

Bcr-Abl Kinetics Suggest Self-Renewing Leukemic Cells are Reduced During Imatinib Treatment

A Stein, T Kalebic, D Bottino

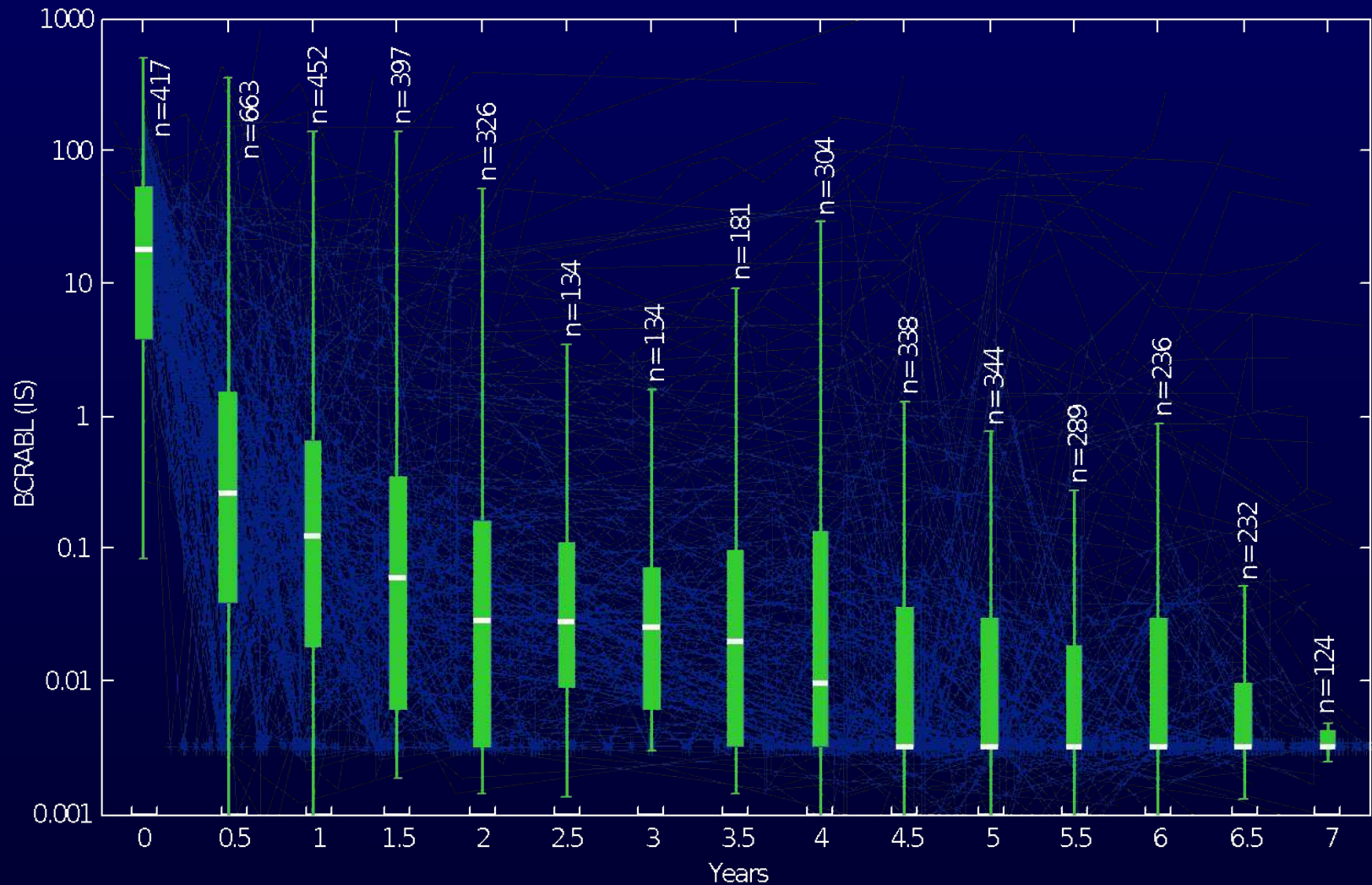
Background: IRIS

- The International Randomized Study of Interferon and STI571 (IRIS) is a phase 3, randomized, multicenter trial which demonstrated the superior safety and efficacy of imatinib over interferon- α plus cytarabine for patients with Philadelphia positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP)¹
- Patients randomized to imatinib achieved the following response rates at 8 years follow-up:²
 - Complete cytogenetic response, 83%
 - Overall survival, 85%
 - Event-free survival, 81%
 - Freedom from progression to accelerated phase/blast crisis, 92%
- Long-term follow-up from IRIS show high, durable rates of hematologic, cytogenetic and molecular response with a proven survival benefit supported by more than 8 years of clinical follow up

1. O'Brien et al. *N Eng J Med*. 2003; 348:994-1004.

2. Deininger et al. *Blood*. 2009; Volume 114, Abstract 1126.

Introduction: BCR-ABL levels decrease over time on imatinib



Does imatinib impact leukemic self-renewing cells (LSCs)?

- Leukemic 'stem cells' have been described as the basis of CML and may contribute to relapse¹
- In preliminary studies of imatinib discontinuation in a small patient populations, the majority of patients relapsed after stopping imatinib¹⁻⁷
- In vitro, quiescent stem cells (CD34⁺) are insensitive to imatinib and nilotinib over 3–12 day experiments⁸⁻⁹

1. Ross et al. ESH meeting, Bordeaux, Sept. 2009: CML – Biological basis of therapy.
2. Rousselot et al. *Blood*. 2007;109:58-60.
3. Mahon et al. *J Clin Oncol*. 2009; 15s:Abst.7084. 4. Koskenvesa et al. *Blood*. 2008;112:212.
5. Russo et al. *Haematologica*. 2009;94(s2):194.
6. Goh et al. *Leukemia & Lymphoma*. 2009;50:944-951.
7. Janssen et al. *Curr Stem Cell Res Ther*. 2009 Sep;4:224-236.
8. Graham et al. *Neoplasia*. 2002;99:319-325.
9. Jorgensen et al. *Neoplasia*. 2007;109:4016-4020.

Goal: investigate if imatinib therapy can reduce the LSCs in patients

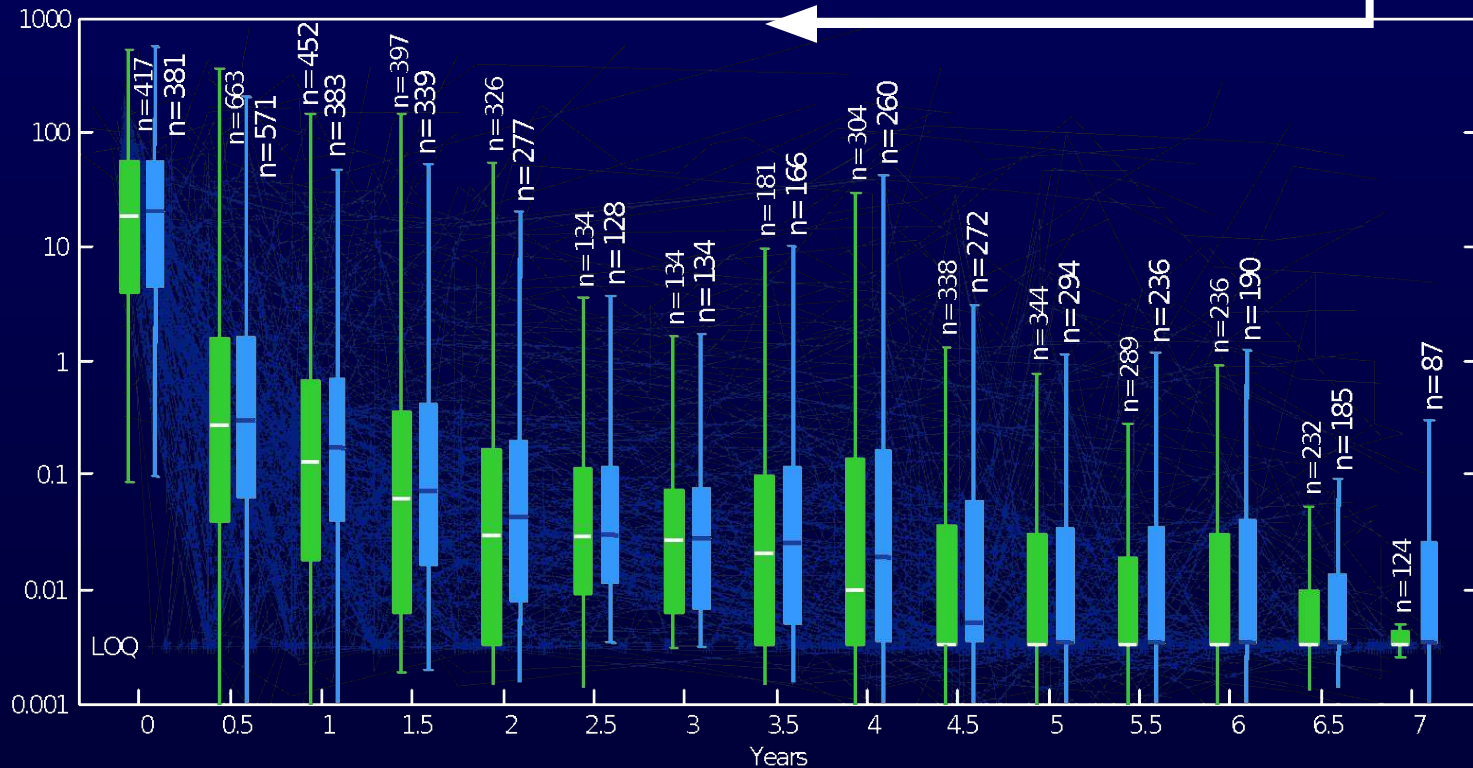
- We have used:
 - Molecular response data from IRIS patients (7 years)
 - Information about early progenitor kinetics, and
 - Mathematical modeling
- (i) To characterize the BCR-ABL time-profiles
- (ii) To infer dynamics of LSCs
in patients treated with imatinib

Methods

1106 patients in IRIS
(7-year follow up)

553 patients
randomized to imatinib

327 patients with ≥ 4
BCR-ABL observations



Empirical model
selection (AIC)¹

mono bi tri-exp

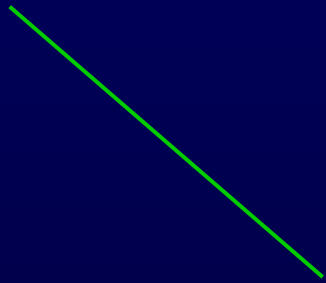
AIC, Akaike Information Criterion

1. Akaike, H. *IEEE Transactions on Automatic Control*. 1974;19(6):716-723.

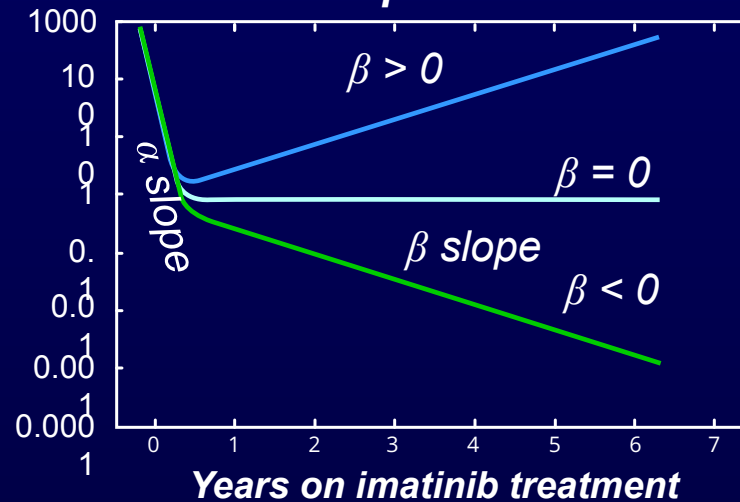
Stein A, et al. *Blood*. 2009;114(22):209. Abs # 506 (oral).

Empirical characterization of patient PCR profiles: *Multi-exponential regression & model selection*

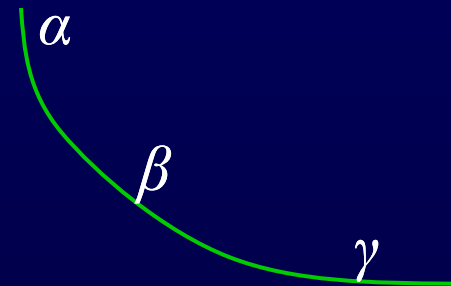
Monoexponential



Bi-exponential



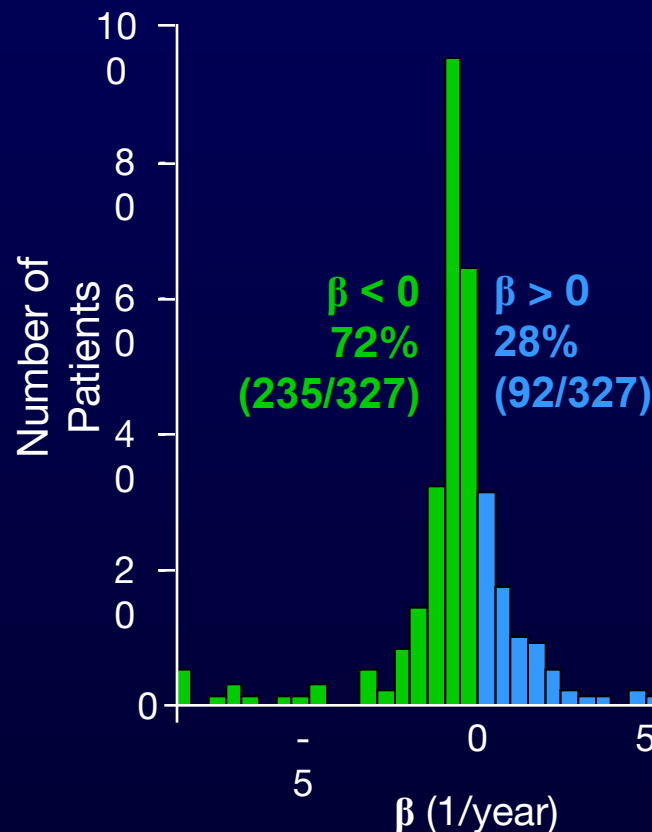
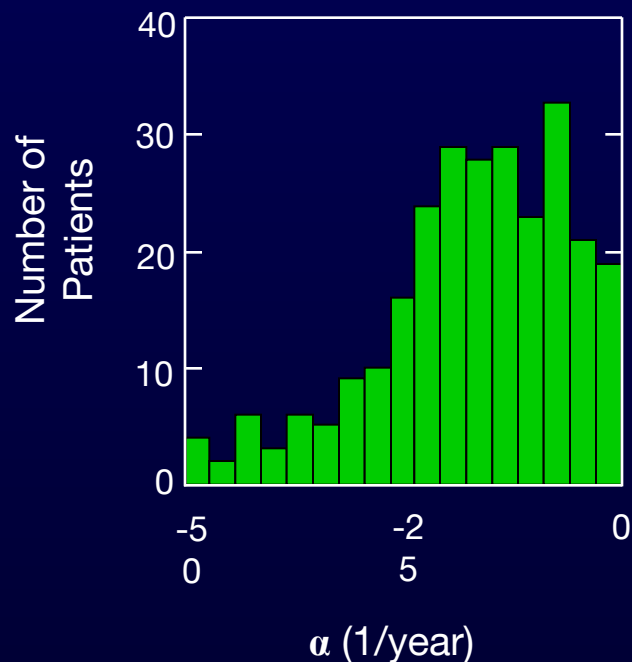
Tri-exponential



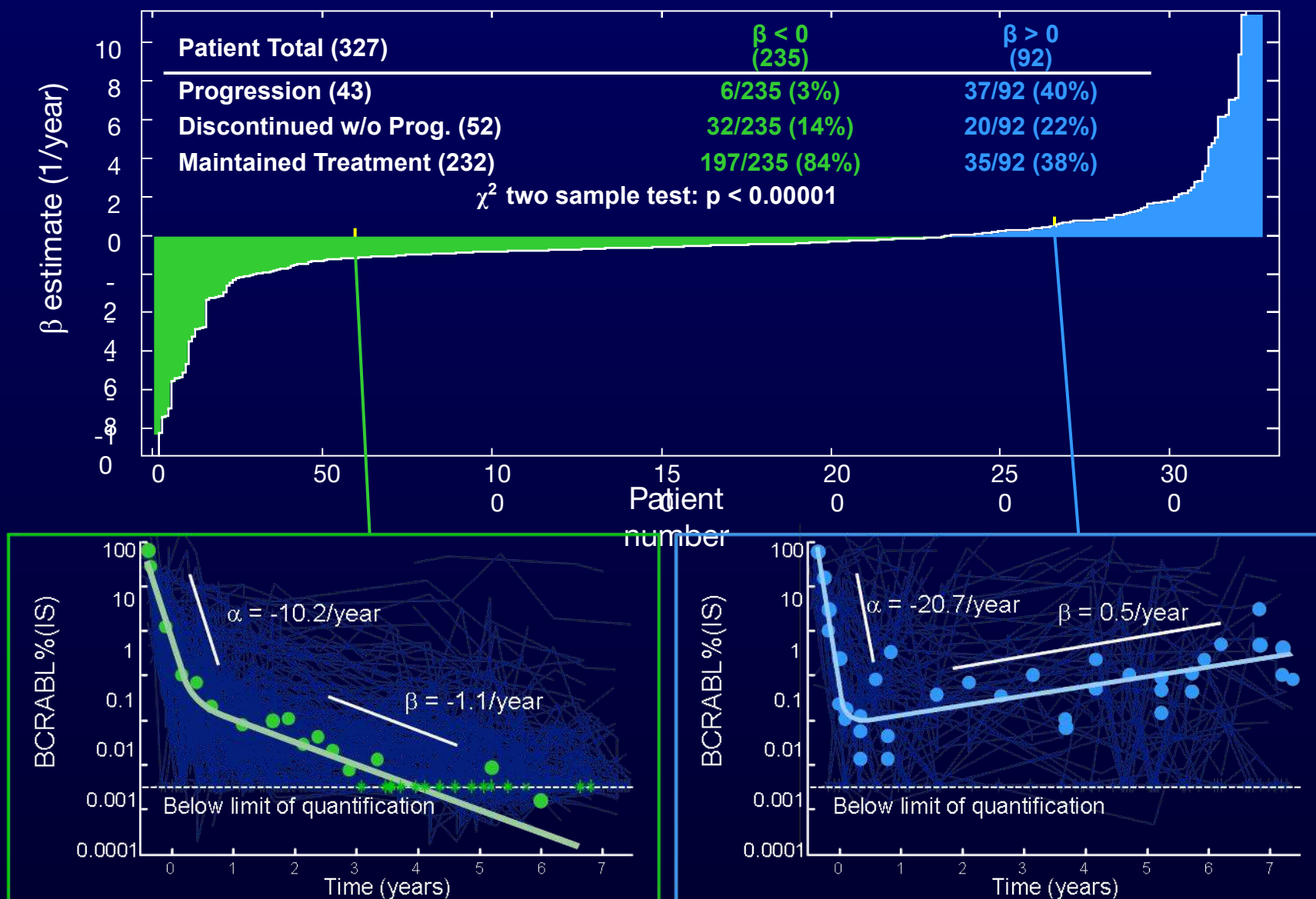
- Standard statistical methods (Akaike Information Criterion [AIC]) used to find simplest multi-exponential function that explained the data
- Tri-exponential was rejected for all but 4 patients via AIC, suggesting β -decline continues to decline below detection threshold
- Bi-exponential function: $Ae^{\alpha t} + Be^{\beta t}$, $\alpha < \beta$, t = time in years
 - $\alpha < 0$ represents the initial slope of BCR-ABL decline (up to ~6 months)
 - β represents the longer slope (~ 6 months and beyond)

Patient parameter estimates for the bi-exponential model

Distribution of β slopes: 72% $\beta < 0$, 28% $\beta > 0$

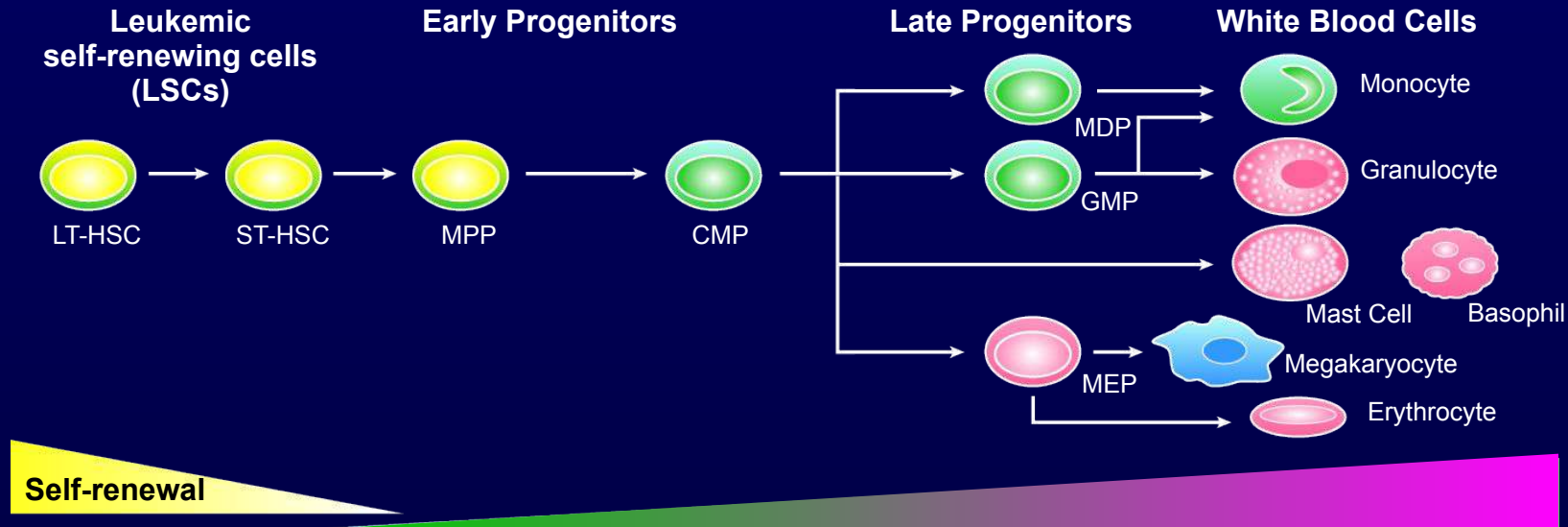


Typical individual profiles for $\beta < 0$ and $\beta > 0$



What drives the α and β slopes?

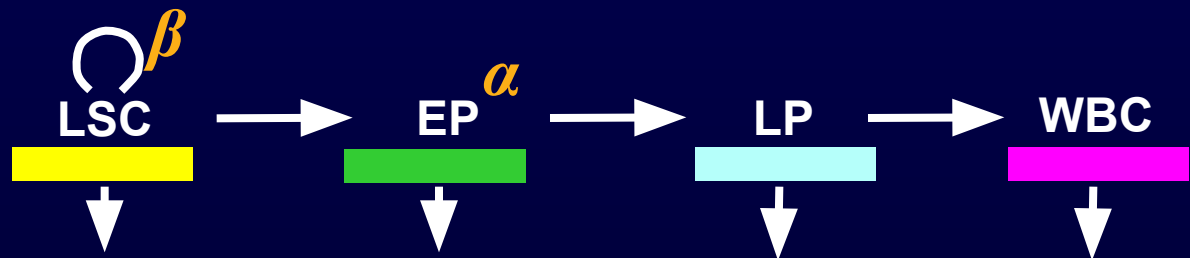
Two hypotheses with distinct implications for LSCs



1: EP-LSC Hypothesis

α ~ decline of EPs

β ~ decline of LSCs

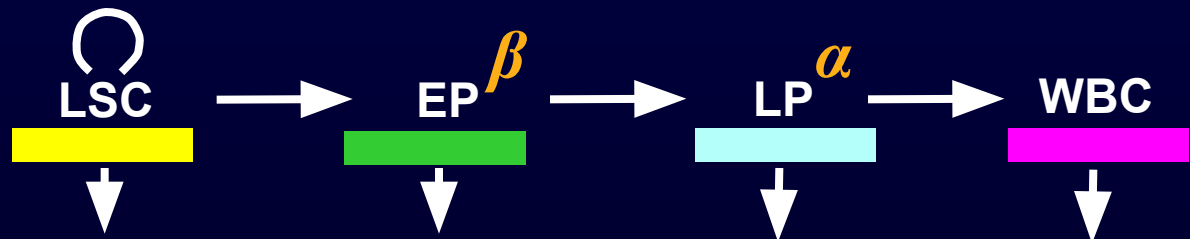


2: LP-EP Hypothesis

α ~ decline of LPs

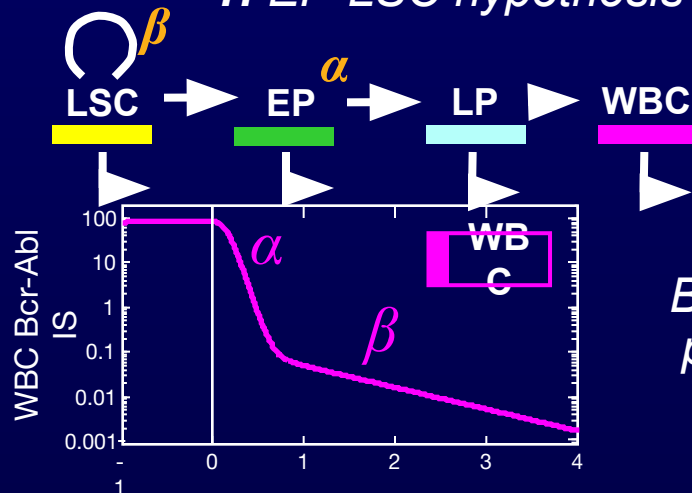
β ~ decline of EPs

LSCs untouched

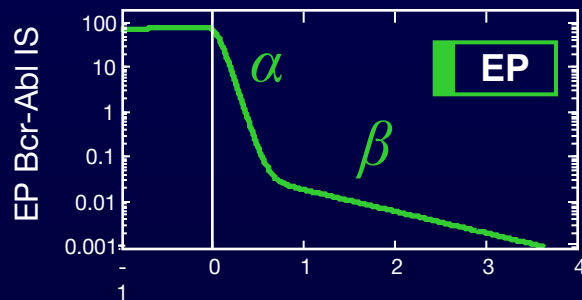


Model Simulations

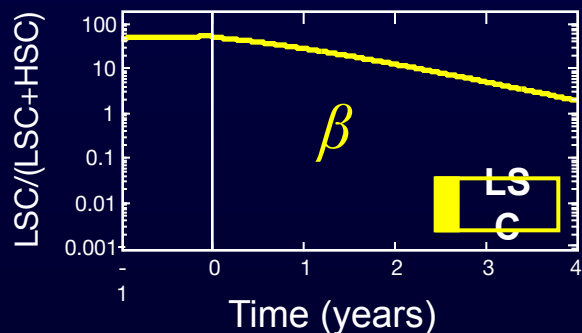
1: EP-LSC hypothesis



Both models can predict biphasic WBC response

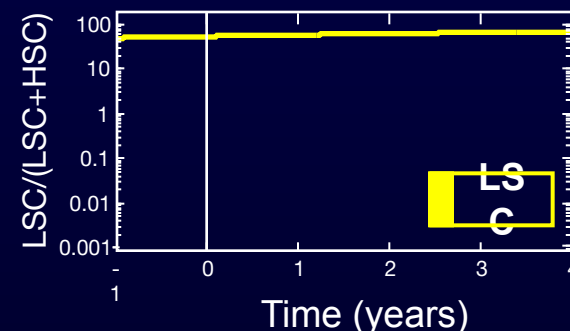
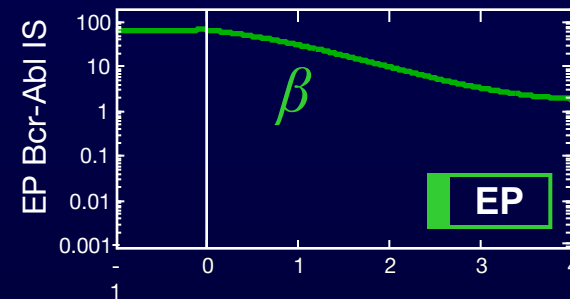
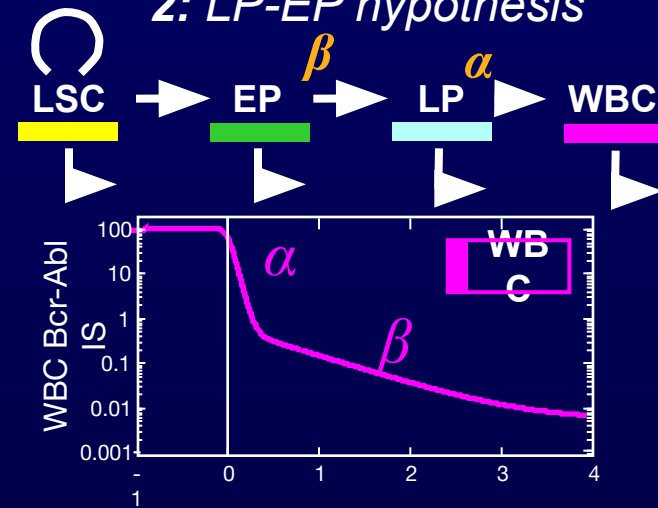


Models make different predictions of EP kinetics

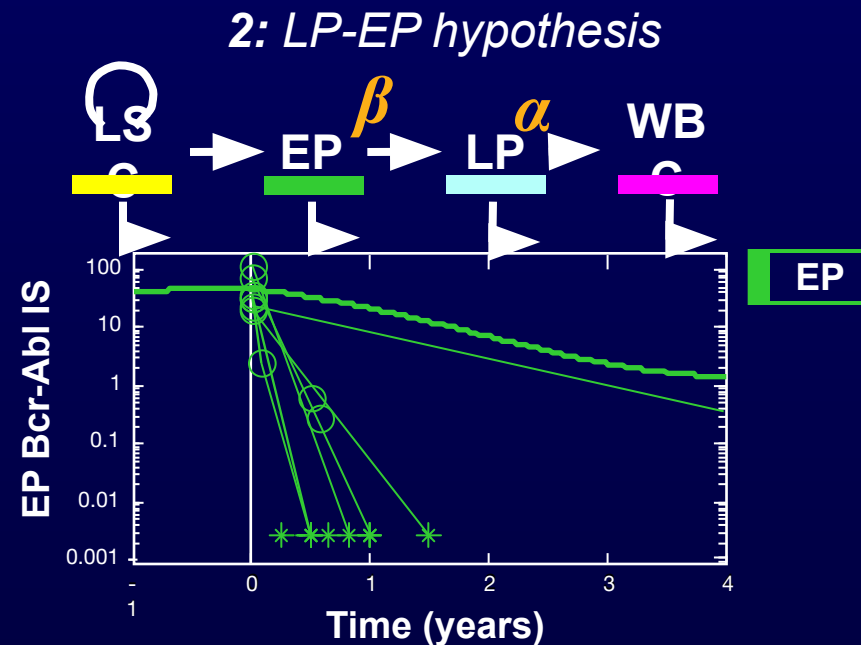
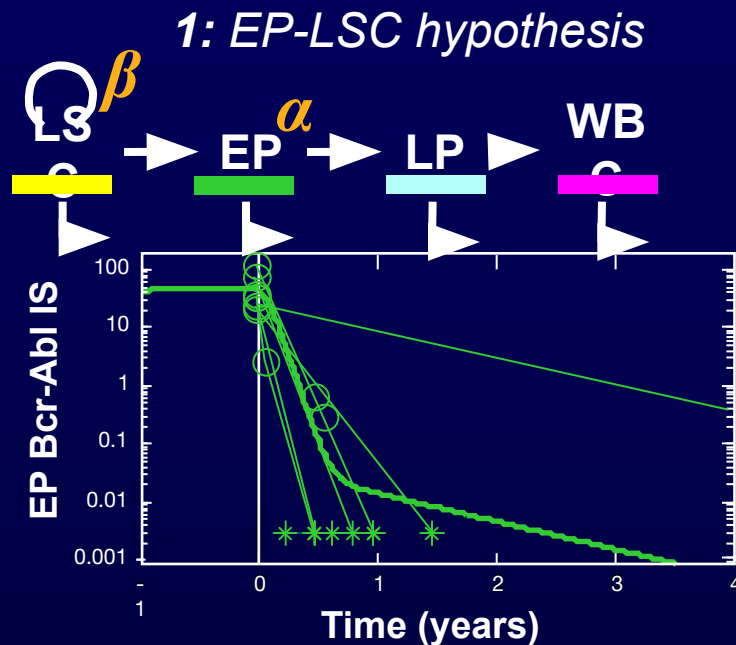


Models make different predictions of LSC kinetics

2: LP-EP hypothesis



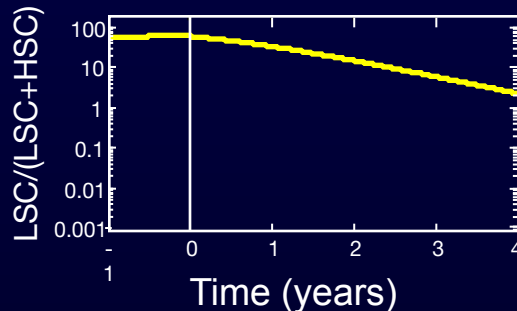
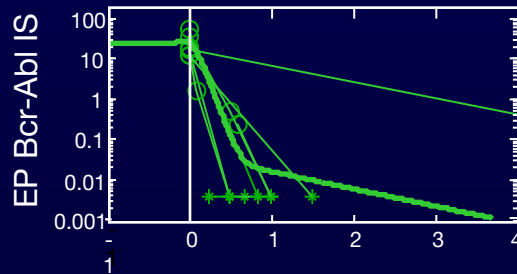
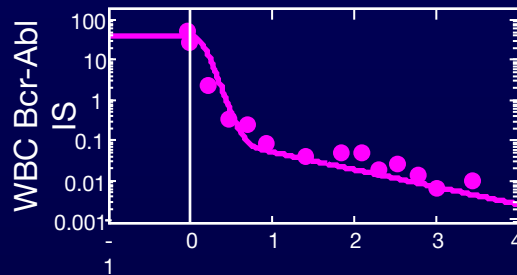
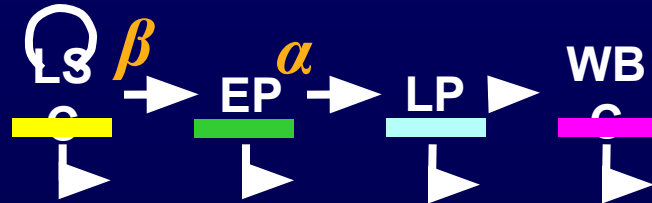
Experimental observations suggest EP decline is much faster than observed β slope



- Healthy hematopoiesis occurs within weeks^{2,3} suggesting that healthy EPs do not persist in bone marrow for years
- Long-term bone marrow transplantation dynamics have been attributed to stem cells (not EPs) in mice⁴
- Preliminary findings show leukemic EPs undetectable by PCR within 1 year¹

LSC reduction model is the only one that can explain both EP and WBC BCRABL kinetics

1: EP-LSC hypothesis



BCRABL
(typical $\beta < 0$ case)

WB
C

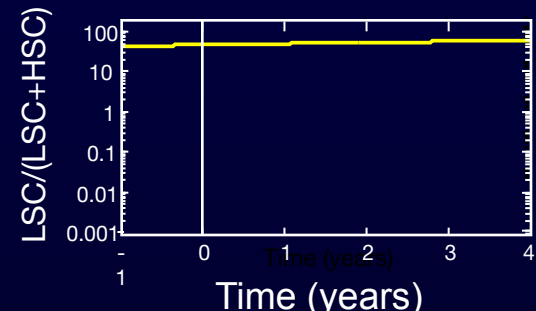
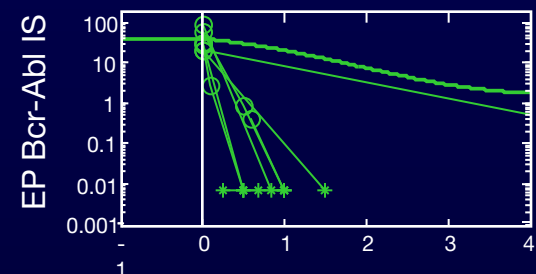
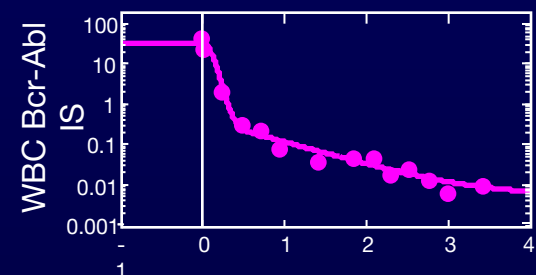
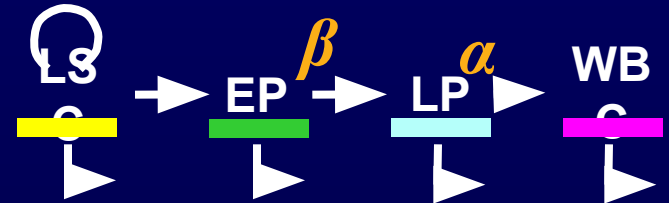
EP kinetics

EP
C

Predicted LSC
kinetics

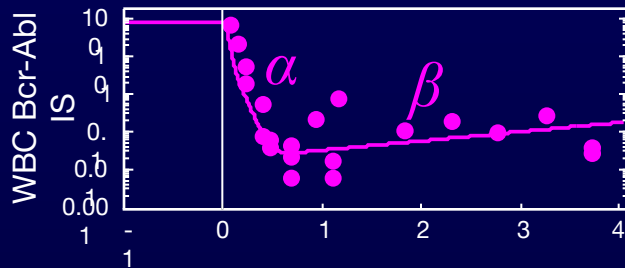
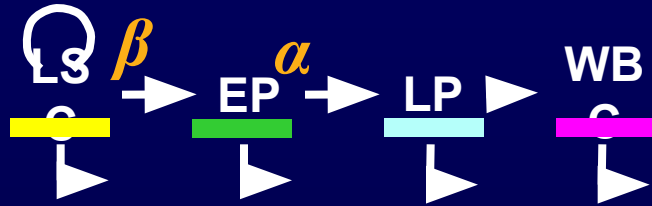
LS
C

2: LP-EP hypothesis



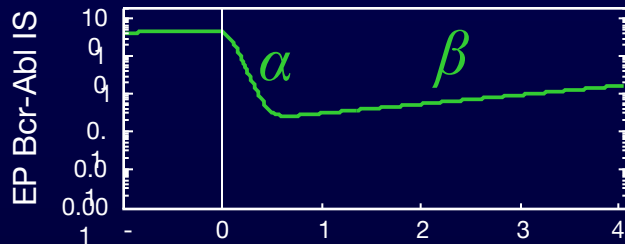
Both models predict that patients with $\beta > 0$ experience LSC increase at rate β

1: EP-LSC hypothesis



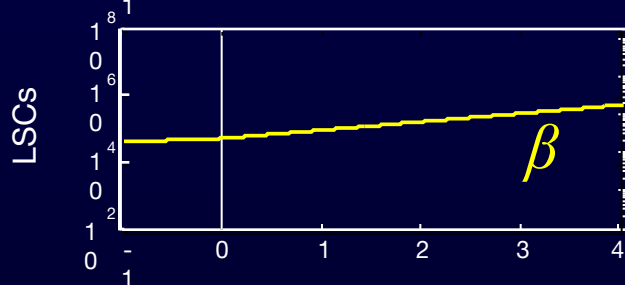
BCRABL
(typical $\beta < 0$ case)

WB
C



Predicted EP
kinetics

EP
C

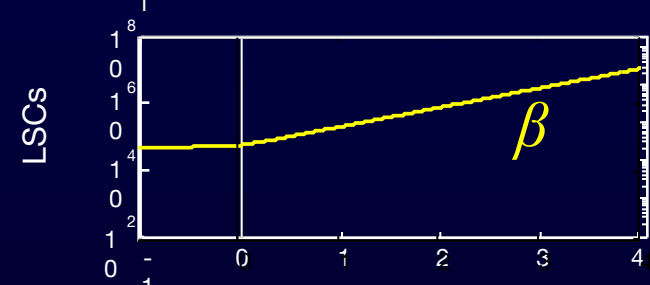
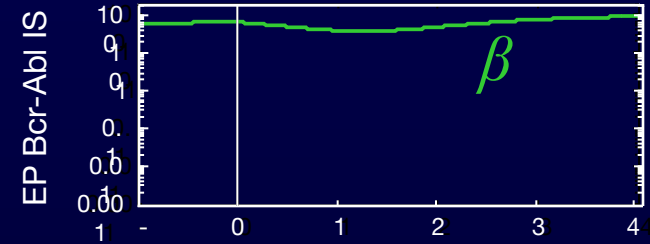
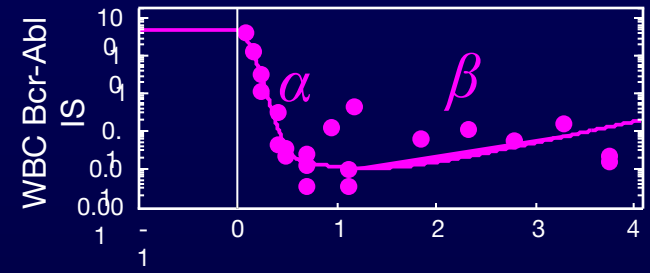
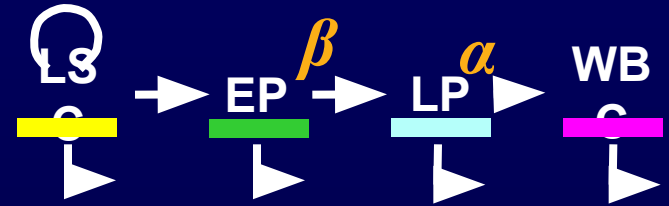


Time (years)

Predicted LSC
kinetics

LS
C

2: LP-EP hypothesis



Time (years)

Conclusions

IRIS data + EP understanding + modeling suggest:

- Majority of study patients well-described by bi-exponential
 - α : initial rapid BCR-ABL ratio decline
 - β : long-term decline or increase
- β corresponds to kinetics of LSCs during IM treatment.
 - 235/327 (72%): $\beta < 0$ □ gradual decline in LSC burden
 - 92/327 (28%): $\beta > 0$ □ gradual increase in LSC burden
- Modeling does not distinguish among various plausible mechanisms for predicted stem cell decline ($\beta < 0$)
- Future analysis will include nilotinib patients

Acknowledgements

- Yen Lin Chia
- Ovidiu Chiparus
- James Dunyak
- Insa Gathmann
- Alan Hatfield
- Gabriel Helmlinger
- Tillmann Krahne
- Vijay Modur
- Jerry Nedelman
- The IRIS investigators