

Horizon Scanning in Oncology

Nilotinib (Tasigna[®]) for the 1st-line
treatment of Philadelphia
chromosome positive chronic
myeloid leukemia in the chronic
phase



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Health Technology Assessment

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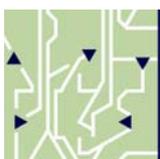
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1 Drug description

Generic/Brand name/ATC code:

Nilotinib, AMN107 / Tassigna[®] / L01XE08

nilotinib (Tassigna[®])

Developer/Company:

Novartis Europharm Ltd

Novartis Europharm Ltd

Description:

Nilotinib is a synthetic aminopyrimidine and an analogue of imatinib¹ that inhibits the BCR-ABL tyrosine-kinase [1]. BCR-ABL is the oncogenic product of the Philadelphia (Ph+) chromosome, which is present in >90% of cancer cells of all adult patients suffering from chronic myeloid leukaemia (CML). The BCR-ABL fusion protein acts as a tyrosine-kinase inhibitor (TKI) mediating the development and maintenance of CML through interaction with multiple downstream signalling partners, resulting in altered cellular adhesion, activation of mitogenic signalling and inhibition of apoptosis, leading to the transformation of hematopoietic stem cells. Briefly, TKIs have the ability to significantly reduce the proliferation of BCR-ABL positive CML cells by inhibiting the BCR-ABL pathway [2].

90% of adult CML are Ph+

reduction of proliferation by inhibition of the BCR-ABL pathway

The current standard of care in 1st-line therapy is imatinib, the first in-class TKI. Studies show that nilotinib is highly selective for BCR-ABL, binding to wild-type BCR-ABL with 10-50 times the affinity of imatinib. Further, nilotinib shows in vitro activity against imatinib-resistant mutants [1, 3].

highly selective for BCR-ABL

Both, the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (US FDA) recommend nilotinib at a dose of 400mg, administered orally twice a day for the treatment of CML patients in the chronic or accelerated phase who are intolerant or resistant to imatinib [4-5]. For the 1st-line therapy of Ph+ CML, the US FDA recommends 300mg given twice daily, whereas the EMA has not yet published a recommended dose of nilotinib for the 1st-line treatment of Ph+ CML [6-7]. Nilotinib should be administered as long as the patient continues to benefit [3]. The median duration of nilotinib 1st-line therapy in Ph+ CML-CP can only be estimated [8]. Nilotinib has to be used with caution in patients having severe problems with their liver or who suffer from certain heart problems [3].

1st-line therapy: 300mg twice daily

2nd-line therapy: 400mg twice daily

median treatment duration not yet known

2 Indication

Nilotinib is indicated for the 1st-line treatment of patients with Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase (CP) (Ph+ CML-CP).

1st-line therapy of Ph+ CML-CP

¹ Imatinib is another tyrosine kinase inhibitor (TKI), which is currently standard of care in the 1st-line therapy of Ph+ CML-CP. For details see Chapters 4 and 5.

3 Current regulatory status

2006: orphan drug designation

2007: approval for 2nd-line therapy

2010: CHMP recommends approval for 1st-line therapy

FDA: approved for 1st- and 2nd-line therapy

Orphan drug designation for nilotinib was granted for the treatment of CML in May 2006 by the EMA. In November 2007, the European Commission approved Tasigna[®] for the treatment of adult patients with chronic phase and accelerated phase Ph+ CML with intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis were not available [7].

In September 2010, EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of marketing authorisation for the medicinal product Tasigna[®]. The CHMP adopted a positive opinion to recommend nilotinib for the treatment of adult patients with newly diagnosed Ph+ CML-CP patients [7].

The US FDA approved nilotinib for the 2nd-line therapy in adult patients with Ph+ CML-CP in October 2007 and for the 1st-line therapy of Ph+ CML-CP patients in June 2010 [9].

4 Burden of disease

a clonal haematopoietic stem-cell disorder

CML is initially diagnosed by typical findings in the blood

3 phases – chronic phase, accelerated phase and blast crisis

CML is a clonal haematopoietic stem-cell disorder resulting in a dysregulated production and uncontrolled proliferation of mature and maturing granulocytes (i.e. white blood cells) [10]. CML is one of the few malignant diseases triggered by a single oncogene – the BCR-ABL fusion protein, which acts as an active kinase. Thus, kinase inhibitors such as imatinib, nilotinib and dasatinib are efficacious in the CML-CP therapy by blocking the activity of BCR-ABL [11]. CML is initially diagnosed by typical findings in the blood and in the bone marrow. Blood tests at diagnosis include a complete blood count with microscopic differential count, assessment of BCR-ABL mRNA transcripts, assessment of serum tryptase level, cytogenetic analysis, and HLA-typing [12]. Investigations for the staging of CML include a chest X-ray, electrocardiogram and echocardiogram, if needed (e.g. when a relevant co-existing cardiac disease is suspected). Further, depending on the clinical situation and symptoms, a computed tomography, neurologic tests or a lumbar puncture may be required. Details about diagnosis and staging are described in more detail elsewhere [12-14].

CML has basically three different stages – chronic phase, accelerated phase and blast crisis. The initial chronic phase (CP) can be asymptomatic and if left untreated the disease will progress at random to an accelerated phase (AP) and then to fatal blast crisis (BC) within 3 to 5 years [15]. After 2002, with the introduction of imatinib as 1st-line therapy in CML, the 5-year survival rate improved from 53% (1999-2005) to 89% [15].

Despite different definitions of accelerated phase and blast crisis, the phase of the disease strongly influences the response to therapy, the duration of the response and overall survival (OS) with better results for chronic phase than for accelerated phase and for accelerated phase than for blast crisis [16]. Typical symptoms of CML are fatigue, weight loss, sweating and abdominal discomfort from an enlarged spleen [14].

CML accounts for approximately 15-20% of all adult leukaemia patients [3, 17] with a yearly incidence of 1 in 100,000 of population in Western countries [3]. CML is uncommon in children and accounts for less than 5% of all childhood leukaemias. Men are generally more often affected than women (3:2) and the incidence increases steadily [3] with age. Median age is 55-66 years at time of diagnosis [2, 15].

Approximately 90-95% of patients are diagnosed in the CP of their disease [18] and more than 90% of CML patients are Philadelphia chromosome positive [2].

In the treatment management of CML, several prognostic factors have been identified, which can be categorised in baseline factors and response-related factors. Whereas baseline factors such as phase of the disease and risk scores (e.g.: encompassing phase of the disease, blast cell counts, basophils, spleen size and cytopenias [12]) can be identified *prior to* the treatment, response-related factors like cytogenetic, hematologic and molecular response (CyR, HR, MoLR) are prognostic factors that can be identified *during* the treatment of CML [16, 19]. As these prognostic factors were established based on efficacy data of the 1st-line treatment of CML patients with imatinib and recombinant interferon-alpha (rIFN α), the European LeukemiaNet [20] points out that these prognostic factors cannot necessarily be applied to nilotinib or dasatinib, two second-generation TKIs targeting the BCR-ABL fusion gene due to several reasons – short follow-up of existing studies and more rapid responses to dasatinib and nilotinib therapy compared to imatinib therapy, saying that if a patient has not achieved a CyR at 3 months or a less than minor CyR at 6 months, the probability of achieving a complete CyR (CCyR) later on is small. Thus, prognostic factors regarding the 1st-line therapy in Ph+ CML-CP with nilotinib or dasatinib are not yet finally established [20].

In Austria, the overall incidence of leukaemia was 894 patients, of which 489 are male and 405 female in 2008 [21]. Applying the above mentioned estimates, the incidence of newly diagnosed Ph+ CML-CP patients is approximately 110 per year in Austria.

phase of disease as prognostic factor

symptoms: fatigue, weight loss, sweating, abdominal discomfort

CML accounts for ~20% of leukaemia

median age at diagnosis: 55-66 years

90% of CML patients are Ph+

prognostic factors: differentiation between baseline factors and response-related factors

prognostic scores not finally established for therapy with second-generation TKIs

~ 110 Ph+ CML-CP patients newly diagnosed per year

5 Current treatment

Since December 2002, imatinib mesylate (IM) at a dose of 400mg once daily is approved as 1st-line therapy for CML and is currently considered to be standard of care in newly diagnosed CML-CP patients [14, 17, 22].

The motivation for treatments other than IM are intolerance or excess toxicity, treatment failure, development of BCR-ABL resistant mutations and suboptimal response [16]. Therapy options for those patients are:

- Imatinib dose escalation to 600-800mg/kg,

standard of care: imatinib 400mg once daily

<p>other treatment options: rIFNα, hydroxyurea, low-dose arabinosyl cytosine or alloHSCT</p> <p>alloHSCT: potential to cure CML</p> <p>intolerance and resistance to imatinib</p> <p>treatment options for imatinib resistant or intolerant patients: second-generation TKIs</p> <p>CHMP recommends approval of nilotinib and dasatinib for 1st-line therapy</p> <p>NCCN guidelines: category 1 treatment options</p>	<ul style="list-style-type: none"> - rIFNα, - chemotherapeutic drugs such as hydroxyurea , low-dose arabinosyl cytosine - or allogeneic hematopoietic stem cell transplantation (alloHSCT), for those patients who are eligible [14, 23]. <p>Though, alloHSCT is considered to be the only possible treatment to cure CML, imatinib is still the 1st-line therapy of choice for CML-CP. This is because of transplant-associated morbidity and mortality and also because of limited efficacy (e.g., 5-year survival rate: 25-70% for alloHSCT vs. 6-year survival rate of 88% with imatinib therapy) and tolerability [11].</p> <p>Despite the positive results of the pivotal imatinib study (IRIS), 18% of patients do not achieve a CCyR, approximately 10% of patients who achieve CCyR eventually lose their response and 4% to 8% are intolerant to imatinib. This results in 30-35% of patients whose outcome with imatinib is not optimal [22]. Some population-based series even describe an higher necessity for 2nd line treatments of 51% as presented at the 2010 annual meeting of the American Society of Hematology [24].</p> <p>Therefore, new strategies for the treatment of imatinib intolerant or resistant patients need to be established. Current options for these patients are:</p> <ul style="list-style-type: none"> - Higher doses of imatinib, or combination therapy - or the use of second-generation TKI like dasatinib, nilotinib and bosutinib [22]. <p>In vitro and clinical study results show that these newer TKIs are generally more potent inhibitors of BCR-ABL kinase activity and are active against most imatinib-resistant tumours harbouring BCR-ABL kinase domain mutations. Nilotinib and dasatinib have already demonstrated high efficacy with a favourable toxicity profile in CML after failure of imatinib [22].</p> <p>For both new second-generation TKIs, nilotinib and dasatinib, the CHMP adopted a positive opinion recommending these new agents for the 1st-line treatment of Ph+ CML-CP [7, 25].</p> <p>Within the latest version of the CML clinical practice guideline of the National Comprehensive Cancer Network (NCCN) all three TKIs, imatinib, nilotinib and dasatinib, are considered to be category 1² treatment options for 1st-line therapy of adult patients with Ph+ CML-CP [17].</p>
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² Category 1 recommendation: based on high-level evidence (i.e., high-powered randomized clinical trials or meta-analyses), and the NCCN Guidelines Panel has reached uniform consensus that the recommendation is indicated. In this context, uniform means near unanimous positive support with some possible neutral positions [26].

6 Evidence

Based on a literature search, limited to the last five years, one phase III trial and two phase II trials evaluating the efficacy and safety of nilotinib as 1st-line therapy in Ph+ CML-CP patients were identified.

1 phase III and 3 phase II trials

The phase III trial, called Evaluating Nilotinib Efficacy and Safety in Clinical Trials- Newly Diagnosed Patients (ENESTnd), investigated in three treatment arms the efficacy and safety of two different dosing regimens of nilotinib (300mg and 400mg twice daily), both compared to imatinib 400mg once daily. Based on the analysis of the primary and key secondary endpoint, both nilotinib arms were considered to be more potent than imatinib. Whereas, hematologic adverse events (AEs) occurred more frequent in the imatinib treated group, non-hematologic AEs and laboratory abnormalities occurred more often in the nilotinib treated groups. The majority of the AEs were of grade 1 and 2 and all were considered to be clinically manageable [8, 27].

ENESTnd – pivotal phase III trial

**nilotinib 300mg/
nilotinib 400mg twice
daily vs. imatinib
400mg once daily**

The aim of two phase II trials was to investigate the efficacy and safety of nilotinib 400mg in newly diagnosed Ph+ CML-CP patients. The results of both trials indicate that nilotinib as front-line therapy is both, clinically effective and safe [22, 28].

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title: A Study of Imatinib Versus Nilotinib in Adult Patients With Newly Diagnosed Philadelphia Chromosome Positive (Ph+) Chronic Myelogenous Leukemia in Chronic Phase (CML-CP) (ENESTnd)			
Median 14-months follow-up: Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia [8]			
Median 18-months follow-up: ENESTnd Update: Continued Superiority of Nilotinib Versus Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) [27]			
Study identifier	ClinicalTrial.gov: NCT00471497, CAMN107A2303, EUDRACT 2007-000208-34		
Design	randomized (1:1:1 ratio), open-label, multicenter		
	Duration of main phase	Data of the 12-month visit of the last patient randomized and 18-months median follow-up are available; Study start: July 2007; Estimated primary completion date: May 2013	
Hypothesis	Superiority – 90% power to detect 15% (55% vs. 40%) increase in MMR rate for the nilotinib arms vs. imatinib arm		
Treatment groups	Intervention 1	Oral nilotinib 300mg twice daily, 282 patients	
	Intervention 2	Oral nilotinib 400mg twice daily, 281 patients	
	Control	Oral imatinib 400mg once daily, 283 patients	
Endpoints and definitions [8, 20]	Major molecular response rate	MMR	a \geq 3.0 log reduction in BCR-ABL transcripts compared to the standardized baseline or \leq 0.1 % BCR-ABL/ABL % by international scale as measured by RQ-PCR, confirmed by duplicate analysis of the same sample
	Complete cytogenetic response	CCyR	0% Ph+ metaphases

	Progression to accelerated phase (AP) or blast crisis (BC)	Progression to AP or BC	the time from the date of randomization to the date of earliest progression-defining event (limited to transformation to blast crisis, accelerated phase disease, or death from any cause).	
	Time to MMR	-	time from the date of randomization to the date of the first documented MMR	
Database lock	September 2, 2009 (on the basis of the 12-month visit of the last patient who underwent randomization [8]); ENESTnd Update: 18-months median follow-up data [27] Estimated primary completion date: May 2013			
Results and analysis				
Analysis description	Primary analysis: intention-to-treat analysis			
Analysis population and time point description	<p>Characteristics: 846 patients with a median age of 47 years (range 18-85), Sokal risk group well balanced across all three study groups – low: 37% (n=310); intermediate: 36% (n=302); high: 28% (n=234)</p> <p>Inclusion: Ph+ CML-CP as determined by conventional cytogenetic analysis of bone marrow, ECOG ≤2</p> <p>Exclusion: prior TKI therapy</p>			
Results	Treatment group	Intervention 1	Intervention 2	Control
	Number of subjects	282	281	283
	MMR at 12 months, %	44 p < 0.001*	43 p < 0.001*	22
	at 18 months, %	66 p < 0.0001*	62 p < 0.0001*	40
	CCyR at 12 months, %	80 p < 0.001*	78 p < 0.001*	65
	at 18 months, %	85 p < 0.001*	82 p = 0.017*	74
	Progression to AP or BC at 12 months, no (%)	2 (<1) p = 0.01**	1 (<1) p = 0.004**	11 (4)
	at 18 months (including clonal evolution), no (%)	2 (0.7) p < 0.001**	3 (1.2) p = 0.003**	12 (4.2)
	MMR by Sokal risk score at 12 months, % <i>low</i> <i>intermediate</i> <i>high</i>	 n.r. n.r. 41	 n.r. n.r. 32	 n.r. n.r. 17
	at 18 months, % <i>low</i> <i>intermediate</i> <i>high</i>	 70 67 59	 69 63 51	 51 39 28
	Median time to MMR, months	8.6	11	Median not yet achieved
	Estimated OS rate at 18 months, %	98.5 p = 0.28**	99.3 p = 0.03**	96.9
	Notes	<ul style="list-style-type: none"> An escalation of the imatinib dose to 400 mg twice daily was permitted in patients who had a suboptimal response or treatment failure, as defined by the European LeukemiaNet [20] Crossover was not permitted according to the study protocol. Instead, patients were eligible to participate in an extension study. 		

* Cochran-Mantel-Haenszel test stratified by Sokal risk group vs imatinib

** Log-rank test stratified by Sokal vs imatinib for time to AP/BC and OS

n.r. – not reported

Table 2: Most frequent adverse events (AE)

		ENESTnd – NCT00471497		
Grade	Outcome (%)	Group A (n= 279)	Group B (n=277)	Group C (n=280)
Non-hematologic AEs				
All Grades	Rash	31%	36%	11%
	Headache	14%	21%	8%
	Nausea	11%	19%	31%
	Pruritus	15%	13%	5%
Grade 3 or 4	Rash	<1%	3%	1%
	Headache	1%	1%	0%
	Nausea	<1%	1%	0%
	Fatigue	0%	1%	<1%
	Vomiting	0%	1%	0%
	Diarrhoea	1%	0%	1%
Hematologic abnormalities				
Any grade	Neutropenia	43%	38%	68%
	Thrombocytopenia	48%	49%	56%
	Anaemia	38%	38%	47%
Grade 3 or 4	Neutropenia	12%	10%	20%
	Thrombocytopenia	10%	12%	9%
	Anaemia	3%	3%	5%
Biochemical abnormalities				
Any grade	Increased total bilirubin	53%	62%	10%
	Increased glucose	36%	41%	20%
	Increased ALT	66%	73%	20%
	Increased AST	40%	48%	23%
Grade 3 or 4	Increased total bilirubin	4%	8%	<1%
	Decreased phosphate	5%	5%	8%
	Increased glucose	6%	4%	0%
	Increased lipase	6%	6%	3%
	Increased ALT	4%	9%	2%

846 patients newly diagnosed with Ph+ CML-CP were randomly allocated to three different study groups and stratified according to the Sokal risk³ score at time of diagnosis. Even though durable major molecular response rate was defined as the key secondary endpoint, the main secondary outcome for this publication, which reports interim results after the 12-months visit of the last randomized patient was CCyR. Statistically improved outcomes for both groups treated with nilotinib in comparison to imatinib were found for MMR rate and CCyR rate.

**random allocation
stratified according to
Sokal risk score**

³ The Sokal risk score is based on age, spleen size, and peripheral-blood platelet count and blast count. Patients are classified as being low-risk (Sokal score, <0.8), intermediate-risk (0.8-1.2), or high-risk (>1.2) [8].

<p>dose reductions more frequent in nilotinib treated pts than in imatinib group</p> <p>9 pts died</p>	<p>Besides the above mentioned non-hematologic, hematologic AEs and laboratory abnormalities the following events have to be pointed out. Dose reductions or interruptions occurred in 59% of nilotinib 300mg group, 66% of the nilotinib 400mg group and in 52% of the imatinib 400mg group. All in all, 5%, 9% and 7% of patients of the nilotinib 300mg and 400mg groups and the imatinib 400mg group, respectively, discontinued the study due to AEs and 9 patients died until time of data cut-off at the 12-months visit of the last randomized patient. Within the nilotinib 300mg group, 2 patients died during the study (one from suicide and the other one from a small-intestine obstruction) and one patient died during follow-up after bone marrow transplantation. Two patients in the nilotinib 400mg group discontinued treatment due to disease progression and both died during follow-up - one due to gastric cancer. Within the imatinib group four patients discontinued treatment because of disease progression and died during follow-up. At the 18-month median follow-up analysis, 16 patients had died. 11 (2, 1, 8 in the intervention 1, 2 groups and control group respectively) of these deaths were considered to be CML-related.</p>
<h2>6.2 Efficacy and safety - further studies</h2>	
<p>98% of pts achieved CCyR at any time</p> <p>24% pts achieved CMR</p>	<p>Cortes et al. 2010 [22] investigated nilotinib (400mg twice daily) as 1st-line therapy for the treatment of early chronic phase (ECP) CML in a single-arm phase II study. 61 patients with a median age of 46 years were included. Prior to nilotinib therapy, 12 patients had received imatinib. Out of the 61 patients, 51 had been observed for at least 3 months and were thus evaluable for cytogenetic and molecular response analysis. 98% of patients achieved a CCyR at any time, 76% achieved a MMR and 24% patients achieved a complete molecular response (CMR).</p>
<p>nilotinib side-effects are clinically manageable and tolerable</p>	<p>Regarding AEs, the most common non-hematologic ones of grade 3-4 were elevations of the liver enzyme bilirubin (7%), hyperglycaemia, non-neutropenic fever and lipase elevations (each 5%). The most common hematologic AEs of any grade (Grade 3-4) were neutropenia 52% (12%), anaemia 49% (5%) and thrombocytopenia 43% (11%). All in all, 24 patients (37%) required at least one treatment interruption and dose reductions were required in 11 patients (17%). 4 patients discontinued therapy due to adverse events and 2 due to progression to blast crisis.</p>
<p>at 12 months:</p> <p>97% CHR</p> <p>96% CCyR</p>	<p>The GINEMA CML Working Party [28] conducted an open-label, single-stage, multicentric phase II trial (ClinicalTrials.gov: NCT00481052) to investigate the safety and efficacy of 400mg nilotinib twice daily in patients with ECP Ph+ CML. 73 patients with a median age of 51 years were enrolled. At 12 months 71 patients (97%) showed complete hematologic response (CHR) and 70 patients (96%) had CCyR. Non-hematologic AEs of all grades occurring in at least 20% of patients were skin rash (grade 3: 5%), bone/muscle/joint pain (grade 3: 4%), headache, dry eyes, fatigue and pruritus (grade 3: 4%). Biochemical laboratory abnormalities occurring in at least 20% of patients were elevations of bilirubin (any grade: 53% / grade 3: 16%), ALT (42% / 8%), γ-GT (36% / 7%), AST (29% / 3%) and lipase (29% / 8%). Hematologic AEs (grade \leq2/3/4) were anaemia (16%/NR/NR), neutropenia (10/3/1%) and thrombocytopenia (1/1/1%). At least one temporary dose interruption is reported in 38 patients (52%) due to biochemical laboratory abnormalities and non-hematologic AEs [28]. After</p>

30 months the overall survival, progression-free survival and failure-free survival were 99% and the event-free survival was 92% [29].

7 Estimated costs

Currently, no price estimates are available for nilotinib in Austria. However, the price for one package imatinib including 30 pieces of 400mg tablets is € 2,677 [30]. As the approved daily dose of imatinib is 400mg, monthly treatment costs for imatinib are around € 2,700.-. Due to expiring patents for imatinib, these costs are estimated to drop sharply in the near future. Like imatinib, nilotinib is a TKI targeting the BCR-ABL protein and is expected to be approved for 1st-line therapy of Ph+ CML-CP soon. Even though data of the pivotal ENESTnd trial indicate that nilotinib is more effective than imatinib, long-term follow-up data are required to compare duration of response and survival data of nilotinib and imatinib. Provided that their efficacy profile is comparable, diagnostic tests for specific BCR-ABL mutations might be necessary to choose the best therapy.

no price for nilotinib available in Austria

Further, no data on the median duration of 1st-line nilotinib therapy are available yet. As imatinib is able to suppress leukemic cell growth for prolonged time periods but cannot eradicate the disease, life-long imatinib therapy appears to be required in patients responding to the therapy [12]. Considering that nilotinib is able to reduce the proliferation of BCR-ABL positive CML cells, but does not cure CML, these considerations might also hold true for nilotinib therapy [2].

life-long therapy?

8 On-going research

By searching www.clinicaltrial.gov (search restrictions: nilotinib + phase III) 16 phase III trials assessing the efficacy and safety in nilotinib in different indications were identified. Besides 10 phase III trials of nilotinib as 1st- or 2nd-line therapy in CML, 5 trials for gastrointestinal stromal tumours (GIST) and one trial for melanoma were registered by November 2010 at ClinicalTrials.gov [31].

16 phase III trials assessing the efficacy and safety of nilotinib registered at ClinicalTrials.gov

1st-line CML therapy:

- [NCT00471497 \(ENESTnd\)](https://clinicaltrials.gov/ct2/show/study/NCT00471497): first interim results of this pivotal phase III trial are presented in Chapter 6.1. The primary completion date is estimated to be May 2013.
- [NCT01061177 \(ENEST1st\)](https://clinicaltrials.gov/ct2/show/study/NCT01061177): a phase IIIb, multicenter, open-label trial evaluating the safety and efficacy of nilotinib in adult patients newly diagnosed with Ph+/BCR-ABL positive CML-CP. The primary completion date is estimated to be December 2013.

1st-line nilotinib in CML – 2 phase III studies registered

2nd-line CML therapy:

- [NCT00519090 \(ENEST\)](https://clinicaltrials.gov/ct2/show/study/NCT00519090): a randomized, open-label, multicenter phase III study evaluating the efficacy and safety of nilotinib

400mg twice daily compared to imatinib 400mg once daily in Ph+ CML-CP patients with suboptimal cytogenetic response to imatinib. The study has been terminated in 2009.

- NCT00802841 (LASOR): a phase III trial evaluating the efficacy of nilotinib compared to imatinib in CHML patients with suboptimal response to standard-dose imatinib. The study started in June 2009 and primary completion date is estimated to be March 2013.
- NCT00760877 (ENESTcmr): a phase III open-label, randomized trial with the aim to determine the rate of confirmed best cumulative complete molecular response within the first year of study therapy with imatinib or nilotinib in patients with CML-CP. The primary completion time for the primary outcome data collection is November 2013.
- NCT00905593 / NCT01126892 / NCT00786812 (ENACT): an open-label, non-randomized multi-center phase III trial evaluating the long-term safety and efficacy of nilotinib in patients with imatinib resistant or intolerant CML in blast crisis, accelerated or chronic phase. It is estimated that approximately 20 patients of the ongoing CAMN107A2109 trial in three Mexican centers will be enrolled to this study. The primary completion date is estimated to be April 2011.
- NCT00718263: this extension study of a phase III multicenter, open-label randomized trial of imatinib versus nilotinib is evaluating the safety and efficacy of nilotinib after the failure of imatinib therapy or imatinib after nilotinib failure. The estimated primary completion date is expected to be May 2018.
- NCT00413270: an open-label, multicenter study to evaluate the safety of nilotinib in CML patients with imatinib intolerance or resistance in all three phases – chronic, accelerated phase and blast crisis. Estimated completion date of this study is not mentioned.
- NCT01126892: an open-label, multicenter phase III study evaluating the safety and efficacy of nilotinib in adult patients with Ph+ CML patients who are resistant or intolerant to imatinib. The primary completion date is expected to be January 2011.
- NCT00302016: an open-label, multicenter expanded access study of nilotinib in adult CML patients with imatinib intolerance or resistance. The study has already been completed.

other indications: AML, ALL, GIST, melanoma, acoustic neuromas, ...

Additionally to these phase III trials, several phase I and II trials evaluating the safety and efficacy in nilotinib in the following indications are registered at www.clinicaltrials.gov:

Acute myeloid leukaemia, acute lymphoblastic leukaemia, GIST, melanoma, acoustic neuromas (also known as vestibular schwannoma), systemic sclerosis, pigmented villonodular synovitis/diffuse-type giant cell tumour/tenosynovial giant cell tumour, malignant gliomas and non-Hodgkin's lymphoma.

9 Commentary

Since 2002, imatinib is the therapy of choice for 1st-line treatment of Ph+ CML-CP patients. As approximately 30% to 51% of these patients develop resistance or are intolerant to imatinib therapy, therefore other therapy options are needed. Two second-generation TKIs, nilotinib and dasatinib are active in 2nd-line therapy of Ph+ CML-CP patients resistant or intolerant to imatinib and are more potent against BCR-ABL in vitro [1, 23]. The frequency of BCR-ABL mutations conferring resistance to TKI treatment seems to be higher with imatinib [32]. The efficacy and safety of both agents in the 1st-line therapy of Ph+ CML-CP is currently studied in ongoing phase III studies [1].

The CHMP of the EMA adopted a positive opinion recommending nilotinib for the 1st-line treatment of Ph+ CML-CP patients in October 2010. During the same meeting, the CHMP also adopted a positive opinion for the approval of dasatinib (Sprycel®), another 2nd-generation TKI targeting BCR-ABL mutations against which imatinib is resistant, for the frontline therapy in Ph+ CML-CP patients. Nilotinib and dasatinib are already approved for the 2nd-line therapy of Ph+ CML-CP patients which are resistant or intolerant to imatinib [25].

Saglio et al. (2010) conducted a phase III trial investigating whether nilotinib is more effective than imatinib in the 1st-line treatment of Ph+ CML-CP. The results of the first interim analysis at the 12-months visit of the last randomized patient and an update at a median follow-up at 18 months are presented in chapter 6.1. Overall 846 patients were included in this study. With a median age of 47 years the study population was slightly younger than patients usually are at diagnosis. The surrogate endpoints major molecular response (MMR) and complete cytogenetic response (CCyR) indicate that nilotinib is more effective than imatinib with a MMR of 66% and 62% vs. 40%, for nilotinib 300mg, nilotinib 400mg and imatinib 400mg, respectively. Also the key secondary endpoint (CCyR), confirmed the superiority of nilotinib to imatinib with a CCyR of 85% in the nilotinib 300mg group, 82% in the nilotinib 400mg group and 74% in the imatinib 400mg group at 12 months [33]. Progression to AP and BC was significantly lower in both nilotinib treated groups compared to the imatinib treated group with 0.7% (p=0.006) in the nilotinib 300mg group, 0.4% (p=0.003) in the nilotinib 400mg group and 4.2% in the imatinib 400mg group [27]. Whereas both drugs showed good safety profiles with the majority of AEs being of grade 1 or 2, some differences between nilotinib and imatinib have to be pointed out. The most frequent grade 3/4 AEs are neutropenia around 11% vs. 20%, thrombocytopenia 11% vs. 9%, anaemia 3% vs. 5%, increased total bilirubin 6% vs. <1%, decreased phosphate 5% vs. 8%, increased glucose 5% vs. 0%, increased ALT 7% vs. 2% and increased AST 2% vs. 1% for the nilotinib groups compared to the imatinib group, respectively. The authors concluded that the observed AEs were clinically manageable and acceptable [8].

~30% of pts are resistant or intolerant to imatinib

CHMP adopted positive opinion to recommend nilotinib and dasatinib as 1st-line therapy in Ph+ CML-CP pts

surrogate endpoints MMR and CCyR – both indicate that nilotinib is more effective than imatinib

median age at diagnosis vs. pts included in the trial: 55-66 vs. 46-47 years

AE profile is considered to be clinically manageable and tolerable

no data on PFS or OS available	Though, the interim results of the pivotal trial indicate that nilotinib is more effective in the treatment of newly diagnosed Ph+ CML-CP patients, a few issues have to be pointed out. Hematologic response and CyR are considered to be surrogate endpoints reasonably likely to predict the clinical effectiveness in CML-CP patients [34] but the question is how these favourable response rates translate into progression-free survival (PFS) and finally into overall survival (OS). Therefore, further follow-up is essential to provide information on the durability of the responses, on the development of potential treatment resistance and to further investigate the toxicity and AE profile of nilotinib in the 1 st -line therapy of CML [8].
further follow-up is necessary	
QoL data not yet available	The evaluation of the quality-of-life (QoL) of Ph+ CML-CP patients treated with nilotinib is another issue that needs to be investigated within clinical trials. Ideally, the QoL evaluation will also be conducted in patients treated with imatinib and dasatinib and compared to each other.
head-to-head comparison of nilotinib and dasatinib	Both, nilotinib and dasatinib have been directly compared to imatinib and have shown favourable results [8, 35] confirmed by a systematic review and meta-analysis [36]. To be able to estimate the different therapeutic effects of these two 2 nd -generation TKIs, a head-to-head trial comparing the efficacy and safety of these two agents is needed.
	Currently, no price for nilotinib is available in Austria. Therefore, the costs of nilotinib therapy cannot be directly compared to the costs of imatinib therapy. As, both are TKIs targeting the BCR-ABL and are indicated for the treatment of Ph+ CML-CP, the monthly treatment costs can be assumed to be comparable until the patent of imatinib expires.
	Despite the fact that the results of the 12-month and 18-month median follow-up data are encouraging and are expected to have the potential to be at least as effective as imatinib in the frontline therapy of Ph+ CML-CP [13, 23], mature data on PFS, OS, safety profile and QoL have to be awaited to confirm these estimates.

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