Response to Nilotinib in Patients With Imatinib-Resistant or -Intolerant Chronic Myeloid Leukemia in Chronic Phase (CML-CP) With Different BCR-ABL Transcript Types

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INTRODUCTION

- Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) is caused by the BCR-ABL fusion gene
- Ph+ CML arises from a reciprocal translocation of most of the cellular ABL gene on chromosome 9 to the BCR gene on chromosome 22
- Various breakpoints in the BCR and ABL genes have been described
  - Most cases are BCR exon 13 or 14 fused to the ABL exon 2 (a2), resulting in the b2a2 and b3a2 transcripts, respectively
- Variations in BCR-ABL transcript types may result in differences in disease prognosis and response to therapy

OBJECTIVE

- To investigate the correlation between BCR-ABL transcript type and responses to nilotinib in the second-line setting

METHODS

Study Design and Patient Population

- Open-label, multicenter, single-arm, phase 2 study of nilotinib (400 mg twice daily) in patients with imatinib-resistant or -intolerant Ph+ CML in chronic phase (N = 321)
- Median exposure to nilotinib was 561 days

Analysis Dataset Population

- Patients with a baseline BCR-ABL transcript type measurement were analyzed (n = 251)
  - Incidence of different BCR-ABL transcript types was described
  - Mutational status, clinical responses including complete hematologic response (CHR), cytogenetic response (CyR), and major molecular response (MMR), and event-free survival (EFS) were evaluated in patients with different BCR-ABL transcript types

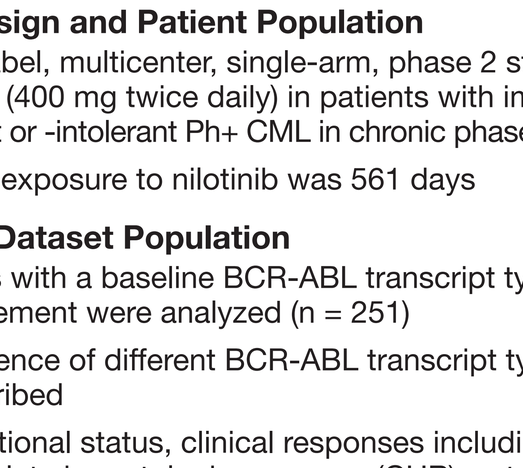
MODELING METHOD

- We analyzed the molecular response dynamics (BCR-ABL transcript by international scale [IS]) of a subset of the patient population (n = 107) with at least 3 PCR measurements and 90% dose intensity during the first 6 months of treatment, and a baseline BCR-ABL (IS) of >10%
- The time course of BCR-ABL transcript reduction (IS) was modeled as a biexponential function ($R(t) = Ae^{\alpha t} + Be^{\beta t}$), as found previously.[1] Patient parameters were estimated using nonlinear mixed effects modeling. The alpha parameter describes the initial decline in $\log_{10}$ (R) upon treatment start, while β describes the shallower slope of the subsequent $\log_{10}$ (R) dynamics in patients. It has been found among nilotinib second-line patients that α has a bimodal distribution, such that some exhibit a shallow decline (α > –5/year) and others exhibit a steep decline (α < –5/year). Steep decline has been shown to be associated with superior response

1. Stein A, et al. *Blood.* 2009;114(22):209 [abstract 506].

RESULTS

Figure 1. Patient Population Breakdown Based on Transcript Type



Breakpoint Type (N = 251)	n	%
b3a2	163	65
b2a2	78	31
b2a2 + b3a2	7	3
b3a3 or e1a2	3	1

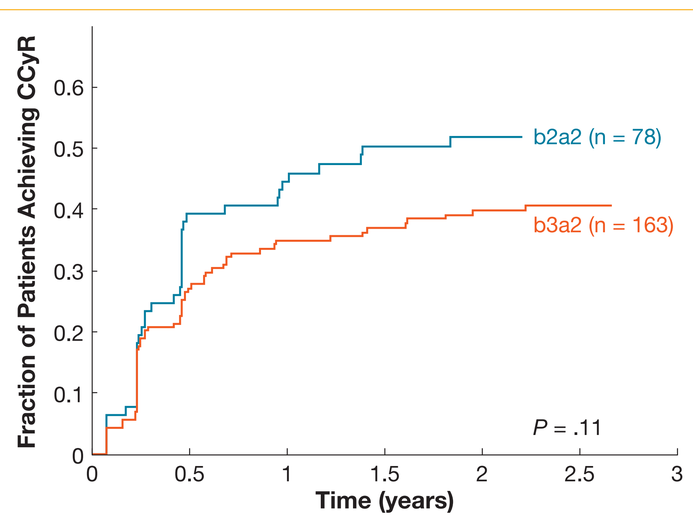
- 99% of patients had typical b2a2 or b3a2 transcripts
- 1% of patients had atypical transcripts

Table 1. Best Response to Nilotinib by Transcript Type

		Best Response					
	All Patients	Complete Hematologic Response (CHR) n (%)	Complete Cytogenetic Response (CCyR) n (%)	Partial Cytogenetic Response (PCyR) n (%)	Major Molecular Response (MMR) n (%)	Progression-Free Survival (PFS) at 24 Months n (%)	Baseline Mutation n (%)
b3a2	163	131 (80.4)	52 (31.9)	18 (11.0)	39 (23.9)	56 (34.4)	76 (46.6)
b2a2	78	70 (89.7)	34 (43.6)	9 (11.5)	20 (25.6)	32 (41.0)	23 (29.5)
P value: comparing b2a2 vs b3a2 using χ^2 2-sample test		.07	.17		.77	.31	.01

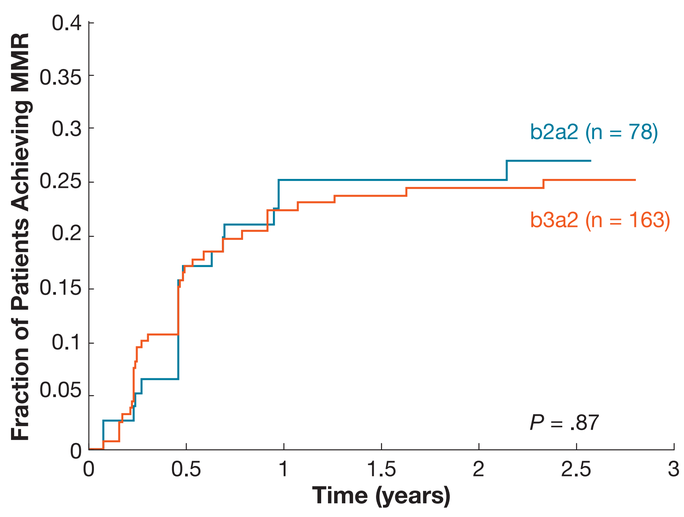
- Transcript type (b3a2 or b2a2) did not influence the response or PFS in patients receiving nilotinib
- The incidence of baseline mutations was higher in patients with b3a2 transcripts compared with b2a2 (*P* = .01)
- Of the 3 patients with atypical transcripts (b3a3 or e1a2), all achieved CHR, 1 achieved CCyR, and 1 achieved PCyR

Figure 2. Time to Complete Cytogenetic Response Based on Transcript Type



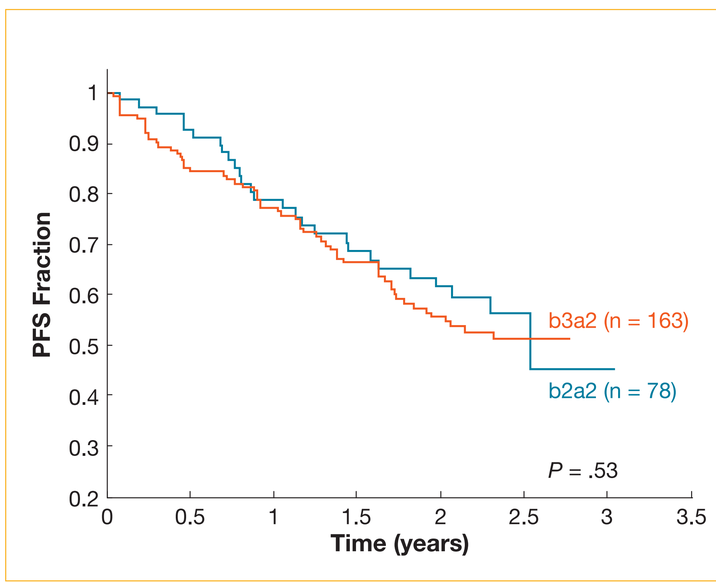
- Cytogenetic response to nilotinib did not exhibit a statistically significant difference between b2a2 and b3a2 transcript types

Figure 3. Time to Major Molecular Response for Different Transcript Types



- Molecular response to nilotinib was similar regardless of transcript type

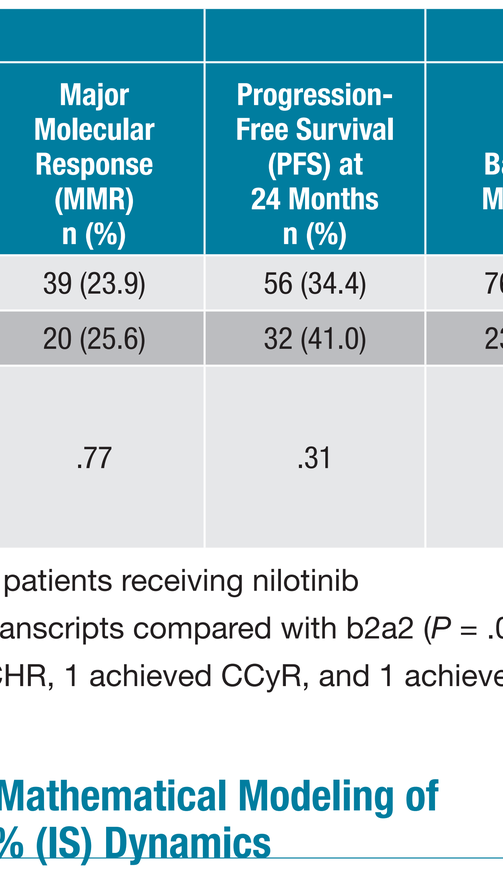
Figure 4. Progression-Free Survival for Different Transcript Types*



* No patient with b3a3 or e1a2 (n = 3) progressed.

- PFS was similar for b2a2 and b3a2

Figure 5. Mathematical Modeling of BCR-ABL% (IS) Dynamics



	All Patients	Shallow α	Steep α
b3a2	64	44 (68.8)	20 (31.3)
b2a2	38	27 (71.1)	11 (28.9)

- Dynamics of response in patients with b2a2 and b3a2 transcripts were similar

CONCLUSIONS

- The b3a2 and b2a2 BCR-ABL transcript types were observed in the majority of patients
- Regardless of transcript type, hematologic, cytogenetic, and molecular responses were similar in nilotinib-treated patients
- The incidence of baseline mutations was higher in patients with b3a2 transcripts compared with b2a2 (*P* = .01)
- Patients with b3a2 and b2a2 had similar patterns of response to nilotinib and long-term outcomes
- CHR, CyR, MMR, and EFS were not significantly different between the b3a2 and b2a2 patient populations
- Data indicate that nilotinib therapy was effective in patients with imatinib intolerance and resistance with all transcript types, including the atypical transcripts (e1a2, b3a3)

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