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.

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

Giuseppe Saglio, Timothy P. Hughes, Dong-Wook Kim, Benjamin Hanfstein, Enrico Gottardi, Susan Branford, Harriet Goh, Lan Beppu, Simona Soverini, Yaping Shou, Andrew M. Stein, Richard C. Woodman, Hagop M. Kantarjian, Jerald P. Radich, Andreas Hochhaus, Giovanni Martinelli

Background: Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) is characterized by the BCR-ABL fusion gene which 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 although in most cases BCR exon 13 or 14 is fused to the ABL exon 2 (a2), resulting in the b2a2 and b3a2 transcripts, respectively.

Aims: Variations in BCR-ABL transcript types may result in differences in disease prognosis and response to therapy. Consequently, an analysis was conducted to investigate the correlation between BCR-ABL transcript type and responses to nilotinib in the second-line setting.

Methods: Imatinib-resistant or -intolerant patients with Ph+ CML-CP (N = 321) enrolled on the phase 2 registration trial for nilotinib were included. BCR-ABL transcript types were analyzed in 301 (94%) patients in order to determine if transcript type influenced response dynamics. In addition, the BCR-ABL transcript dynamics were modeled as previously described (Stein et al. *Blood.* 2009;114(22):209).

Results: Median exposure to nilotinib was 561 days. The majority of patients (95%) had typical b3a2 (63%) and b2a2 (32%) BCR-ABL transcript types; 3% of patients had both b3a2 and b2a2 transcripts and 2% had atypical transcripts (e1a2, e19a2, b3a3). Patients with b3a2 transcripts had a higher incidence of baseline mutations compared with patients with b2a2 transcripts (46% vs 32%, $P = .03$). Transcript type did not influence response to nilotinib treatment (Table). A two-sample χ^2 test of the four endpoints (CHR, CyR, MMR, and EFS) did not show a significant difference ($P > .05$) between the b2a2 and b3a2 populations. Modeling results demonstrated no statistically significant difference in the response dynamics between the major BCR-ABL transcript types.

Conclusion: In this analysis, nilotinib was shown to be effective regardless of transcript type, including in patients with rare atypical transcripts. Patients with typical b3a2 and b2a2 transcripts had similar patterns of response to nilotinib in the second-line setting.

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

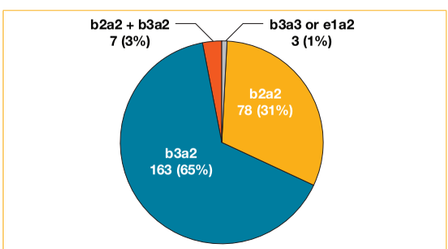
MODELING METHOD

- 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

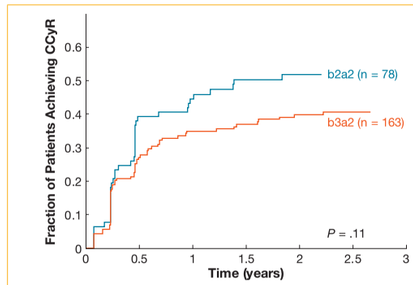
RESULTS

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

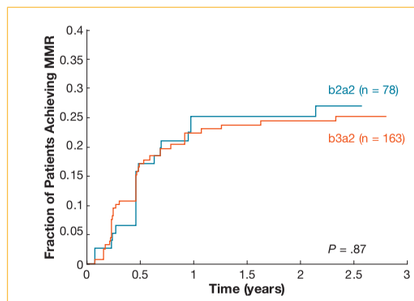
- Transcript type (b3a2 or b2a2) did not influence the response or PFS in patients receiving nilotinib
- The incidence of baseline mutations was higher in patients with b3a2 transcripts compared with b2a2 (*P* = .01)
- Of the 3 patients with atypical transcripts (b3a3 or e1a2), all achieved CHR, 1 achieved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

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



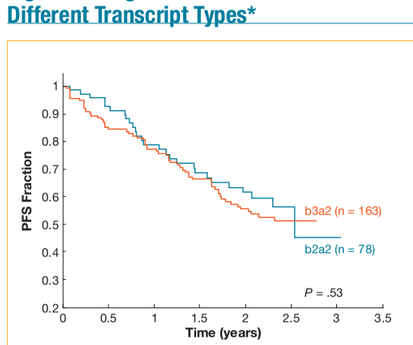
- Cytogenetic response to nilotinib did not exhibit a statistically significant difference between b2a2 and b3a2 transcript types

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



- Molecular response to nilotinib was similar regardless of transcript type

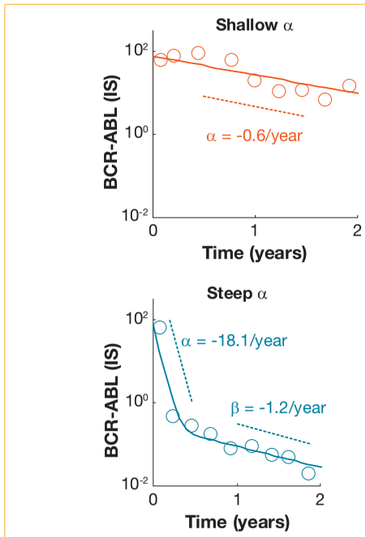
Figure 4. Progression-Free Survival for Different Transcript Types*



* 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)

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