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Nilotinib in Chronic Myeloid Leukemia Patients in Chronic Phase (CML-CP) With Imatinib Resistance or Intolerance: 24-Month Follow-Up Results of a Phase 2 Study

Hagop M Kantarjian[1], Francis Giles[2], Kapil N. Bhalla[3], Javier Pinilla[4], Richard A. Larson[5], Norbert Gattermann[6], Oliver G. Ottmann[7], Jim Wang[8], Neil J. Gallagher[9], Michele Baccarani[10], and Philipp D. le Coutre[11]

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Background

Nilotinib is a potent and highly selective BCR-ABL inhibitor approved for treatment of Ph+ CML patients in CP or accelerated phase who are resistant or intolerant to prior therapy including imatinib.

Aims

This study evaluated the efficacy and safety of nilotinib in CML-CP patients resistant or intolerant to imatinib.

Methods

Intolerant patients must not have had a major cytogenetic response (MCyR) at study entry, since only these patients could be appropriately assessed for the primary study endpoint. Primary endpoint was MCyR. Secondary endpoints included complete cytogenetic response (CCyR), complete hematologic response (CHR), MCyR duration, overall survival (OS), and safety. In this analysis, we evaluated the kinetics and duration of CCyR, along with other parameters described below.

Results

CML-CP patients (N=321) with a minimum follow-up of 19 months were evaluated. Overall, 70% of patients were imatinib resistant and 30% were imatinib intolerant. Patients were heavily pretreated, with 72% having received ≥ 600 mg/day imatinib prior to enrollment. Median duration of CML was 58 (range 5-275) months, and prior imatinib treatment was 32 (range 1-94) months. Median dose intensity of nilotinib was 790 (range 151-1110) mg/day, closely approximating the planned dose of 800 mg/day. Nilotinib led to rapid and durable hematologic and cytogenetic responses. CHR was achieved or maintained in 94% of patients, with 75% of patients with no baseline CHR achieving a new CHR, at a median of 1 month following initiation of nilotinib therapy. MCyR was achieved in 59% of patients at a median of 2.8 months following initiation of nilotinib therapy. In patients with a baseline CHR, 73% achieved MCyR. Overall, 44% of patients achieved a CCyR with a median time to first CCyR of 3.3 (range 0.9-23.5) months. Responses were durable, with 78% of patients maintaining MCyR, and 83% maintaining CCyR at 24 months. Overall, major molecular response (MMR) was achieved in 25% of patients. Estimated time to discontinuation of study drug was 578 (range 1-958) days. Estimated OS rate was 88% at 24 months. Nilotinib was generally well-tolerated and no new safety issues emerged with 24 months of follow-up. The most frequent grade 3/4 biochemical laboratory abnormalities were elevated lipase (17%), hypophosphataemia (16%), hyperglycemia (12%), and total bilirubin (8%). All biochemical abnormalities were transient and clinically asymptomatic. Grade 3/4 nonhematologic adverse events were infrequent, with rash, headache, and diarrhea occurring in 2% of patients. The most common grade 3/4 hematologic laboratory abnormalities were neutropenia (31%), thrombocytopenia (31%), and anemia (10%). Brief dose interruptions were successful in managing most adverse events. Pleural or pericardial effusions occurred in 2% of patients (all grades), and grade 3/4 were uncommon (< 1%).

Conclusions

These results demonstrate that nilotinib was highly effective, inducing rapid and durable cytogenetic responses in CML-CP patients failing prior imatinib therapy due to resistance or intolerance. Nilotinib was well tolerated with a favorable risk/benefit profile in this study. The estimated 88% OS rate at 24 months in this heavily pretreated patient population suggests that nilotinib is effective and can provide favorable long-term outcomes for patients.

Nilotinib in Chronic Myeloid Leukemia Patients in Chronic Phase (CML-CP) With Imatinib Resistance or Intolerance: 24-Month Follow-Up Results of a Phase 2 Study

Hagop M. Kantarjian[1], Francis J. Giles[2], Kapil N. Bhalla[3], Javier Pinilla[4], Richard A. Larson[5], Norbert Gattermann[6], Oliver G. Ottmann[7], Jim Wang[8], Neil J. Gallagher[9], Michele Baccarani[10], and Philipp D. le Coutre[11]

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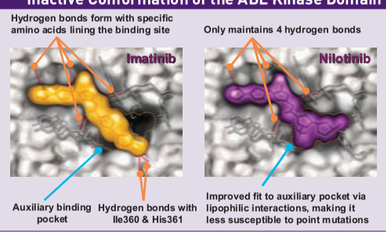
INTRODUCTION

- Nilotinib (Tasigna®) is a rationally designed, potent, highly selective BCR-ABL kinase inhibitor
- Nilotinib binds to ABL with higher affinity and improved topological fit compared with imatinib; it inhibits most imatinib-resistant BCR-ABL mutants (not T315I)
- Nilotinib is approved for the treatment of patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) or accelerated phase (AP) resistant to or intolerant of prior therapy, including imatinib
- The present analysis includes patients with CML-CP with a minimum follow-up of 24 months of exposure

Figure 1. Nilotinib Strategically Designed for a Better Fit to Inactive Conformation of the ABL Kinase Domain



OBJECTIVES

- To evaluate the efficacy and safety of nilotinib in CML-CP patients with resistance to or intolerance of imatinib
- To evaluate the kinetics and duration of complete cytogenetic response (CCyR)
- To characterize the safety and tolerability of nilotinib, including acute and chronic toxicities, in patients with imatinib-resistant or imatinib-intolerant CML-CP

METHODS

Study design

- Phase 2, open label, single treatment arm

Patient population

- Adults with imatinib-resistant or -intolerant Ph+ CML-CP
  - Standard eligibility criteria
  - QTc >450 msec not eligible
- Nilotinib was given 400 mg orally twice daily (2 hours following meals)

Cytogenetic response characterized by:

- Complete (0% Ph+ cells)
- Partial (1%-35% Ph+ cells)
- Major (complete + partial)

Definition of Imatinib Resistance and Intolerance

Imatinib resistance

- Defined as either treatment with imatinib ≥ 600 mg/day with disease progression (≥ 50% increase in WBC, blasts, basophils, or platelet counts), no hematologic response in bone marrow after 4 weeks, or patients receiving < 600 mg/d with any other following mutations: L248, G250, Q252, Y253, E255, T315, F317, H396.

Primary resistance

- No complete hematologic response (CHR) at or after 3 months
- No minimal cytogenetic response (CyR) at or after 6 months
- No major cytogenetic response (MCyR) at or after 12 months

Secondary resistance

- Loss of CHR
- Loss of minimal Cyr, loss of MCyR, loss of CCyR, or cytogenetic relapse
- Development of clonal evolution

Imatinib intolerance with resistance

- Patients without an MCyR* who discontinued for:
  - Persistent grade 3/4 imatinib-related adverse event (AE), despite optimal supportive care
  - Persistent grade 2 imatinib-related AE, despite optimal supportive care
    - Persisting ≥ 1 month, or
    - Recurring > 3 times with imatinib dose reduction

* Patients without MCyR were chosen because they were fully and appropriately assessable for the primary study endpoints.

RESULTS

Table 1. Baseline Demographics (N = 321)

Median age, years (range)	58 (21-85)
Median duration of CML, months (range)	58 (5-275)
Median duration of prior imatinib therapy, months (range)	32 (<1-94)
Active disease prior to therapy, n (%)	206 (64)
Imatinib resistant/intolerant, (%)	70/30
Prior highest imatinib dose ≥ 600 mg/day, n (%)	232 (72)
Other prior therapy	
Hydroxyurea, n (%)	266 (83)
Interferon, n (%)	187 (58)
Cytarabine, n (%)	78 (24)

- 72% of patients received prior doses of imatinib > 600 mg/day

Table 2. Patient Disposition (N = 321)

	n (%)
Ongoing treatment	124 (39)
Discontinued treatment	197 (61)
Disease progression	88 (27)
Adverse event(s)	61 (19)
Drug related	50 (16)
Non-drug related	11 (3)
Abnormal test	4 (1)
Abnormal lab value	2 (< 1)
Other*	39 (12)
Death	3 (< 1)

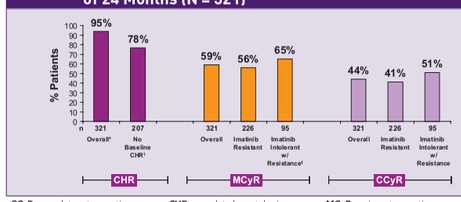
* Includes protocol violation, patient withdrew consent, lost to follow up, not stated, and administrative problems.

Table 3. Nilotinib Exposure (N = 321)

Median duration of nilotinib, days (range)	561 (1-1096)
Median dose intensity, mg/days (range)	789 (151-1110)
Patients with dose interruption, n (%)	176 (55)
Median cumulative duration of dose interruption, days (range)	20 (1-345)
Median percent of dose interruption, % days (range)	4 (<1-62)
Patients with dose reduction, n (%)	84 (26)

- Median dose delivered was close to the planned dose of 800 mg/day

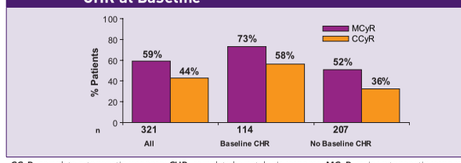
Figure 2. Response in Patients With a Minimum Follow-Up of 24 Months (N = 321)



CCyR, complete cytogenetic response; **CHR,** complete hematologic response; **MCyR,** major cytogenetic response.
* Patients who achieved (without baseline CHR) or maintained CHR (had CHR at study entry).
† Patients with no CHR at baseline.
‡ See definition of imatinib-intolerant with resistance in the Methods sections.

- The rate of MCyR for patients with primary resistance was 55%
- The overall rate of major molecular response (MMR) at 24 months was 38% for all patients with post-baseline PCR data available and baseline CHR (n = 105)
- The median time to CHR was 1.0 month in patients without CHR at baseline

Figure 3. Cytogenetic Responses in Patients With and Without CHR at Baseline



CCyR, complete cytogenetic response; **CHR,** complete hematologic response; **MCyR,** major cytogenetic response.

- Patients entering the study with CHR at baseline had higher rates of MCyR than those without baseline CHR

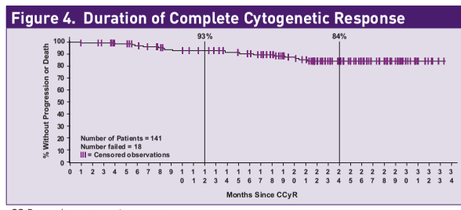
Table 4. Median Time to Cytogenetic Response by Baseline CHR Status

	All Patients	Baseline CHR	No Baseline CHR
MCyR	**(n = 190)**	**(n = 83)**	**(n = 107)**
Median time to response, months (range)	2.8 (1-28)	1.4 (1-19)	2.8 (1-28)
CCyR	**(n = 141)**	**(n = 66)**	**(n = 75)**
Median time to response, months (range)	3.3 (1-27)	3.2 (1-24)	3.3 (1-27)

CCyR, complete cytogenetic response; **CHR,** complete hematologic response; **MCyR,** major cytogenetic response.

- Time to MCyR was faster in patients entering study in CHR

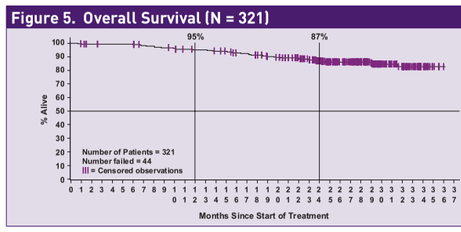
Figure 4. Duration of Complete Cytogenetic Response



CCyR, complete cytogenetic response.

- CCyR remains durable at 24 months

Figure 5. Overall Survival (N = 321)



- 87% of patients were estimated to be alive on nilotinib therapy at 24 months

Table 5. Most Frequent (> 10%) Drug-Related Nonhematologic Adverse Events (N = 321)

Adverse Event	All Grades (%)	Grades 3/4 (%)
Rash	31	2
Pruritus	26	<1
Nausea	25	<1
Fatigue	20	1
Headache	18	2
Diarrhea	12	2
Vomiting	13	<1
Constipation	13	<1

- Severe nonhematologic AEs were infrequent on nilotinib therapy

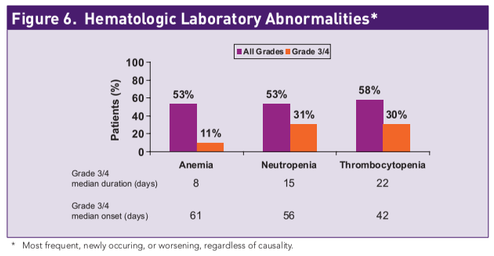
Table 6. Biochemical Laboratory Abnormalities* (N = 321)

	Any (%)	Grades 3/4 (%)
Lipase elevation	47	18
Hypophosphatemia	56	17
Hyperglycemia	70	12
Bilirubin elevation (total)	72	7
ALT elevation	69	4
AST elevation	55	3
Hypocalcemia	51	2
Creatinine	24	1
Hypomagnesemia	17	< 1

ALT, alanine aminotransferase; **AST,** aspartate aminotransferase.
* Most frequent newly occurring or worsening, regardless of causality.

- Biochemical laboratory abnormalities were generally mild, transient, and easily managed

Figure 6. Hematologic Laboratory Abnormalities*



* Most frequent, newly occuring, or worsening, regardless of causality.

- Myelosuppression events were predictable and generally easily managed

Table 7. Laboratory Abnormalities Associated With Treatment Discontinuation (N = 321)

	n (%)
Discontinuation	
Myelosuppression	20 (6)
AST/ALT elevation	2 (<1)
Hyperbilirubinemia	1 (<1)
Lipase elevation or pancreatitis	4 (1)
Discontinuation due to any adverse event	61 (19)
Drug related	50 (16)
Non-drug related	11 (3)

ALT, alanine aminotransferase; **AST,** aspartate aminotransferase.

Table 8. Drug-Related Adverse Events Associated With Fluid Retention and Bleeding (N = 321)

	All Grades n (%)	Grades 3/4 n (%)
Peripheral edema	20 (6)	0 (0)
Pericardial effusion	2 (<1)	1 (<1)
Pleural effusion	4 (1)	1 (<1)
Pulmonary edema	1 (<1)	1 (<1)
CNS bleeding	1 (<1)	1 (<1)
GI bleeding	3 (<1)	1 (<1)

CNS, central nervous system; **GI,** gastrointestinal.

- Severe fluid retention or bleeding events were rare on nilotinib therapy

CONCLUSIONS

- Nilotinib was highly effective, inducing rapid and durable cytogenetic responses in patients with CML-CP who failed prior imatinib therapy due to resistance or intolerance
  - All patients in this study were highly resistant, with the majority requiring high doses of imatinib for at least 3 months and with imatinib-intolerant patients required not to be in MCyR at study entry
- Nilotinib was well tolerated with a favorable benefit/risk profile in this study
- The estimated 87% overall survival at 24 months in this heavily pretreated patient population suggests that nilotinib is effective and can provide favorable long-term outcomes for patients