Acknowledgments

Australia: P Bardy, TP Hughes, CH Hui, B To, I Lewis, F Szabo, N Horvath, M Hughes, SH Lee, D Thomas, N Hurst, H Mangos, M Sobieraj-Teague, M Al-Muslahi, H Sia, A Schwarer, S Avery, C Arthur, L Coyle, K Fay, C Ward, A Johnston; **Belgium:** D Bron, P Martiat, P Lewalle, G Verhoef, J Maertens, M Delforge, K Theunissen, A Bosly, A Delannoy; **Canada:** DC Roy, PJ Laneuville; **Denmark:** H Vestergaard, K Vissing; **France:** FX Mahon, F Guilhot, G Martineau, T Facon, S Corm, P Rousselot, M Michallet, FE Nicolini, M Tulliez, S Giraudier, C Pautas, M Kuentz, AP Guerci-Bresler, N Vey, A Charbonnier, D Bordessoule, MP Chauny, D Caillot, JN Bastie, O Casasnovas, C Dauriac, T Lamy, M Escoffre, S de Guibert, S Nimubona; **Germany:** OG Ottmann, B Wassmann, P Brueck, G Bug, H Pfeifer, L Wunderle, J Chromik, U Duenzinger, A Hochhaus, S Saussele, A Leitner, T Fischer, PD le Coutre, G Baskaynak, J Westermann, N Gattermann, E Mueller-Leydig, T Bruemmendorf, F Honecker, P Schafhausen, F Schneller, J Duyster, N von Bubnoff, A Dickhut; **Italy:** G Rosti, M Baccarani, P Piccaluga, M Rondoni, G Martinelli, F Castagnetti, G Saglio, D Cilloni, E Messa, C Fava, S Ulisciani, G Mattioli, G Alimena, I Carmosino, R Latagliata, M Breccia, F Gentilini, E Abruzzese, M Trawinska, E Morra, M Draisci, L Pezzetti, A Scaccianoce, F Nobile, B Martino, E Oliva, I Vincilli, G Marino, D Ielo, M Gobbi, M Miglino, R Varaldo, AM Carella, E Lerma, G Leone, F Sorà, S Sica; **Korea:** D-W Kim, KH Lee, JH Lee, HJ Kim; **Netherlands:** GJ Ossenkoppele, J Janssen, OJ Visser, PC Huijgens, AA van Loosdrecht; **New Zealand:** P Browett; **Norway:** I Dybedal, Ø Melien, E Kvan; **Poland:** L Konopka, B Ceglarek, K Kos; **Spain:** F Cervantes, A Alvarez, A Muntañola, M Granell, J Berlanga, C Boque, D Gallardo; **Sweden:** J Richter, M Lindblom; **Switzerland:** Al Rovo, A Gratwohl, D Heim, M Stern, M Heizmann, M Decker, A Theocharides, C Arber, M Grob, JP Sigle, G Stuessi, M Weisser, T Silzle, B Roth, C Forster, J Studt; **United Kingdom:** SG O'Brien, AL Lennard, M Collin, G Jackson, AR Green, P Campbell, G Follows, T Holyoake, M Copeland, L Mitchell, JF Apperley, D Marin, G Smith, D Bowen; **United States:** HM Kantarjian, FJ Giles, KN Bhalla, J Lancet, J Pinilla, R Hoffman, RA Larson, BJ Druker, DA Rizzieri, M Wadleigh, R Stone, SE Coutre, J Gotlib, CA Schiffer, HP Erba, BL Powell, BD Smith, R Bhatia, J Fuloria, M Milder, B Abbott, T Pacheco, MH Jagasia, JE Kolitz, SL Goldberg, CM Jones, LP Akard.

Special acknowledgment to Ovidiu Chiparus, Alison Carter, and Gabriel Helmlinger for their contributions.

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

Andrew M. Stein, Yaping Shou, Dean Bottino, Yen Lin Chia, Richard C. Woodman, Giovanni Martinelli, Timothy P. Hughes, Martin C. Müller, Lan Beppu, Enrico Gottardi, Susan Branford, Simona Soverini, Harriet Goh, Andreas Hochhaus, Dong-Wook Kim, Giuseppe Saglio, Jerald P. Radich

Background: A mathematical model established using molecular data from patients with newly diagnosed CML-CP who were randomized to the imatinib arm of the International Randomized Study of Interferon and STI571 (IRIS) trial demonstrated that the majority of patients experienced a biphasic decline in BCR-ABL transcripts, with a rapid initial decline (α) followed by a steady long-term decline (β).

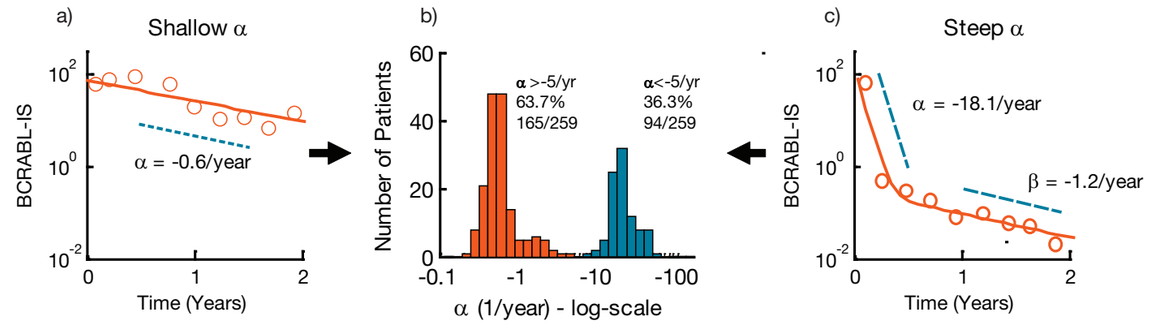
Aims: Here we have applied this model to the molecular response data from patients with CML-CP with prior resistance or intolerance to imatinib treated with nilotinib 400mg bid.

Methods: Patients from the nilotinib phase 2 registration study who had at least 24 months of follow-up and a sufficient number of PCR data points to support parameter estimation were included in the model (N = 259). The time course of BCR-ABL transcript reduction (IS) was modeled as a biexponential function ($R(t) = Ae^{\alpha t} + Be^{\beta t}$). Patient parameters were estimated using nonlinear mixed effects modeling. The α 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.

Results: As with patients treated with imatinib on IRIS, the patient population was well-described by this model. However, unlike in IRIS, the majority of patients displayed monophasic dynamics where only the α slope was observable. Also in contrast to IRIS, the α parameter showed a bimodal distribution (Fig 1b), with patients displaying 1 of 2 typical responses, a shallow α slope corresponding to a lesser initial decline in BCR-ABL transcripts (> -5/yr; n = 165) or a steep α slope (< -5/yr; n = 94) (Fig 1a, 1c). A steep α slope (36% of pts) was associated with superior responses and event-free survival (EFS), with 24 month rates of complete cytogenetic response, major molecular response, and EFS of 94%, 77%, and 83% for patients with $\alpha < -5$/yr versus 25%, 6%, and 40% for patients with $\alpha > -5$/yr ($P < .0001$ for all comparisons). Three PCR data points collected within months 3-6 of therapy could reliably estimate the α slope. The β parameter, generally observable only in patients with a steep α, was similar to that seen in IRIS, with a median yearly steady state reduction in $\log_{10}$ transcript levels of -0.66/yr (range, -3.5/yr-5.9/yr). Only 9 (3.6%) patients had $\beta > 0$ with 95% confidence, suggestive of molecular relapse.

Conclusions: Mathematical modeling demonstrated that treatment with nilotinib can be described by 2 main parameters: an initial decline in BCR-ABL transcript levels (α) and a longer, more sustained decline (β). Two patterns emerged in the slope of the initial decline, steep ($\alpha < -5$/yr) or shallow ($\alpha > -5$/yr). A steep α was shown to be associated with superior response and EFS outcomes. This bimodal distribution of α, which could be estimated using PCR data collected during the first 3-6 months of therapy, may be an early predictive tool for longer-term outcomes of patients on second-line nilotinib who have failed prior imatinib therapy.

Figure 1. a) Typical shallow α patient; b) Distribution of α slopes; c) Typical steep α patient.



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

Andrew M. Stein[1], Yaping Shou[1], Dean Bottino[2], Yen Lin Chia[1], Richard C. Woodman[2], Giovanni Martinelli[3], Timothy P. Hughes[4], Martin C. Müller[5], Lan Beppu[6], Enrico Gottardi[7], Susan Branford[8], Simona Soverini[3], Harriet Goh[9], Andreas Hochhaus[10], Dong-Wook Kim[9], Giuseppe Saglio[7], Jerald P. Radich[6]

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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

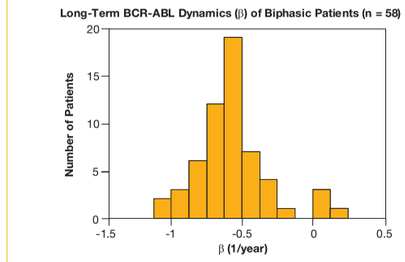
Predictive Analysis Dataset

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

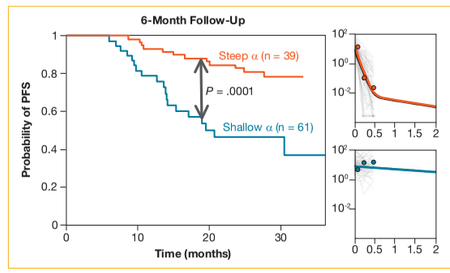
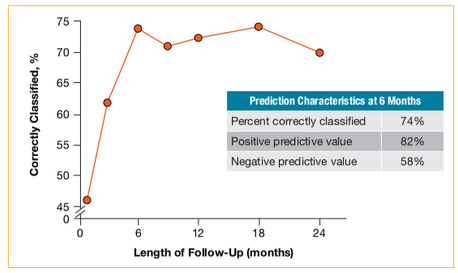


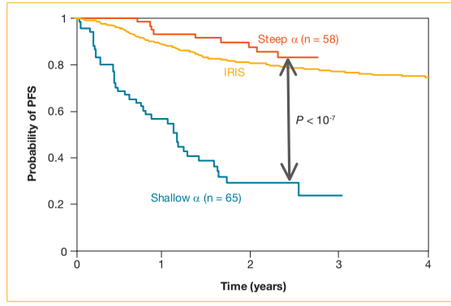
Figure 5. Using the α Slope to Predict Outcome



BCR-ABL Response Dynamics	All Pts	Best Response Achieved Over 24-Month Follow-Up: CHR	CCyR	MMR	Patient Characteristics: 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.

Figure 3. PFS According to α Slope

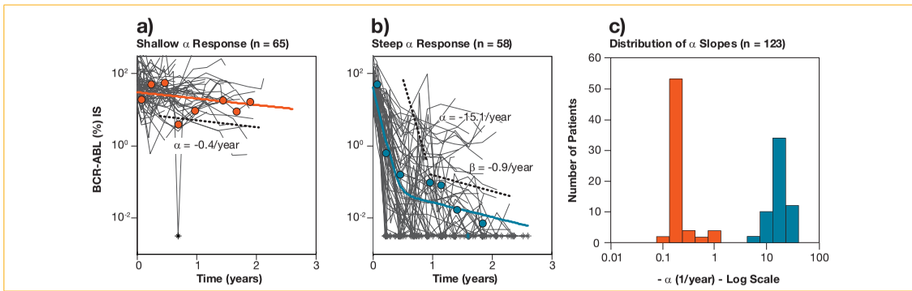


- Patients with a steep α slope had significantly improved PFS
- Six months of time was sufficient to observe the bimodal distribution of α and predict PFS at 24 months (Figures 4 and 5). Similar results to the full dataset were observed

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

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

Poster Presentation at the 15th Congress of EHA, June 10-13, 2010, Barcelona, Spain.