

Inference of Imatinib Effects on Leukemic Stem Cell Compartment via Mathematical Modeling of IRIS Treatment Response Data

Dean Bottino¹, Yen Lin Chia², Andrew Stein², Anna Georgieva¹, Gabriel Helmlinger^{2*}, Thea Kalebic¹

¹Novartis Pharmaceutical Corporation, East Hanover, NJ, USA; ²Novartis Institutes for Biomedical Research, Cambridge, MA, USA.



Background

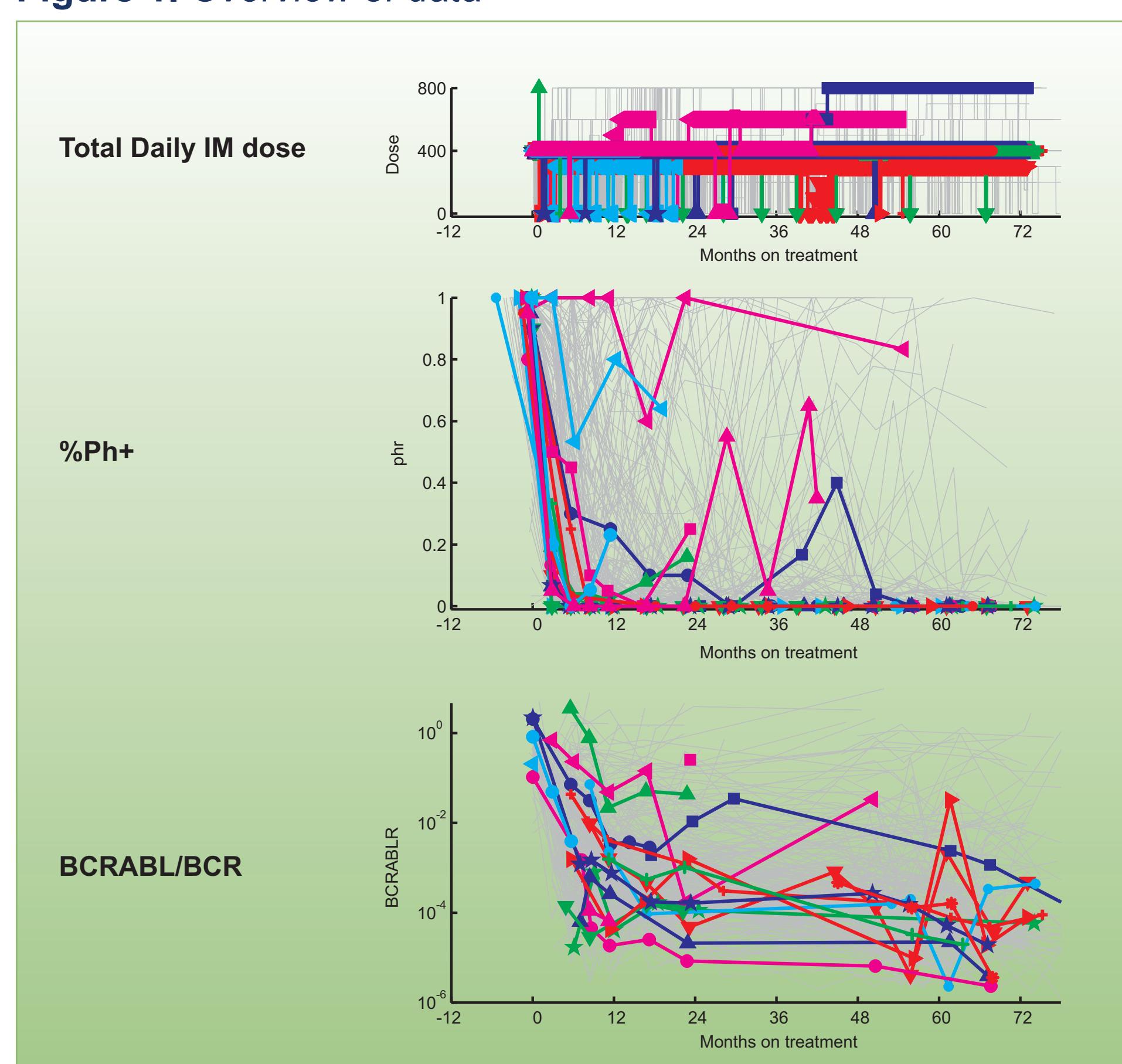
- Continuous treatment with imatinib (IM) induces durable responses in majority of chronic phase leukemia (CML-CP) patients with a decreasing rate of relapse.¹
- Here, we present a mechanistic mathematical model to explore IM effects on leukemic stem cells (LSCs) across the patient population.

Methods

Data used in the analysis

- A 6.5-year follow up data from the international randomized study of interferon versus ST1571 (IRIS) trial² (Figure 1).

Figure 1. Overview of data



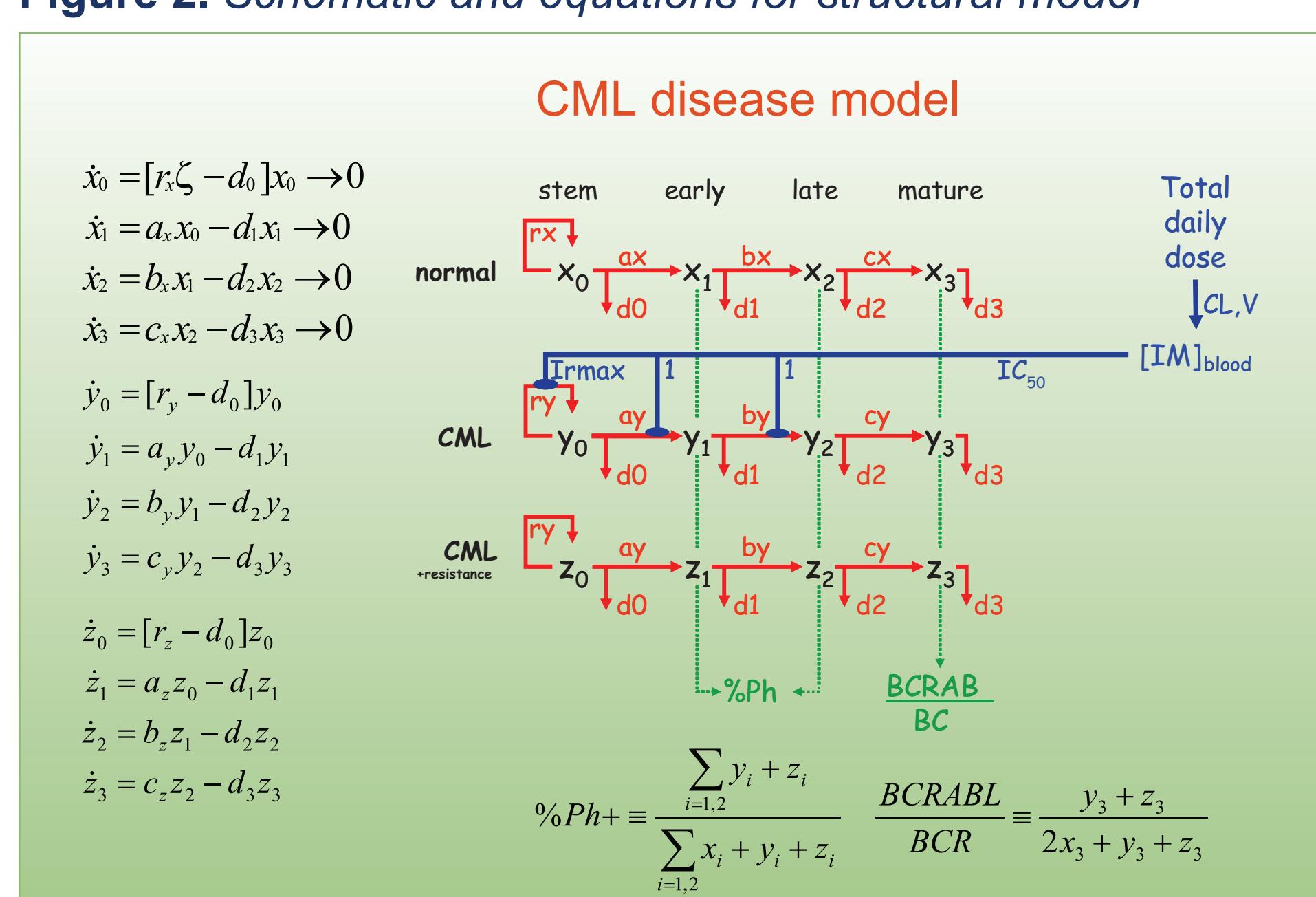
Patient subset

- 1106 CML-CP patients in IRIS trial.
- 553 in IM arm of trial.
- 455 have pharmacokinetic (PK) data.
- 425 used in this study.

CML disease model

- CML was modeled as independent evolution of up to three cellular subpopulations: normal, Ph+ (CML), and Ph+ (IM) resistant.
- For any subpopulation, hemopoiesis was assumed to be a 4-step process of stem, early progenitor, late progenitor, and mature cell compartments. CML subpopulations were assumed to have higher proliferation/differentiation rates than their normal counterparts. IM-resistant cells were assumed to have same rates as IM-sensitive cells in the absence of IM (Figure 2).
- Cytogenetic status (% Ph+) is modeled as ratio of leukemic to total progenitor cells.
- Molecular status (BCRABL/BCR) is modeled as ratio of leukemic cells to total cells in peripheral blood, with a correction for copy number.

Figure 2. Schematic and equations for structural model



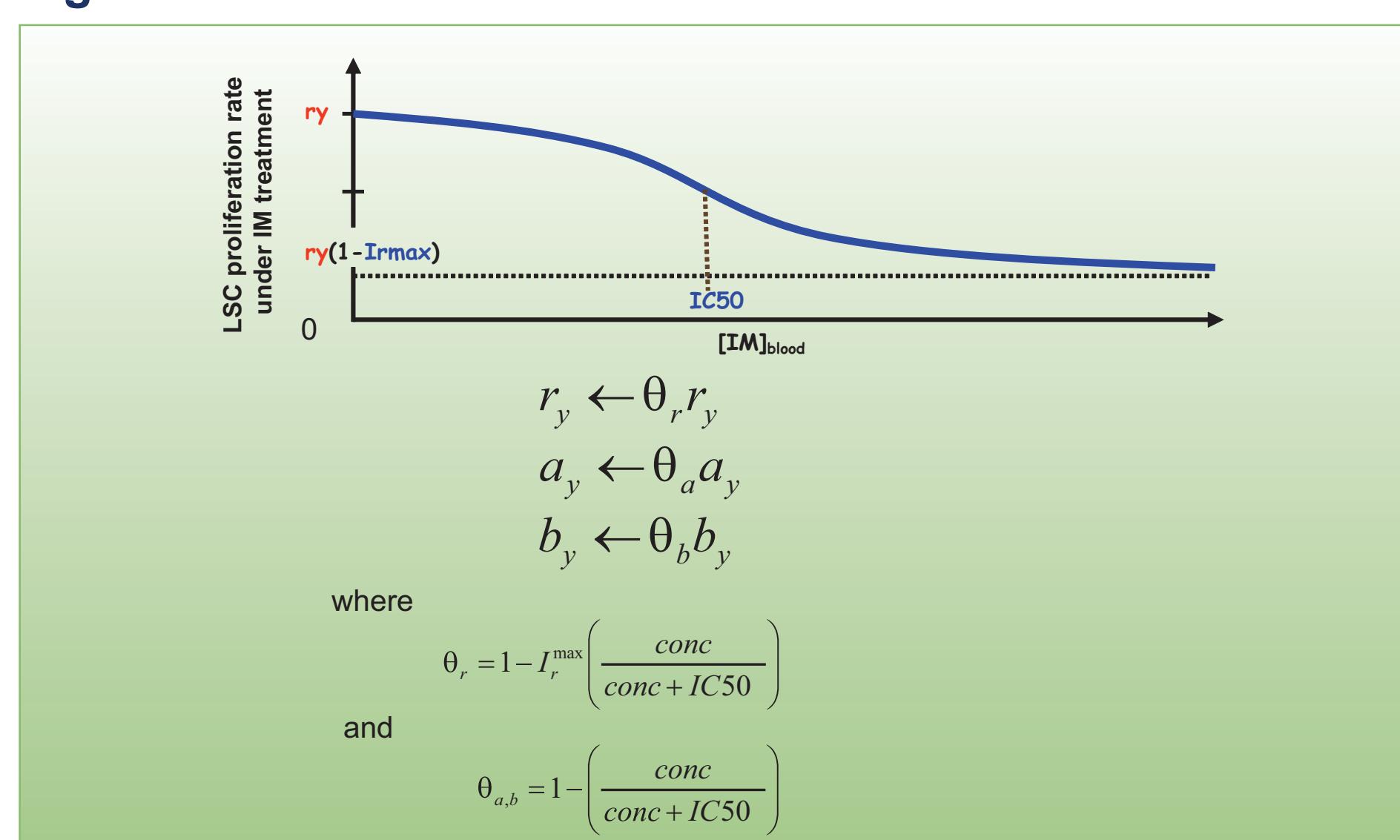
Dose-exposure model

- Daily dose exposure for each patient was estimated from the total daily dose (TDD) records and individual PK parameters of previous PK study.³ IM exposure was assumed to be constant during periods of constant TDD.
- Individual PK parameters were assumed to remain constant after Day 28 (last PK observation).

Concentration-inhibition model

- IM-sensitive cells were assumed to have the same IC₅₀ to IM irrespective of maturation state, but maximum level of inhibition (I_{max}) could vary according to the maturation state (Figure 3).
- I_{max} parameter describes the maximum inhibition of IM on Ph+ wt LSC proliferation/self-renewal. In previous publications with similar structural models, I_{max} was assumed to be zero. In this study, we allowed the I_{max} parameter to be estimated based on IRIS response profiles.

Figure 3. Concentration-inhibition model



Parameter estimation

- We used non-linear mixed effects approach as implemented in MONOLIX.
- Key model parameters were subject to either fixed or mixed effects parameter estimation:
 - Mixed: $0 < \Phi_L < 1$, the initial ratio of Ph+: total stem cells.
 - Fixed: $IC_{50} > 0$, the IM blood exposure causing 50% of maximum inhibition of leukemic cell proliferation.
 - Mixed: $0 < I_{max} < 1$, the maximum inhibition by IM on Ph+ stem cells.
 - Mixed (ture): $-Inf < Tres < +Inf$, the initial time of formation of a resistant clone. This was modeled as a mixture distribution to reflect the fact that a minority of patients develop resistance.
 - Fixed: ry , rate of LSC proliferation/self renewal.
- Different combinations of fixed and random effects on the above parameters were attempted until a satisfactory fit to the data was obtained.

Figure 4. IM effect on LSC required to explain clinical observation

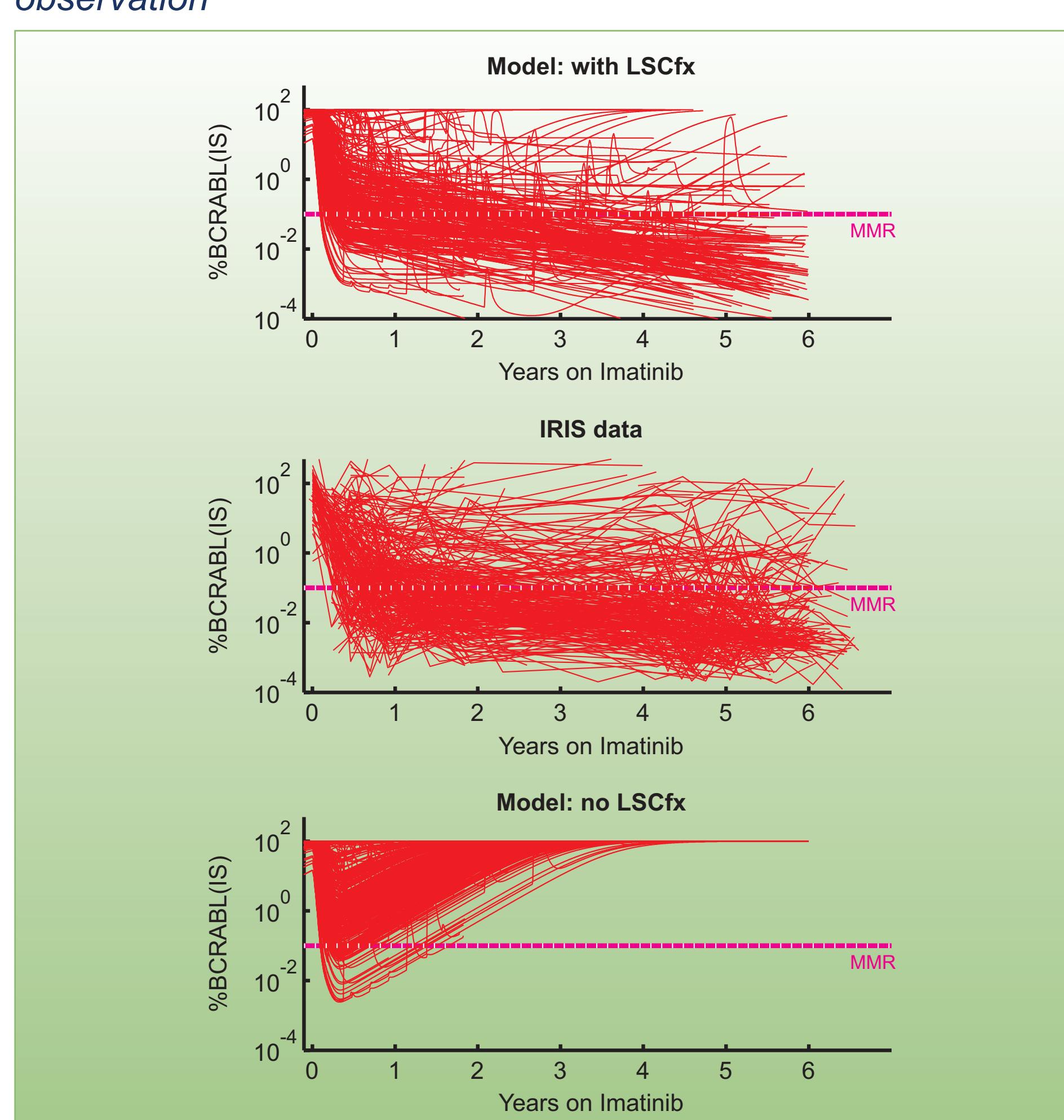


Figure 5. Distribution of individual estimates of I_{max} (maximum LSC inhibition by IM) and sensitivity of response profiles to that parameter

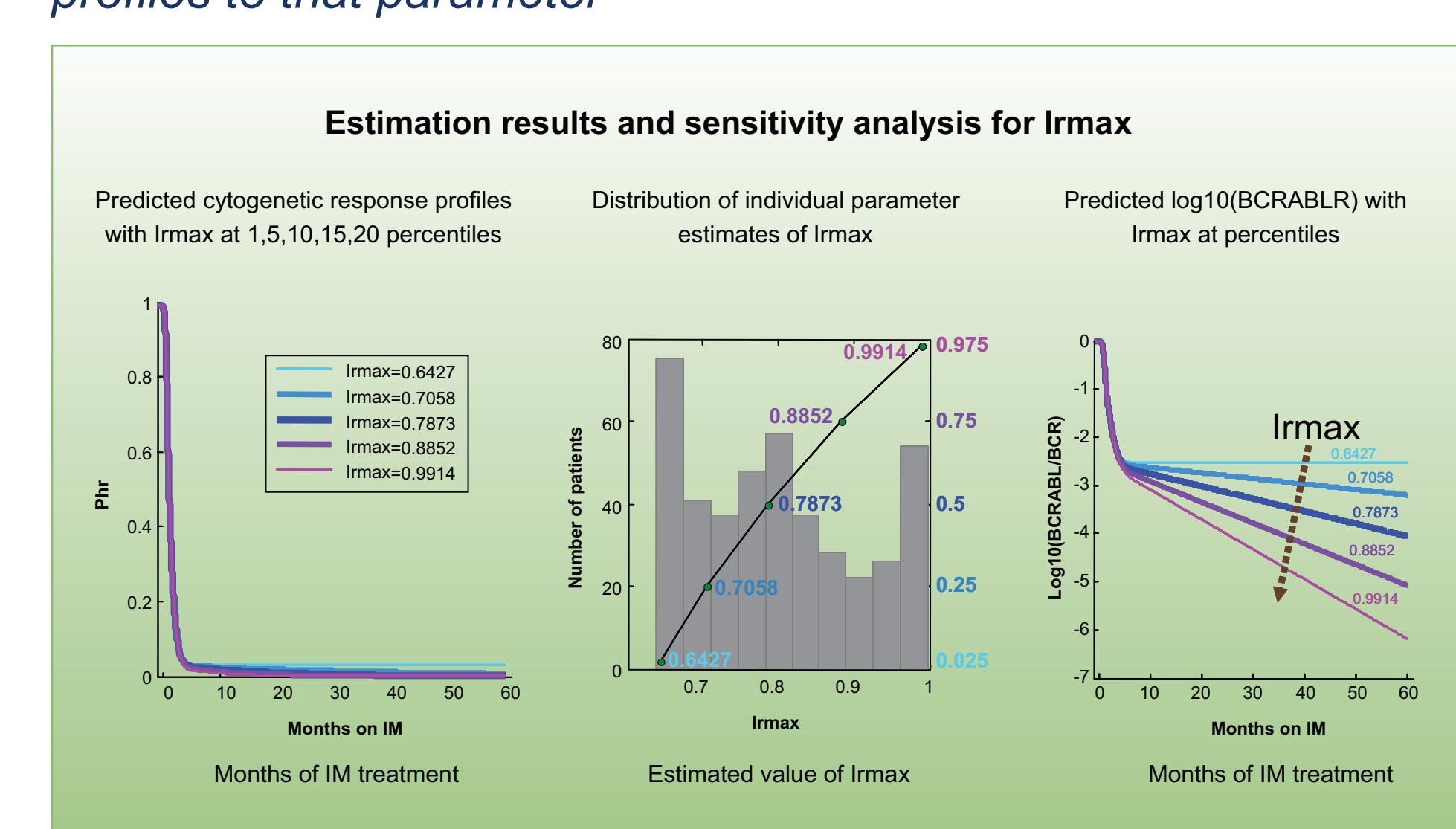
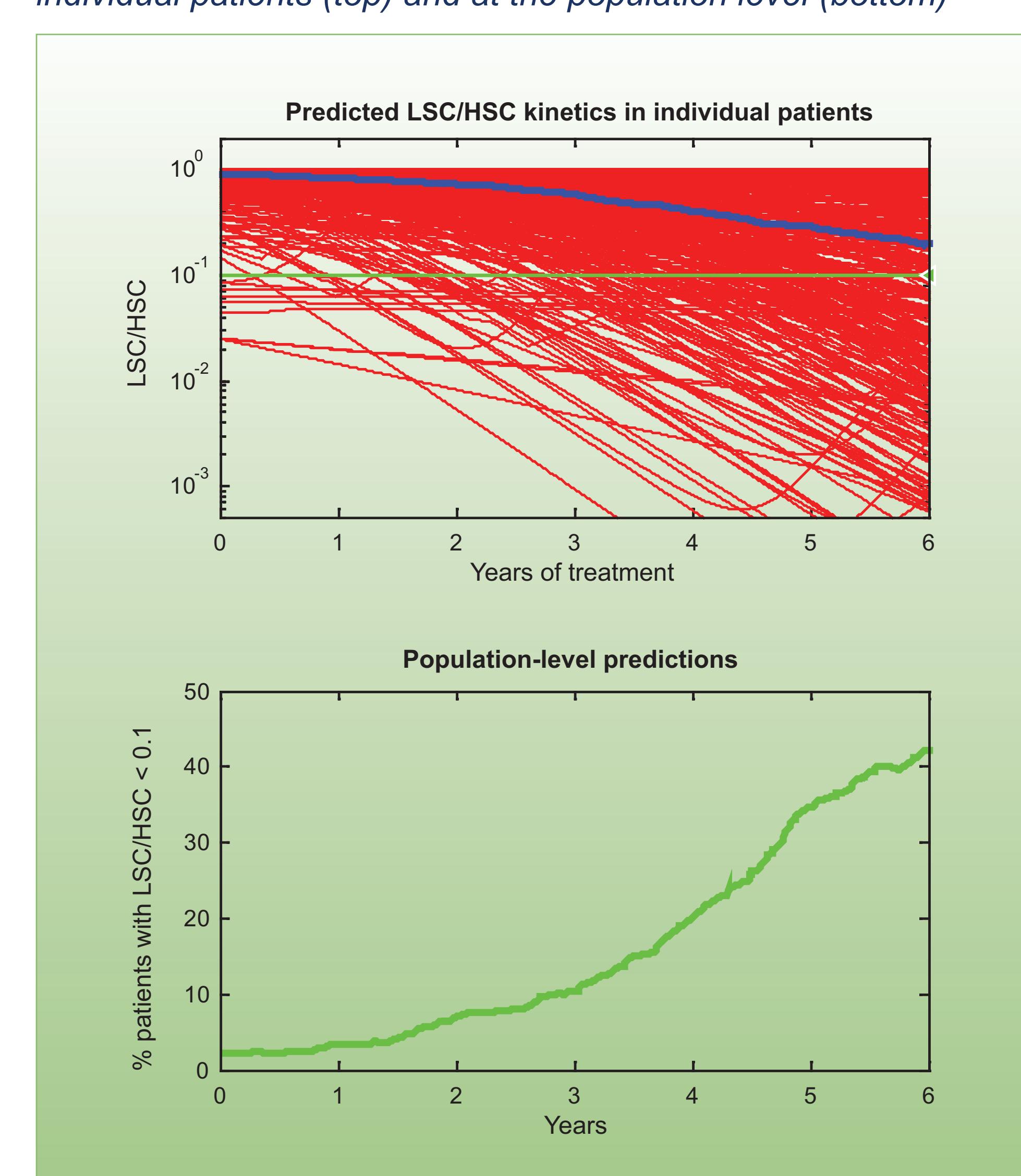


Figure 6. Model predictions of LSC burden reduction in individual patients (top) and at the population level (bottom)



Results/Conclusions

- A mechanistic model of CML-CP response to IM treatment was fit to individual cytogenetic and molecular response time-courses in 425 CML-CP patients with follow-up of up to 6.5 years.
- Non-linear mixed effects modeling suggests that the following parameters must vary across the population to account for the range of response trajectories observed (Figure 5):
 - Φ_L , the pre-treatment ratio of leukemic to total stem cells.
 - T_{res} , the initial time of formation of a resistant clone, in the small population of patients with clinical resistance (primary or acquired).
 - I_{max} , the maximum inhibition of Ph+ stem cell (LSC) proliferation by IM.
- Previous modeling efforts,⁴ which assume $I_{max} = 0$ (no IM stem cell effect), can explain early (12 months) response data but cannot explain durable responses observed in IRIS and other long-term studies (Figure 4).
- The presented model can explain the 6.5-year IRIS data and further predicts that most patients undergo a reduction in their LSC to total hemopoietic stem cell (HSC) ratio over the course of treatment, and that after 6 years of treatment, 45% of patients will have an LSC/HSC ratio < 0.1 (Figure 6).

References

- Hochhaus A. et al. Blood. 2007;110:15a-6a. Abstract No. 25.
- O'Brien SG. et al. N Engl J Med. 2003;348:994-1004.
- Schmidli H. et al. Br J Clin Pharmacol. 2005;60(1):35-44.
- Michor F. et al. Nature. 2005;435(7046):1267-70.