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Nilotinib

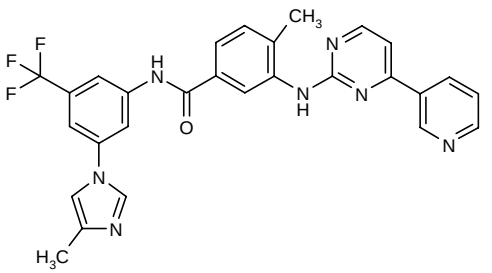
Rec INN; USAN

Bcr-Abl Kinase Inhibitor
Apoptosis Inducer
Oncolytic

AMN-107
Tasigna®

4-Methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[4-(3-pyridyl)pyrimidin-2-ylamino]benzamide

InChI=1/C28H22F3N7O/c1-17-5-6-19(10-25(17)37-27-33-9-7-24(36-27)20-4-3-8-32-14-20)26(39)35-22-11-21(28(29,30)31)12-23(13-22)38-15-18(2)34-16-38/h3-16H,1-2H3,(H,35,39)(H,33,36,37)



$C_{28}H_{22}F_3N_7O$
Mol wt: 529.5161

CAS: 641571-10-0

EN: 386178

Abstract

Nilotinib (AMN-107, Tasigna®; Novartis) is a phenylaminopyrimidine derivative structurally related to imatinib mesilate (STI-571, Gleevec®/Glivec®). It acts as a signal transduction inhibitor that potently and selectively inhibits the tyrosine kinase Bcr-Abl, with additional activity against the stem cell factor receptor Kit and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. As a result of its ability to target tyrosine kinases, nilotinib has been investigated in chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL) and other hematological malignancies, such as systemic mastocytosis and hypereosinophilic syndrome/chronic eosinophilic leukemia, with preclinical and clinical data indicating efficacy against imatinib-resistant, clinically problematic tyrosine kinase mutations. Novartis is currently pursuing phase II/III trials in these conditions, and the company submitted the drug for approval in the U.S. and E.U. in 2006 in adult patients with Philadelphia chromosome-positive (Ph+) CML displaying resistance and/or intolerance to imatinib. Studies have also demonstrated activity against gastrointestinal stromal tumors (GISTs) and phase I trials are ongoing.

Synthesis

The condensation of 3-fluoro-5-(trifluoromethyl)benzonitrile (I) with 2-methylimidazole (II) in hot *N,N*-dimethylacetamide affords the imidazolyl benzonitrile (III), which is hydrolyzed to the corresponding benzoic acid (IV) employing NaOH in aqueous dioxan. Subsequent Curtius rearrangement of acid (IV) in *tert*-butanol in the presence of diphenylphosphoryl azide, followed by acidic hydrolysis of the resulting *tert*-butyl carbamate (V), yields 3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)aniline (VI). The condensation of 3-amino-4-methylbenzoic acid methyl ester (VII) with cyanamide in refluxing ethanolic HCl gives the 3-guanidinobenzoate (VIII) (1). Claisen condensation of 3-acetylpyridine (IX) with ethyl formate by means of sodium metal in hot toluene, followed by treatment with dimethylamine, gives the enamino ketone (X) (2), which is cyclized with guanidine (VIII) in refluxing ethanolic NaOH to produce the pyridylpyrimidine (XI). After saponification of ethyl ester (XI) with NaOH in hot aqueous ethanol, the 4-methyl-3-[4-(3-pyridyl)pyrimidin-2-ylamino]benzoic acid (XII) obtained is finally coupled with aniline (VI) employing diethyl cyanophosphate to furnish the corresponding amide nilotinib (1). Scheme 1.

Background

Chronic myelogenous leukemia (CML) accounts for approximately 20% of all leukemia cases and is generally believed to develop when a single multipotent hematopoietic stem cell (HSC) undergoes genetic rearrangement between chromosomes 9 and 22, resulting in an abnormal truncated chromosome 22 known as the Philadelphia (Ph) chromosome. This translocation also involves the fusion of part of the *BCR* (breakpoint cluster region) gene from chromosome 22 (region q11) with part of the *ABL* (Abelson leukemia) gene on chro-

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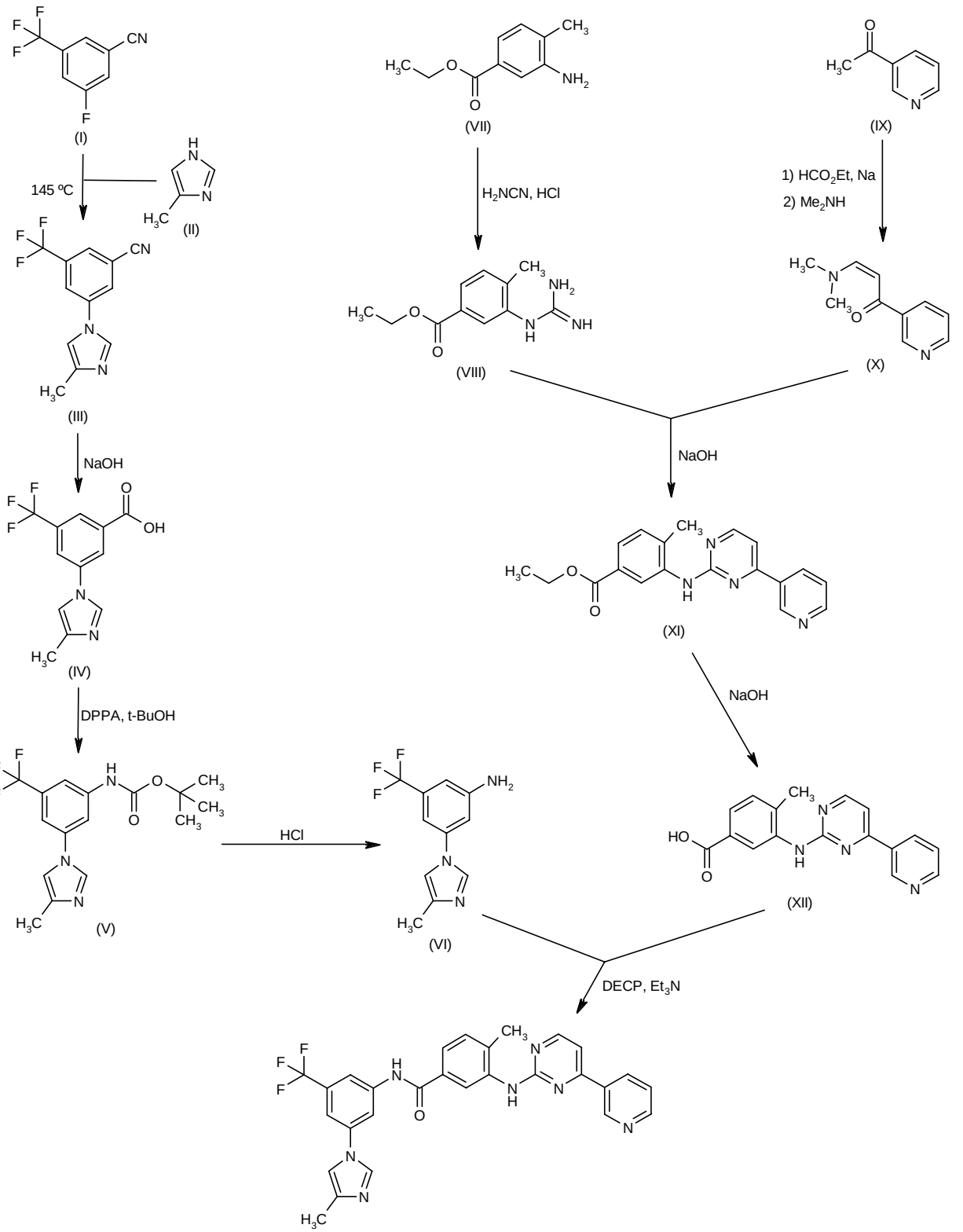
Scheme 1: Synthesis of Nilotinib



mosome 9 (region q34). The *BCR-ABL* fusion gene transcript is constitutively expressed and, being a tyrosine kinase, triggers uncontrolled activation of a number of cell cycle-controlling proteins, accelerating cell division and contributing to malignant transformation of normal bone marrow progenitor cells (3-10). Allogeneic stem cell transplantation (SCT) is the only known curative therapy for CML. However, many patients are not eligible for this therapy because of advanced age or lack of a suitable stem cell donor (3, 11, 12). The discoveries that Bcr-Abl is required for CML pathogenesis and that the tyrosine kinase activity of Abl is essential for Bcr-Abl-mediated transformation have exposed the Abl kinase as an attractive target for therapeutic intervention (3).

Imatinib mesilate (STI-571, Gleevec®/Glivec®), a potent inhibitor of the oncogenic tyrosine kinase Bcr-Abl, has shown remarkable clinical activity in patients with CML. However, resistance as a result of emerging Bcr-Abl mutations has been documented, especially in advanced stages of the disease, driving the development of new agents (13-16). Nilotinib (AMN-107, Tasigna®; Novartis) is a phenylaminopyrimidine derivative structurally related to imatinib that selectively inhibits the Bcr-Abl tyrosine kinase. It has been submitted for U.S. and E.U. approval as a new option for patients displaying resistance and/or intolerance to imatinib for certain forms of Ph+ CML (17).

Preclinical Pharmacology

In vitro assays have shown that nilotinib reduces cellular Bcr-Abl autophosphorylation in (IC_{50} = 42, 60 and 23 nM, respectively) and the proliferation (IC_{50} = 11, 8 and 23 nM, respectively) of the CML cell lines K-562 and KU812F and the pro-B-cell line Ba/F3 expressing wild-type Bcr-Abl, with enhanced potency compared to imatinib (autophosphorylation IC_{50} = 470, 399 and 231 nM, respectively; proliferation IC_{50} = 272, 80 and 643 nM, respectively). This was also evident in cells expressing the imatinib-resistant Bcr-Abl mutants M351T, F317L and E255V, where nilotinib gave IC_{50} values for inhibition of autophosphorylation of 33, 43 and 245 nM, respectively, compared to respective values for imatinib of 595, 818 and 6499 nM, and IC_{50} values for inhibition of proliferation of 30, 77, 684 nM, respectively, *vs.* values for imatinib of 1285, 1583, 6294 nM, respectively. Nilotinib did not affect the Bcr-Abl mutants T315I and G250E at concentrations below 8 μM and had no effect on the proliferation of control Ba/F3 cells at up to 10 μM. Nilotinib was also shown to inhibit the cellular tyrosine kinase activity of platelet-derived growth factor receptor β (PDGFRβ) and c-Kit (IC_{50} = 85 and 192 nM, respectively) in cell-based assays, with similar activity to imatinib (IC_{50} = 74 and 96 nM, respectively) (18).

Nilotinib showed enhanced activity compared to imatinib in Bcr-Abl+ leukemic cell lines (imatinib *vs.* nilotinib IC_{50} = 250 nM *vs.* 80 nM, 450 nM *vs.* 30 nM and 80 nM *vs.* 7.5 nM, respectively, in K-562, KCL-22 and LAMA-84 cells) and in primary cells derived from 2 Bcr-Abl+ CML patients resistant to imatinib (imatinib *vs.* nilotinib IC_{50} = 750 nM *vs.* 100 nM and 4000 nM *vs.* 400 nM) and 1 newly diagnosed CML patient (imatinib *vs.* nilotinib IC_{50} = 5000 nM *vs.* 2500 nM). Complete inhibition of Bcr-Abl tyrosine kinase activity and induction of apoptosis was achieved at lower concentrations in nilotinib-treated samples when compared to imatinib (10 nM *vs.* 5000 nM and 5 nM *vs.* 250 nM, respectively). Nilotinib showed enhanced uptake into cells compared to imatinib, particularly in MDR1-overexpressing cells (19, 20).

Studies have also demonstrated that nilotinib is more effective than imatinib against other CML cell lines. The compound inhibited the proliferation of imatinib-sensitive KBM5 and KBM7 cells with 43-60-fold greater potency than imatinib (IC_{50} = 11.3 nmol/l *vs.* 480.5 nmol/l and 4.3 nmol/l *vs.* 259 nmol/l, respectively). Importantly, nilotinib blocked the proliferation of imatinib-resistant KBM5-STI571R1.0 and KBM7-STI571R1.0 CML cell lines with IC_{50} values of 2418 and 97.2 nmol/l, respectively, compared to respective values for imatinib of 6361 and 2497 nmol/l. Nilotinib was also more effective than imatinib in inhibiting Bcr-Abl phosphorylation (21, 22).

In K-562 leukemia cells, nilotinib 50 nM was found to downregulate the phosphorylation of Bcr-Abl Tyr177, which has been implicated in the pathogenesis of CML, and Tyr412, but not Tyr735, whereas imatinib had no effect at 200 nM. The title compound was also much more potent than imatinib in blocking these cells in the G1 phase, while it had no effect in Bcr-Abl-negative cell lines. Significantly increased apoptosis was seen in CML blasts from patients incubated with low concentrations of nilotinib, while much higher concentrations of imatinib were needed. Furthermore, nilotinib treatment was associated with decreased levels of the p85 regulatory subunit of phosphoinositide 3-kinase (PI3K), STAT5, CBL, CRKL and Akt phosphorylation, and expression of the antiapoptotic protein Bcl-X_L (23-25).

Additional studies confirmed G1 phase accumulation and apoptosis in CML blast-crisis K-562 and LAMA-84 cells treated with nilotinib, and these effects were enhanced when it was combined with LBH-589, a histone deacetylase (HDAC) inhibitor. The synergistic effects in K-562 cells were associated with further attenuated levels of the progrowth and prosurvival proteins phosphorylated CRKL, phosphorylated ERK1/2, Bcl-X_L and c-Myc, and further enhanced expression of the proapoptotic proteins p27 and Bim. Enhanced apoptosis and Bcr-Abl depletion were also seen with co-treatment in Ba/F3 cells expressing wild-type Bcr-Abl or the imatinib-resistant mutants Bcr-AblE255K and Bcr-AblT315I, as well as a greater loss of viability in primary CML blast-crisis cells, including those expressing Bcr-AblT315I (26-28).

It has been suggested that nilotinib may be superior to imatinib in terms of resistance development. Cell-based mutagenesis assays revealed that, in comparison to imatinib, Bcr-Abl kinase mutations recovered in the presence of nilotinib are limited and markedly decrease with increasing concentrations; at 2000 nM, a concentration achievable in patient plasma, only T315I mutations were detected. However, several novel mutations emerged,

most of which also appeared to be resistant to imatinib (29-32). The resistance profiles of nilotinib, imatinib and dasatinib, alone and in combination, were also compared. Nilotinib and dasatinib were associated with fewer Bcr-Abl kinase domain mutations than imatinib, and the number was further reduced at higher drug concentrations, only T315I being detected at high concentrations. Dual combinations of these agents more effectively prevented the outgrwoth of resistant clones (32).

The efficacy of nilotinib was further assessed against a range of imatinib-resistant Bcr-Abl kinase domain mutants comprising > 90% of clinically observed mutations. Nilotinib effectively inhibited the growth of 13 of 16 with an IC_{50} of 200 nM or less (33, 34). Combined application of nilotinib and imatinib against several wild-type and imatinib-resistant Bcr-Abl-expressing cell lines provided an additive or synergistic effect (35).

Using two Ph+ acute lymphoblastic leukemia (ALL) cell lines (Z-119 and Z-181), nilotinib was found to be 30-40 times more potent than imatinib in inhibiting proliferation (IC_{50} = 19.3 and 1.6 nM, respectively, *vs.* 620 and 63.9 nM, respectively). Nilotinib was also more effective than imatinib in inhibiting phosphorylation of p190 Bcr-Abl tyrosine kinase in these cell lines (complete inhibition at concentrations of nilotinib of 125 nM and above compared to 2.5 μM and above for imatinib). Similar results were obtained in primary ALL cells from patients. No effect was observed for either drug in Ph-negative Z-138 ALL lines (36, 37).

Drugs targeting tyrosine kinases, given alone or in combination, may be useful in treating systemic mastocytosis where the Kit mutation D816V is present, which includes the majority of patients. This was confirmed in a study in which PKC-412 (midostaurin) and nilotinib were tested against Ba/F3 cells with inducible Kit D816V expression, as well as human mast cell leukemia HMC-1 cells with the Kit mutation. PKC-412 demonstrated effective growth inhibition of HMC-1 cells and Ba/F3 cells with and without Kit D816V, while nilotinib had a much greater effect on cells without Kit D816V. Enhanced antiproliferative effects were seen with combinations of PKC-412 and nilotinib in HMC-1 cells, with synergistic activity observed in Kit D816V-negative cells and additive effects in Kit D816V-positive cells (38-42). On the other hand, although nilotinib and imatinib displayed similar potency in mast cells carrying the wild-type codon 816 c-Kit (IC_{50} = 108 and 74 nM, respectively), neither agent showed activity against cells with a mutation in codon 816 of c-Kit (CD117), which is commonly associated with the pathogenesis of systemic mastocytosis (43, 44).

Further studies demonstrated that, like imatinib, nilotinib is active *in vitro* and *ex vivo* against the FIP1L1-PDGFRα tyrosine kinase associated with myeloproliferation that occurs in hypereosinophilic syndrome (HES). In MTS assays, the IC_{50} of imatinib and nilotinib against EOL-1 cells harboring the FIP1L1-PDGFRα oncoprotein were 1.2 and 0.54 nM, respectively. Both agents effectively induced apoptosis and reduced phosphorylation of PDGFRα. This effect was also seen in cells from a patient with HES (45).

In vitro studies of nilotinib were performed in imatinib-sensitive GIST882 and imatinib-resistant GIST430 and GIST48 human gastrointestinal stromal tumor (GIST) cell lines. Cell proliferation IC_{50} values for nilotinib and imatinib were 190 and 330 nM, respectively, in GIST882, 900 and > 5000 nM, respectively, in GIST48 and 2000 and > 5000 nM, respectively, in GIST430 cells. Nilotinib more potently inhibited Kit in the imatinib-resistant GIST cell lines (IC_{50} = 20-28 nM *vs.* 105 nM in GIST882) (46). In other experiments, both nilotinib and imatinib potently inhibited the proliferation of GIST882 cell (IC_{50} = 40 and 30 nmol/l, respectively), whereas neither compound inhibited the proliferation of the imatinib-resistant GIST GDG1 cell line. HPLC analysis revealed increased uptake for nilotinib compared to imatinib, suggesting that nilotinib may be less susceptible to multidrug resistance pump-driven imatinib resistance (47, 48).

Experiments in SCID mice with advanced blast-phase CML induced by injecting human KBM5 cells showed that nilotinib treatment (10, 20 and 30 mg/kg/day i.p. for 20 days) prolonged survival by 144%, 159% and 182%, respectively, compared to untreated controls (21).

In mice bearing 32D.p210-luciferase cells, nilotinib (75 mg/kg/day p.o.) reduced the accumulation of leukemia cells in the marrow, lymph nodes, liver and spleen. While 15 of 20 animals survived over 100 days following 16-day nilotinib treatment, all but 1 vehicle-treated animal died within 36 days of cell injection. Nilotinib also prolonged survival in mice transplanted with marrow cells infected with a p210Bcr-Abl retrovirus and in mice transplanted with a Bcr-Abl mutant associated with imatinib resistance (49, 50). Significant and dose-dependent decreases in tumor burden were also seen in athymic nude mice bearing 32D.p210-luciferase cells treated with nilotinib once or twice daily. Daily administration of 50 mg/kg over a period of 14 days resulted in an almost complete inhibition of tumor cell proliferation and spleen weights were observed to be within the disease-free range (51). Further studies in these mice demonstrated that combined nilotinib and imatinib (75 mg/kg) facilitated an overall lower tumor burden compared to mice treated with vehicle or either agent alone (35).

In an *in vivo* bone marrow transplantation assay, nilotinib (75 mg/kg/day p.o. starting on day 11 post-transplantation) effectively treated myeloproliferative disease induced by TEL-PDGFRβ and FIP1L1-PDGFRα, significantly increasing survival (+26 days) and disease latency and reducing disease severity (significantly reduced total white blood cell count and spleen weight compared to placebo) as assessed by histopathology and flow cytometry (52).

Pharmacokinetics and Metabolism

The pharmacokinetics, metabolism and safety of nilotinib were investigated following oral administration to 4 healthy fasting male volunteers. A single dose of 400 mg was well tolerated; mild headache was reported in 3 of 4 of the subjects, although this resolved spontaneously.

Peak serum levels were reached at approximately 4 h postdose, with the terminal half-life calculated as approximately 16 h, supporting once- or twice-daily dosing. Oral absorption was incomplete, with no significant retention of drug and metabolites. Unchanged compound accounted for over two-thirds of the dose recovered, and a carboxylic acid derivative was the major circulating metabolite (53).

Data from patients with CML or Ph+ ALL treated once or twice daily with nilotinib (50-1200 mg/day p.o.) indicated that systemic exposure was dose-dependent, but increased less than proportionally to dose at doses over 400 mg once daily. Exposure was greater following 400 mg b.i.d. than following 800 mg once daily and the former dose provided serum drug levels well above the IC_{50} for inhibition of Bcr-Abl phosphorylation, with a half-life of 15 h. In healthy subjects, administration with a high-fat meal markedly increased bioavailability (54).

Clinical Studies

A phase I/II study was conducted in patients with imatinib-resistant advanced-phase CML, blast-crisis CML and Ph+ ALL, with several reports presenting preliminary data (55-58). More recent clinical data were presented on a total cohort of 119 patients. Oral nilotinib at doses of 50, 100, 200, 400, 600, 800 and 1200 mg once daily and 400 and 600 mg twice daily was generally well tolerated, with myelosuppression (grade 3 or 4 thrombocytopenia in 20%, neutropenia in 13% and anemia in 6%), transient indirect hyperbilirubinemia and skin rash among the most common adverse events. The estimated maximum tolerated dose (MTD) was 600 mg b.i.d., and the dose of 400 mg b.i.d. was associated with similar efficacy and better tolerability. Treatment was active in patients with CML. Of 33 patients with blastic-phase disease, 13 (39%) displayed a hematological response and 9 (27%) had a cytogenetic response. Of 46 patients with accelerated-phase disease, 33 (72%) exhibited a hematological response and 22 (48%) had a cytogenetic response. Complete hematological remission was seen in 11 of 12 patients in the chronic phase. However, only 2 of 13 patients (15%) with Ph+ ALL responded (59-62). Results from this and several of the following studies are shown in Table I.

Additional assays examined the effect of nilotinib on levels of phosphorylated CRKL, a downstream effector of Bcr-Abl, in these patients. Significant reductions in the proportion of phosphorylated CRKL were observed from a dose level of 200 mg/day nilotinib, indicating effective suppression of Bcr-Abl activity in patients despite imatinib resistance (63).

Preliminary results from an ongoing phase II study of nilotinib (400 mg b.i.d.) in imatinib-resistant or -intolerant patients with Ph+ CML in blast crisis (n=18) or relapsed/refractory Ph+ ALL (n=6) demonstrated that 7 (38%) blast-crisis CML patients had a hematological response (5 complete and 2 marrow responses/no evidence of leukemia) and 3 had a cytogenetic response; complete remission was obtained in 2 ALL patients. At the time of analysis, 7 patients remained on nilotinib and 17 had discontinued due to death (sudden cardiac death and death due to disease progression), adverse events (3), progressive disease (9) or other causes (2). Adverse events, except for thrombocytopenia (grade 3 or 4 in 29%), neutropenia (grade 3 or 4 in 25%) and anemia (grade 3 or 4 in 17%), were generally mild to moderate, the most frequent being rash, fever, nausea, vomiting, fatigue, diarrhea and headache (64).

Nilotinib (400 mg b.i.d.) was also shown to be active in an ongoing open-label study of imatinib-resistant (n=39) or -intolerant (n=27) patients with CML in the chronic phase. Complete hematological response was observed in 83% of patients after a median treatment duration of 129 days; major cytogenetic responses were obtained in 19% of patients. In addition to grade 3 or 4 thrombocytopenia (13%) and neutropenia (12%), the most frequent nonhematological adverse events were headache, fatigue, pruritus, nausea, rash and diarrhea (65).

Preliminary data for 22 accelerated-phase CML patients (77% resistant and 23% intolerant to imatinib) exposed to nilotinib (400 mg b.i.d.) for a median of 124 days documented a hematological response in 14 patients (10 complete responses, 3 marrow responses/no evidence of leukemia and 1 return to chronic phase) and a cytogenetic response in 6 patients. Adverse events were similar to in other studies and 2 deaths occurred in 1 patient with thrombocytopenia who had a CNS bleed and another patient who had disease progression (66).

Eight CML patients who had received prior treatment with dasatinib (n=2) or nilotinib (n=6) underwent allogeneic stem cell transplantation. Molecular response was seen in 5 patients after a median follow-up of 8 months and 3 patients relapsed within 3 months. Prior treatment with these tyrosine kinase inhibitors did not appear to increase transplant-related toxicities (67).

Preliminary results from 5 patients with newly diagnosed Ph+ chronic-phase CML who had reached the 3-month evaluation on nilotinib (400 mg b.i.d. p.o.) showed a complete cytogenetic response in all subjects. Three of 13 patients treated so far in this trial experienced grade 3-4 myelosuppression, which led to temporary interruption and subsequent resumption of nilotinib treatment; transient elevation of bilirubin was observed in 1 patient (68).

Early studies examined the effect of nilotinib administered to a single patient with GIST. A dose of 400 mg p.o. b.i.d. was well tolerated and induced disease stabilization, as revealed by serial CT scans (69). A subsequent international phase I study evaluated nilotinib (200 or 400 mg once daily or 400 mg b.i.d.) alone or in combination with imatinib (400 mg b.i.d.) in patients with imatinib-resistant metastatic GISTs. Of 37 patients treated as of March 2006, 17 showed disease stabilization, 9 on nilotinib alone, and 2 had partial responses. Dose-limiting toxicity of grade 3 bilirubin elevation and grade 3 skin rash was seen in 2 patients, and the combination of 400 mg b.i.d. nilotinib and 400 mg b.i.d. imatinib was associated with excessive skin toxicity requiring dose reduction. No clini-

Table I: Clinical studies of nilotinib (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Leukemia, chronic myeloid	Open	Nilotinib, 50 mg o.d. x 12-200 d (n=6) Nilotinib, 100 mg o.d. x 12-200 d (n=5) Nilotinib, 200 mg o.d. x 12-200 d (n=7) Nilotinib, 400 mg o.d. x 12-200 d (n=9) Nilotinib, 600 mg o.d. x 12-200 d (n=1) Nilotinib, 800 mg o.d. x 12-200 d (n=14) Nilotinib, 1200 mg o.d. x 12-200 d (n=9) Nilotinib, 400 mg b.i.d. x 12-200 d (n=1)	52	Nilotinib demonstrated significant anti-tumor activity in patients with imatinib-resistant Bcr/Abl-positive chronic myeloid leukemia	56
Leukemia, chronic myeloid	Open	Nilotinib, 50 mg p.o. o.d. x 2-267 d (n=6) Nilotinib, 100 mg p.o. o.d. x 2-267 d (n=5) Nilotinib, 200 mg p.o. o.d. x 2-267 d (n=7) Nilotinib, 400 mg p.o. o.d. x 2-267 d (n=8) Nilotinib, 600 mg p.o. o.d. x 2-267 d (n=3) Nilotinib, 800 mg p.o. o.d. x 2-267 d (n=14) Nilotinib, 1200 mg p.o. o.d. x 2-267 d (n=9) Nilotinib, 400 mg p.o. b.i.d. x 2-267 d (n=17) Nilotinib, 600 mg p.o. b.i.d. x 2-267 d (n=10)	78	Nilotinib showed significant antitumor activity in patients with imatinib-resistant chronic myeloid leukemia	57
Leukemia, acute lymphocytic, Leukemia, chronic myeloid	Open	Nilotinib, 50 mg p.o. o.d. (n=7) Nilotinib, 100 mg p.o. o.d. (n=7) Nilotinib, 200 mg p.o. o.d. (n=10) Nilotinib, 400 mg p.o. o.d. (n=10) Nilotinib, 600 mg p.o. o.d. (n=6) Nilotinib, 800 mg p.o. o.d. (n=19) Nilotinib, 1200 mg p.o. o.d. (n=10) Nilotinib, 400 mg p.o. b.i.d. (n=32) Nilotinib, 600 mg p.o. b.i.d. (n=18)	119	Nilotinib was generally well tolerated and active in patients with chronic myeloid leukemia or acute lymphoblastic leukemia. Overall response rates were similar in patients with and without Bcr-Abl mutations at baseline. Patients who developed new mutations showed lower response rates compared with patients who did not develop new mutations	59, 62
Leukemia, acute lymphocytic, Leukemia, chronic myeloid	Open Multicenter	Nilotinib, 400 mg b.i.d.	24	Nilotinib was associated with clinical activity and a favorable safety and tolerability profile in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis or acute lymphoblastic leukemia	64
Leukemia, chronic myeloid	Open Multicenter	Nilotinib, 400 mg p.o. b.i.d.	67	Nilotinib demonstrated antitumor activity and an acceptable safety and tolerability profile in patients with chronic-phase chronic myeloid leukemia	65
Leukemia, chronic myeloid	Open Multicenter	Nilotinib, 400 mg p.o. b.i.d.	22	Nilotinib was well tolerated and demonstrated antitumor activity in patients with chronic myeloid leukemia in accelerated phase	66
Leukemia, chronic myeloid	Open	Nilotinib, 400 mg p.o. b.i.d. x 3 mo	13	Nilotinib showed promising antileukemic activity in patients with newly diagnosed chronic myeloid leukemia in chronic phase	68
Cancer, gastrointestinal (stromal)	Open	Nilotinib, 400 mg p.o. b.i.d. Nilotinib, 200 mg p.o. o.d. + Imatinib, 400 mg p.o. b.i.d. Nilotinib, 400 mg p.o. o.d. + Imatinib, 400 mg p.o. b.i.d. Nilotinib, 400 mg p.o. b.i.d. + Imatinib, 400 mg p.o. b.i.d.	37	Preliminary results suggested that nilotinib was well tolerated as monotherapy or in combination with imatinib at doses up to 400 mg/d, and exhibited antitumor activity in patients with gastrointestinal stromal tumors	70
Leukemia, acute lymphocytic, Leukemia, chronic myeloid	Open Multicenter	Nilotinib	18	This study will investigate if nilotinib provides an improved safety and efficacy profile in patients with hematological malignancies refractory to previous imatinib therapy	76

cally significant pharmacokinetic interaction between the two drugs was observed (70, 71).

Administration of nilotinib (400 mg b.i.d) in an open-label phase II trial to 23 patients with systemic mastocytosis produced 2 incomplete remissions and 1 minor response after a median exposure time of 144 days. Treatment was well tolerated and grade 3/4 adverse events included headache, fatigue, nausea, pruritus, hypotension, muscle spasms, diarrhea, extremity pain, dizziness and increased ALT (72).

Phase II/III clinical trials continue in patients with CML resistant to or intolerant of imatinib; a phase II trial is eval-

uating nilotinib in patients with CML and other hematological malignancies (Ph+ ALL, hypereosinophilic syndrome/chronic eosinophilic leukemia [HES/CEL] and systemic mastocytosis), and a phase I/II study is evaluating the safety and efficacy of nilotinib in patients with CML and Ph+ ALL (73-76).

Source

Novartis AG (CH).

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