Rapid Initial Decline in BCR-ABL Levels is Associated With Superior Responses in Patients With Imatinib-Resistant or -Intolerant Chronic Myeloid Leukemia in Chronic Phase Treated With Nilotinib

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INTRODUCTION

- A mathematical model defined using molecular data from patients randomized to the imatinib arm on the International Randomized Study of Interferon and STI571 (IRIS) trial demonstrated a biphasic decline in BCR-ABL transcript levels[1]
- In this analysis, the model was applied to data from patients resistant to or intolerant of imatinib who were subsequently treated with nilotinib in the phase 2 registration study (2101)
- The goal of this analysis was to determine if BCR-ABL kinetics in patients treated with nilotinib were similar to those treated with imatinib and whether kinetics observed early in treatment may predict long-term outcomes

METHODS – ANALYSIS

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-CP (N = 321)
- Median exposure to nilotinib was 561 days

Analysis Dataset Population

- Patient subset for modeling analysis was chosen (n = 123) such that each patient had
  - At least 3 polymerase chain reaction (PCR) measurements in the first 6 months
  - An average daily dose of 720 mg (90% of the target dose) during the first 6 months
  - BCR-ABL by international scale (IS) transcript ratios greater than 10% at baseline
- The time course of BCR-ABL transcript levels was modeled as a biexponential function $R(t) = Ae^{\alpha t} + Be^{\beta t}$
- Patient parameters were estimated using nonlinear mixed effects modeling
  - α parameter represents the initial decline in BCR-ABL transcript levels ($\log_{10}[R]$). α was permitted to have a bimodal distribution via a mixture model
  - β parameter represents the shallower subsequent decline in BCR-ABL transcript levels

METHODS – PREDICTION

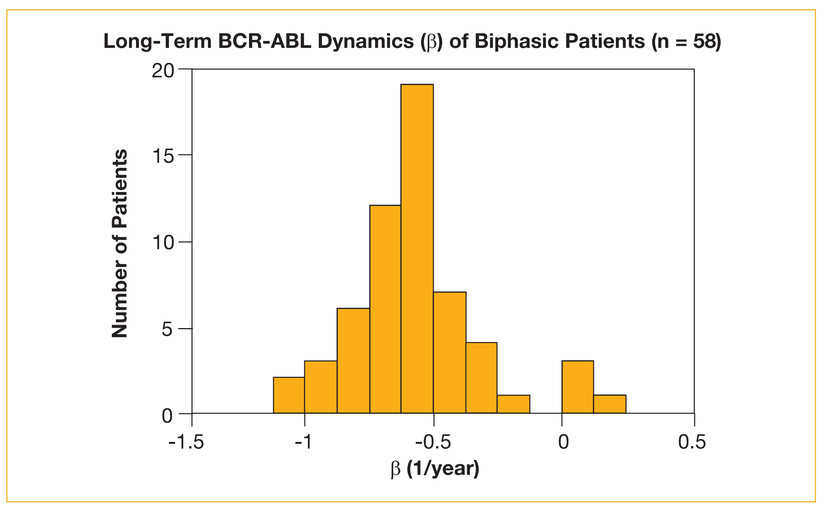
Predictive Analysis Dataset

- The α parameter was then estimated for each patient by refitting the model to the 1-, 3-, 6-, 9-, 12-, 18-, and 24-month datasets to patients who had not yet progressed. In the refitting process, we assumed that the population means and variances of the model parameters did not change
- Using the α estimate at an early time point, the model was then used to predict progression-free survival (PFS) at 24 months. The positive and negative predictive value of α were reported

RESULTS

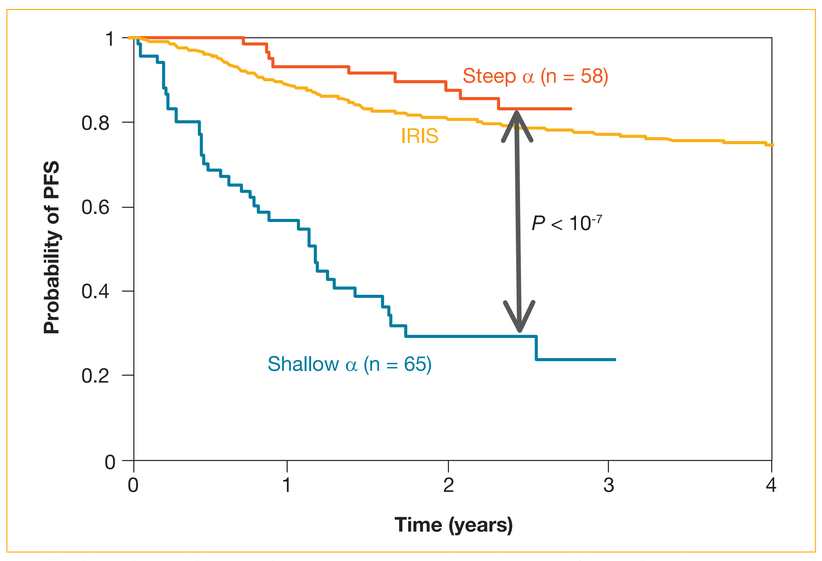
- Patients were well described by the $R(t) = Ae^{\alpha t} + Be^{\beta t}$ model
- They had 1 of 2 typical responses:
  - Response type 1: Monophasic response with shallow α > -5/year (n = 65) such that the BCR-ABL (%) IS drops by approximately 0.02 $\log_{10}$ in the first 6 months (Figure 1a)
  - Response type 2: Biphasic response with steep α < -5/year, such that the BCR-ABL (%) IS drops by approximately 1 $\log_{10}$ in the first 6 months (Figure 1b)
- Unlike patients randomized to imatinib in the IRIS trial,[1] most patients (53%) in the nilotinib registration trial conformed to scenario 1, with monophasic dynamics where only the shallow α slope was observable
- The α parameter showed a bimodal distribution, with patients exhibiting either a steep or shallow α slope (Figure 1c)
- The β parameter was observed mostly in patients with a steep α slope, and was similar to that seen in imatinib-treated patients in IRIS,[1] with a yearly reduction of $\log_{10}$ transcript levels of –0.58/year (range, –1.0/year to 0.14/year; Figure 2)

Figure 2. Distribution of β Slopes Among Patients With a Steep α



- Patients with a steep α slope demonstrated significantly better hematologic, cytogenetic, and molecular response (Table), and better PFS (Figure 3)
- Patients with a steep α slope had a lower incidence of insensitive mutations (IC_{50} > 150 nm)
- Patients with imatinib intolerance were more likely to have a steep α (16/23) and the imatinib-resistant patients were more likely to have a shallow α (58/100); *P* = .017

Figure 3. PFS According to α Slope



- Patients with a steep α slope had significantly improved PFS
- Six months of time was sufficient to observe the bimodal distribution of α and predict PFS at 24 months (Figures 4 and 5). Similar results to the full dataset were observed

Figure 4. Using the α Slope Based on First 6 Months of Data to Subdivide the Patient Population

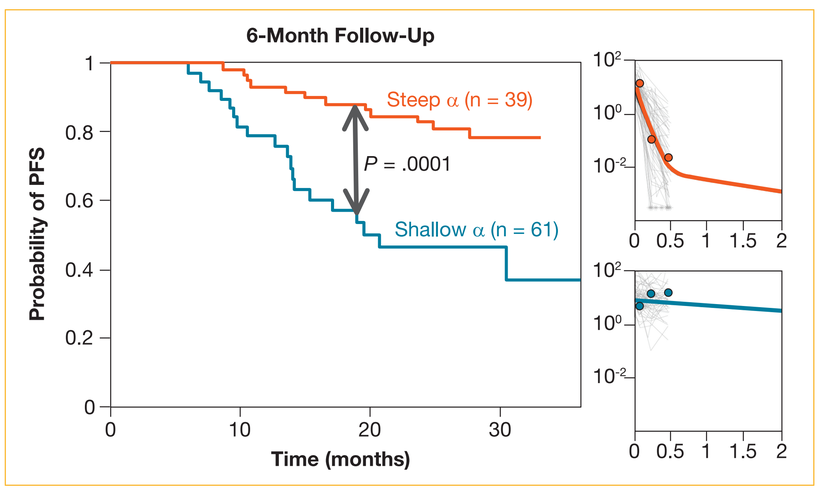
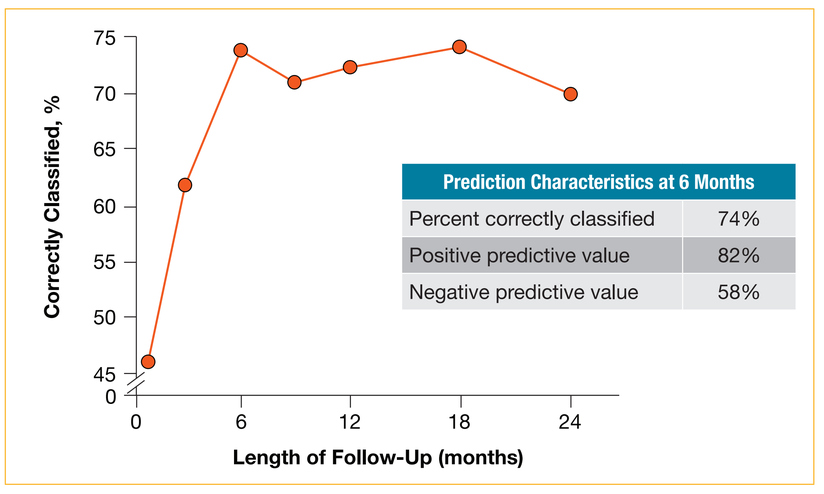


Figure 5. Using the α Slope to Predict Outcome



		Best Response Achieved Over 24-Month Follow-Up			Patient Characteristics			
BCR-ABL Response Dynamics	**All Pts**	**CHR**	**CCyR**	**MMR**	**Sensitive baseline mutation (IC_{50}<150 nm)**	**Insensitive baseline mutation (IC_{50}>150 nm)**	**Resistant**	**Intolerant**
Shallow α	65	47 (72.3)	5 (7.7)	1 (1.5)	21 (32.3)	18 (27.7)	58 (89.2)	7 (10.8)
Steep α	58	57 (98.3)	51 (87.9)	41 (70.7)	18 (31.0)	2 (3.4)	42 (72.4)	16 (27.6)
***P* value**		.0001	< .0001	< .0001	.88	.0003	.017	

CHR, complete hematologic response; **CCyR**, complete cytogenetic response; **MMR**, major molecular response.

CONCLUSIONS

- In contrast to patients randomized to imatinib in the frontline setting in the IRIS trial,[1] the majority of patients receiving nilotinib in the second line typically demonstrated a monophasic pattern of BCR-ABL transcript decline
- A bimodal distribution for the slope of the initial BCR-ABL transcript decline was observed with one group exhibiting a 6-month reduction of approximately 1 $\log_{10}$ (median α = –18.4/year; biphasic patients) and another group exhibiting a 6-month reduction of approximately 0.02 $\log_{10}$ (median α = –0.36/year; monophasic patients)
- Patients with a steep α had better rates of response and PFS at 24 months versus those with a shallow α. In fact, PFS outcomes for second-line nilotinib-treated patients with a steep α were comparable to frontline imatinib patients in the IRIS trial
- The α slope could be estimated using PCR data from the first 6 months of therapy
- The α slope may serve as an early predictive tool for long-term outcomes in patients treated with nilotinib after failure or intolerance of imatinib
- Further validation with this tool is required

Figure 1. α Slopes in Patients in 2101 Trial: a) Typical Patient With Shallow α Slope; b) Typical Patient With Steep α Slope; c) Distribution of α Slopes

- Asterisks (*) correspond to measurements below the limit of quantification of the PCR assay, assumed to be 0.0032% for all labs

REFERENCE

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

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