SUPPLEMENTARY APPENDIX

Dynamics of chronic myeloid leukemia response to dasatinib, nilotinib, and high-dose imatinib

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SUPPLEMENTARY INFORMATION

Dynamics of chronic myeloid leukemia response to dasatinib, nilotinib, and high-dose imatinib

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STUDY GROUP

Patient selection

We utilized four cohorts in this analysis: 233 patients treated with dasatinib, 215 patients treated with nilotinib and 281 patients treated with high-dose imatinib within the phase II trial at the MD Anderson Cancer Center[1-2], as well as 22 patients treated with low-dose imatinib (400mg daily) within the IRIS trial[3-4]. We employed the following criterion to select patients from the study group for inclusion in our various analyses. Only patients with measurements at the first five time points were included, which were at 0, 3, 6, 9, and 12 months.

Patient cohorts

Based on the above patient selection criteria, we obtained data of 92 patients treated with dasatinib, 75 patients treated with nilotinib and 123 patients treated with high-dose imatinib within the phase II trial at the MD Anderson Cancer Center[1-2]. We also obtained data of 13 patients treated with low-dose imatinib (400mg daily) within the IRIS trial[3-4]. For each patient, the disease burden was quantitated using the International Scale standardized methodology over the entire course of the trial.

DETAILS OF MATHEMATICAL MODELING APPROACH

To investigate the parameters of the mathematical model, we first conducted statistical model fitting to data of each patient cohort.

Individual model fitting

We fit two models to each individual patient to identify the better fit: a single exponential curve and a bi-phasic exponential curve with a turning point. These models were chosen since the leukemic cell burden is expected to decrease (or increase) at an exponential rate. When fitting these two models, we first performed a logarithmic transformation of the original data and then fit a bi-phasic linear or linear model to the transformed data.

The log-transformed data is of the form (t_{ij}, y_{ij}), $i = 1, \ldots, N$; $j = 1, \ldots, n_i$, where i is the patient-specific index and n_i is the total number of BCR-ABL1% value measurements for patient i; here y_{ij} is logarithmically transformed. Then the linear model for each patient i is given by

$$M_0 : E(y_{ij}) = \alpha_i + \beta_i t_{ij}, i = 1,\ldots,N; j = 1,\ldots,n_i,$$

where α_i and β_i are parameters to be estimated for each individual based on data of each individual patient *i;* while the bi-phasic linear model is given by

$$M_1 : E(y_{ij}) = (\alpha_i + \beta_i t_{ij}) I_{\{t_{ij} \le \tau_i\}} + (\alpha_i^{'} + \beta_i^{'} t_{ij}) I_{\{t_{ij} > \tau_i\}}, \qquad \alpha_i + \beta_i \tau_i = \alpha_i^{'} + \beta_i^{'} \tau_i .$$

where α_i, β_i, $\alpha_i^{'}$, $\beta_i^{'}$ and τ_i are parameters to be estimated for each individual based on data of each individual patient *i.*

To determine the model with the best fit for each individual patient's data, choosing among the above linear versus bi-phasic linear models, we utilized the joinpoint software, which is publicly available on the NCI website, http://surveillance.cancer.gov/joinpoint/. We chose to use this

software because it was designed to identify segmented models that best fit to longitudinal data. Within this framework, we utilized the permutation test approach since it controls the error probability of selecting the wrong model at a given significance level, for instance 0.05. This option was chosen over other approaches (such as the BIC) since the latter does not provide an estimate of the error probability.

For each model with k turning points, we estimated a total of $2k + 2$ parameters (k = 0 or 1 in our study). For the parameter estimation, we utilized Hudson's Method[5], as it provides more accurate estimates compared to the Grid Search method[6], even though it is computationally more expensive. For details of the parameter estimation and the hypothesis testing see Kim et al.[7]. In brief, for any linear model with k turning points, Hudson's method first partitions the observed data into k+1 consecutive subsets. For each subset, an ordinary least squares method is applied to obtain the intercept and slope estimates over the data range of that subset. The turning points are then directly calculated as the intersections of two adjacent linear segments. If these intersection points divide the observed data into the same partitions as chosen originally, then the fit is admissible and its sum of squared error (SSE) is noted. Otherwise, the fit is not admissible and further adjustments are made. The least squares estimates for the linear model with k turning points are then obtained from the fit, which provides the smallest SSE over all feasible partitions.

After the parameter estimation outlined above, the following permutation test procedure is performed to determine the better fit between the linear model M_0 and the bi-phasic linear model M_1. This approach[5] can be summarized in several steps:

1. Fit the original data set with the null hypothesis model with *0* turning points.
2. Permute the residuals from the null hypothesis model and add them back to the means from the null hypothesis model to obtain a new permutation data set.
3. For this permutation data set, fit both the null model with *0* turning points and the alternative model with *1* turning points and calculate a scalar goodness-of-fit measure. This measure is a ratio, SSEN/SSEA, where SSEN is the sum of squared errors (SSE) from the null model M_0 and SSEA is the SSE from the alternative model M_1.
4. Repeat steps 2 and 3 N_p-1 times. Denote the ratios, SSEN/SSEA, from the permutation data sets p as $\{T_p, p = 1, \ldots, N_p\text{-}1\}$. Also calculate this ratio for the original data set and denote it as T_0. Values of the ratio close to 1 represent the case in which the alternative is not much better than the null hypothesis model, while larger ratios signify that the alternative is much better.
5. The p-value of testing the hypothesis M_0 versus M_1 for the original data set is determined from the permutation distribution of the goodness-of-fit statistics. Then p-value = (number of times that $[T_p \geq T_0]$ for $p = 1, \ldots, N_p\text{-}1$) / N_p.

The permutation tests are used to investigate whether there is enough evidence to require a model with a larger number of turning points than the one in the null hypothesis. This approach controls the error probability of selecting the wrong model at a significance level of 0.05.

For the dasatinib treatment response data, 35 out of 69 patients had the bi-phasic model as better fitting. For the nilotinib treatment response data, 26 out of 51 patients had the bi-phasic model as better fitting. For the high-dose imatinib treatment response data, 54 out of 123 patients had the bi-phasic model as better fitting. For the low-dose imatinib treatment response data, all 13 patients had the bi-phasic model as better fitting (**Supplementary Table S3**).

Whole cohort model fitting

We then identified the model with the best fit to the entire patient cohort. When fitting each model to data of each patient individually as stated in the above section, we obtained the corresponding SSE_i as well as SST_i (Total Sum of Squares) for each subject *i*. The total SSE and total SST of the model were then calculated as $\sum_i SSE_i$ and $\sum_i SST_i$ separately. We defined the final R^2 for each model over the whole cohort as 1 - total SSE/total SST = 1 - $\sum_i SSE_i / \sum_i SST_i$. Let R_0^2 be the final R^2 of the model M_0 and R_1^2 be the final R^2 of the model M_1.

For the dasatinib treatment response data, 35 out of 69 patients had bi-phasic model as better fitting, R_0^2 was 0.59 , and R_1^2 was 0.92. For the nilotinib treatment response data, 26 out of 51 patients had bi-phasic model as better fitting, R_0^2 was 0.60, and R_1^2 was 0.93. For the high-dose imatinib treatment response data, 54 out of 123 patients had the bi-phasic model as better fitting, R_0^2 was 0.52, and R_1^2 was 0.89. For the low-dose imatinib treatment response data, all 13 patients had the bi-phasic model as better fitting. Also, for the dasatinib, nolotinib and high-dose imatinib cohorts, we obtained *N* subject-specific $R^2 = 1 - SSE_i / SST_i$, $i = 1, \ldots, N$. The summary information (Minimum, 1st Quartile, Median, Mean, 3rd Quartile, Maximum) of the R^2 for each model of different analysis is reported in **Supplementary Table S2**.

We found that the bi-phasic exponential model provided a larger final R^2 and smaller sum of BICs than the exponential model for all cohorts. The difference between the final R^2 was large enough to convince us of the better fit of the bi-phasic model in all four cohorts.

Mathematical model

We utilized a mathematical model of the treatment response of CML cells to TKI therapy [8-9], which describes four layers of the differentiation hierarchy of the hematopoietic system. Stem cells give rise to progenitors, which produce differentiated cells, which in turn produce terminally differentiated cells. This hierarchy applies both to normal and leukemic cells. Only stem cells have the potential for indefinite self-renewal, but progenitor and differentiated cells possess the capability to undergo limited reproduction, which, together with differentiation, leads to an expansion of the cell number at each level of the differentiation hierarchy. The BCR-ABL oncogene is present in all leukemic cells, leading to slow clonal growth of leukemic stem cells and accelerating the rate at which leukemic progenitors and differentiated cells are generated. Imatinib therapy reduces the production rates of leukemic progenitors and differentiated cells, and potentially also inhibits the expansion of leukemic stem cells.

Denote by x_0, x_1, x_2, and x_3 the abundances of normal hematopoietic stem cells, progenitors, differentiated cells, and terminally differentiated cells. Their respective leukemic abundances are given by y_0, y_1, y_2, and y_3. We assume that homeostatic mechanisms maintain the hematopoietic stem cell population at a constant level, and therefore introduce a density dependence term, ϕ, in the stem cell production rate. Leukemic stem cells grow at a slow pace until reaching their maximum number, which may be larger than that of normal stem cells; afterwards, their number is also held constant by a density dependence mechanism. Then the system containing stem cells (SC), progenitor cells (PC), differentiated (DC) and terminally differentiated cells (TC) is described by

healthy cells leukemic cells

$$
\begin{array}{lll}
SC & \dot{x}_0 = [r_x\phi - d_0]x_0 & \dot{y}_0 = [r_y\varphi - d_0]y_0 \\
PC & \dot{x}_1 = a_x x_0 - d_1 x_1 & \dot{y}_1 = a_y y_0 - d_1 y_1 \\
DC & \dot{x}_2 = b_x x_1 - d_2 x_2 & \dot{y}_2 = b_y y_1 - d_2 y_2 \\
TC & \dot{x}_3 = c_x x_2 - d_3 x_3 & \dot{y}_3 = c_y y_2 - d_3 y_3
\end{array}
$$

Here density dependence in the stem cell population is given by $\phi = 1/[1 + p_x(x_0 + y_0)]$ and $\varphi = 1/[1 + p_y(x_0 + y_0)]$. The potentially different carrying capacities of normal and leukemic stem cells are represented by the parameters p_x and p_y. Imatinib dramatically reduces the differentiation rates of cells, a_y to a_y' and b_y to b_y'. This change in rates leads to a bi-phasic decline of the leukemic cell burden.[8] The parameters during imatinib therapy are denoted by r_y', a_y', b_y' etc.

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SUPPLEMENTARY TABLES

Supplementary Table S1. The basic model of the differentiation hierarchy of normal and leukemic cells. The abundances of normal stem cells, progenitors, differentiated, and terminally differentiated cells are given by x_0, x_1, x_2, and x_3, while the respective abundances of leukemic cells are given by z_0, z_1, z_2, and z_3. Normal and leukemic stem cells divide at rates r_x and r_z per day, respectively. The rate constants for the production of progenitors, differentiated cells and terminally differentiated cells are given by a_x, b_x, and c_x for normal and by a_z, b_z, and c_z for leukemic cells. Stem cells die at rate d_0, progenitors at rate d_1, differentiated cells at rate d_2, and terminally differentiated cells at rate d_3 per day. Cells at all levels are assumed to potentially reproduce symmetrically and/or asymmetrically; the limited replication potential of more

differentiated cell types is then considered as part of the differentiation rates. Density dependence is achieved by the functions $\varphi_x = 1/[1+\rho_x(x_0+z_0)]$ and $\varphi_z = 1/[1+\rho_z(x_0+z_0)]$; these functions take into account crowding, limited resources, and interactions with the microenvironment. We assumed that the *BCR-ABL1* oncogene increases the rate at which progenitors and differentiated cells are being produced; $a_z > a_x$ and $b_z > b_x$. Molecularly targeted therapy counteracts the effects of *BCR-ABL1* by reducing the differentiation rates to $a'_z < a_z$ and $b'_z < b_z$, and possibly reducing the growth rate of leukemic stem cells to $r'_z < r_z$.

	Normal	Leukemic
Stem cells	$\dot{x}_0 = [r_x\varphi_x - d_0]x_0$	$\dot{z}_0 = [r_z\varphi_z - d_0]z_0$
Progenitors	$\dot{x}_1 = a_x x_0 - d_1 x_1$	$\dot{z}_1 = a_z z_0 - d_1 z_1$
Differentiated cells	$\dot{x}_2 = b_x x_1 - d_2 x_2$	$\dot{z}_2 = b_z z_1 - d_2 z_2$
Terminally differentiated cells	$\dot{x}_3 = c_x x_2 - d_3 x_3$	$\dot{z}_3 = c_z z_2 - d_3 z_3$

Supplementary Table S2. Summary statistics of the two statistical models for data in the dasatinib, nilotinib and high-dose imatinib patient cohorts. The two statistical models investigated were a single-phasic exponential model (denoted as 1-phase in the following table) and a 2-phasic exponential model (denoted as 2-phase in the following table). Note that summary statistics for the low-dose imatinib cohort were not presented here because all 13 patients in the low-dose imatinib cohort had 2-phasic model as the best fitting model, thus 2-phasic model was obviously the best fitting model for this entire cohort.

	Dasatinib cohort (69 patients)		**Nilotinib cohort** (51 patients)		**High-dose imatinib cohort** (123 patients)	
	2-phase	1-phase	2-phase	1-phase	2-phase	1-phase
Min* of R_i^2	0.230	0.011	0.575	0.005	0.243	0.000
1st Quartile* of R_i^2	0.901	0.449	0.913	0.431	0.864	0.327
Median* of R_i^2	0.960	0.573	0.964	0.551	0.930	0.540
Mean* of R_i^2	0.920	0.569	0.922	0.545	0.883	0.488
3rd Quartile* of R_i^2	0.984	0.736	0.982	0.692	0.973	0.658
Max* of R_i^2	1.000	0.968	0.999	0.948	1.000	0.917
**Final R^2	0.924	0.592	0.934	0.597	0.887	0.521
***Sum of BICs	-26.1****	96.7****	-9.86	-81.66	51.3****	227.8****

* the Minimum/1st Quartile/Median/Mean/3rd Quartile/Maximum of the R_i^2, i = 1, ..., N, calculated from the corresponding fitted model for each patient, where N is the total number of patients and $R_i^2 = 1 - SSE_i / SST_i$;

** Final R^2, calculated as $1 - \sum SSE_i / \sum SST_i$, evaluates the overall fit of the corresponding model to the whole time series data with all patients;

*** Sum of BICs is the sum of BICs over all subjects for each model.

**** One patient in this cohort had SSE being exactly zero when fitting the 2-phasic exponential model which resulted in negative infinite BIC. The Sum of BICs here did not include the BIC from this patient.

Supplementary Table S3. Summary of statistical analysis of 1-phasic versus 2-phasic model comparison in all four patient cohorts. Note that all 2-phasic patients in each cohort had negative first slopes.

	Total # of patients	# of 1-phasic	# of 2-phasic	2-phasic, beta2 >0*	2-phasic, beta2 <0*	2-phasic, beta2 =0*
Dasatinib cohort	69	34	35	15	18	2
Nilotinib cohort	51	25	26	10	13	3
High-dose imatinib cohort	123	69	54	23	24	7
Standard dose imatinib cohort	13	0	13	1	12	0

* zero refers to any number with an absolute value ≤ 10^{-8}.

SUPPLEMENTARY FIGURE LEGENDS

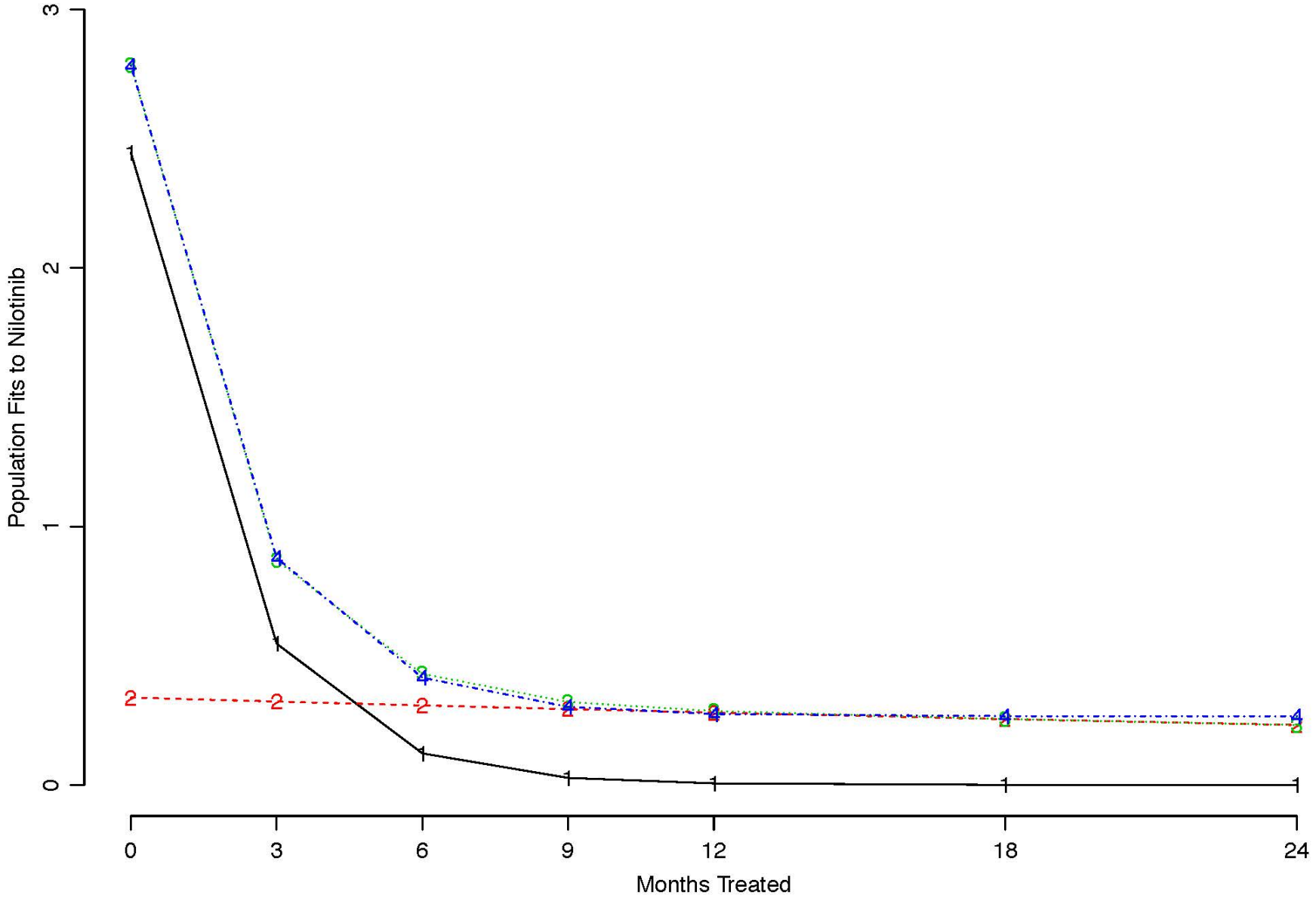
Figure S1. A bi-exponential and an exponential fit to the log-transformed nilotinib curves. The bi-exponential fit is the sum of two exponentials. The curves labeled "1" (black) and "2" (red) are the components of the bi-exponential and the curve labeled "3" (green) is the result. The curve labeled "4" (blue) is a single scaled exponential with an intercept (our model in Statistical Methods). Note its similarity to the bi-exponential. This is because curve "2" is virtually a straight line.

Figure S2. Individual fitting for patients in the imatinib 800mg cohort. The figure displays each individual's *BCR-ABL1*/*ABL1*% data (black circle), together with the bi-phasic fitting curves (red lines). For those patients whose data exhibit a better fitting with a single-phasic model, a dashed green line is shown. The green circles represents value of 0.00001, which is the original zero value.

Figure S3. Individual fitting for patients in the dasatinib cohort. The figure displays each individual's *BCR-ABL1*/*ABL1*% data (black circle), together with the bi-phasic fitting curves (red lines). For those patients whose data exhibit a better fitting with a single-phasic model, a dashed green line is shown. The green circles represents value of 0.00001, which is the original zero value.

Figure S4. Individual fitting for patients in the nilotinib cohort. The figure displays each individual's *BCR-ABL1*/*ABL1*% data (black circle), together with the bi-phasic fitting curves (red lines). For those patients whose data exhibit a better fitting with a single-phasic model, a dashed green line is shown. The green circles represents value of 0.00001, which is the original zero value.

Figure S5. Individual fitting for patients in the imatinib 400mg cohort. The figure displays each individual's *BCR-ABL1*/*ABL1*% data (black circle), together with the bi-phasic fitting curves (red lines). For those patients whose data exhibit a better fitting with a single-phasic model, a dashed green line is shown. The green circles represents value of 0.00001, which is the original zero value.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18
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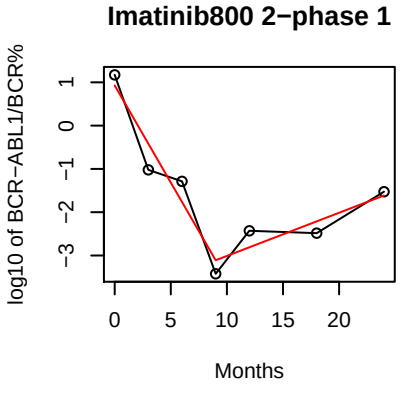
Months Treated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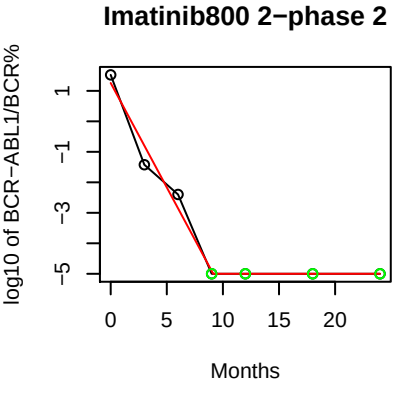
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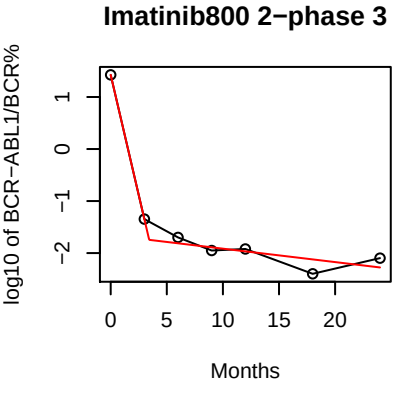
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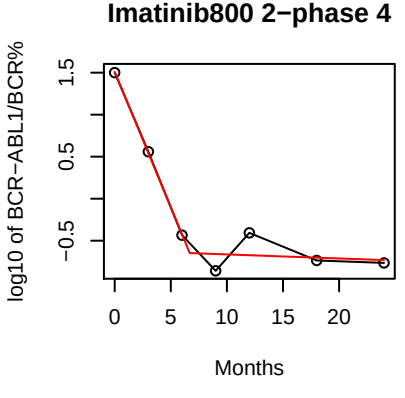
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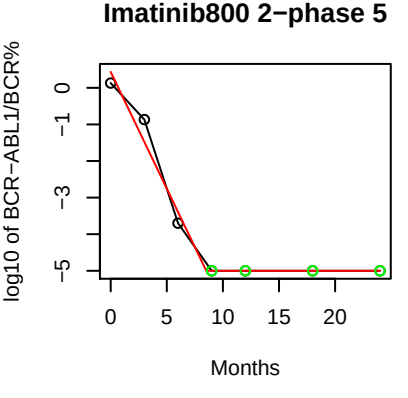
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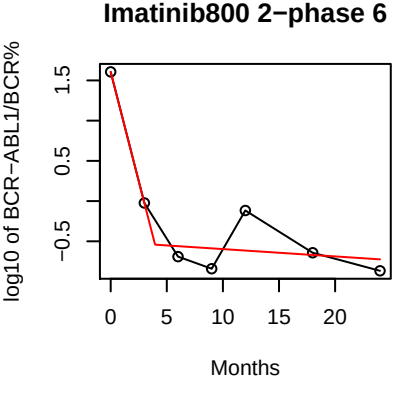
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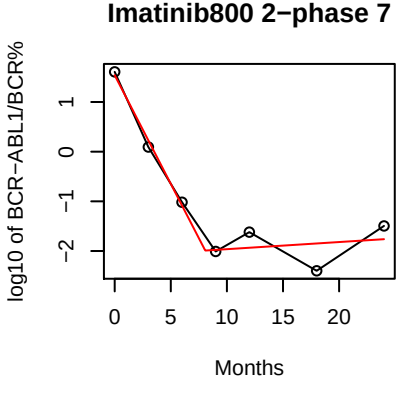
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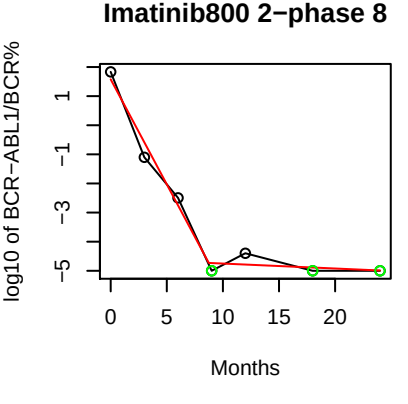
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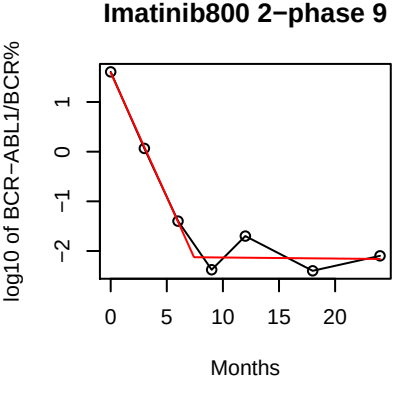
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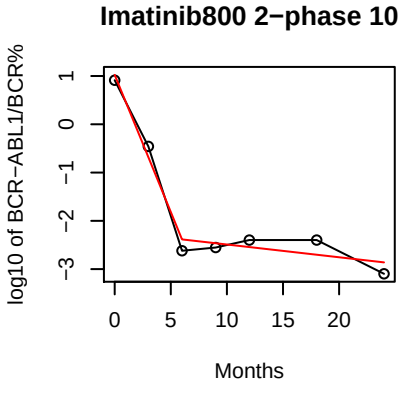
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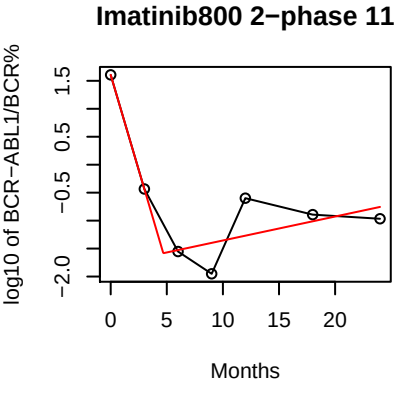
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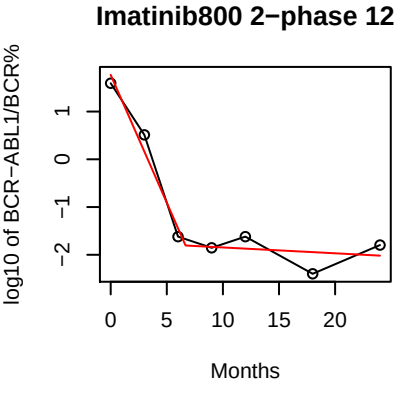
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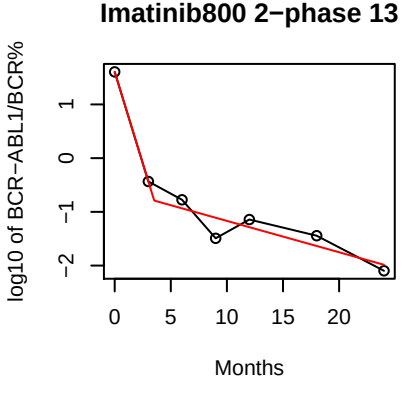
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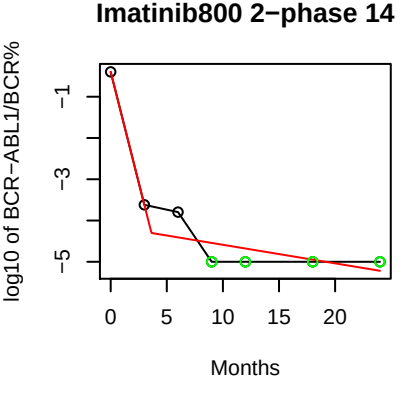
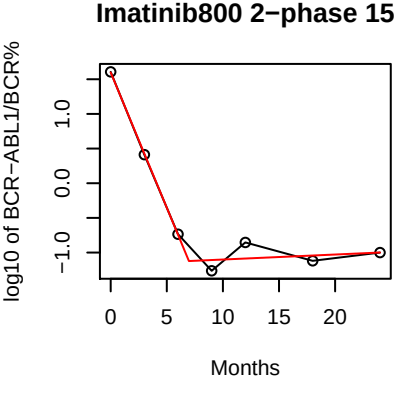
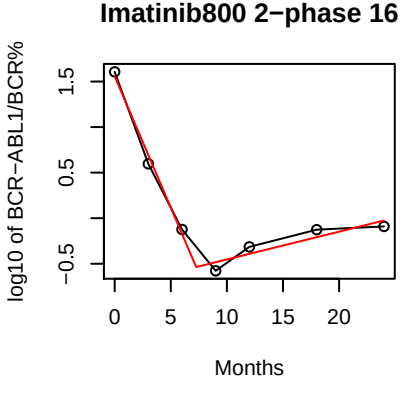
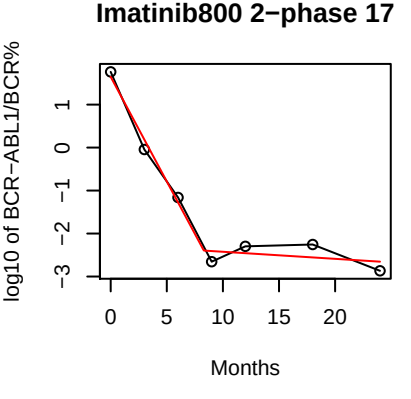
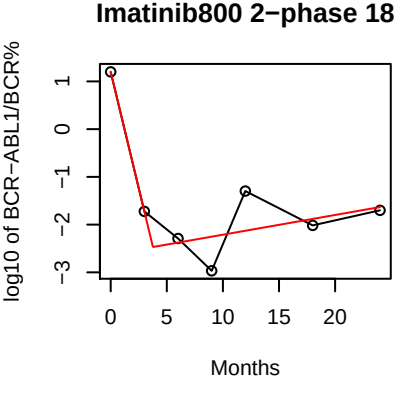
log10 of BCR−ABL1/BCR%
Months

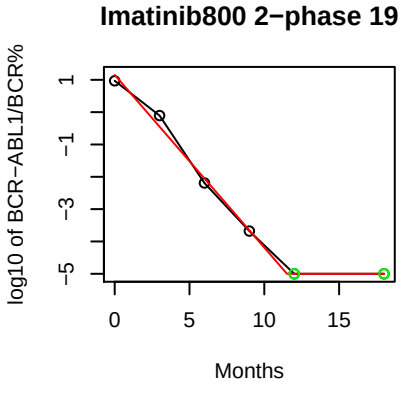

Imatinib800 2−phase 14
log10 of BCR−ABL1/BCR%
Months

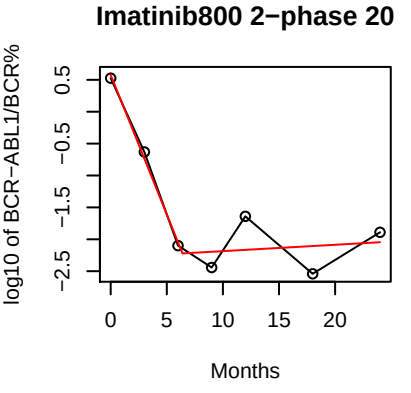

Imatinib800 2−phase 15
log10 of BCR−ABL1/BCR%
Months

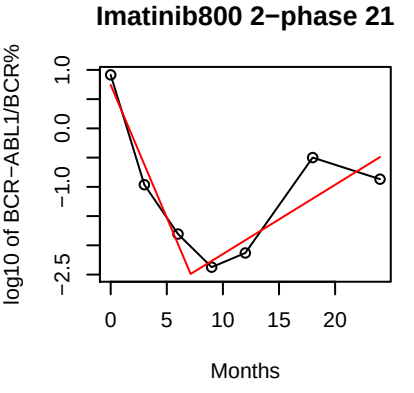

Imatinib800 2−phase 16
log10 of BCR−ABL1/BCR%
Months

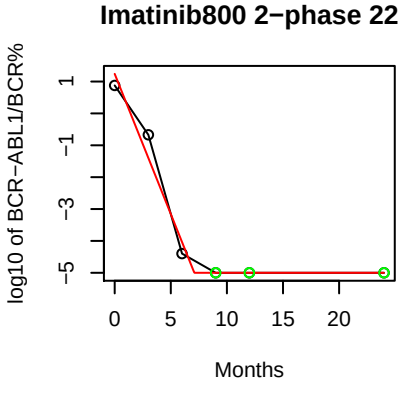

Imatinib800 2−phase 17
log10 of BCR−ABL1/BCR%
Months

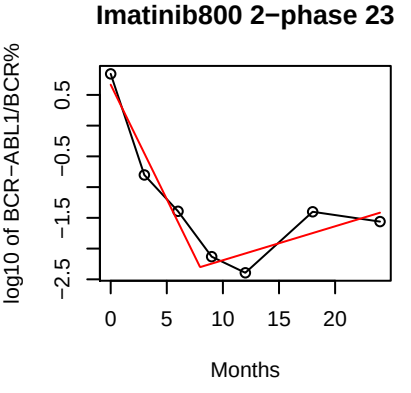

Imatinib800 2−phase 18
log10 of BCR−ABL1/BCR%
Months

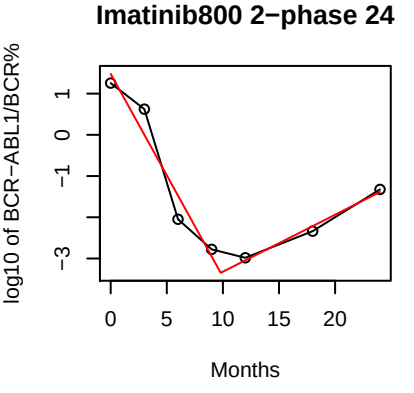

Imatinib800 2−phase 19
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
Months

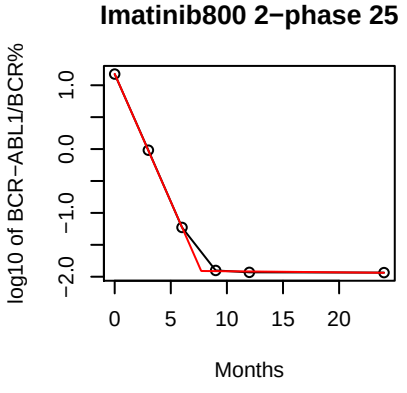

Imatinib800 2−phase 20
log10 of BCR−ABL1/BCR%
0.5
−0.5
−1.5
−2.5
0
5
10
15
20
Months

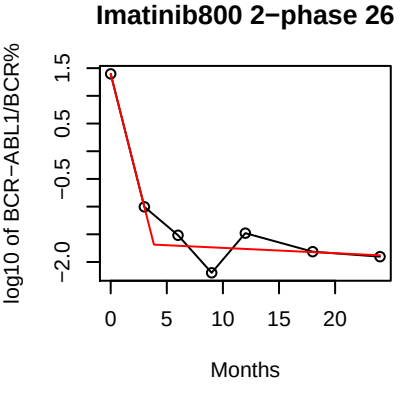

Imatinib800 2−phase 21
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.5
0
5
10
15
20
Months

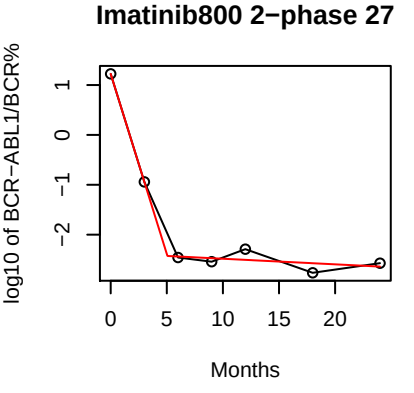

Imatinib800 2−phase 22
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

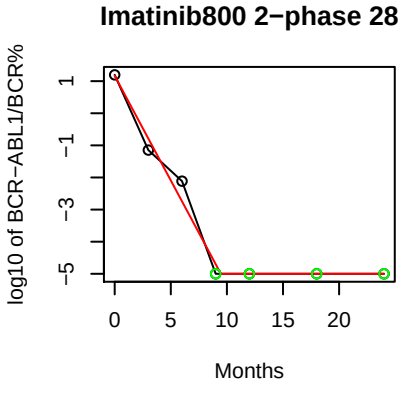

Imatinib800 2−phase 23
log10 of BCR−ABL1/BCR%
0.5
−0.5
−1.5
−2.5
0
5
10
15
20
Months

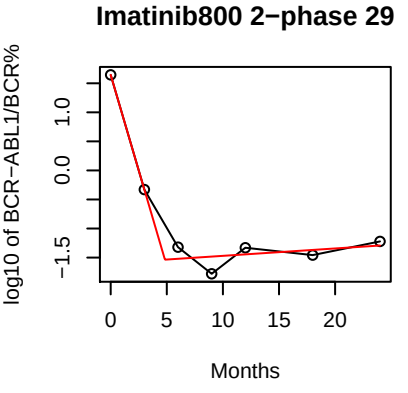

Imatinib800 2−phase 24
log10 of BCR−ABL1/BCR%
1
0
−1
−3
0
5
10
15
20
Months

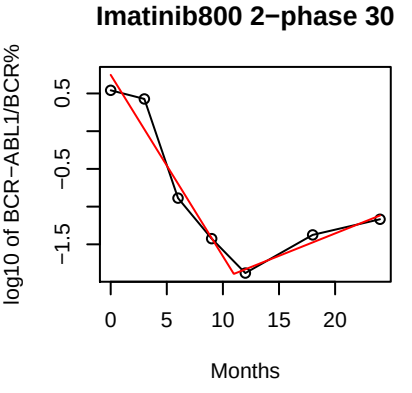

Imatinib800 2−phase 25
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.0
0
5
10
15
20
Months

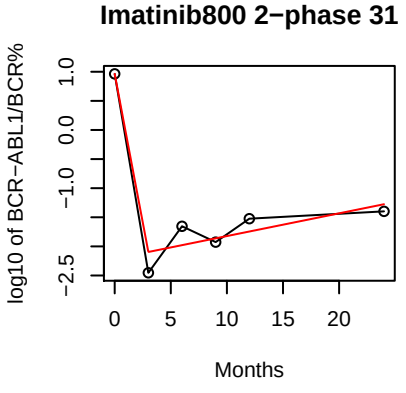

Imatinib800 2−phase 26
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
−2.0
0
5
10
15
20
Months

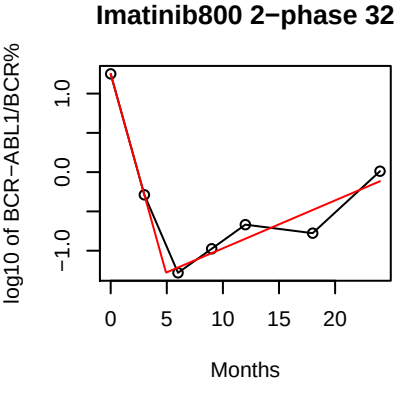

Imatinib800 2−phase 27
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

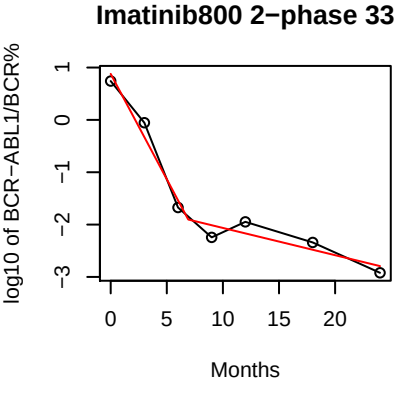

Imatinib800 2−phase 28
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

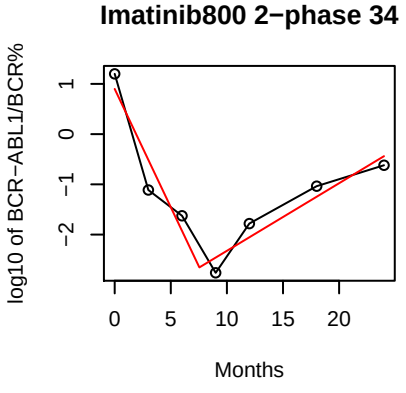

Imatinib800 2−phase 29
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.5
0
5
10
15
20
Months

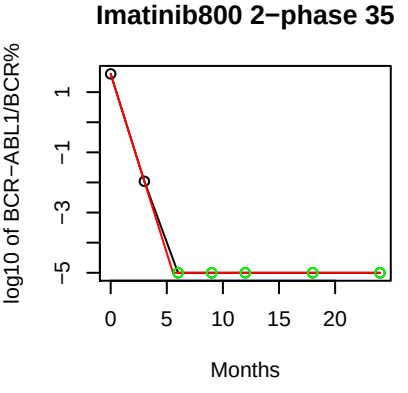

Imatinib800 2−phase 30
log10 of BCR−ABL1/BCR%
0.5
−0.5
−1.5
0
5
10
15
20
Months

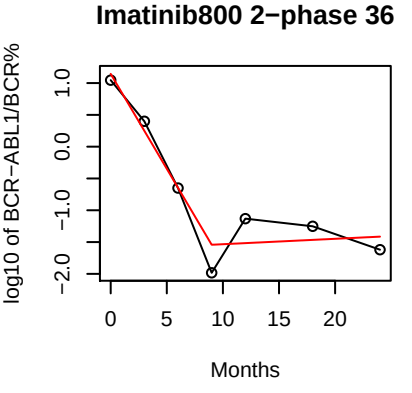

Imatinib800 2−phase 31
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.5
0
5
10
15
20
Months

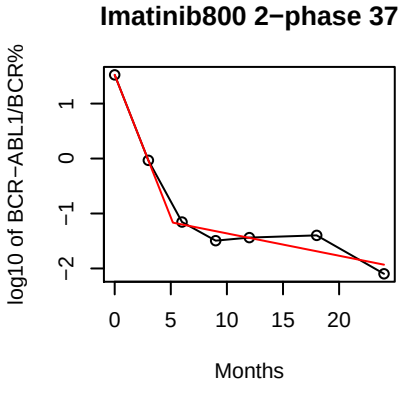

Imatinib800 2−phase 32
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
0
5
10
15
20
Months

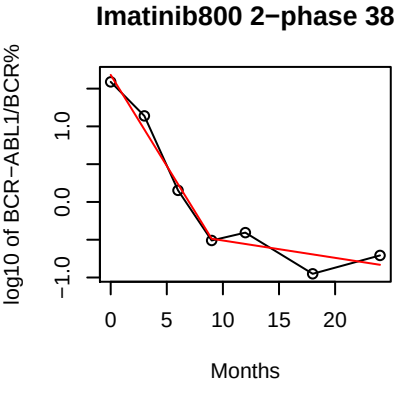

Imatinib800 2−phase 33
log10 of BCR−ABL1/BCR%
1
0
−1
−2
−3
0
5
10
15
20
Months

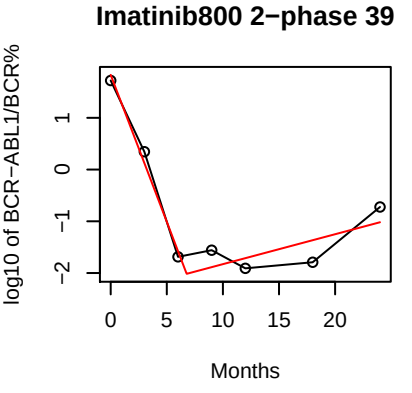

Imatinib800 2−phase 34
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

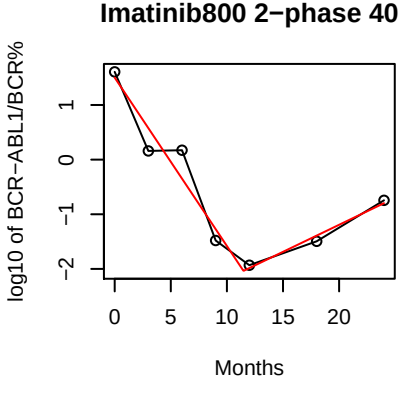

Imatinib800 2−phase 35
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

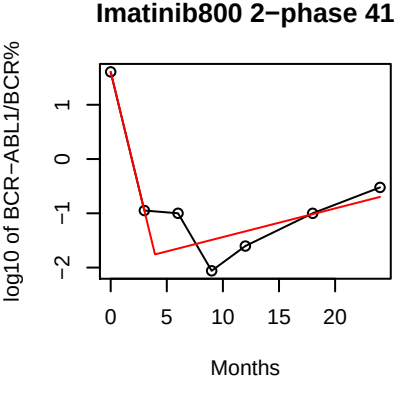

Imatinib800 2−phase 36
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.0
0
5
10
15
20
Months

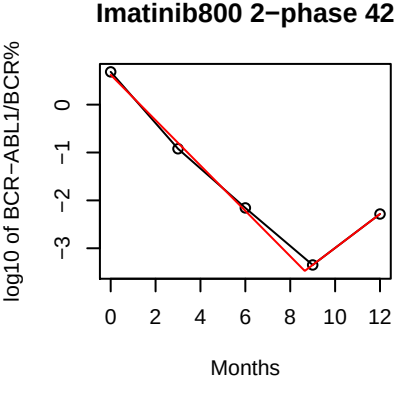

Imatinib800 2−phase 37
log10 of BCR−ABL1/BCR%
Months

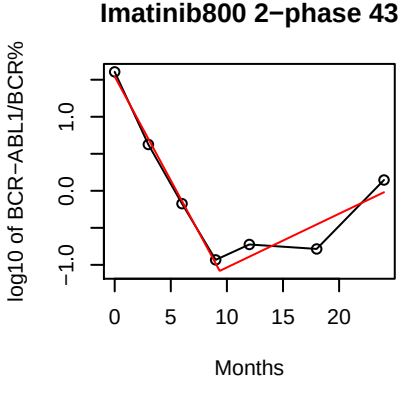

Imatinib800 2−phase 38
log10 of BCR−ABL1/BCR%
Months

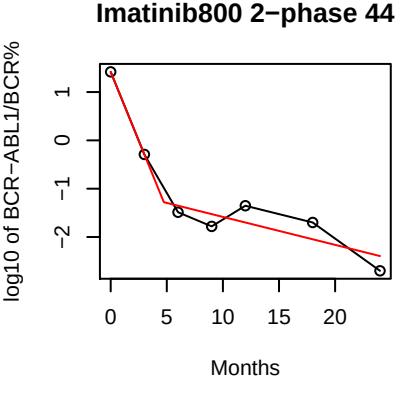

Imatinib800 2−phase 39
log10 of BCR−ABL1/BCR%
Months

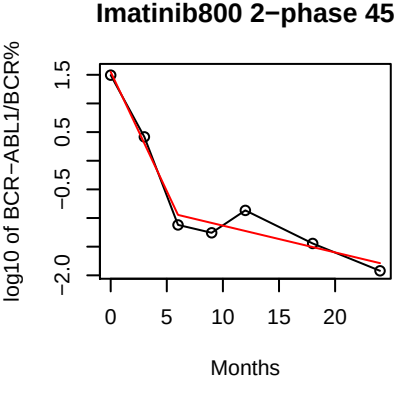

Imatinib800 2−phase 40
log10 of BCR−ABL1/BCR%
Months

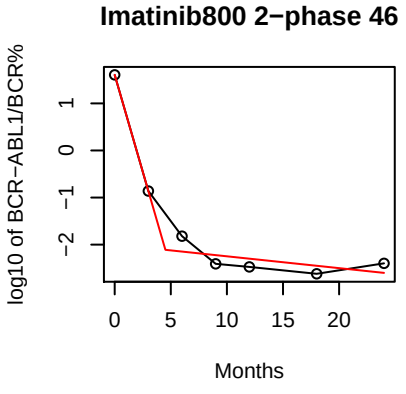

Imatinib800 2−phase 41
log10 of BCR−ABL1/BCR%
Months

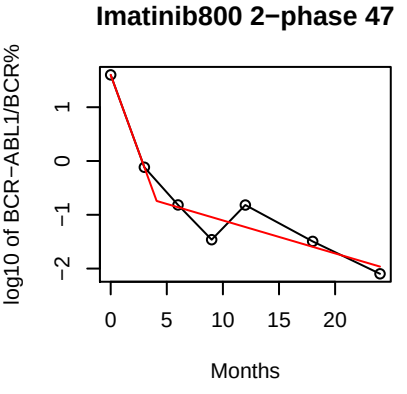

Imatinib800 2−phase 42
log10 of BCR−ABL1/BCR%
Months

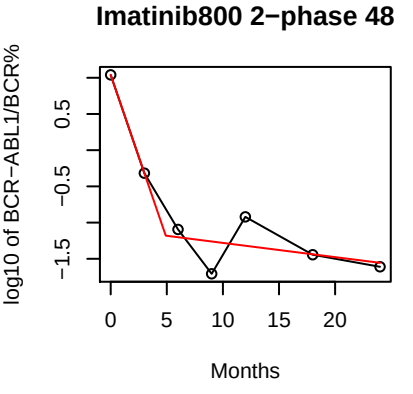

Imatinib800 2−phase 43
log10 of BCR−ABL1/BCR%
Months

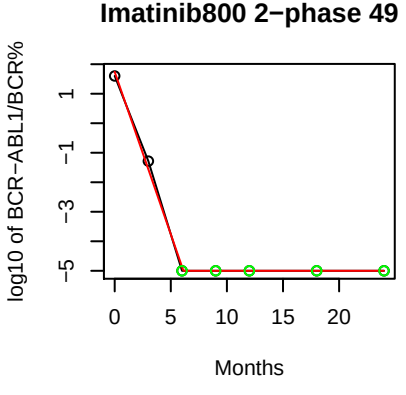

Imatinib800 2−phase 44
log10 of BCR−ABL1/BCR%
Months

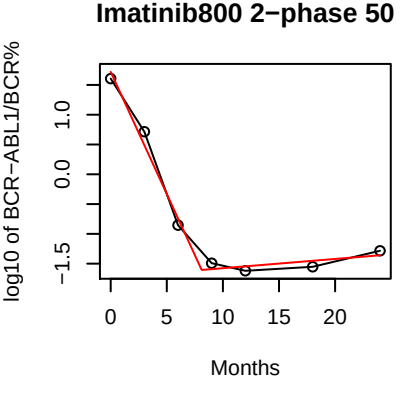

Imatinib800 2−phase 45
log10 of BCR−ABL1/BCR%
Months

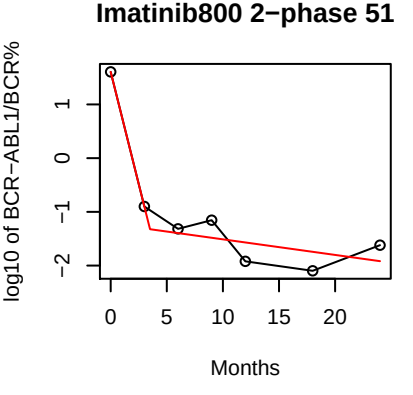

Imatinib800 2−phase 46
log10 of BCR−ABL1/BCR%
Months

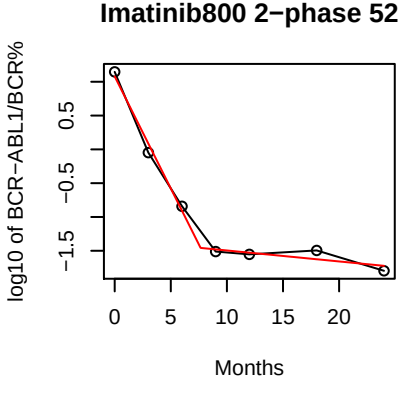

Imatinib800 2−phase 47
log10 of BCR−ABL1/BCR%
Months

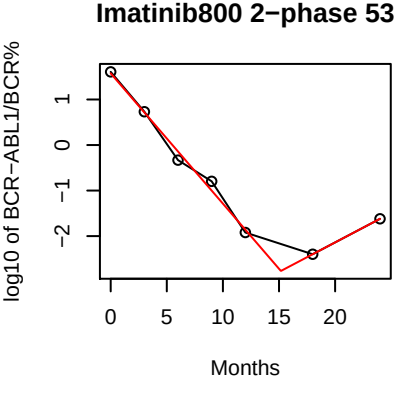

Imatinib800 2−phase 48
log10 of BCR−ABL1/BCR%
Months

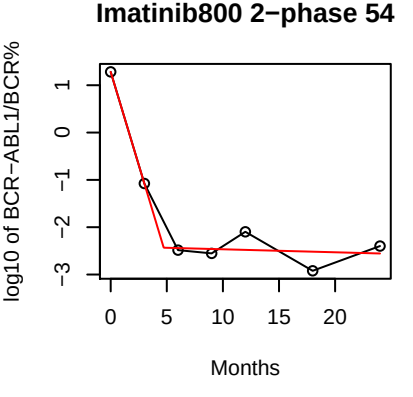

Imatinib800 2−phase 49
log10 of BCR−ABL1/BCR%
Months

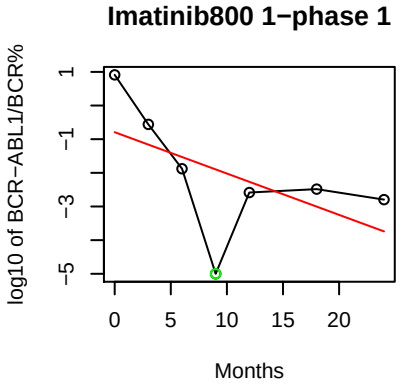

Imatinib800 2−phase 50
log10 of BCR−ABL1/BCR%
Months

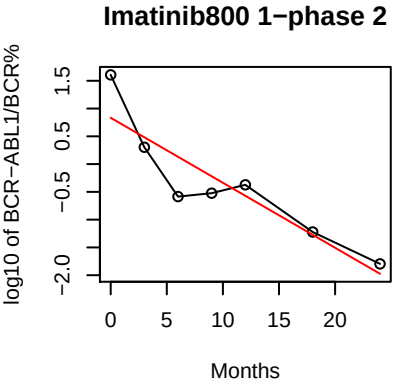

Imatinib800 2−phase 51
log10 of BCR−ABL1/BCR%
Months


Imatinib800 2−phase 52
log10 of BCR−ABL1/BCR%
Months

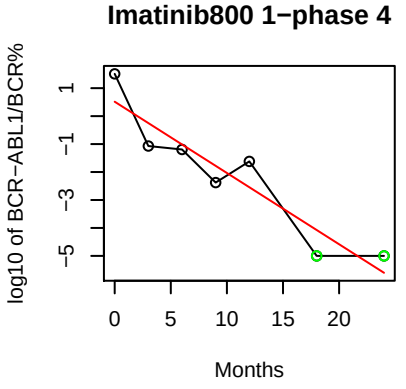

Imatinib800 2−phase 53
log10 of BCR−ABL1/BCR%
Months

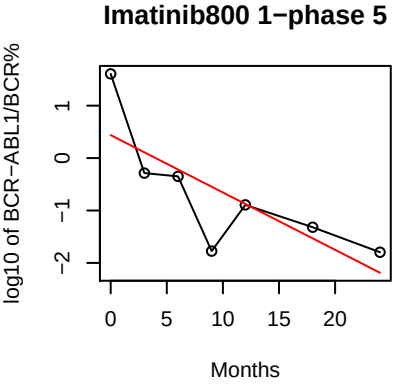

Imatinib800 2−phase 54
log10 of BCR−ABL1/BCR%
Months

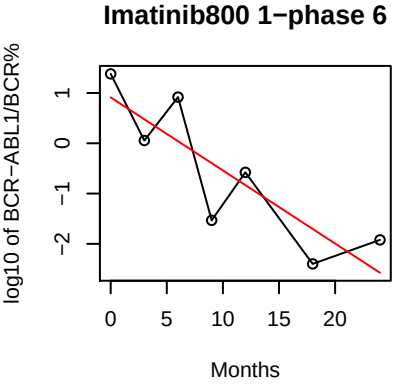

Imatinib800 1−phase 1
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

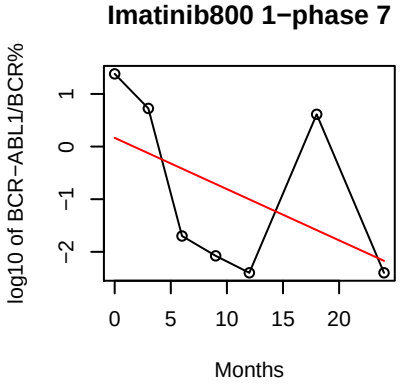

Imatinib800 1−phase 2
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
−2.0
0
5
10
15
20
Months

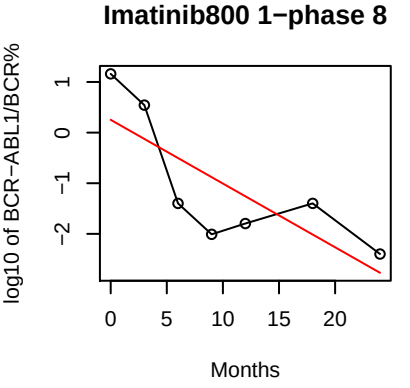

Imatinib800 1−phase 3
log10 of BCR−ABL1/BCR%
0
−2
−4
−6
0
5
10
15
20
Months

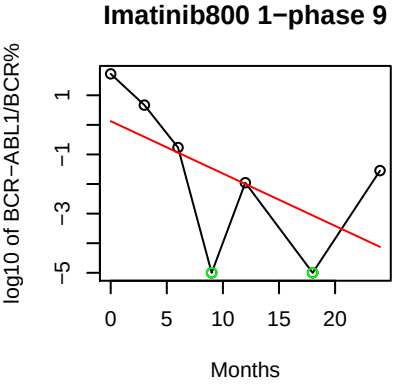

Imatinib800 1−phase 4
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

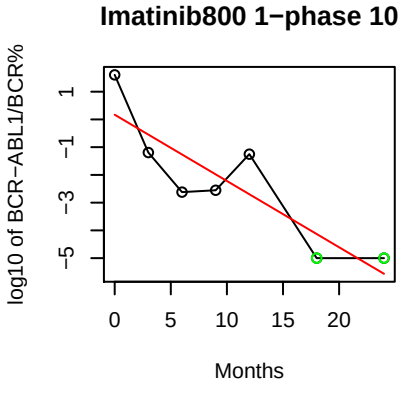

Imatinib800 1−phase 5
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

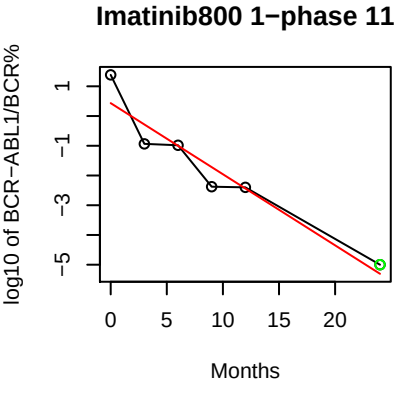

Imatinib800 1−phase 6
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

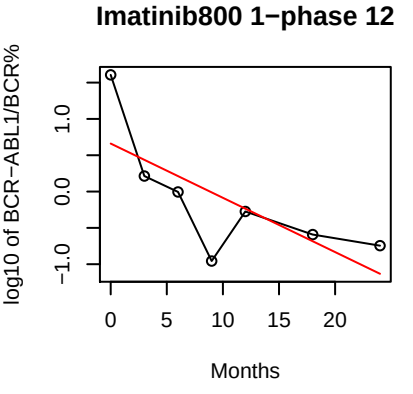

Imatinib800 1−phase 7
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

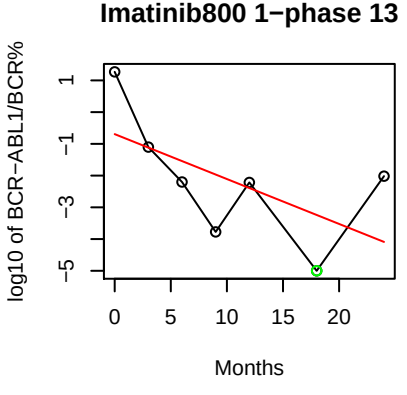

Imatinib800 1−phase 8
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

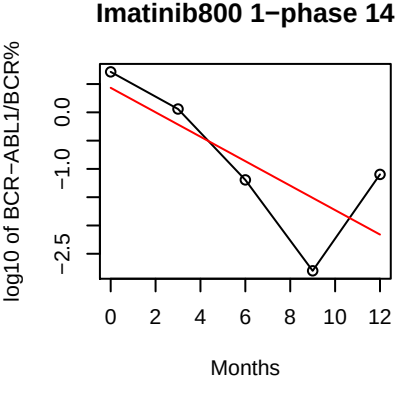

Imatinib800 1−phase 9
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

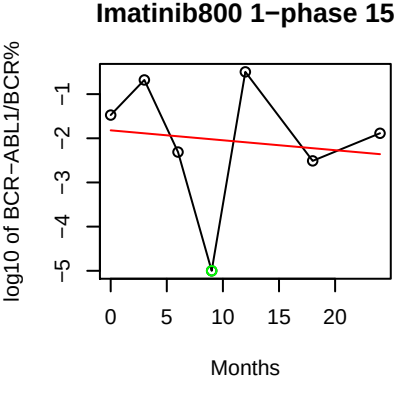

Imatinib800 1−phase 10
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

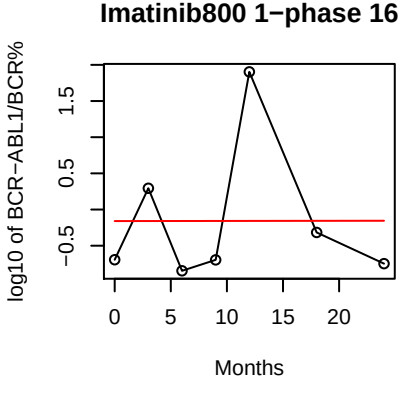

Imatinib800 1−phase 11
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

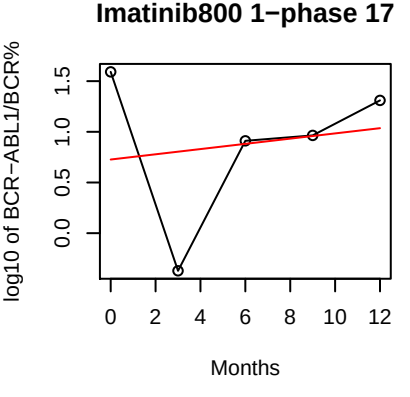

Imatinib800 1−phase 12
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
0
5
10
15
20
Months

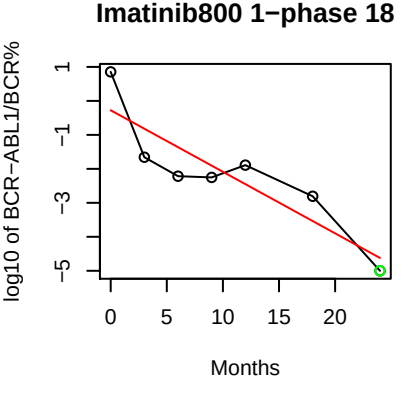

Imatinib800 1−phase 13
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

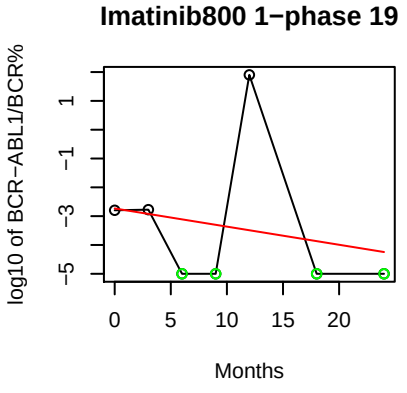

Imatinib800 1−phase 14
log10 of BCR−ABL1/BCR%
0.0
−1.0
−2.5
0
2
4
6
8
10
12
Months

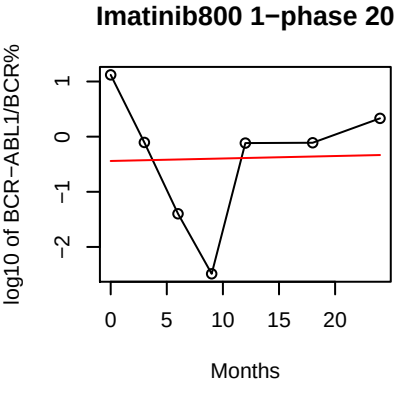

Imatinib800 1−phase 15
log10 of BCR−ABL1/BCR%
−1
−2
−3
−4
−5
0
5
10
15
20
Months

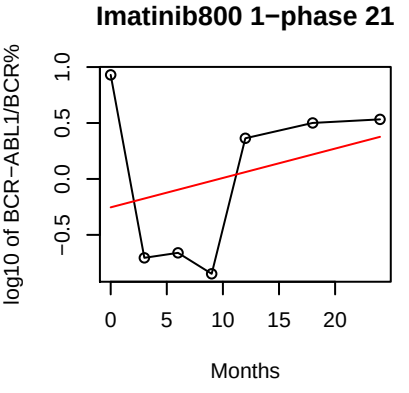

Imatinib800 1−phase 16
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
0
5
10
15
20
Months


Imatinib800 1−phase 17
log10 of BCR−ABL1/BCR%
1.5
1.0
0.5
0.0
0
2
4
6
8
10
12
Months

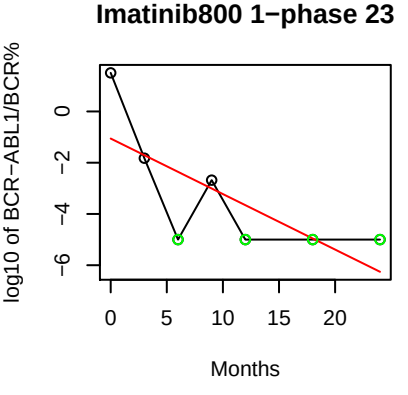

Imatinib800 1−phase 18
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

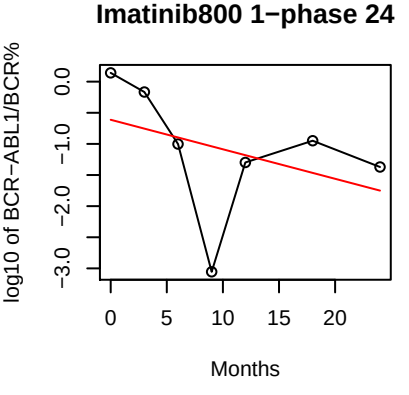

Imatinib800 1−phase 19
log10 of BCR−ABL1/BCR%
−5
−3
−1
1
0
5
10
15
20
Months

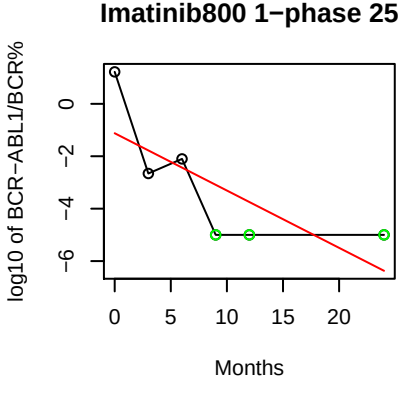

Imatinib800 1−phase 20
log10 of BCR−ABL1/BCR%
−2
−1
0
1
0
5
10
15
20
Months

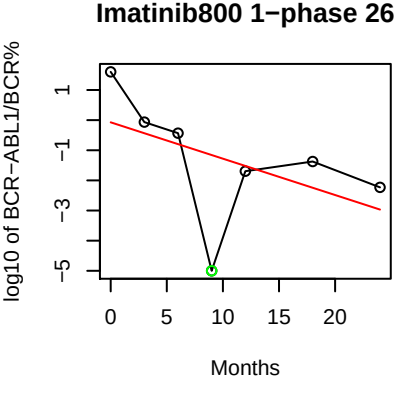

Imatinib800 1−phase 21
log10 of BCR−ABL1/BCR%
−0.5
0.0
0.5
1.0
0
5
10
15
20
Months

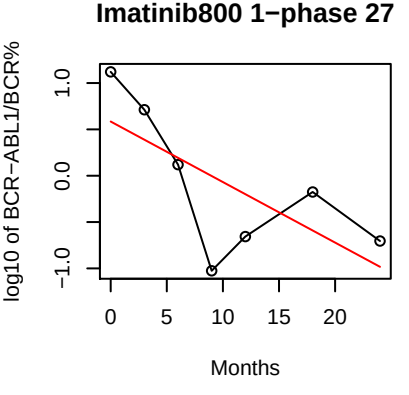

Imatinib800 1−phase 22
log10 of BCR−ABL1/BCR%
0.2
0.6
1.0
1.4
0
5
10
15
Months

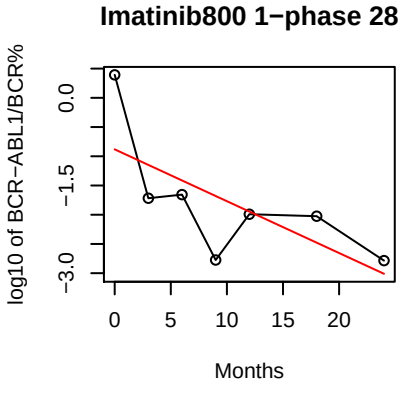

Imatinib800 1−phase 23
log10 of BCR−ABL1/BCR%
−6
−4
−2
0
0
5
10
15
20
Months

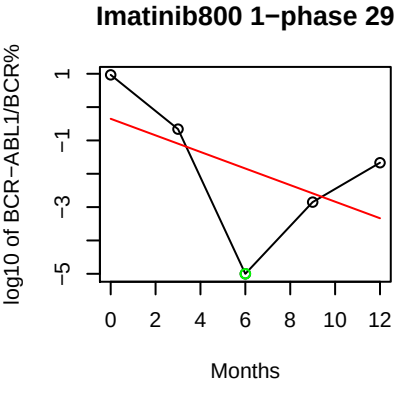

Imatinib800 1−phase 24
log10 of BCR−ABL1/BCR%
−3.0
−2.0
−1.0
0.0
0
5
10
15
20
Months

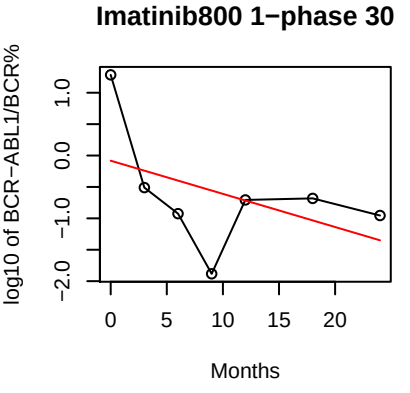

Imatinib800 1−phase 25
log10 of BCR−ABL1/BCR%
−6
−4
−2
0
0
5
10
15
20
Months

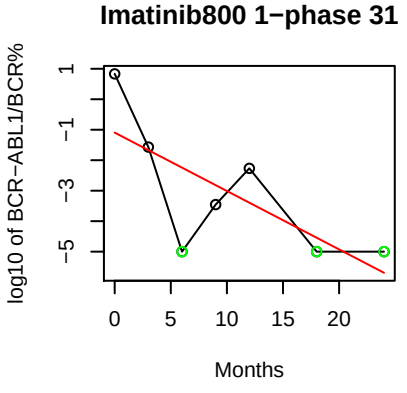

Imatinib800 1−phase 26
log10 of BCR−ABL1/BCR%
−5
−3
−1
1
0
5
10
15
20
Months

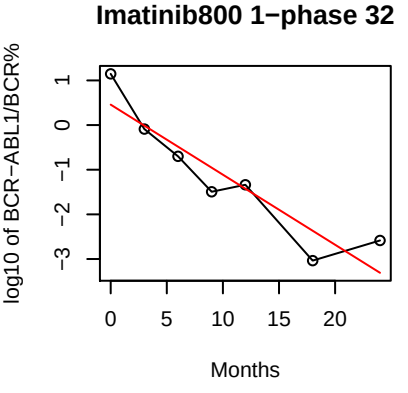

Imatinib800 1−phase 27
log10 of BCR−ABL1/BCR%
−1.0
0.0
1.0
0
5
10
15
20
Months

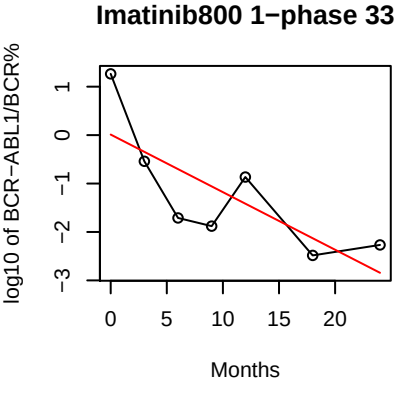

Imatinib800 1−phase 28
log10 of BCR−ABL1/BCR%
0.0
−1.5
−3.0
0
5
10
15
20
Months

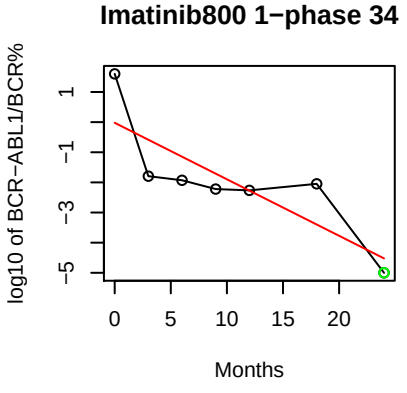

Imatinib800 1−phase 29
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
2
4
6
8
10
12
Months

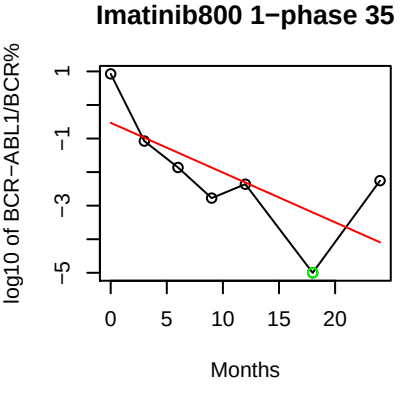

Imatinib800 1−phase 30
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.0
0
5
10
15
20
Months

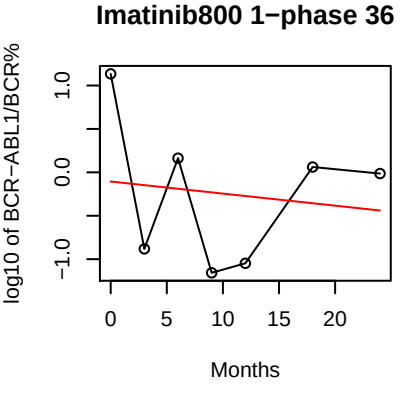

Imatinib800 1−phase 31
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

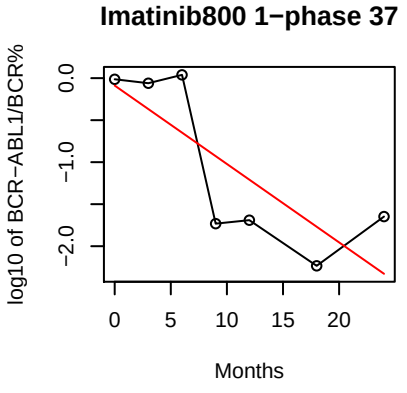

Imatinib800 1−phase 32
log10 of BCR−ABL1/BCR%
1
0
−1
−2
−3
0
5
10
15
20
Months

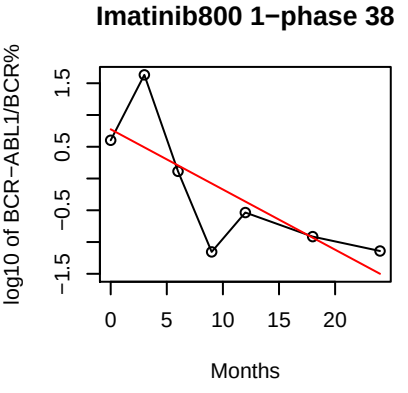

Imatinib800 1−phase 33
log10 of BCR−ABL1/BCR%
1
0
−1
−2
−3
0
5
10
15
20
Months

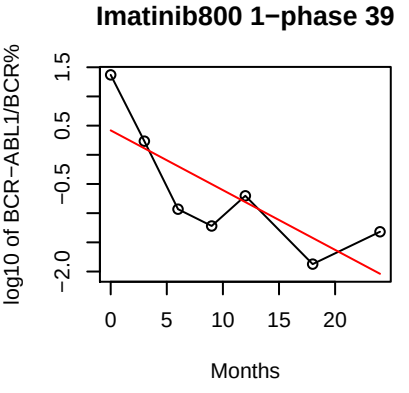

Imatinib800 1−phase 34
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

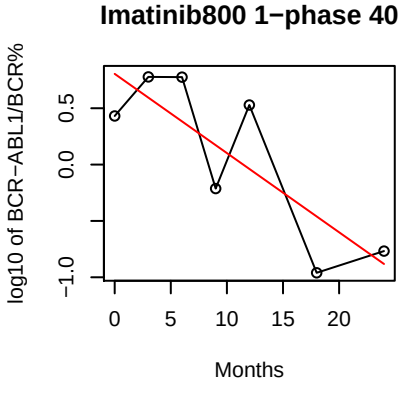

Imatinib800 1−phase 35
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

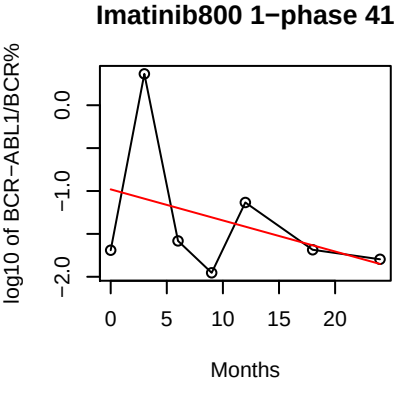

Imatinib800 1−phase 36
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
0
5
10
15
20
Months

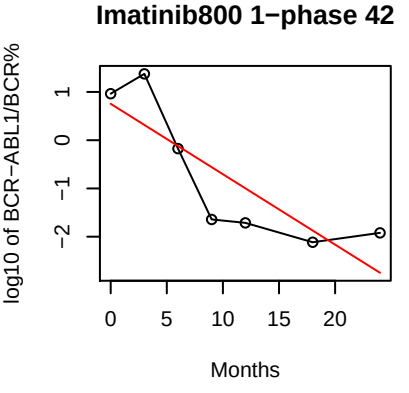

Imatinib800 1−phase 37
log10 of BCR−ABL1/BCR%
0.0
−1.0
−2.0
0
5
10
15
20
Months

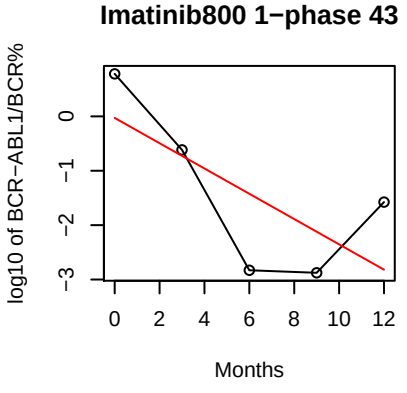

Imatinib800 1−phase 38
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
−1.5
0
5
10
15
20
Months

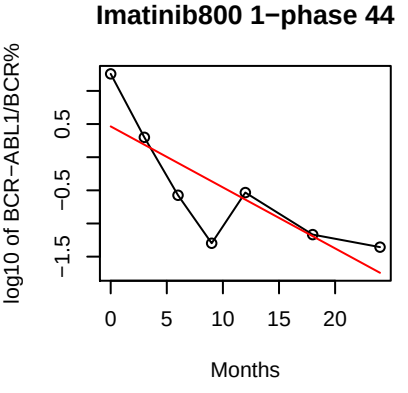

Imatinib800 1−phase 39
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
−2.0
0
5
10
15
20
Months

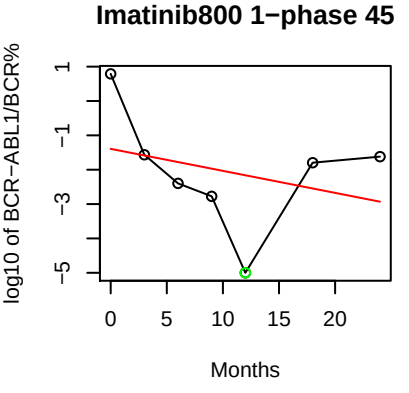

Imatinib800 1−phase 40
log10 of BCR−ABL1/BCR%
0.5
0.0
−1.0
0
5
10
15
20
Months

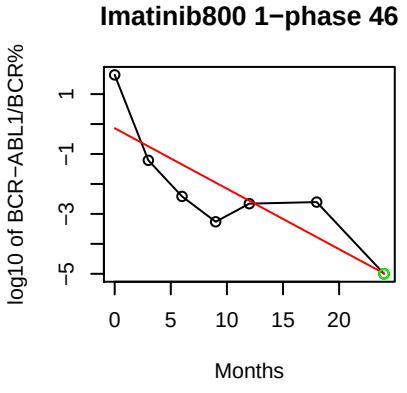

Imatinib800 1−phase 41
log10 of BCR−ABL1/BCR%
0.0
−1.0
−2.0
0
5
10
15
20
Months

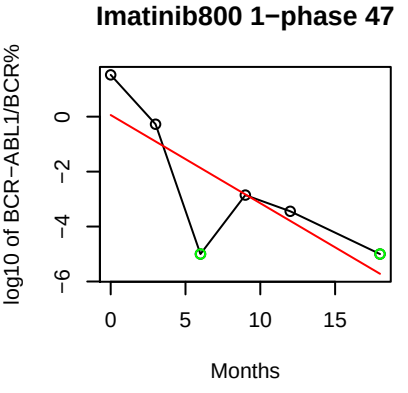

Imatinib800 1−phase 42
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

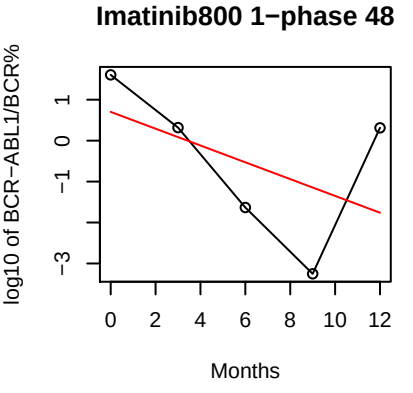

Imatinib800 1−phase 43
log10 of BCR−ABL1/BCR%
0
−1
−2
−3
0
2
4
6
8
10
12
Months

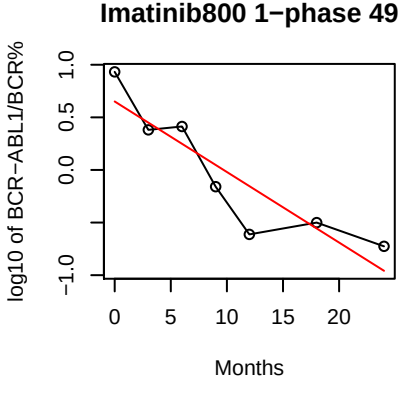

Imatinib800 1−phase 44
log10 of BCR−ABL1/BCR%
0.5
−0.5
−1.5
0
5
10
15
20
Months

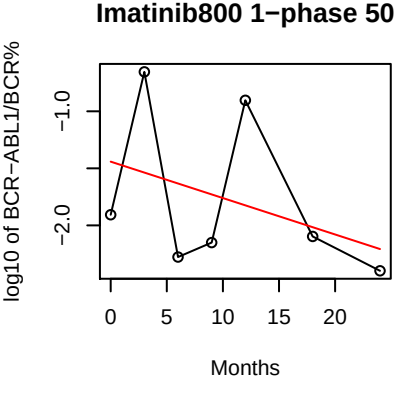

Imatinib800 1−phase 45
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

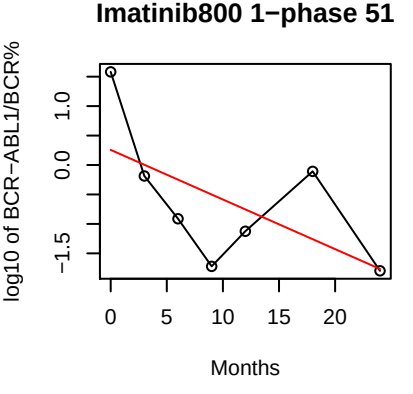

Imatinib800 1−phase 46
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

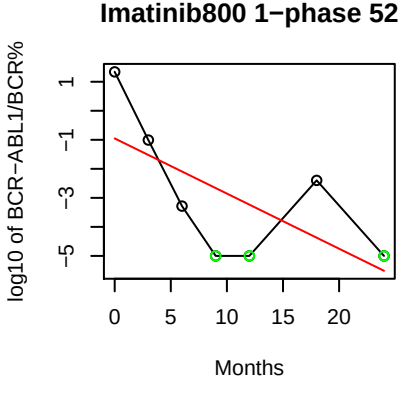

Imatinib800 1−phase 47
log10 of BCR−ABL1/BCR%
0
−2
−4
−6
0
5
10
15
Months

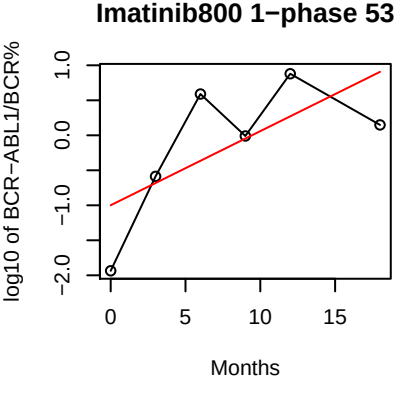

Imatinib800 1−phase 48
log10 of BCR−ABL1/BCR%
1
0
−1
−3
0
2
4
6
8
10
12
Months

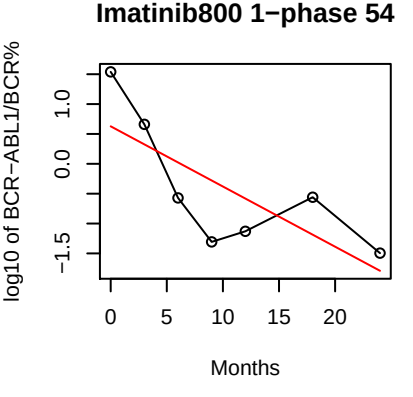

Imatinib800 1−phase 49
log10 of BCR−ABL1/BCR%
1.0
0.5
0.0
−1.0
0
5
10
15
20
Months

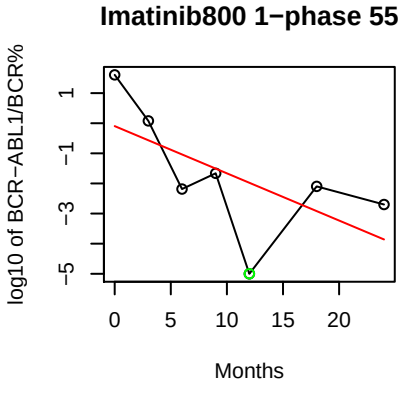

Imatinib800 1−phase 50
log10 of BCR−ABL1/BCR%
−1.0
−2.0
0
5
10
15
20
Months

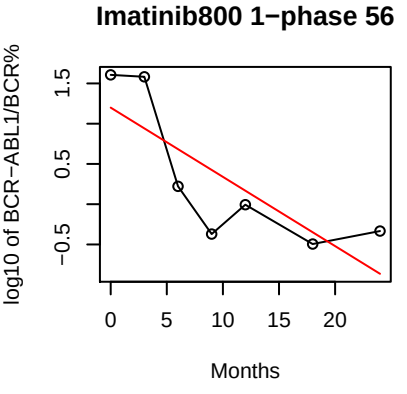

Imatinib800 1−phase 51
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.5
0
5
10
15
20
Months

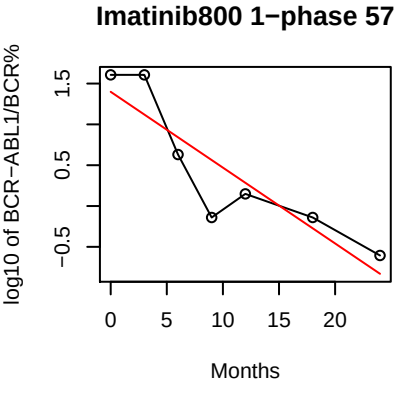

Imatinib800 1−phase 52
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

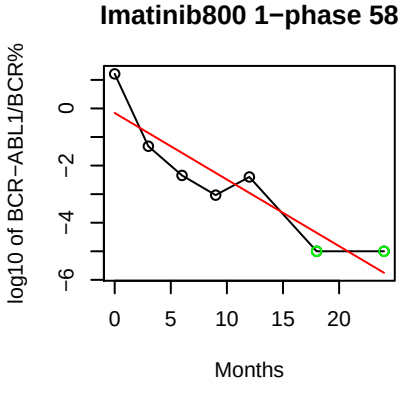

Imatinib800 1−phase 53
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.0
0
5
10
15
Months

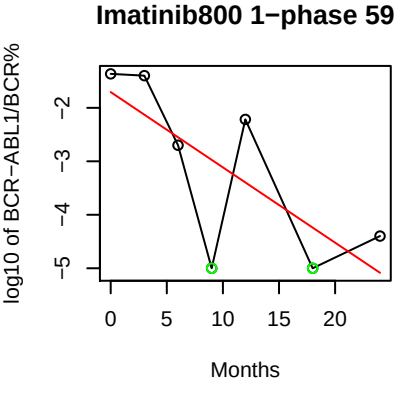

Imatinib800 1−phase 54
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.5
0
5
10
15
20
Months

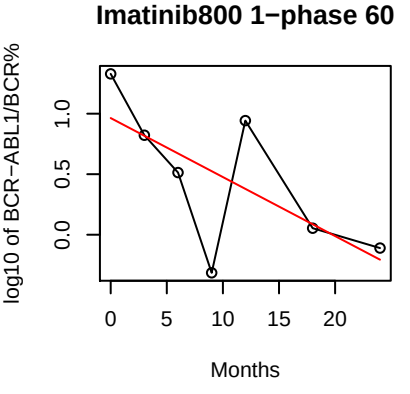

Imatinib800 1−phase 55
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

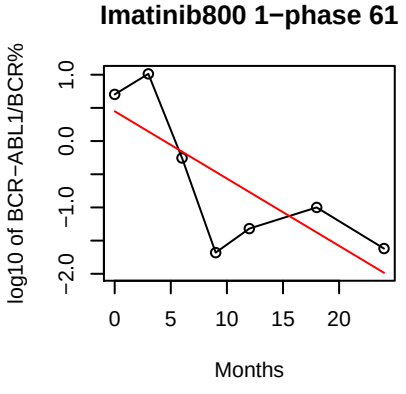

Imatinib800 1−phase 56
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
0
5
10
15
20
Months

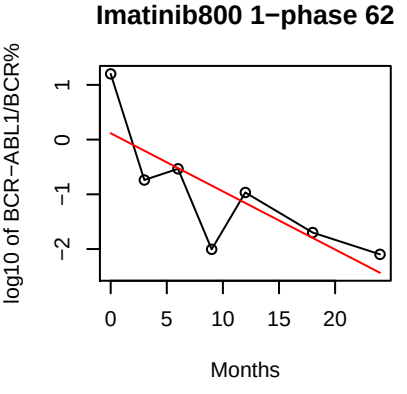

Imatinib800 1−phase 57
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
0
5
10
15
20
Months

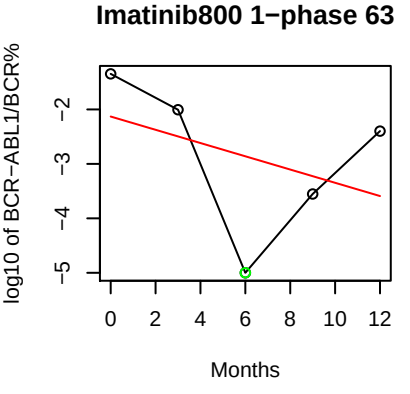

Imatinib800 1−phase 58
log10 of BCR−ABL1/BCR%
0
−2
−4
−6
0
5
10
15
20
Months

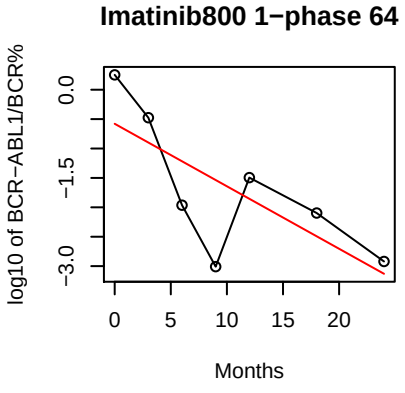

Imatinib800 1−phase 59
log10 of BCR−ABL1/BCR%
−2
−3
−4
−5
0
5
10
15
20
Months

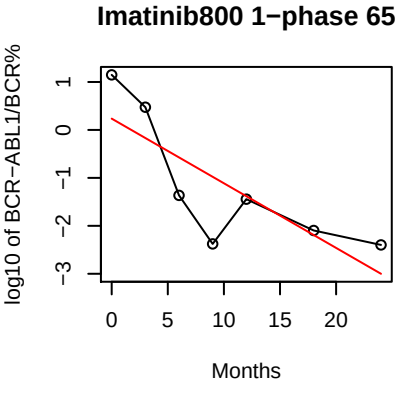

Imatinib800 1−phase 60
log10 of BCR−ABL1/BCR%
1.0
0.5
0.0
0
5
10
15
20
Months

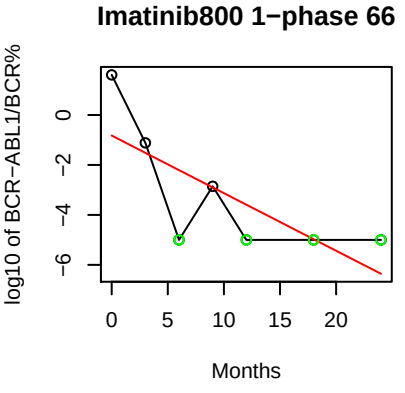

Imatinib800 1−phase 61
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.0
0
5
10
15
20
Months

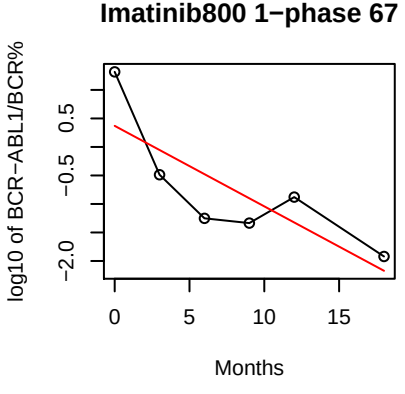

Imatinib800 1−phase 62
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

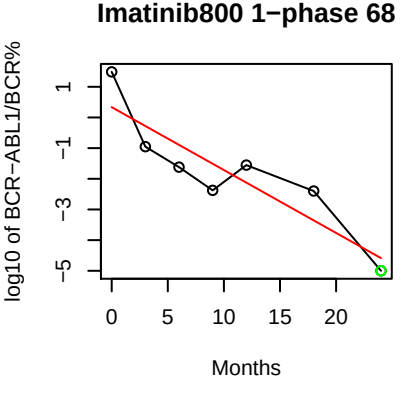

Imatinib800 1−phase 63
log10 of BCR−ABL1/BCR%
−2
−3
−4
−5
0
2
4
6
8
10
12
Months

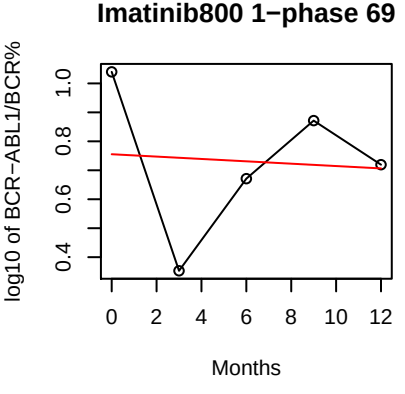

Imatinib800 1−phase 64
log10 of BCR−ABL1/BCR%
0.0
−1.5
−3.0
0
5
10
15
20
Months

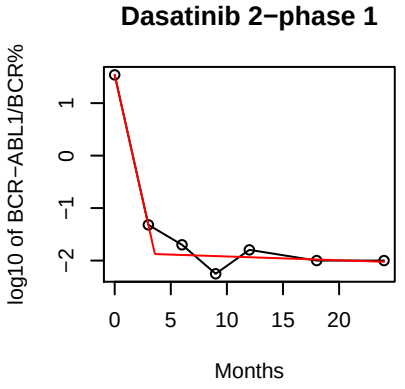

Imatinib800 1−phase 65
log10 of BCR−ABL1/BCR%
1
0
−1
−2
−3
0
5
10
15
20
Months

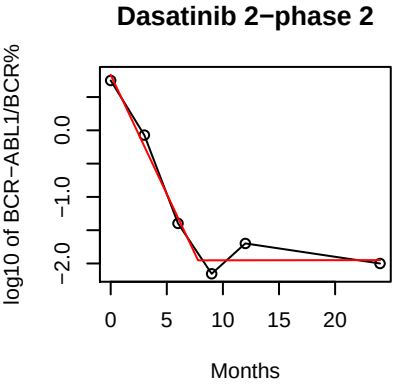

Imatinib800 1−phase 66
log10 of BCR−ABL1/BCR%
0
−2
−4
−6
0
5
10
15
20
Months

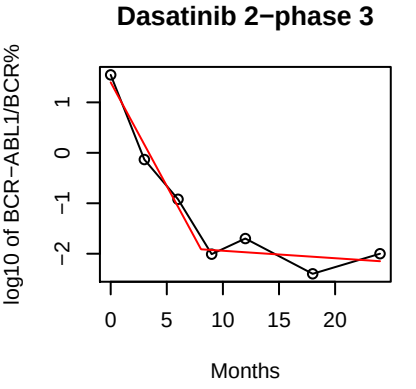

Imatinib800 1−phase 67
log10 of BCR−ABL1/BCR%
0.5
−0.5
−2.0
0
5
10
15
Months

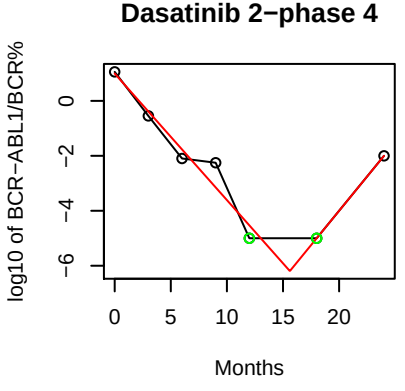

Imatinib800 1−phase 68
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

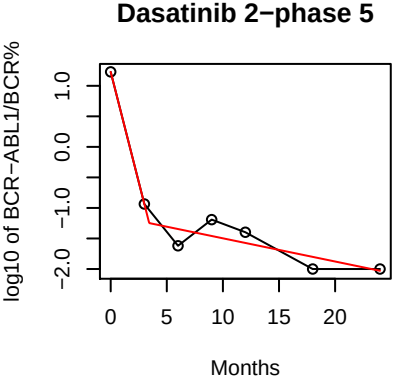

Imatinib800 1−phase 69
log10 of BCR−ABL1/BCR%
1.0
0.8
0.6
0.4
0
2
4
6
8
10
12
Months

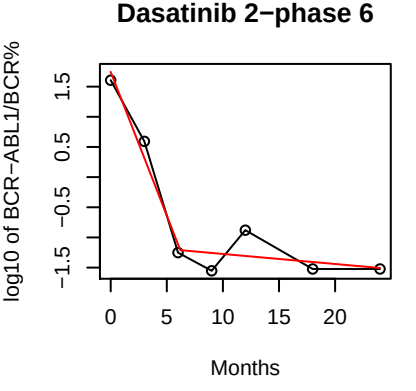

Dasatinib 2−phase 1
log10 of BCR−ABL1/BCR%
Months

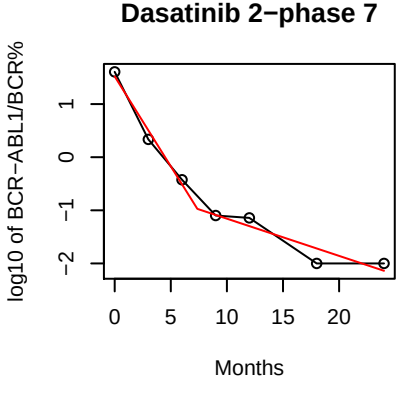

Dasatinib 2−phase 2
log10 of BCR−ABL1/BCR%
Months

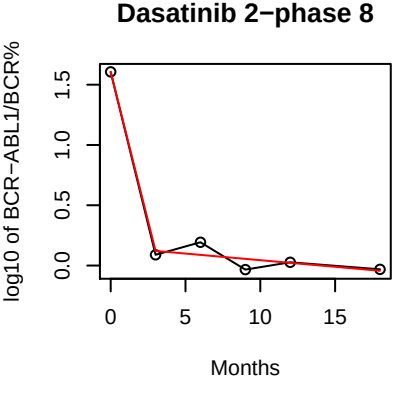

Dasatinib 2−phase 3
log10 of BCR−ABL1/BCR%
Months

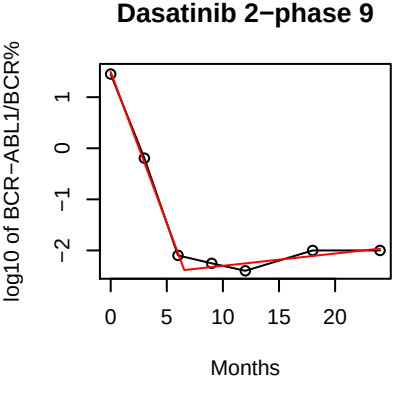

Dasatinib 2−phase 4
log10 of BCR−ABL1/BCR%
Months

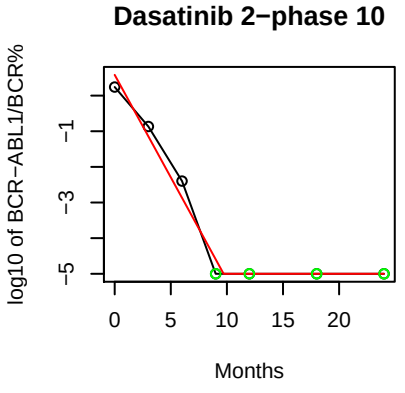

Dasatinib 2−phase 5
log10 of BCR−ABL1/BCR%
Months

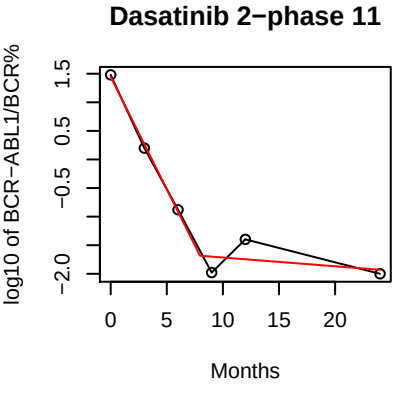

Dasatinib 2−phase 6
log10 of BCR−ABL1/BCR%
Months

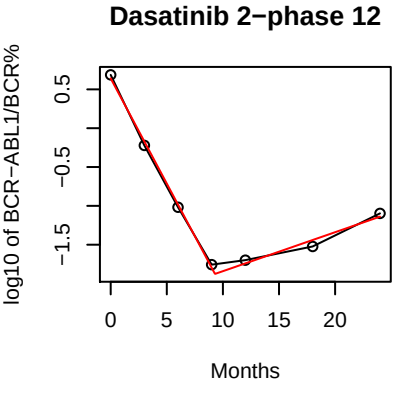

Dasatinib 2−phase 7
log10 of BCR−ABL1/BCR%
Months

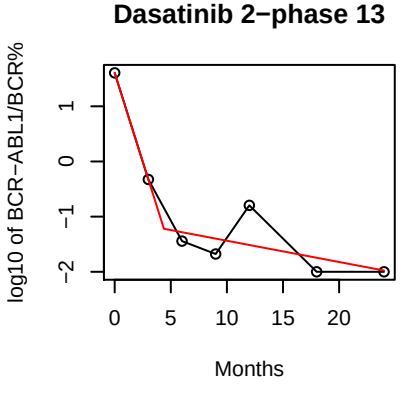

Dasatinib 2−phase 8
log10 of BCR−ABL1/BCR%
Months

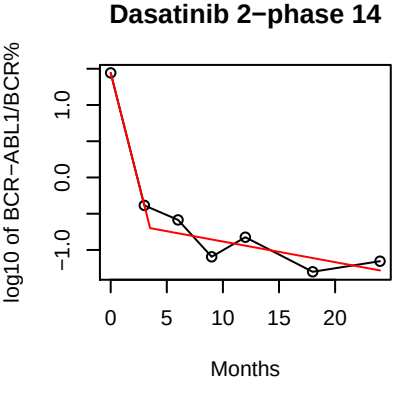

Dasatinib 2−phase 9
log10 of BCR−ABL1/BCR%
Months

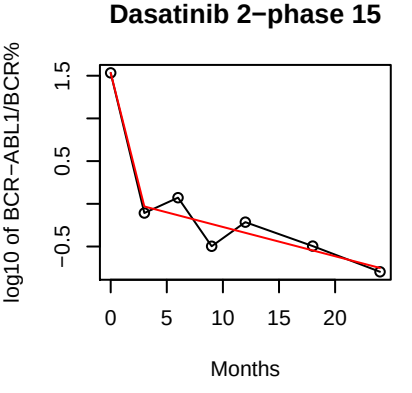

Dasatinib 2−phase 10
log10 of BCR−ABL1/BCR%
−1
−3
−5
0
5
10
15
20
Months

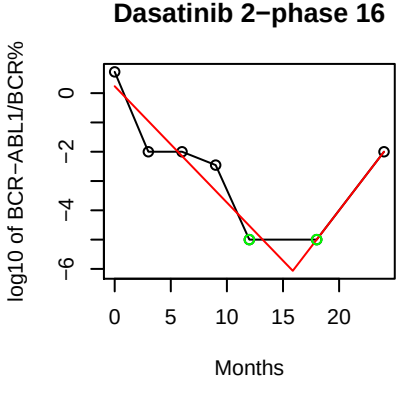

Dasatinib 2−phase 11
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
−2.0
0
5
10
15
20
Months

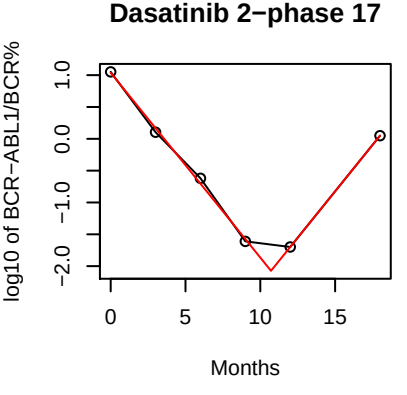

Dasatinib 2−phase 12
log10 of BCR−ABL1/BCR%
0.5
−0.5
−1.5
0
5
10
15
20
Months

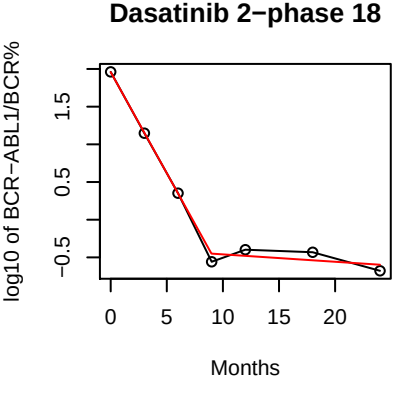

Dasatinib 2−phase 13
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

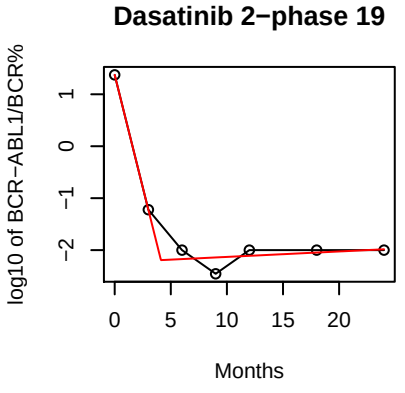

Dasatinib 2−phase 14
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
0
5
10
15
20
Months

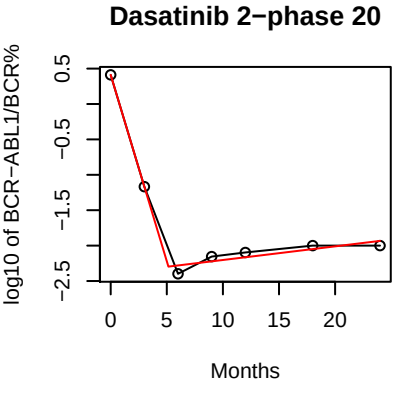

Dasatinib 2−phase 15
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
0
5
10
15
20
Months

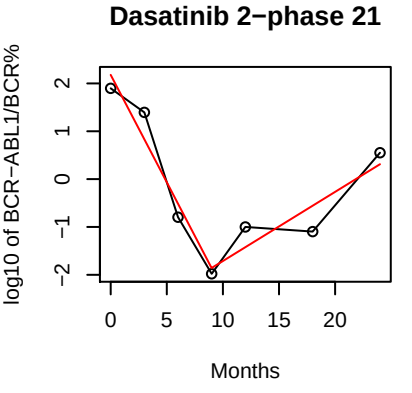

Dasatinib 2−phase 16
log10 of BCR−ABL1/BCR%
0
−2
−4
−6
0
5
10
15
20
Months

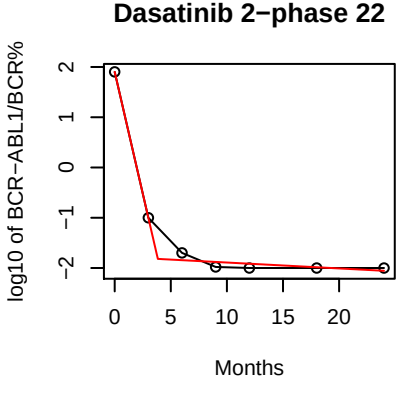

Dasatinib 2−phase 17
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.0
0
5
10
15
Months

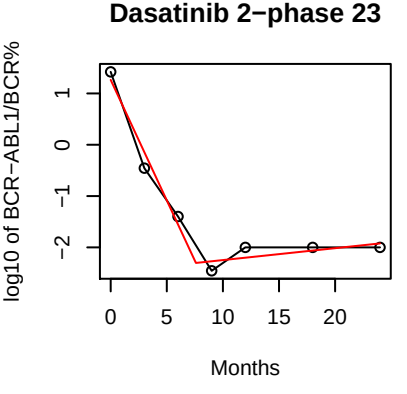

Dasatinib 2−phase 18
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
0
5
10
15
20
Months

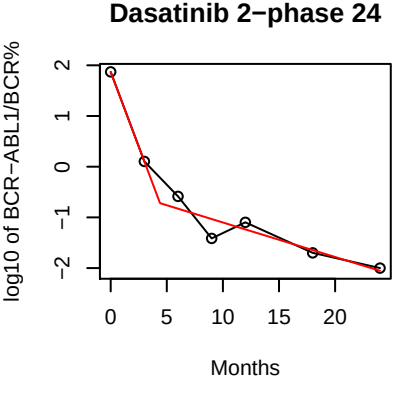

Dasatinib 2−phase 19
log10 of BCR−ABL1/BCR%
Months

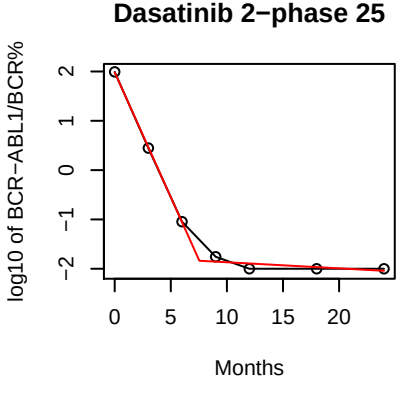

Dasatinib 2−phase 20
log10 of BCR−ABL1/BCR%
Months

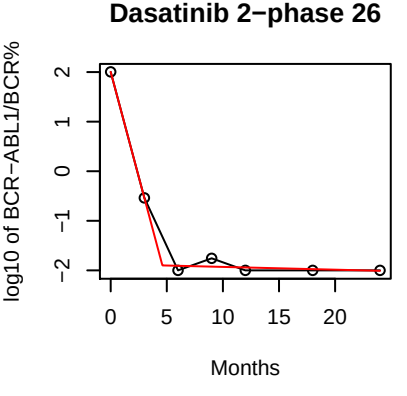

Dasatinib 2−phase 21
log10 of BCR−ABL1/BCR%
Months

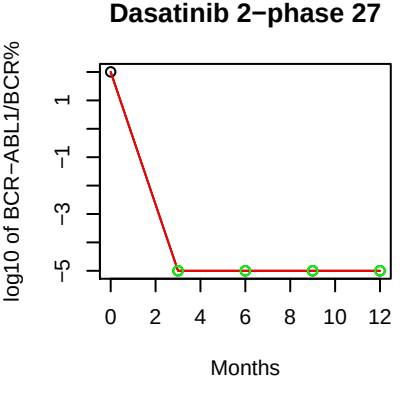

Dasatinib 2−phase 22
log10 of BCR−ABL1/BCR%
Months

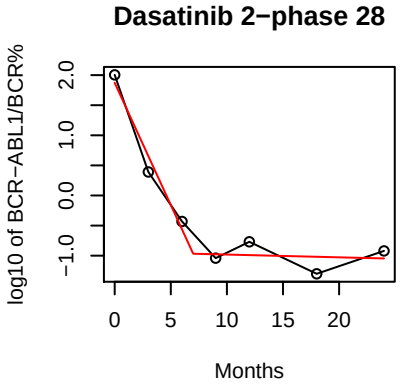

Dasatinib 2−phase 23
log10 of BCR−ABL1/BCR%
Months

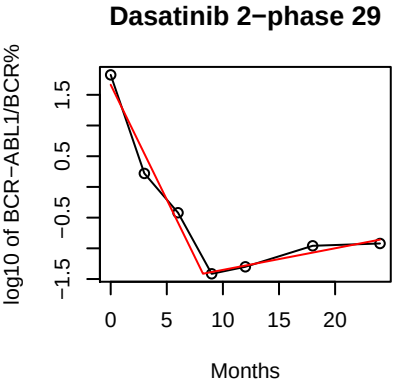

Dasatinib 2−phase 24
log10 of BCR−ABL1/BCR%
Months

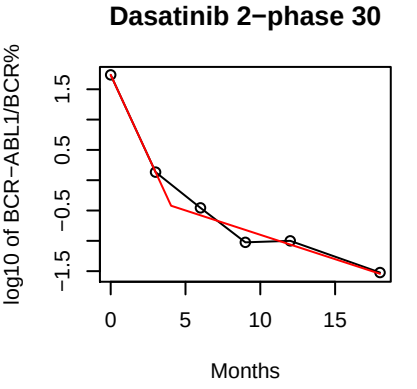

Dasatinib 2−phase 25
log10 of BCR−ABL1/BCR%
Months

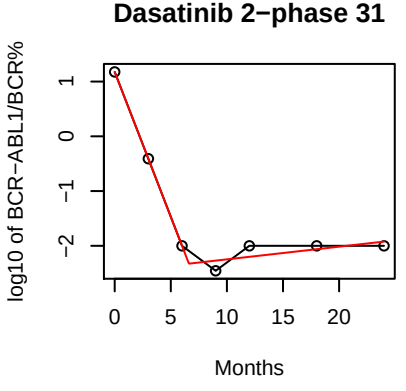

Dasatinib 2−phase 26
log10 of BCR−ABL1/BCR%
Months

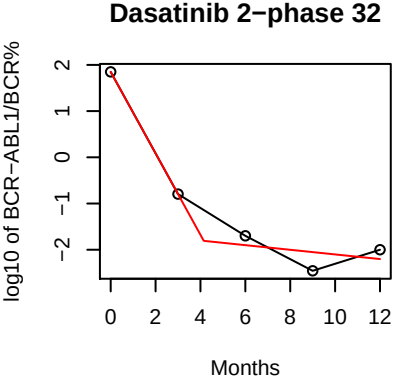

Dasatinib 2−phase 27
log10 of BCR−ABL1/BCR%
Months

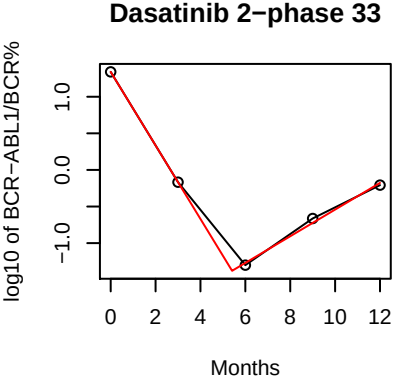

Dasatinib 2−phase 28
log10 of BCR−ABL1/BCR%
−1.0
0.0
1.0
2.0
0
5
10
15
20
Months

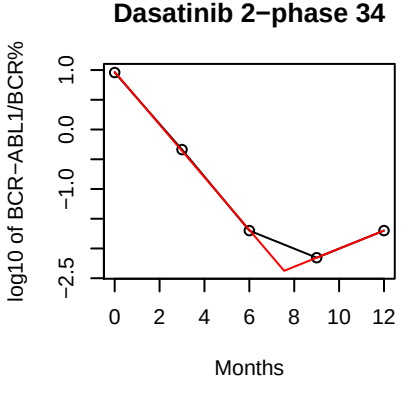

Dasatinib 2−phase 29
log10 of BCR−ABL1/BCR%
−1.5
−0.5
0.5
1.5
0
5
10
15
20
Months

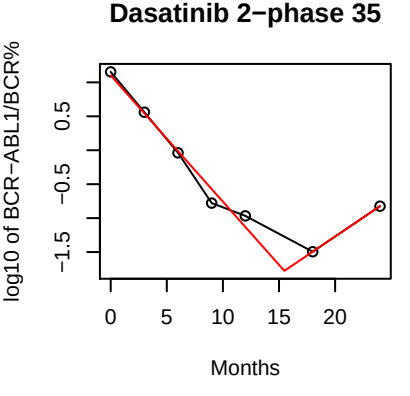

Dasatinib 2−phase 30
log10 of BCR−ABL1/BCR%
−1.5
−0.5
0.5
1.5
0
5
10
15
Months

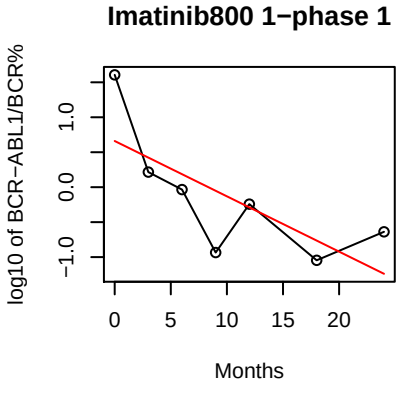

Dasatinib 2−phase 31
log10 of BCR−ABL1/BCR%
−2
−1
0
1
0
5
10
15
20
Months

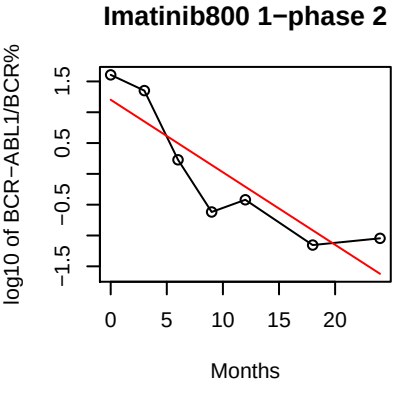

Dasatinib 2−phase 32
log10 of BCR−ABL1/BCR%
−2
−1
0
1
2
0
2
4
6
8
10
12
Months

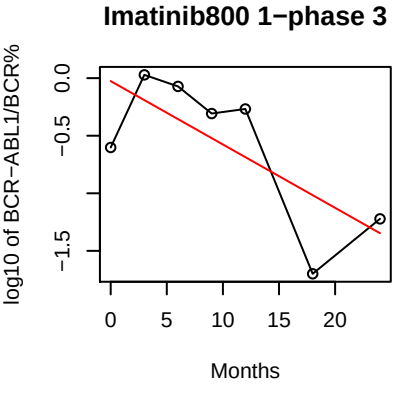

Dasatinib 2−phase 33
log10 of BCR−ABL1/BCR%
−1.0
0.0
1.0
0
2
4
6
8
10
12
Months

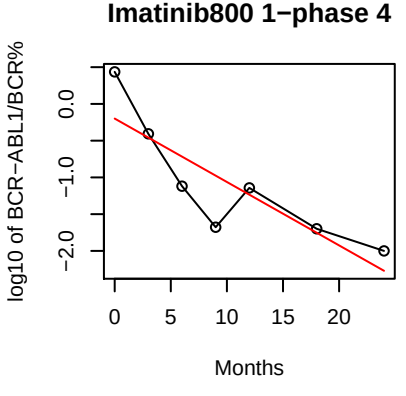

Dasatinib 2−phase 34
log10 of BCR−ABL1/BCR%
−2.5
−1.0
0.0
1.0
0
2
4
6
8
10
12
Months

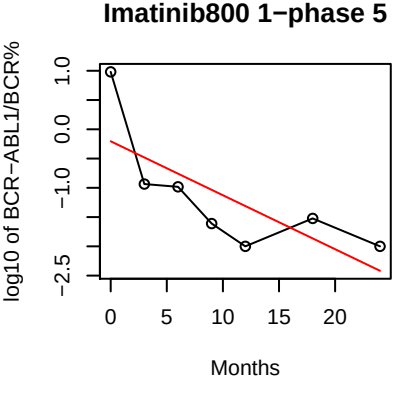

Dasatinib 2−phase 35
log10 of BCR−ABL1/BCR%
−1.5
−0.5
0.5
0
5
10
15
20
Months

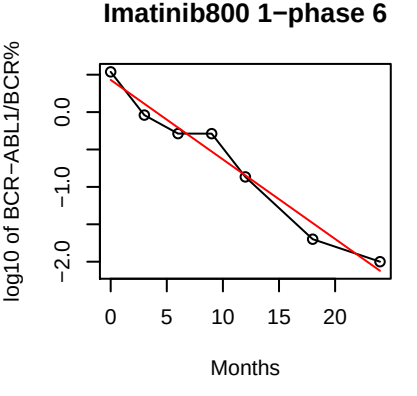

Imatinib800 1−phase 1
log10 of BCR−ABL1/BCR%
−1.0
0.0
1.0
0
5
10
15
20
Months

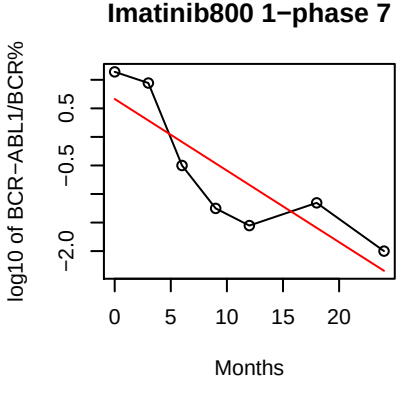

Imatinib800 1−phase 2
log10 of BCR−ABL1/BCR%
−1.5
−0.5
0.5
1.5
0
5
10
15
20
Months

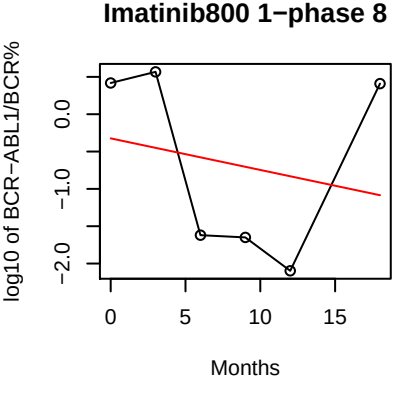

Imatinib800 1−phase 3
log10 of BCR−ABL1/BCR%
−1.5
−0.5
0.0
0
5
10
15
20
Months

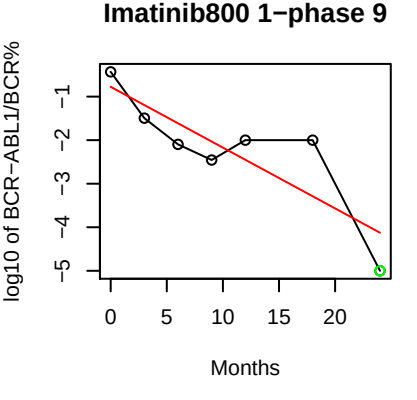

Imatinib800 1−phase 4
log10 of BCR−ABL1/BCR%
−2.0
−1.0
0.0
0
5
10
15
20
Months

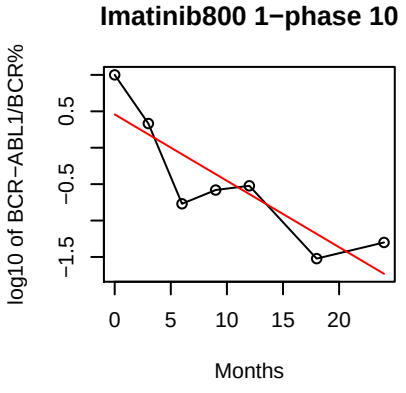

Imatinib800 1−phase 5
log10 of BCR−ABL1/BCR%
−2.5
−1.0
0.0
1.0
0
5
10
15
20
Months

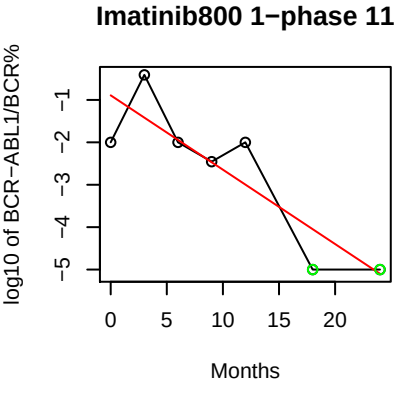

Imatinib800 1−phase 6
log10 of BCR−ABL1/BCR%
−2.0
−1.0
0.0
0
5
10
15
20
Months

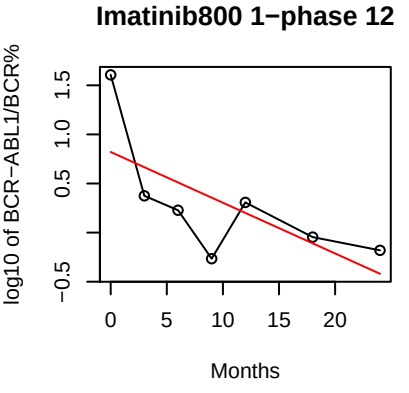

Imatinib800 1−phase 7
log10 of BCR−ABL1/BCR%
−2.0
−0.5
0.5
0
5
10
15
20
Months

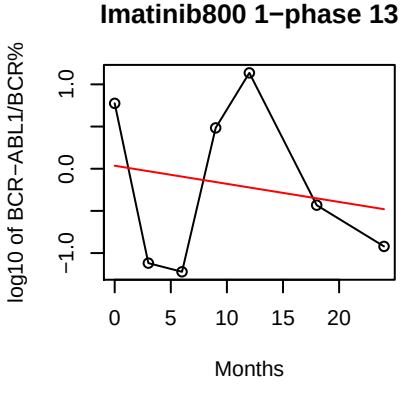

Imatinib800 1−phase 8
log10 of BCR−ABL1/BCR%
−2.0
−1.0
0.0
0
5
10
15
Months

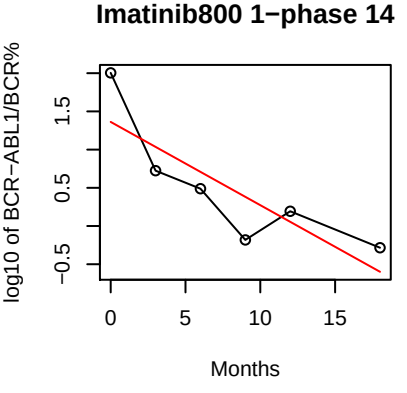

Imatinib800 1−phase 9
log10 of BCR−ABL1/BCR%
−5
−4
−3
−2
−1
0
5
10
15
20
Months

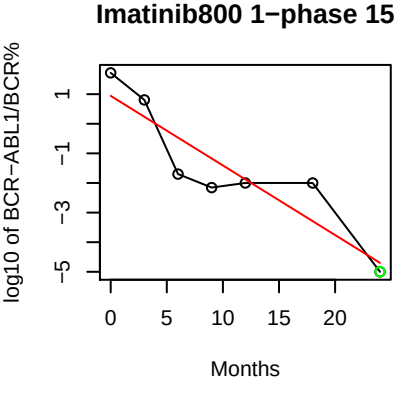

Imatinib800 1−phase 10
log10 of BCR−ABL1/BCR%
0.5
−0.5
−1.5
0
5
10
15
20
Months

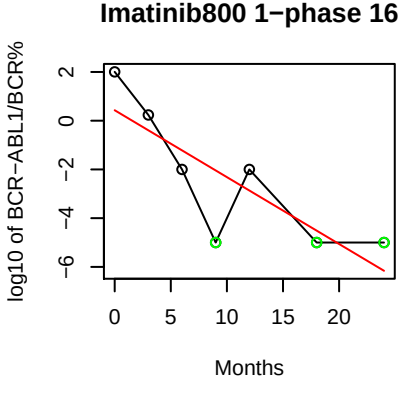

Imatinib800 1−phase 11
log10 of BCR−ABL1/BCR%
−1
−2
−3
−4
−5
0
5
10
15
20
Months

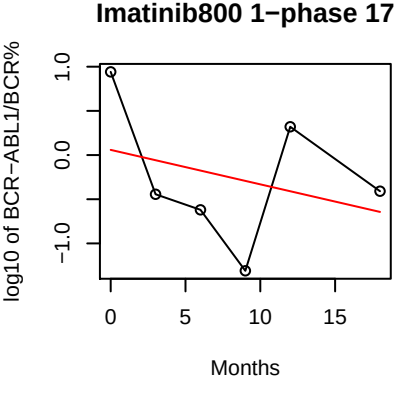

Imatinib800 1−phase 12
log10 of BCR−ABL1/BCR%
1.5
1.0
0.5
−0.5
0
5
10
15
20
Months

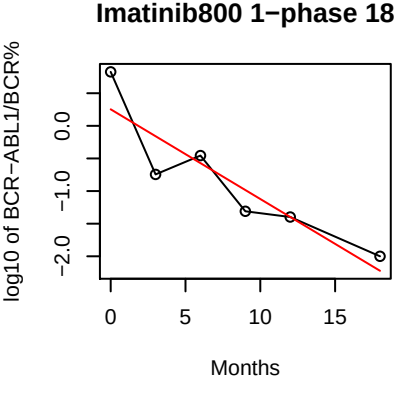

Imatinib800 1−phase 13
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
0
5
10
15
20
Months

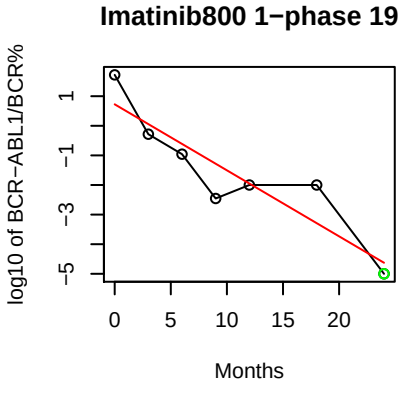

Imatinib800 1−phase 14
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
0
5
10
15
Months

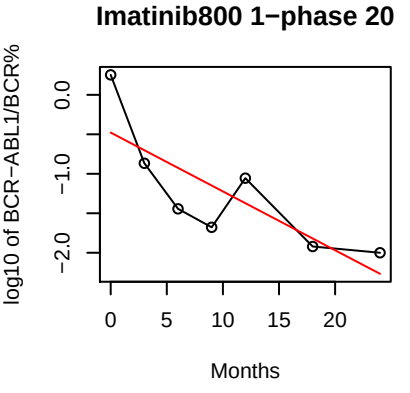

Imatinib800 1−phase 15
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

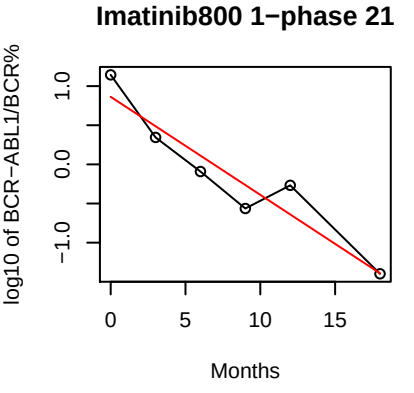

Imatinib800 1−phase 16
log10 of BCR−ABL1/BCR%
2
0
−2
−4
−6
0
5
10
15
20
Months

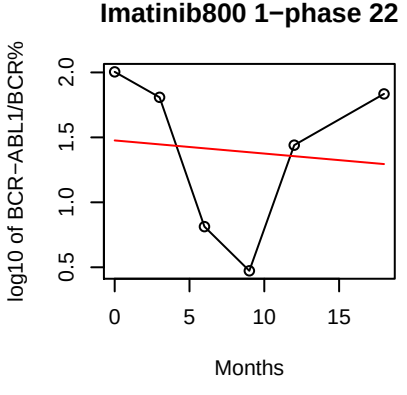

Imatinib800 1−phase 17
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
0
5
10
15
Months

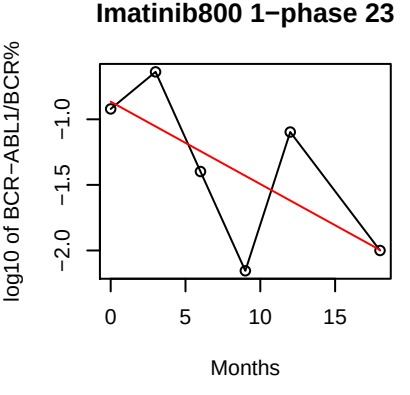

Imatinib800 1−phase 18
log10 of BCR−ABL1/BCR%
0.0
−1.0
−2.0
0
5
10
15
Months

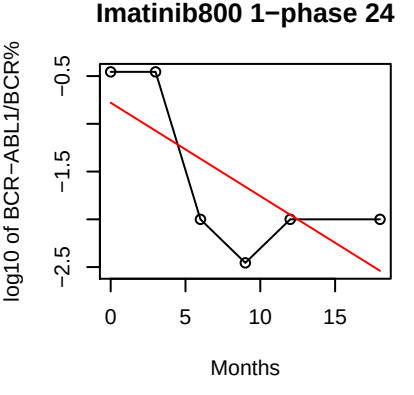

Imatinib800 1−phase 19
log10 of BCR−ABL1/BCR%
Months

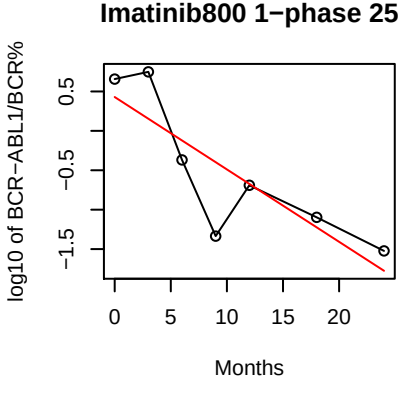

Imatinib800 1−phase 20
log10 of BCR−ABL1/BCR%
Months

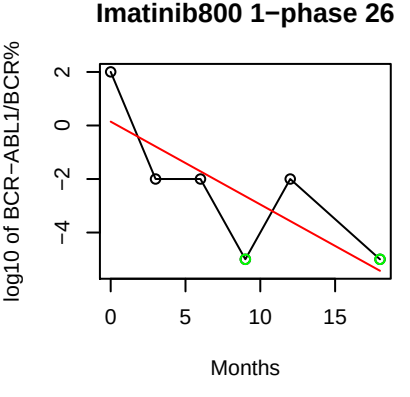

Imatinib800 1−phase 21
log10 of BCR−ABL1/BCR%
Months

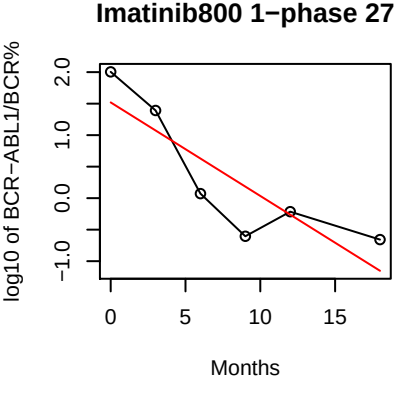

Imatinib800 1−phase 22
log10 of BCR−ABL1/BCR%
Months

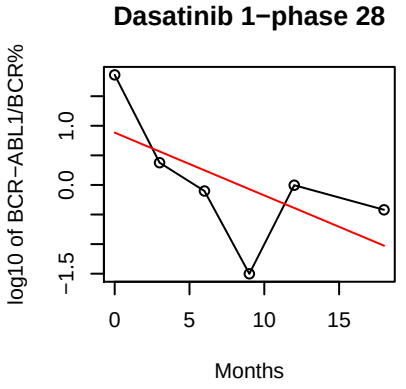

Imatinib800 1−phase 23
log10 of BCR−ABL1/BCR%
Months

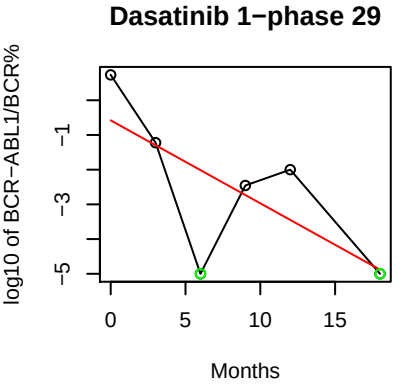

Imatinib800 1−phase 24
log10 of BCR−ABL1/BCR%
Months

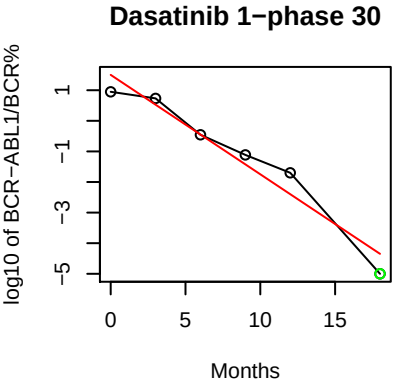

Imatinib800 1−phase 25
log10 of BCR−ABL1/BCR%
Months

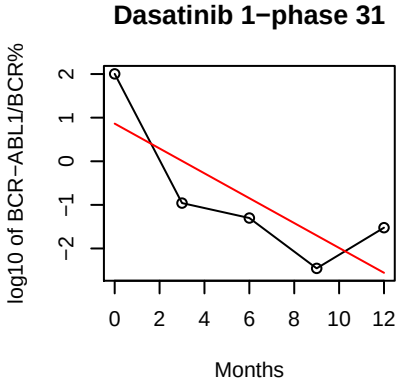

Imatinib800 1−phase 26
log10 of BCR−ABL1/BCR%
Months

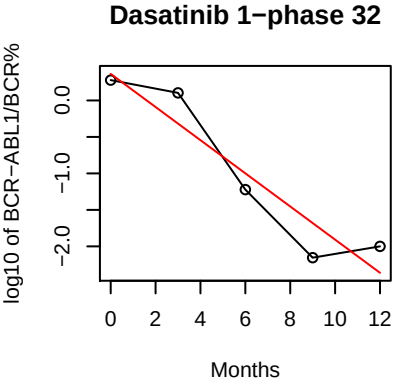

Imatinib800 1−phase 27
log10 of BCR−ABL1/BCR%
Months

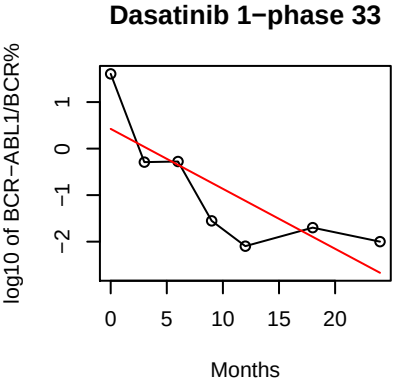

Dasatinib 1−phase 28
log10 of BCR−ABL1/BCR%
−1.5
0.0
1.0
0
5
10
15
Months

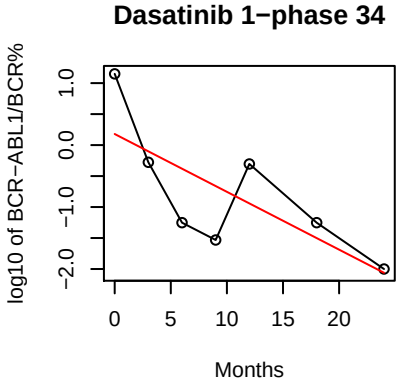

Dasatinib 1−phase 29
log10 of BCR−ABL1/BCR%
−5
−3
−1
0
5
10
15
Months

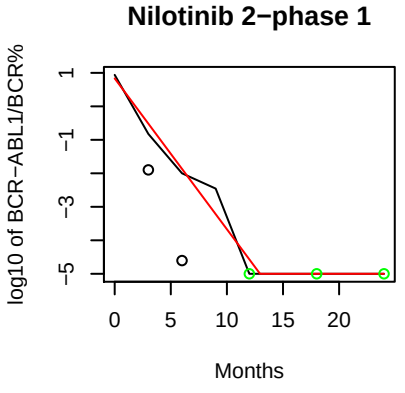

Dasatinib 1−phase 30
log10 of BCR−ABL1/BCR%
−5
−3
−1
1
0
5
10
15
Months

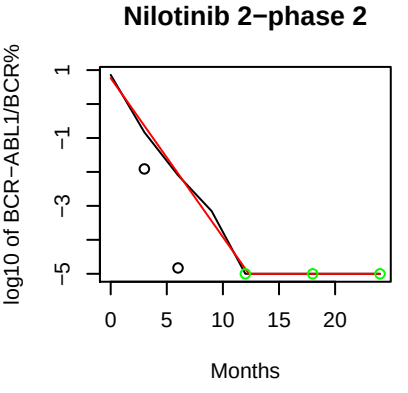

Dasatinib 1−phase 31
log10 of BCR−ABL1/BCR%
−2
−1
0
1
2
0
2
4
6
8
10
12
Months

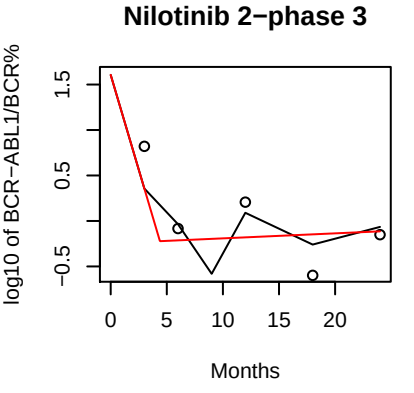

Dasatinib 1−phase 32
log10 of BCR−ABL1/BCR%
−2.0
−1.0
0.0
0
2
4
6
8
10
12
Months

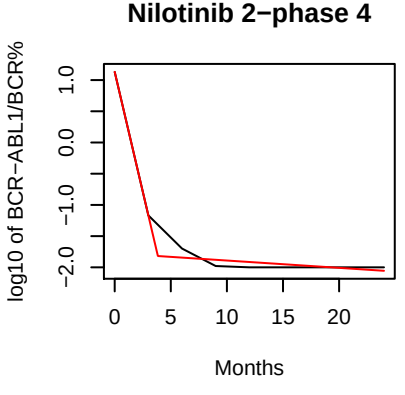

Dasatinib 1−phase 33
log10 of BCR−ABL1/BCR%
−2
−1
0
1
0
5
10
15
20
Months

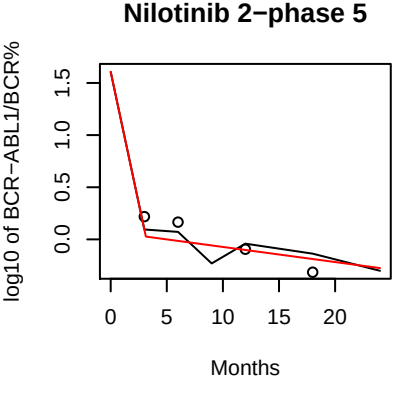

Dasatinib 1−phase 34
log10 of BCR−ABL1/BCR%
−2.0
−1.0
0.0
1.0
0
5
10
15
20
Months

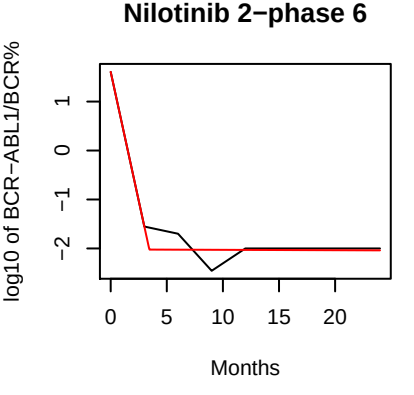

Nilotinib 2−phase 1
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

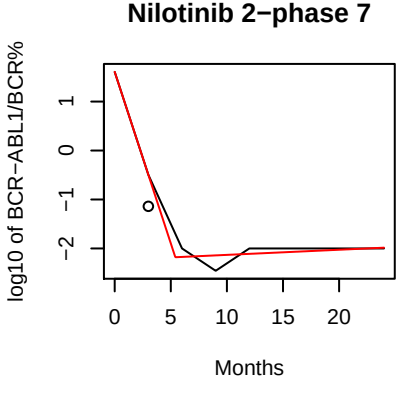

Nilotinib 2−phase 2
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

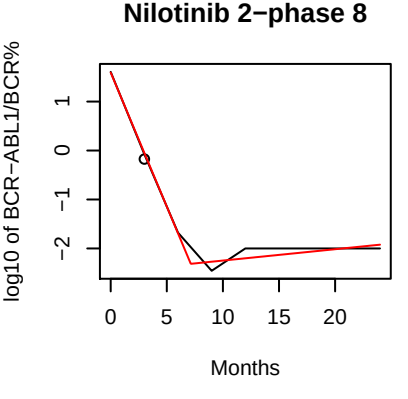

Nilotinib 2−phase 3
log10 of BCR−ABL1/BCR%
1.5
0.5
−0.5
0
5
10
15
20
Months

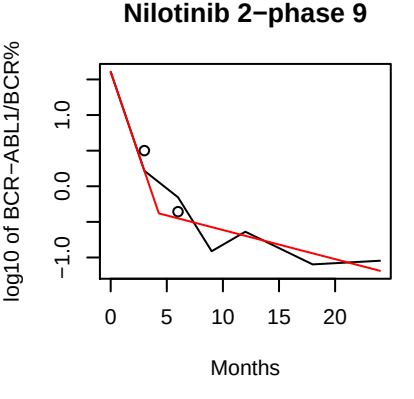

Nilotinib 2−phase 4
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.0
0
5
10
15
20
Months

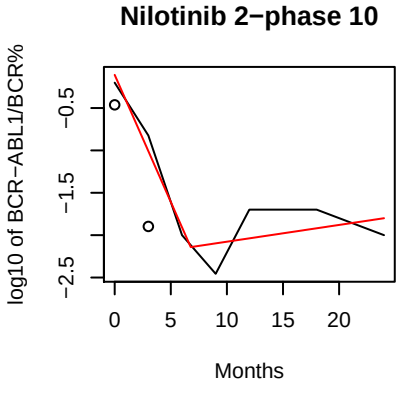

Nilotinib 2−phase 5
log10 of BCR−ABL1/BCR%
1.5
1.0
0.5
0.0
0
5
10
15
20
Months

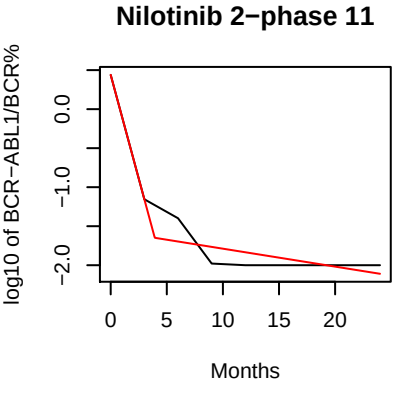

Nilotinib 2−phase 6
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

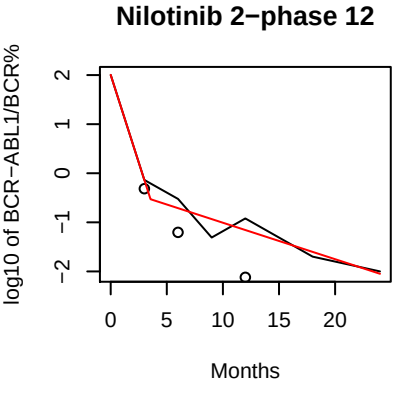

Nilotinib 2−phase 7
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

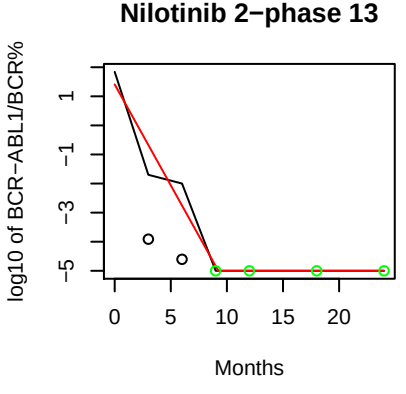

Nilotinib 2−phase 8
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

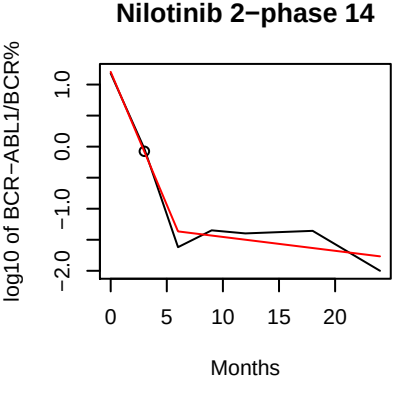

Nilotinib 2−phase 9
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
0
5
10
15
20
Months

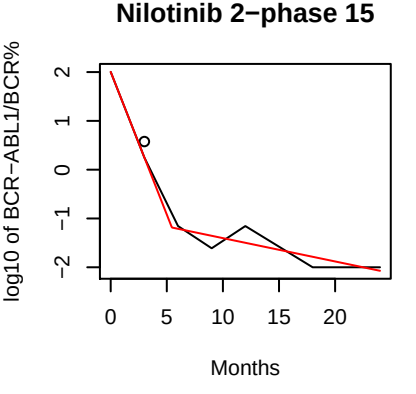

Nilotinib 2−phase 10
log10 of BCR−ABL1/BCR%
−0.5
−1.5
−2.5
0
5
10
15
20
Months

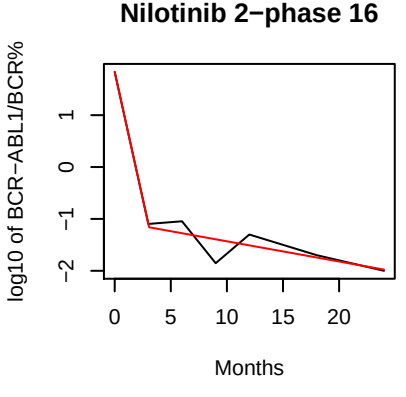

Nilotinib 2−phase 11
log10 of BCR−ABL1/BCR%
0.0
−1.0
−2.0
0
5
10
15
20
Months

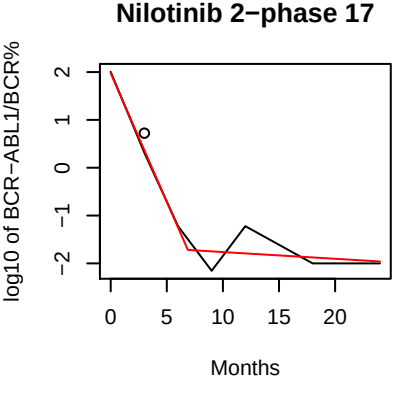

Nilotinib 2−phase 12
log10 of BCR−ABL1/BCR%
2
1
0
−1
−2
0
5
10
15
20
Months

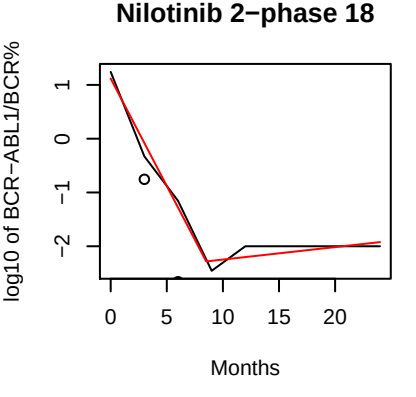

Nilotinib 2−phase 13
log10 of BCR−ABL1/BCR%
1
−1
−3
−5
0
5
10
15
20
Months

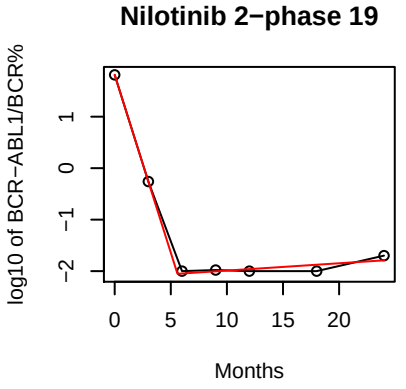

Nilotinib 2−phase 14
log10 of BCR−ABL1/BCR%
1.0
0.0
−1.0
−2.0
0
5
10
15
20
Months

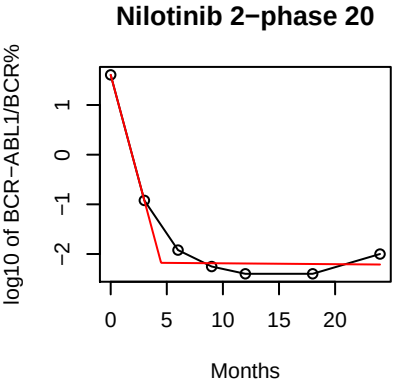

Nilotinib 2−phase 15
log10 of BCR−ABL1/BCR%
2
1
0
−1
−2
0
5
10
15
20
Months

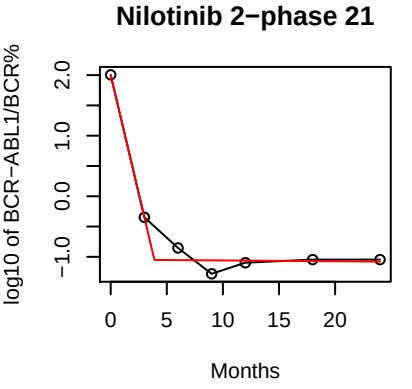

Nilotinib 2−phase 16
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

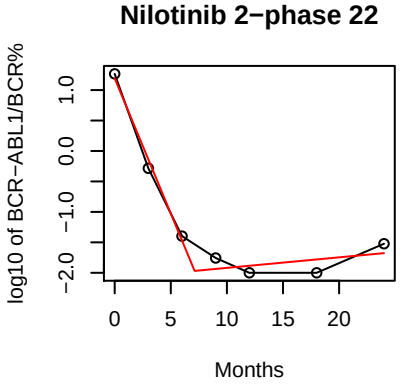

Nilotinib 2−phase 17
log10 of BCR−ABL1/BCR%
2
1
0
−1
−2
0
5
10
15
20
Months

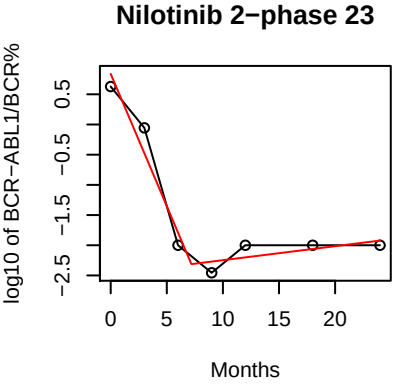

Nilotinib 2−phase 18
log10 of BCR−ABL1/BCR%
1
0
−1
−2
0
5
10
15
20
Months

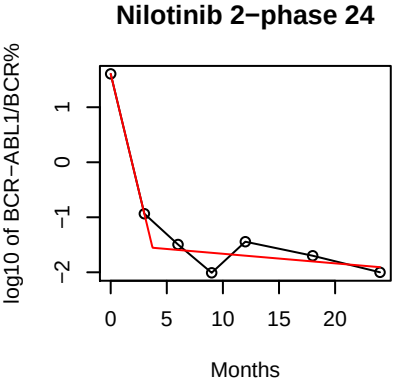

Nilotinib 2−phase 19
log10 of BCR−ABL1/BCR%
−2
−1
0
1
0
5
10
15
20
Months

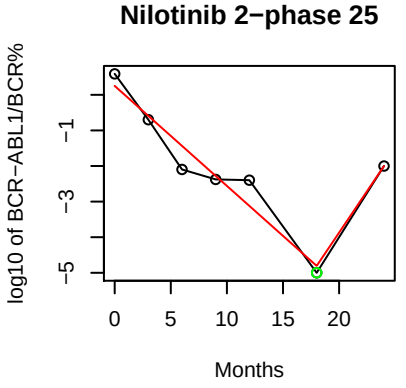

Nilotinib 2−phase 20
log10 of BCR−ABL1/BCR%
−2
−1
0
1
0
5
10
15
20
Months

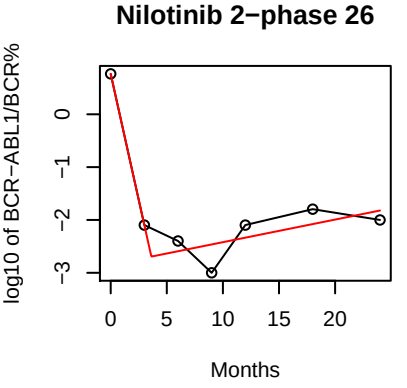

Nilotinib 2−phase 21
log10 of BCR−ABL1/BCR%
−1.0
0.0
1.0
2.0
0
5
10
15
20
Months

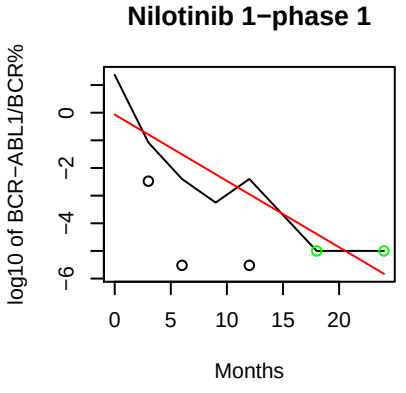

Nilotinib 2−phase 22
log10 of BCR−ABL1/BCR%
−2.0
−1.0
0.0
1.0
0
5
10
15
20
Months

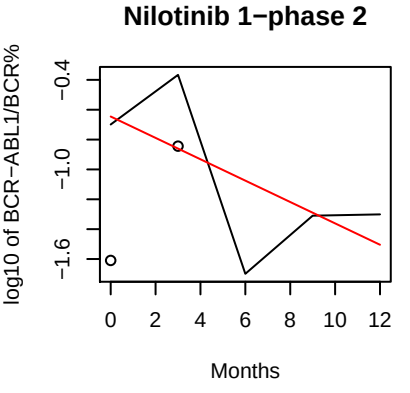

Nilotinib 2−phase 23
log10 of BCR−ABL1/BCR%
−2.5
−1.5
−0.5
0.5
0
5
10
15
20
Months

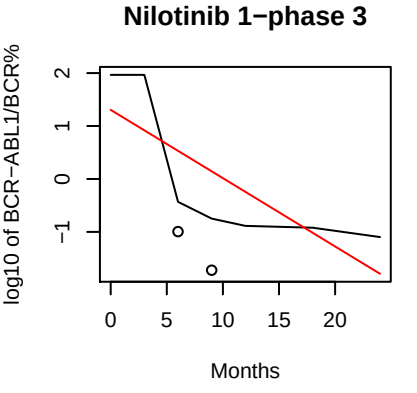

Nilotinib 2−phase 24
log10 of BCR−ABL1/BCR%
−2
−1
0
1
0
5
10
15
20
Months

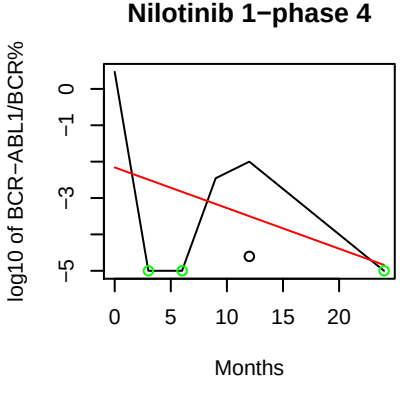

Nilotinib 2−phase 25
log10 of BCR−ABL1/BCR%
−5
−3
−1
0
5
10
15
20
Months

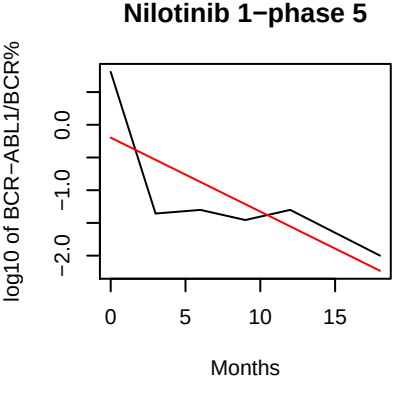

Nilotinib 2−phase 26
log10 of BCR−ABL1/BCR%
−3
−2
−1
0
0
5
10
15
20
Months

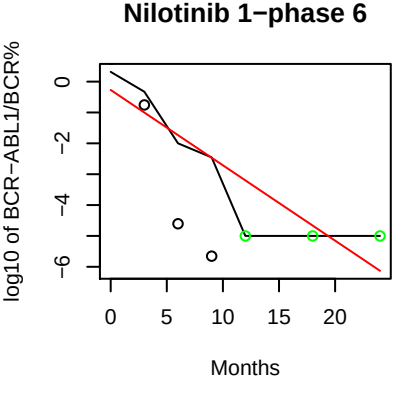

Nilotinib 1−phase 1
log10 of BCR−ABL1/BCR%
Months

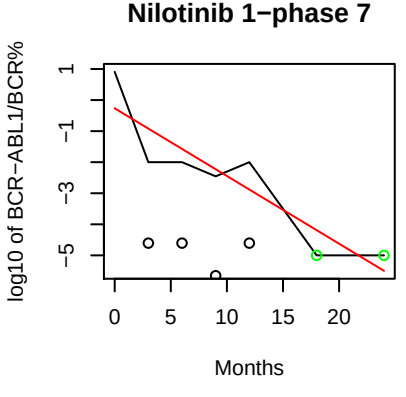

Nilotinib 1−phase 2
log10 of BCR−ABL1/BCR%
Months

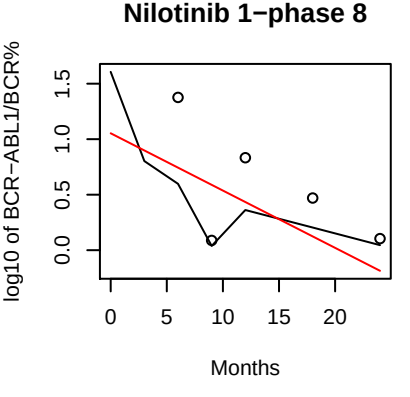

Nilotinib 1−phase 3
log10 of BCR−ABL1/BCR%
Months

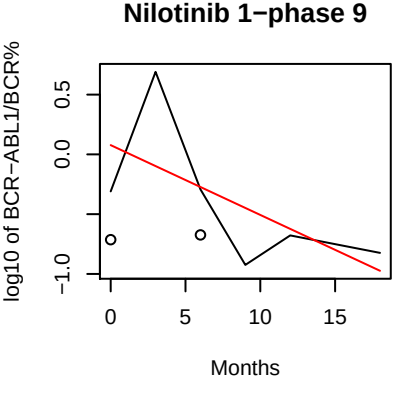

Nilotinib 1−phase 4
log10 of BCR−ABL1/BCR%
Months

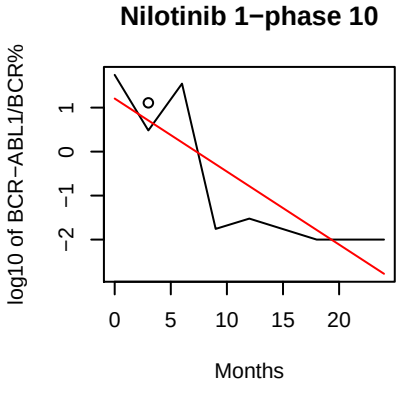

Nilotinib 1−phase 5
log10 of BCR−ABL1/BCR%
Months

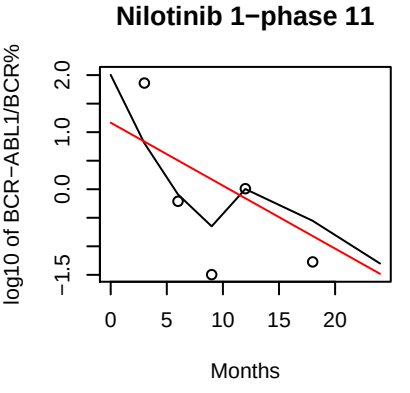

Nilotinib 1−phase 6
log10 of BCR−ABL1/BCR%
Months

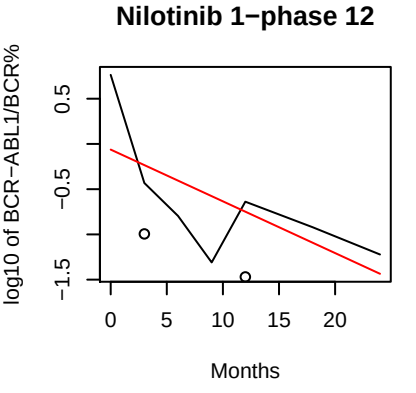

Nilotinib 1−phase 7
log10 of BCR−ABL1/BCR%
Months

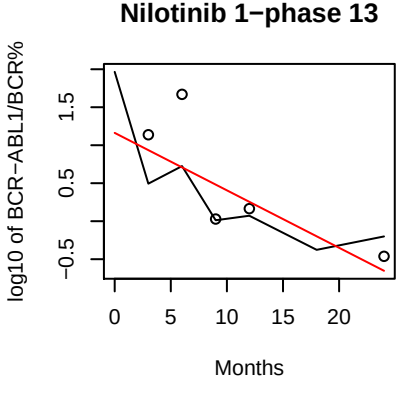

Nilotinib 1−phase 8
log10 of BCR−ABL1/BCR%
Months

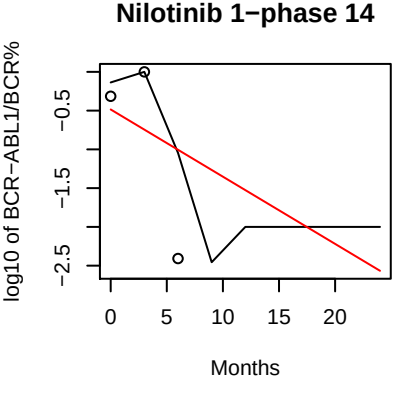

Nilotinib 1−phase 9
log10 of BCR−ABL1/BCR%
Months

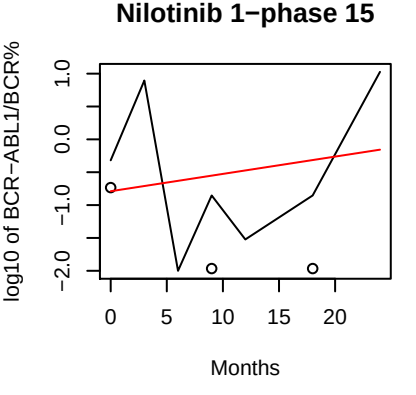

Nilotinib 1−phase 10
log10 of BCR−ABL1/BCR%
−2
−1
0
1
0
5
10
15
20
Months

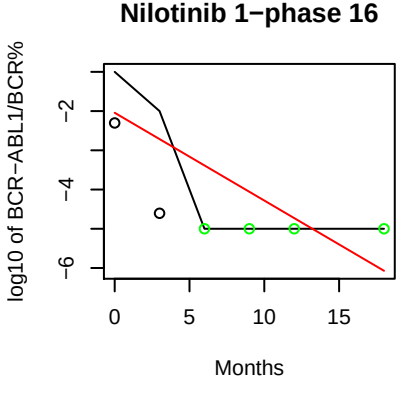

Nilotinib 1−phase 11
log10 of BCR−ABL1/BCR%
−1.5
0.0
1.0
2.0
0
5
10
15
20
Months

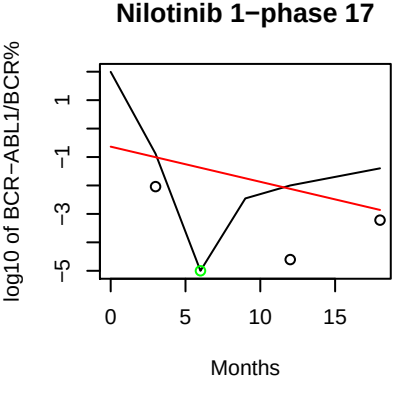

Nilotinib 1−phase 12
log10 of BCR−ABL1/BCR%
−1.5
−0.5
0.5
0
5
10
15
20
Months

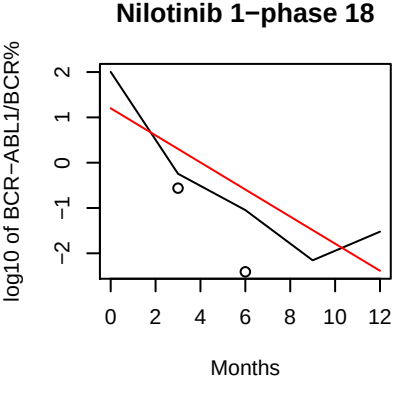

Nilotinib 1−phase 13
log10 of BCR−ABL1/BCR%
−0.5
0.5
1.5
0
5
10
15
20
Months

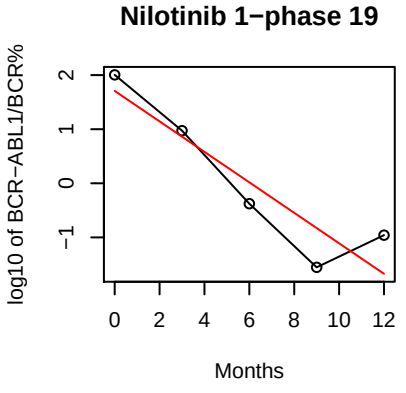

Nilotinib 1−phase 14
log10 of BCR−ABL1/BCR%
−2.5
−1.5
−0.5
0
5
10
15
20
Months

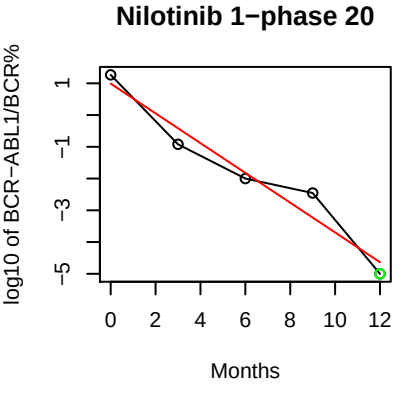

Nilotinib 1−phase 15
log10 of BCR−ABL1/BCR%
−2.0
−1.0
0.0
1.0
0
5
10
15
20
Months

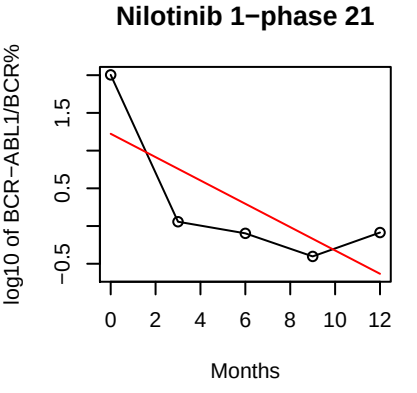

Nilotinib 1−phase 16
log10 of BCR−ABL1/BCR%
−6
−4
−2
0
5
10
15
Months

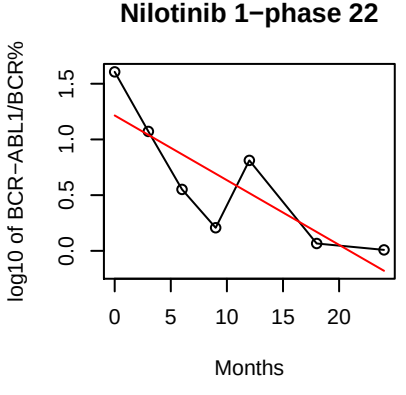

Nilotinib 1−phase 17
log10 of BCR−ABL1/BCR%
−5
−3
−1
1
0
5
10
15
Months

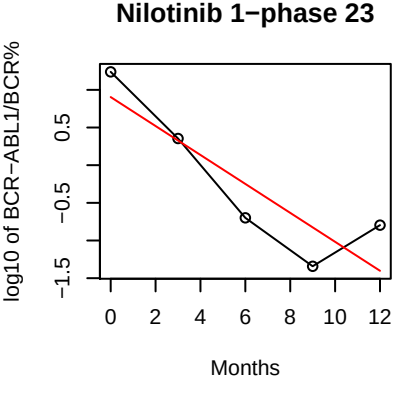

Nilotinib 1−phase 18
log10 of BCR−ABL1/BCR%
−2
−1
0
1
2
0
2
4
6
8
10
12
Months

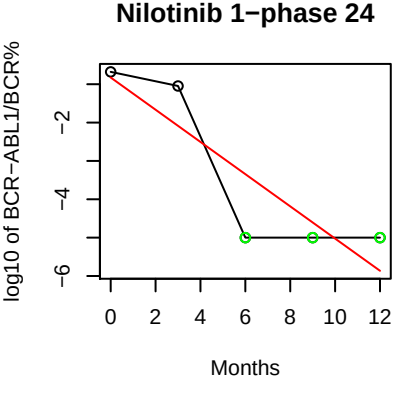

Nilotinib 1−phase 19
log10 of BCR−ABL1/BCR%
Months

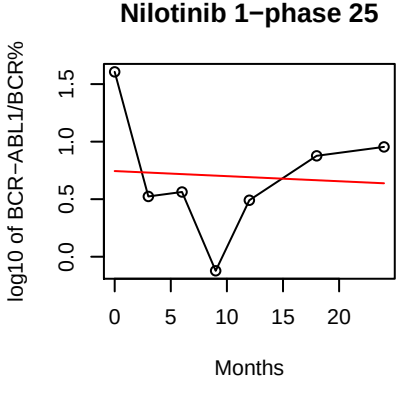

Nilotinib 1−phase 20
log10 of BCR−ABL1/BCR%
Months

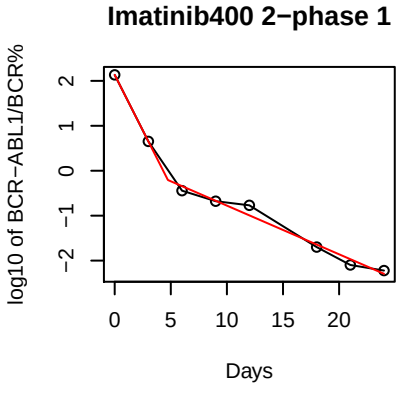

Nilotinib 1−phase 21
log10 of BCR−ABL1/BCR%
Months

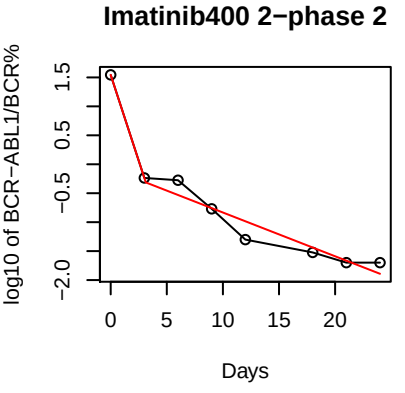

Nilotinib 1−phase 22
log10 of BCR−ABL1/BCR%
Months

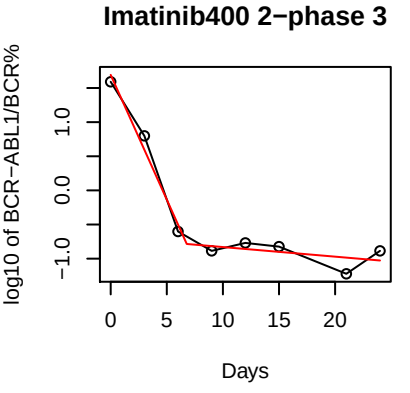

Nilotinib 1−phase 23
log10 of BCR−ABL1/BCR%
Months

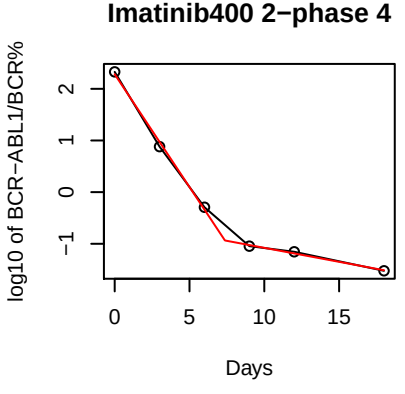

Nilotinib 1−phase 24
log10 of BCR−ABL1/BCR%
Months

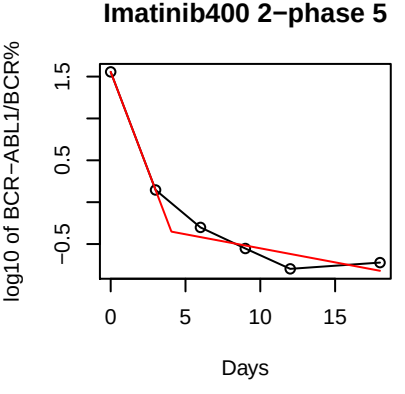

Nilotinib 1−phase 25
log10 of BCR−ABL1/BCR%
Months

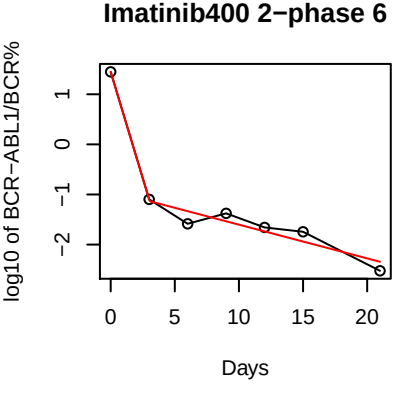

Imatinib400 2−phase 1
log10 of BCR−ABL1/BCR%
Days

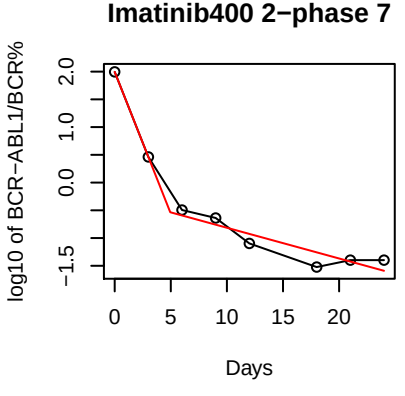

Imatinib400 2−phase 2
log10 of BCR−ABL1/BCR%
Days

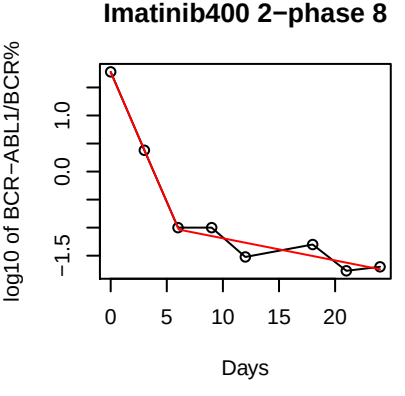

Imatinib400 2−phase 3
log10 of BCR−ABL1/BCR%
Days

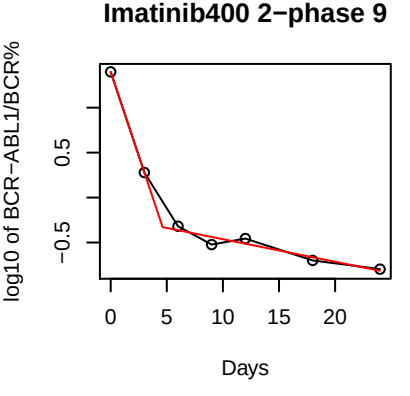

Imatinib400 2−phase 4
log10 of BCR−ABL1/BCR%
Days

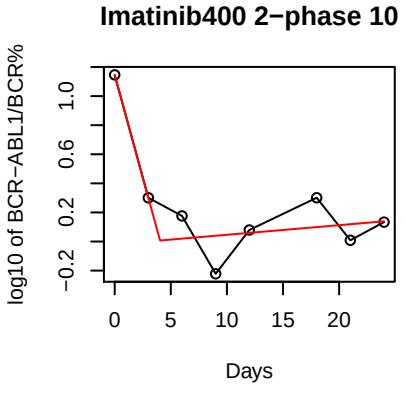

Imatinib400 2−phase 5
log10 of BCR−ABL1/BCR%
Days

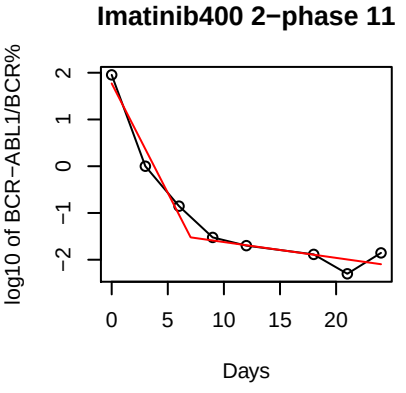

Imatinib400 2−phase 6
log10 of BCR−ABL1/BCR%
Days

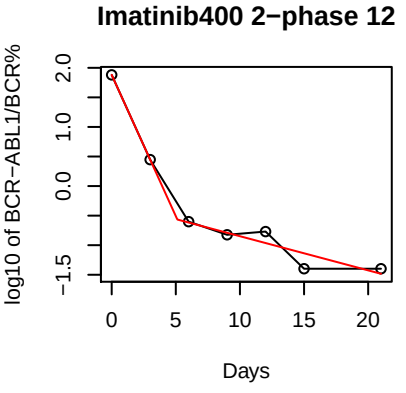

Imatinib400 2−phase 7
log10 of BCR−ABL1/BCR%
Days

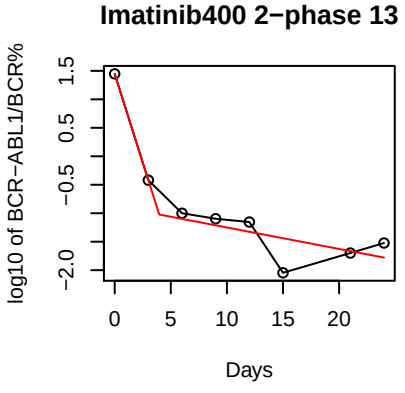

Imatinib400 2−phase 8
log10 of BCR−ABL1/BCR%
Days


Imatinib400 2−phase 9
log10 of BCR−ABL1/BCR%
Days


Imatinib400 2−phase 10
log10 of BCR−ABL1/BCR%
−0.2
0.2
0.6
1.0
0
5
10
15
20
Days


Imatinib400 2−phase 11
log10 of BCR−ABL1/BCR%
−2
−1
0
1
2
0
5
10
15
20
Days


Imatinib400 2−phase 12
log10 of BCR−ABL1/BCR%
−1.5
0.0
1.0
2.0
0
5
10
15
20
Days


Imatinib400 2−phase 13
log10 of BCR−ABL1/BCR%
−2.0
−0.5
0.5
1.5
0
5
10
15
20
Days