

# Metabolism of imatinib and other TK inhibitors: importance of blood level testing

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# Introduction

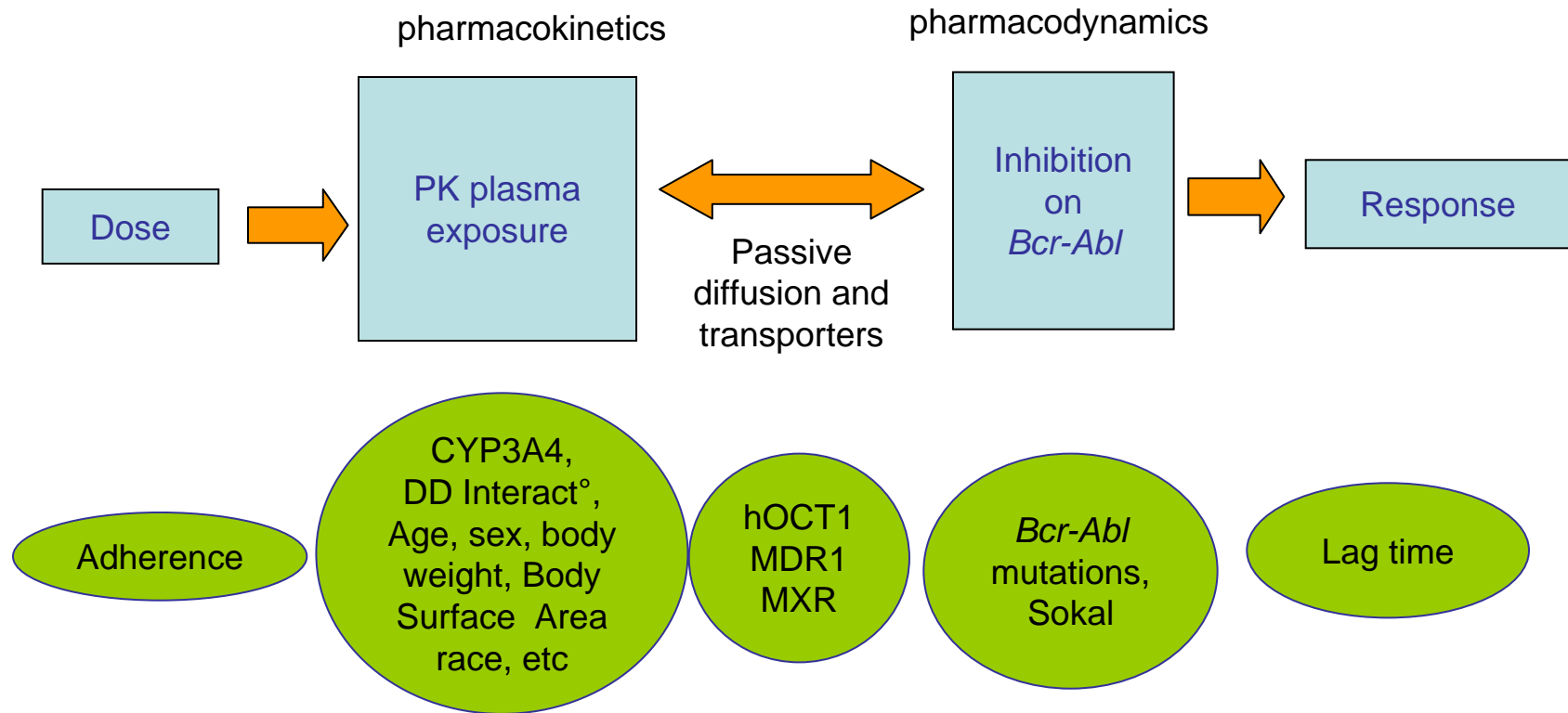
- Despite the impressive efficacy of imatinib suboptimal response and treatment failure are sometimes observed
- A number of factors may underlie this variation :
  - biological factors : BCR-ABL mutations or other genetic variations...
  - clinical features : disease status, the Sokal risk score....
  - pharmacokinetic (PK)-related factors affecting exposure to imatinib recently associated with clinical response

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# Factors affecting clinical response



MXR, multixenobiotic resistance protein

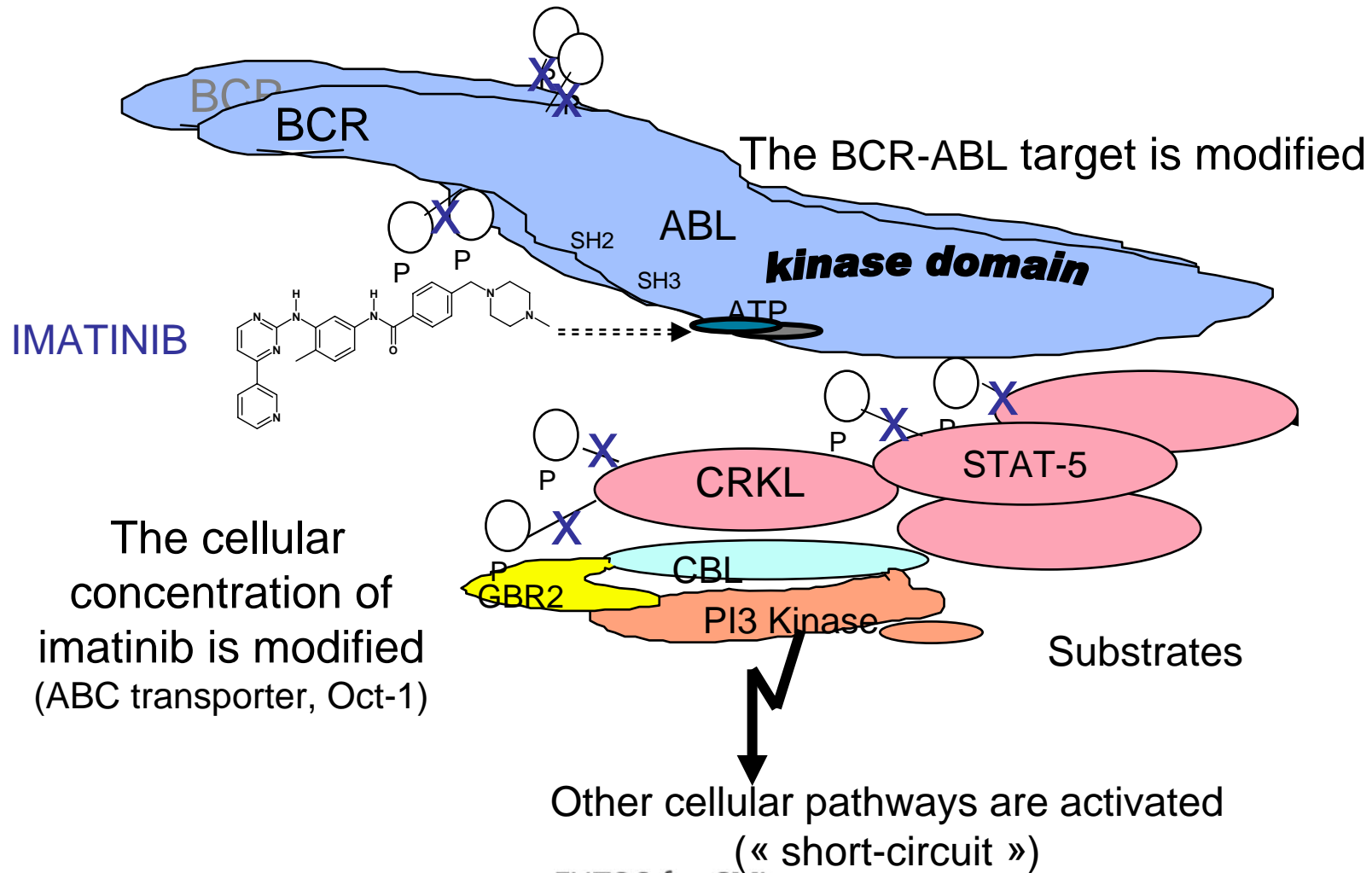
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Pharmacokinetic/pharmacodynamic correlation and blood-level testing in imatinib therapy for chronic myeloid leukemia. JE Cortes et al. Leukemia in press

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# Mechanisms of imatinib resistance

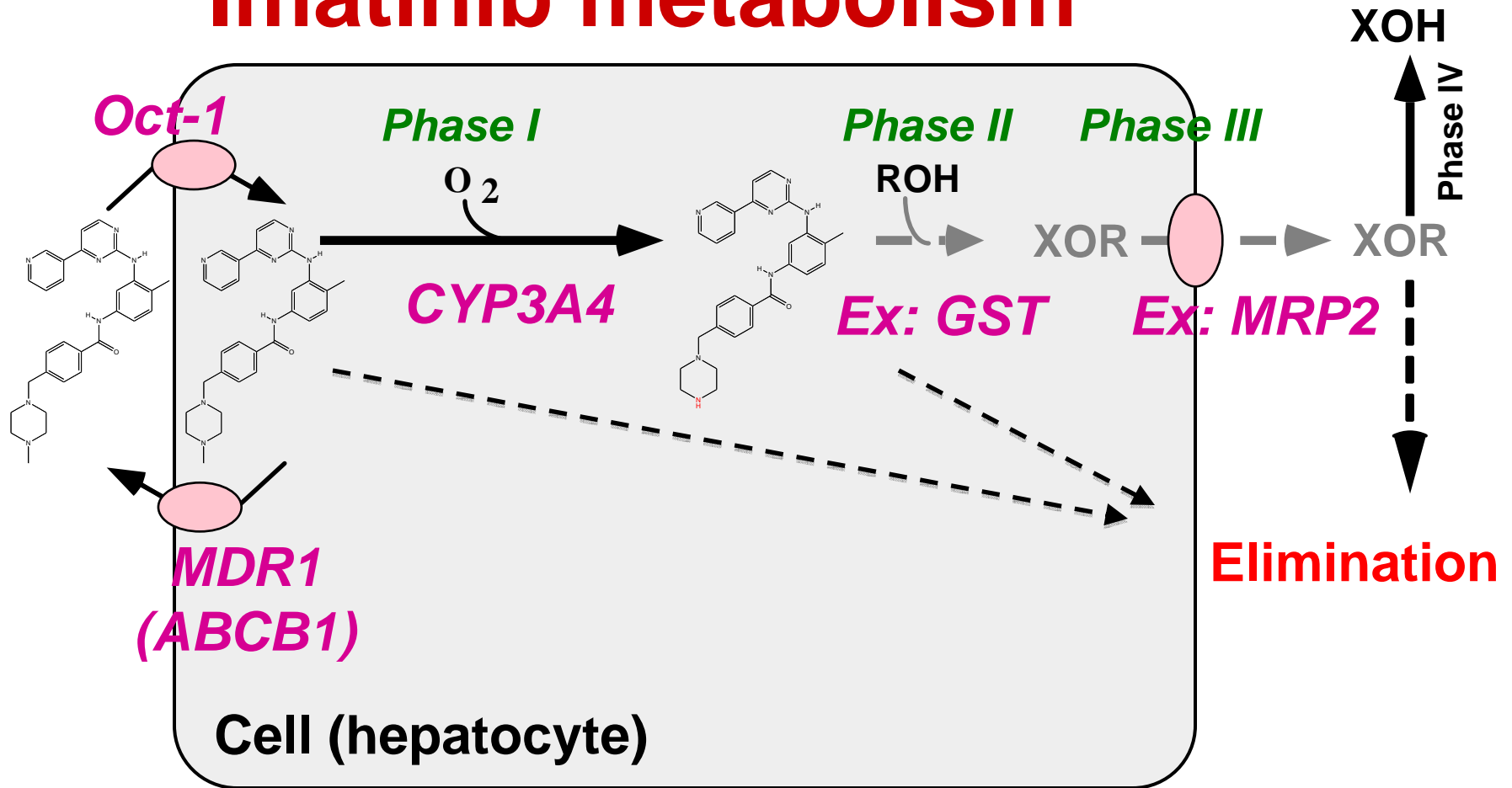


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# Imatinib metabolism



—————▶ Major pathway  
- - - - -▶ Minor pathway

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# Using imatinib plasma level testing in the management of CML

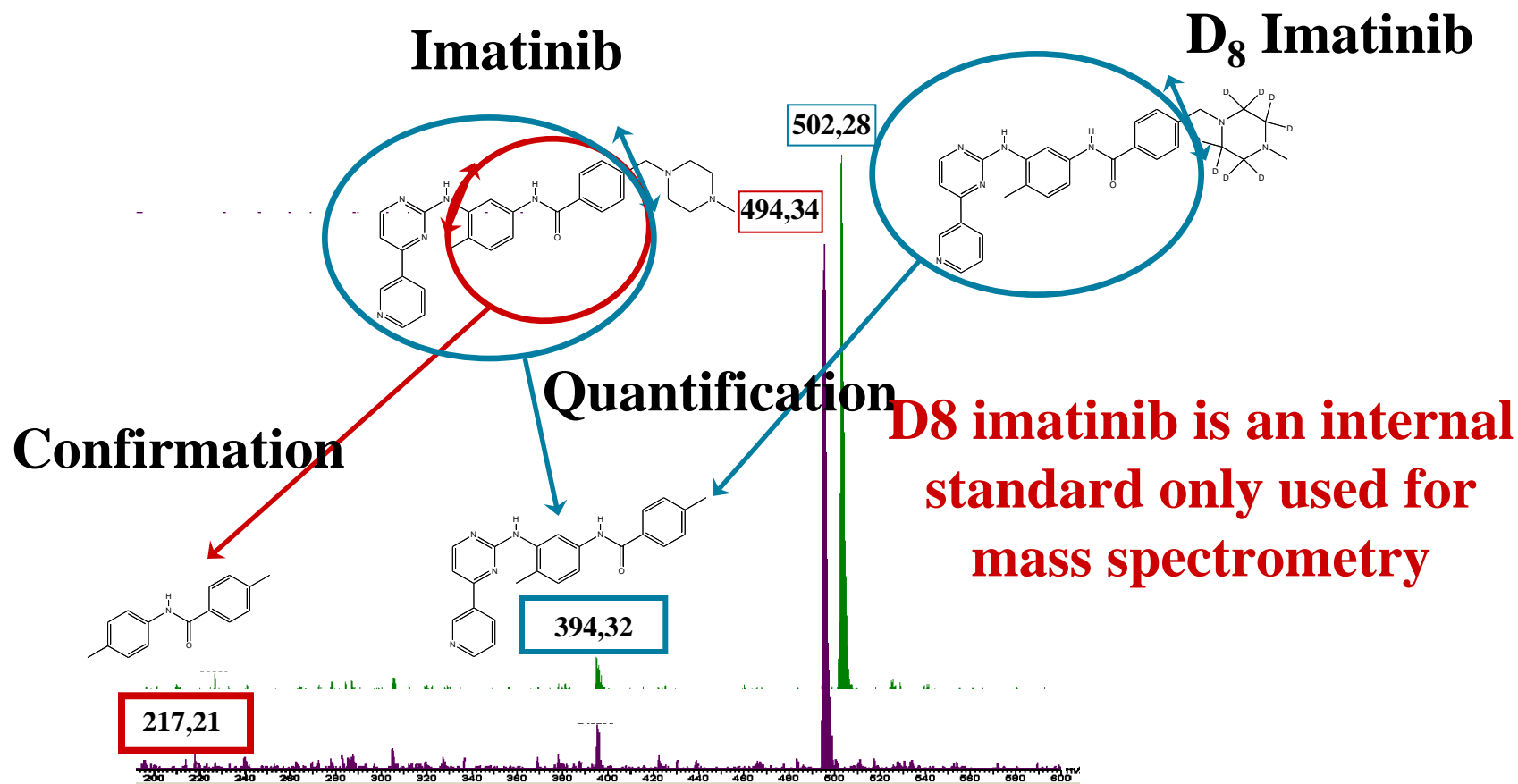
1. How do you measure imatinib plasma concentration?
2. What does the measurement mean ?
3. Why measure imatinib plasma concentration?

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# Quantification of imatinib, in human plasma, by high performance liquid chromatography-tandem mass spectrometry



Titier K *et al.* *Ther Drug Monit.* 2005 Oct;27(5):634-640.

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# Variability of imatinib plasma levels

- Imatinib is highly effective in treating patients with CML
- However, several studies have demonstrated large inter-patient variability in imatinib trough exposure<sup>1-4</sup>
- Effects of age, gender, body weight or surface area are not likely to be clinically significant
- Possible reasons for variations in exposure include:<sup>5-9</sup>
  - Incomplete adherence to therapeutic regimen
  - Drug-drug interactions (via CYP3A4/5)
  - Decreased absorption due to GI abnormalities or disease states
  - Binding to plasma proteins (e.g. alpha 1 acid-glycoprotein)
  - Variability in uptake (e.g. OCT-1) and efflux (e.g. P-glycoprotein) transporters

1. Peng *et al. J Clin Oncol* 2004;22:935–942. 2. Blasdel C *et al.* Paper presented at: American Society of Hematology 48th Annual Meeting; December 9-12, 2006; Orlando, Fla. Abstract 4820. 3. Picard *et al. Blood* 2007;109:3496–3499. 4. Larson *et al. Blood* 2008;ePub ahead of print. 5. Bolton *et al. Cancer Chemother Pharmacol* 2004;53:102–106. 6. Dutreix *et al. Cancer Chemother Pharmacol* 2004;54:290–294. 7. Peng *et al. Clin Pharmacokinet* 2005;44:879–894. 8. Beumer *et al. Pharmacotherapy* 2006;26:903–907. 9. White *et al. Blood* 2007;110:4064–72.

# Blood Level Testing (BLT)

A physician may want to consider imatinib BLT if a patient is

- **Not responding** to imatinib as well as expected
- Thought not to be **adhering** to their imatinib regimen
- Thought to be experiencing **drug–drug interactions**
- Experiencing **side effects** that are unusually severe for the prescribed dosage

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# BLT: drug–drug interactions

There are a number of drugs and other products that may affect imatinib plasma concentrations. Some examples are given below.

Aprepitant  
Clarithromycin / erythromycin  
Cyclosporin  
Itraconazole  
Pimozide  
Grapefruit juice

Those that may **INCREASE**  
imatinib plasma concentration

Barbiturates  
Carbamazepine  
Dexamethasone  
Phenytoin  
St John's wort

Those that may **DECREASE**  
imatinib plasma concentration

Glivec® [Summary of Product Characteristics]. Basel, Switzerland: Novartis Pharma AG. Available at: <http://www.glivec.com/content/tools/espc.jsp>.

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# Imatinib trough blood levels – correlation with clinical response

- Several studies have demonstrated a correlation between trough imatinib exposure and clinical response, including
  - A French BLT study<sup>1</sup>
  - A retrospective analysis of the IRIS trial<sup>2</sup>
  - The TOPS study<sup>3</sup>
  - An assessment of patient samples at the centralized BLT lab in Bordeaux<sup>4</sup>

1. Picard *et al. Blood* 2007;109:3496–3499. 2. Larson *et al. Blood* 2008; ePub ahead of print.  
3. J. Cortes EHA 2008 Oral presentation. 4. Mahon *et al. J Clin Oncol* 2008;26(Suppl): Abstract 7087

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## French BLT study

- Trough plasma levels of imatinib measured in 68 patients with Ph+ CML
  - All received imatinib 400 mg/day or 600 mg/day for >12 months
  - Blood samples collected at  $24 \pm 3$  h after previous imatinib dose
- Results from this study indicated
  - Trough imatinib levels varied greatly (181–2947 ng/mL range). with a plasma ‘threshold’ of 1002 ng/mL
  - Trough plasma levels of imatinib were associated with the likelihood of achieving CCR and MMR

CCR, complete cytogenetic response;  
MMR, major molecular response

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Picard *et al.* *Blood* 2007;109:3496–3499.

## French BLT study

- Trough imatinib plasma concentrations and CCR
  - The mean trough imatinib level was significantly higher in patients who achieved CCR than in those who did not ( $p = 0.03$ )

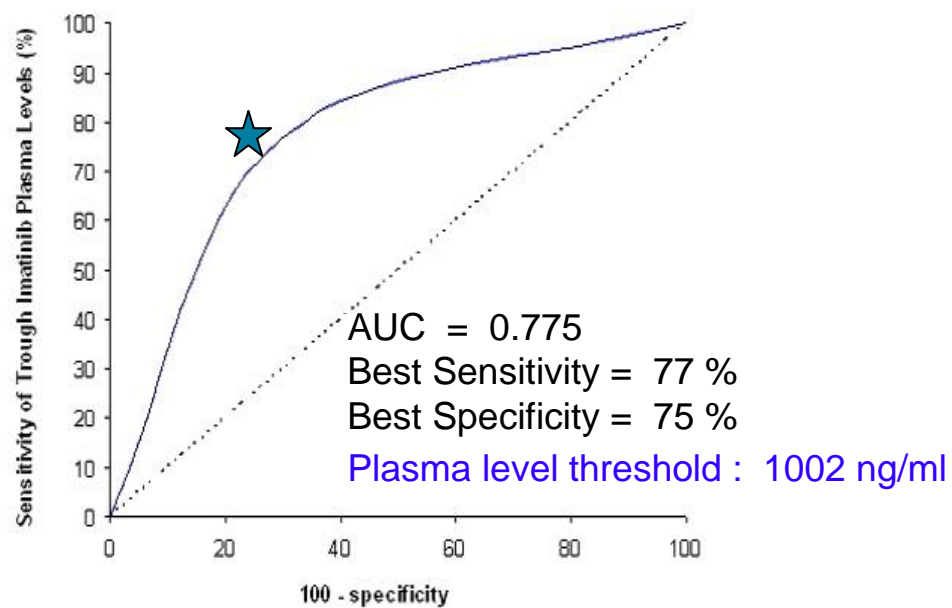
Response	<i>n</i>	Mean trough plasma imatinib level ( $\pm$ SD)
<b>CCR</b>	<b>56</b>	<b>1123 <math>\pm</math> 617 ng/mL</b>
<b>No CCR</b>	<b>12</b>	<b>694 <math>\pm</math> 556 ng/mL</b>

## Definition of efficiency threshold in CML

	<b>Imatinib concentration (mean)</b>	<b>SD</b>
<b>MMR (n = 34)</b>	1452 ng/mL	649
<b>Non-MMR (n = 34)</b>	869 ng/mL	427

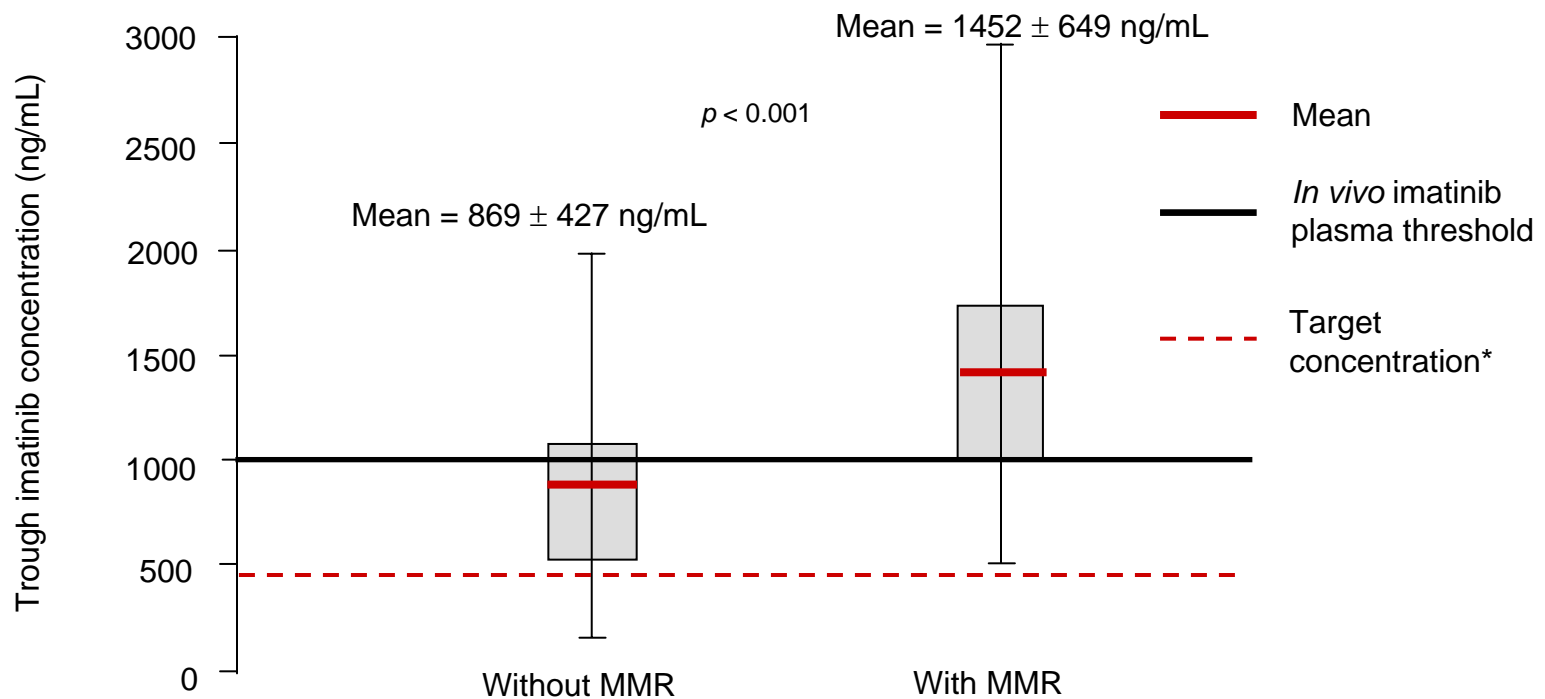
p < 0.0001

### ROC analysis on MMR



# French BLT study

- Trough imatinib plasma concentrations and MMR
  - Mean trough imatinib level was significantly higher in patients who achieved MMR than in those who did not



\*Required to result in *BCR-ABL*-positive cell death *in vitro*.



# Retrospective analysis of the IRIS trial

- Trough plasma concentrations analysed for 351 (of 553) patients with CP-CML on Day 29 of treatment in the IRIS trial
  - All patients randomized to initial imatinib 400 mg/day
  - Blood samples collected 24 h after previous imatinib dose
- Imatinib plasma trough levels were grouped into three plasma concentration categories based on distribution among four quartiles (Q1, Q2–Q3, and Q4)
- These categories were used for retrospective subgroup analysis

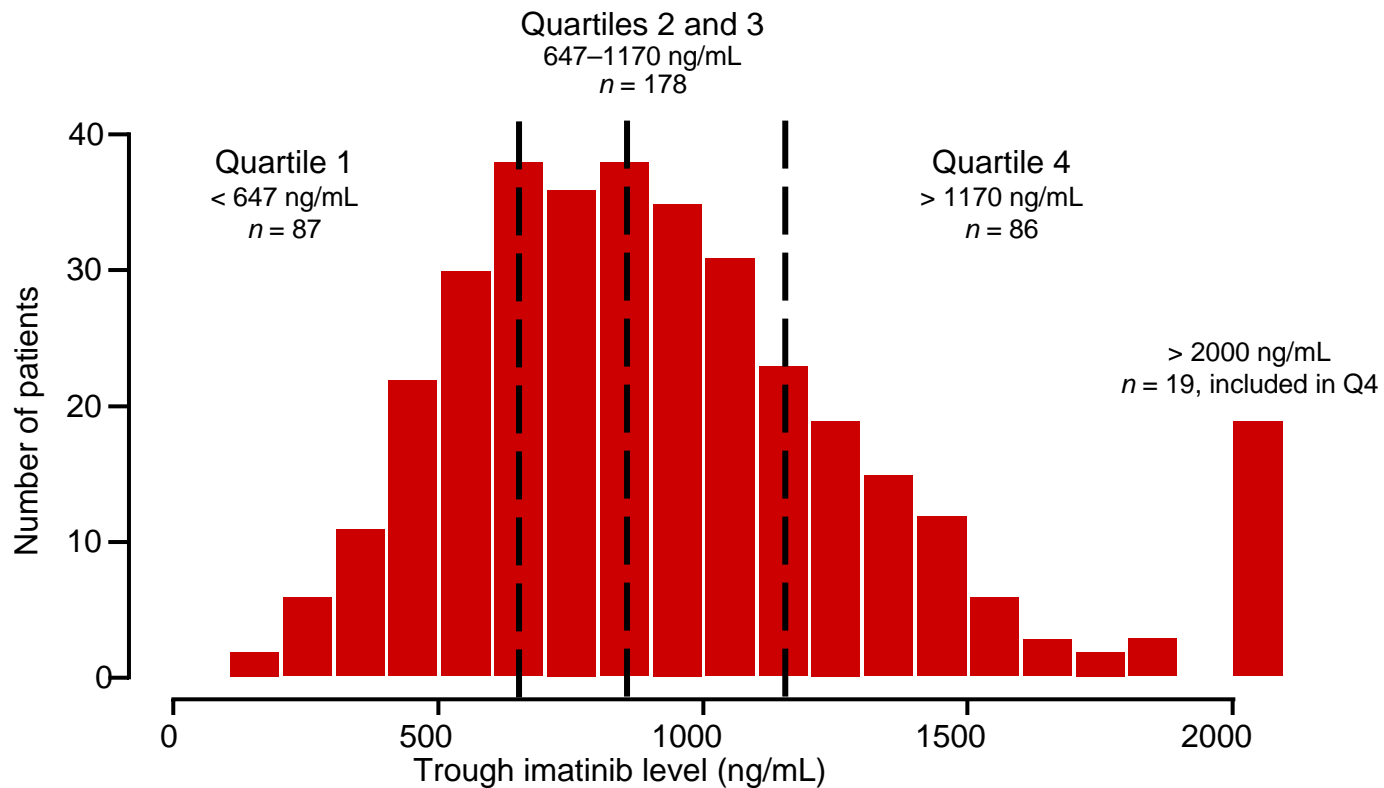
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# Retrospective analysis of the IRIS trial

- Distribution of imatinib trough levels from patients in IRIS study at steady state



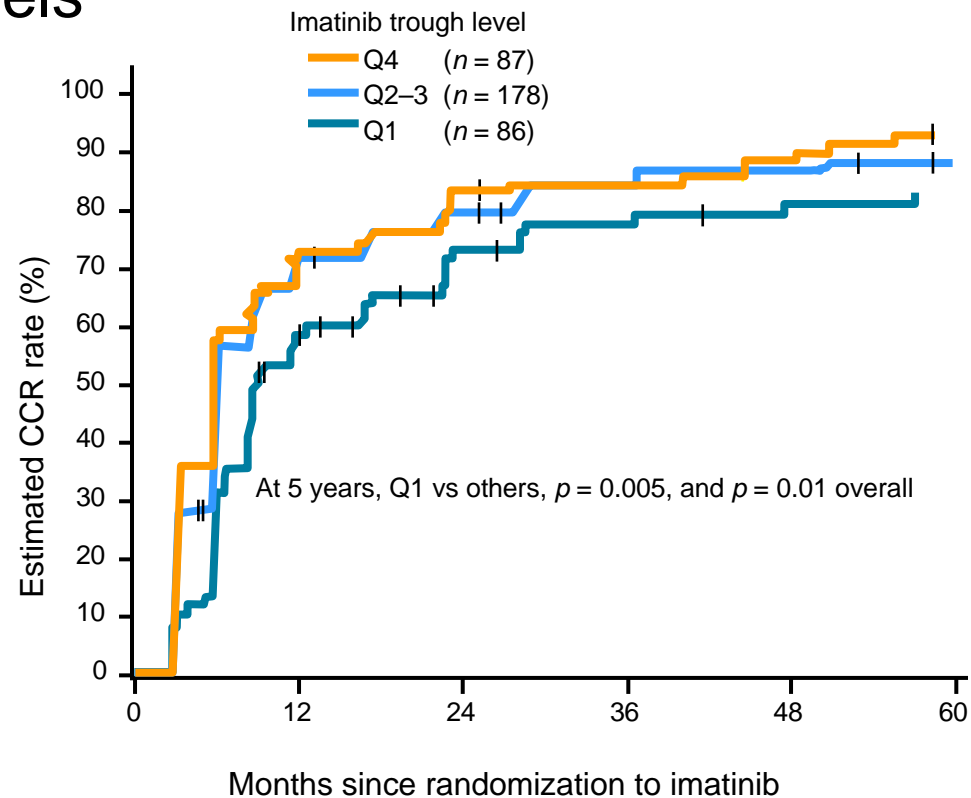
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# Retrospective analysis of the IRIS trial

- Estimated cumulative CCR rates according to imatinib trough levels



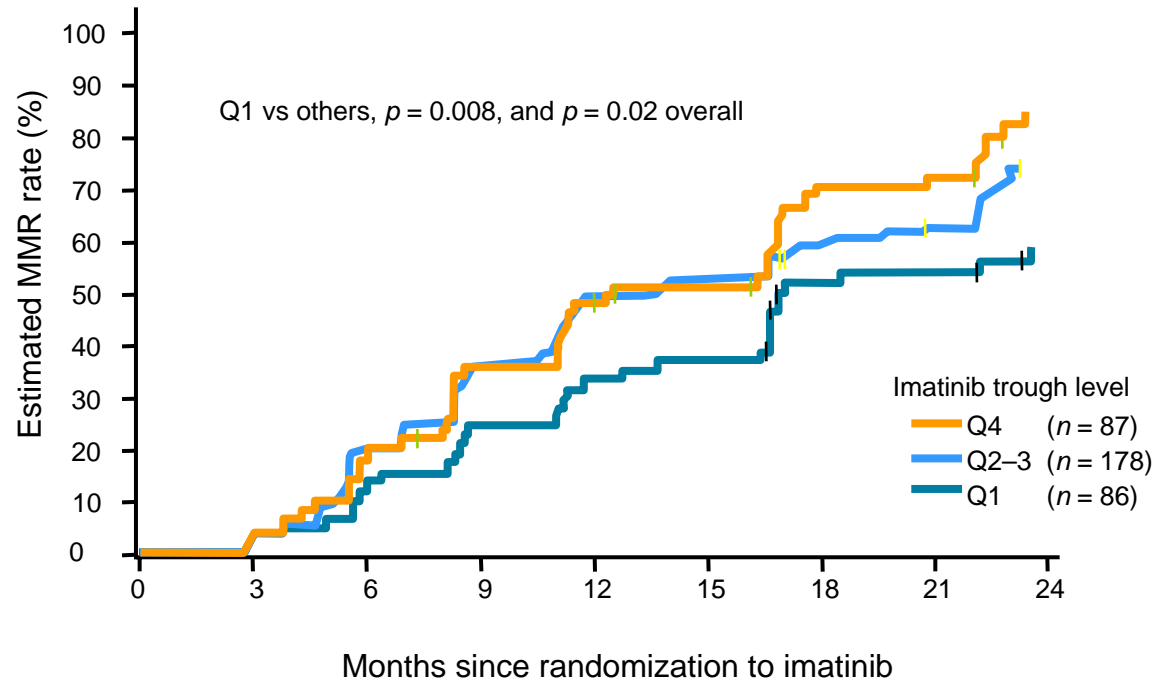
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# Retrospective analysis of the IRIS trial

- Estimated cumulative MMR rates according to imatinib trough levels



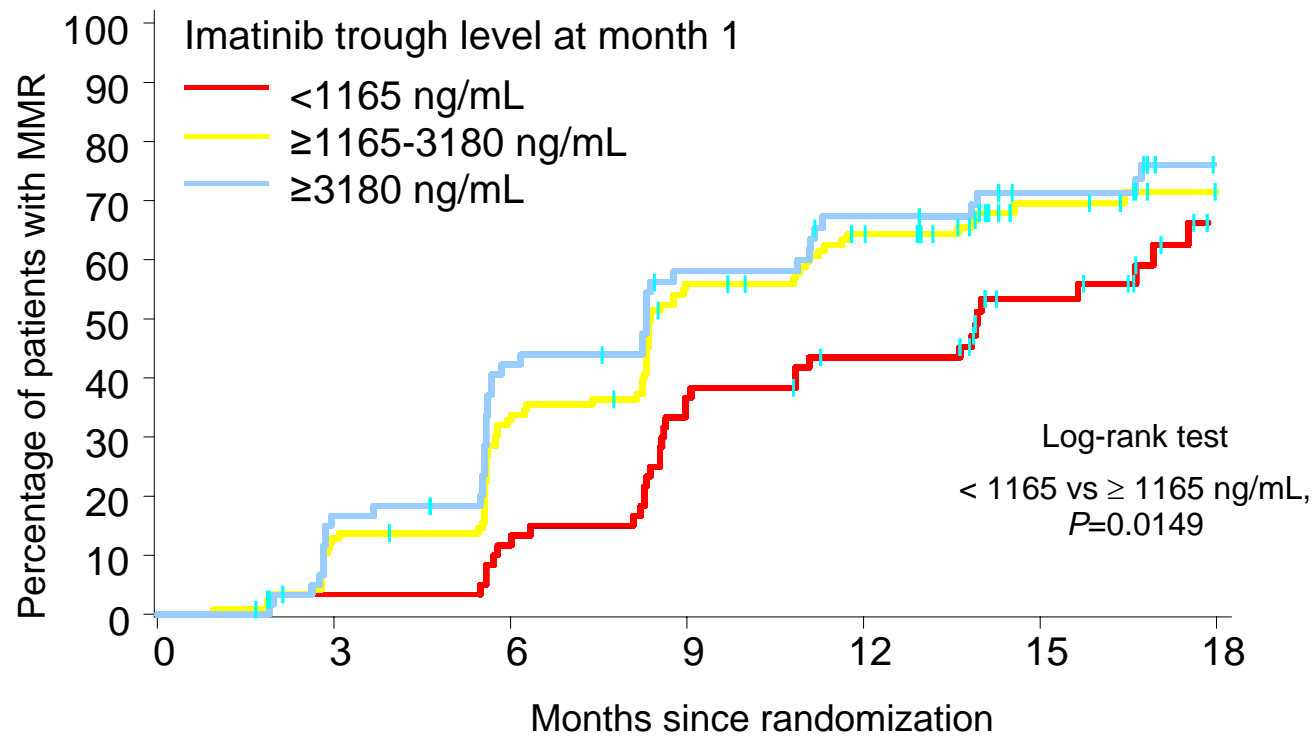
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# TOPS study

- Time to first MMR by imatinib trough level at month 1



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# Patient Not Responding as well as Expected

- A correlation has been demonstrated between imatinib blood levels and clinical response<sup>1,2</sup>
- In some patients, unexpectedly poor response may be due to inadequate imatinib plasma concentrations
- If the imatinib blood level is low, dose escalation may improve response

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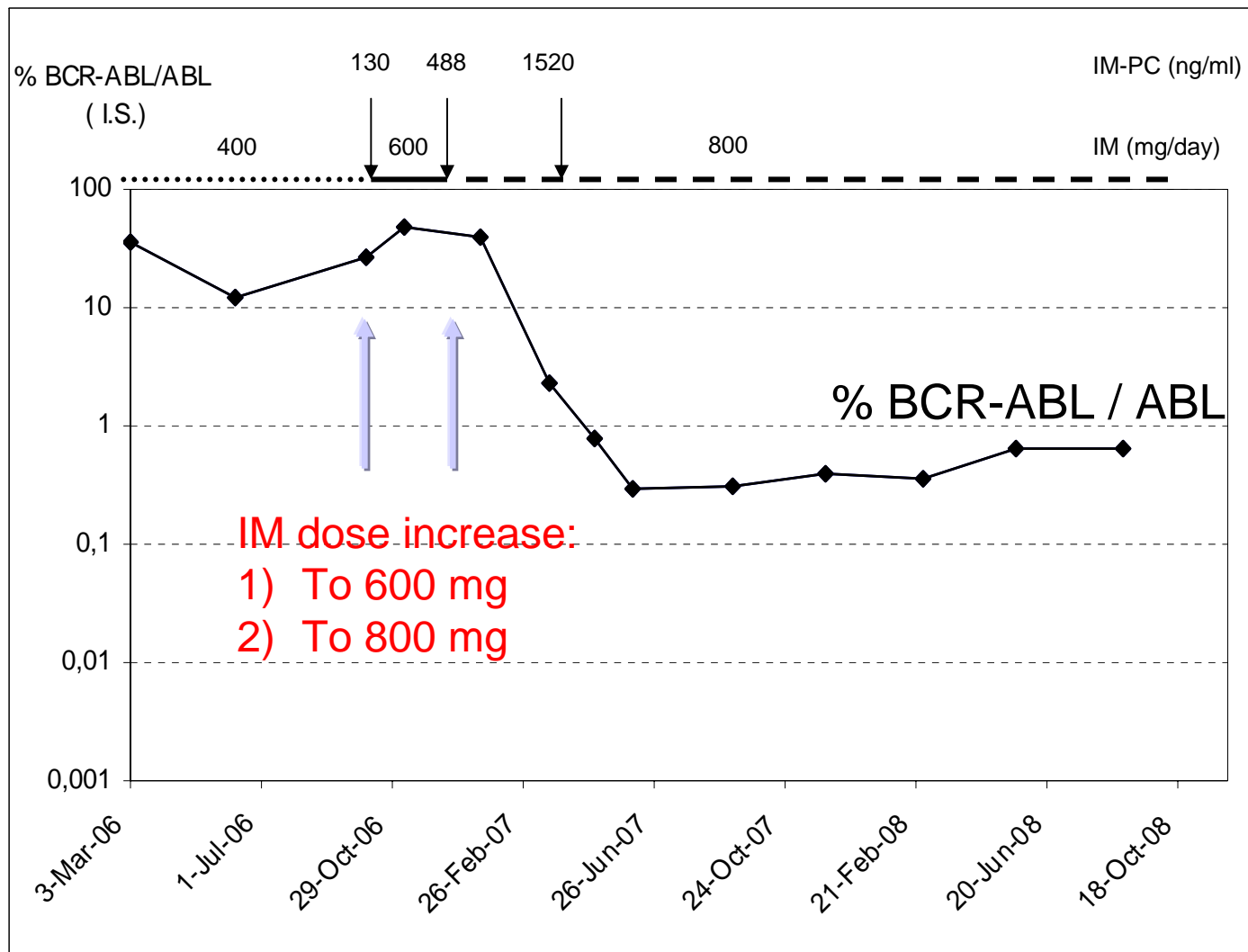


1. Picard et al. Blood 2007;109:3496.

2. Larson et al. Blood 2008;111:4022–8.

# Imatinib Dose Adjustment based on Trough Imatinib Plasma Level in a case of Imatinib Failure

rb2



Data on file courtesy of Dr. Mahon.

## Slide 22

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rb2

I would like to redo the labels to make them a little bit more clear.

rbloechlinger, 03/02/2009

# French Database: patients' characteristics & distribution of trough levels by quartiles

1511 patients with CML, 2147/3121 trough samples

Mean age (median)	55 (56) years
Sex ratio F/H (%)	42/57
Mean Length of treatment (median)	32 (26) months
Only one sample	1142 (75.6%)
More than one sample	369 (24.4%)

	Imatinib trough concentration ng/ml
mean	1010
median	852
quartile 25	584
quartile 75	1280
Interpatient coefficient of variation	61.2%
Intrapatent coefficient of variation (n=327)	31 %

# French database: main indications of drug level testing

Analysed CML samples  
(n=1390)

n (%)

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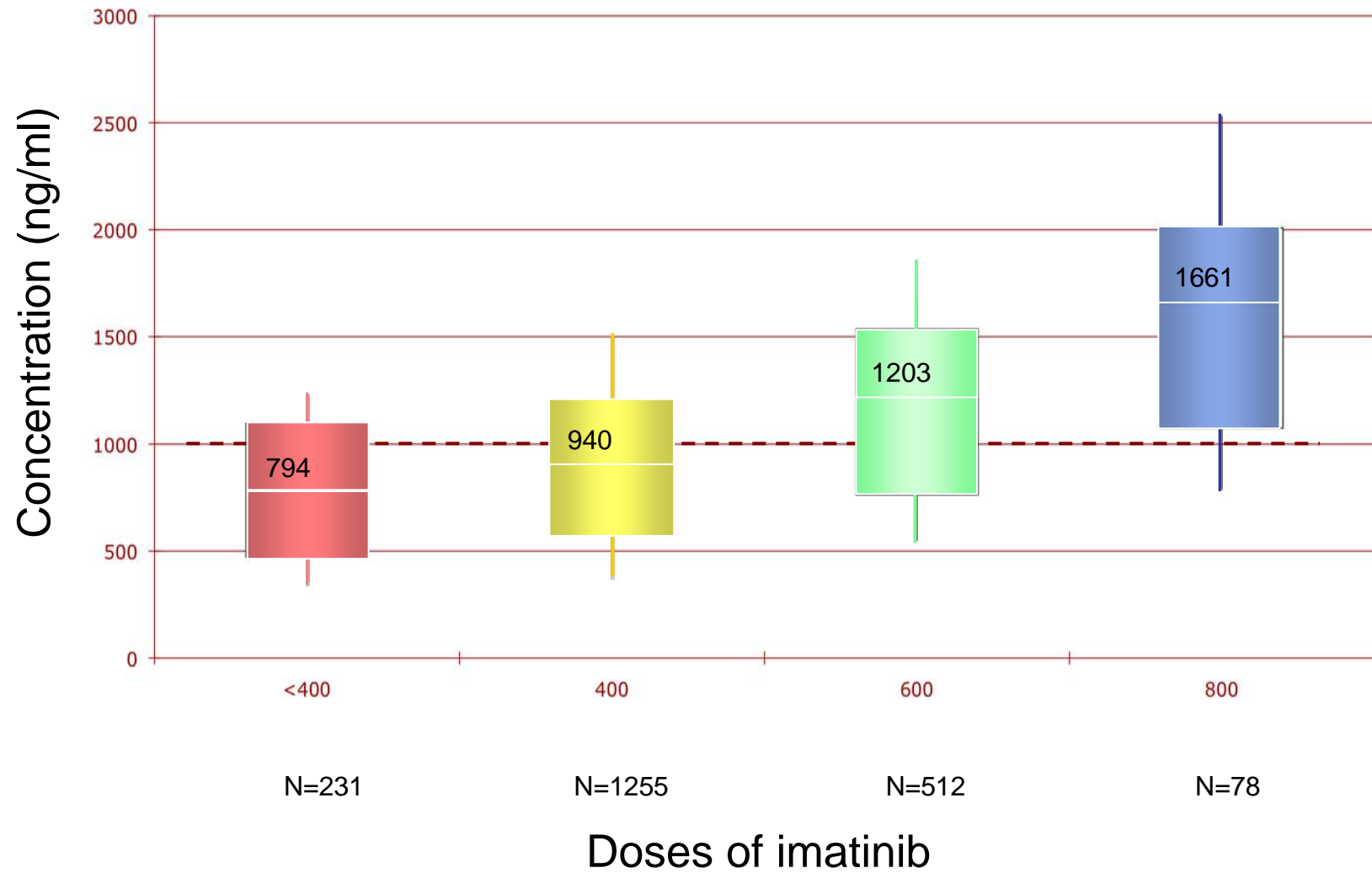
A less-than-expected response to imatinib	770	(55)
Side effects	386	(28)
Compliance concerns	254	(18)
Suspicion of a drug-drug interaction	155	(11)

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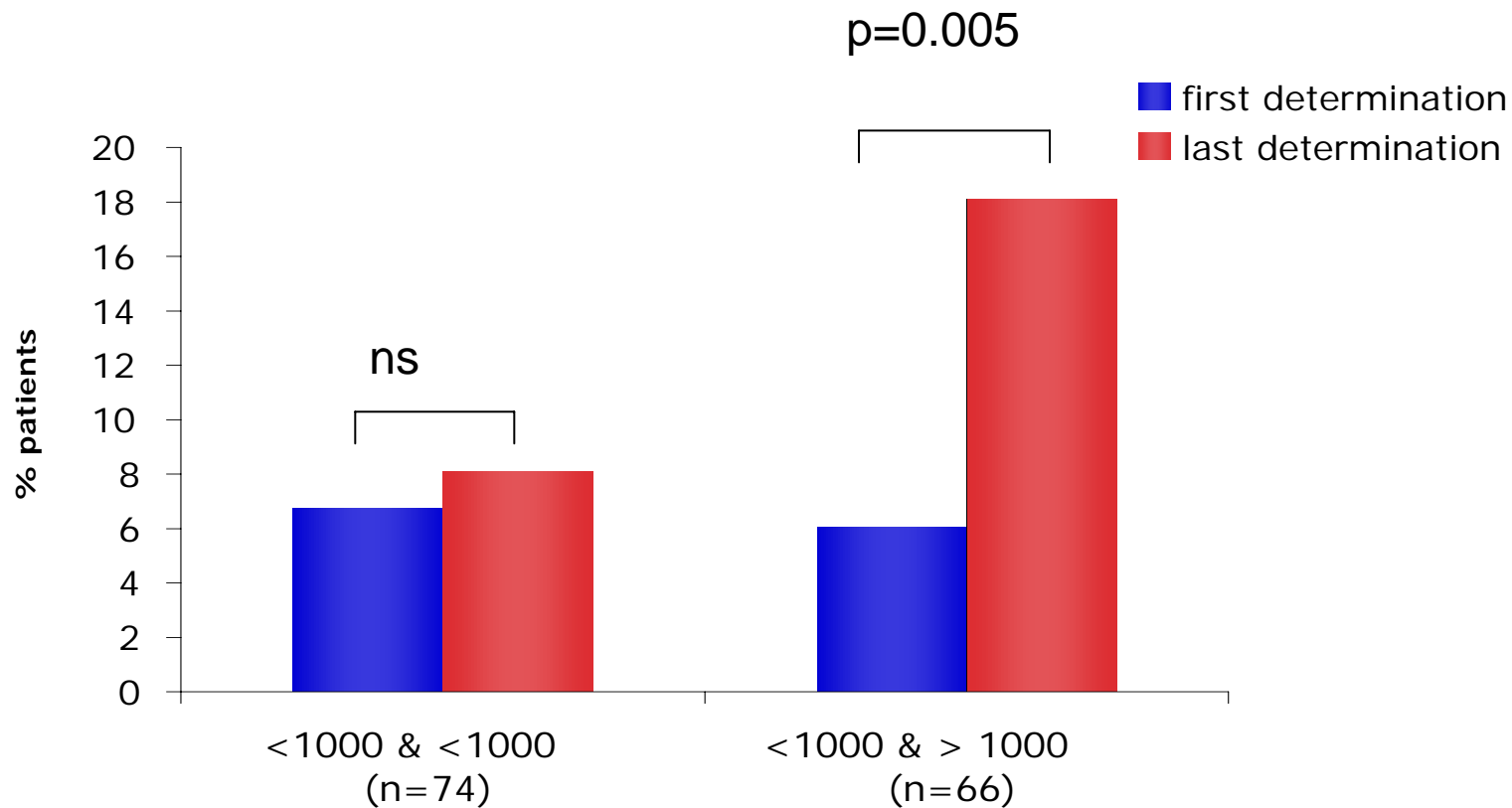


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# Two years experience of imatinib monitoring centralized

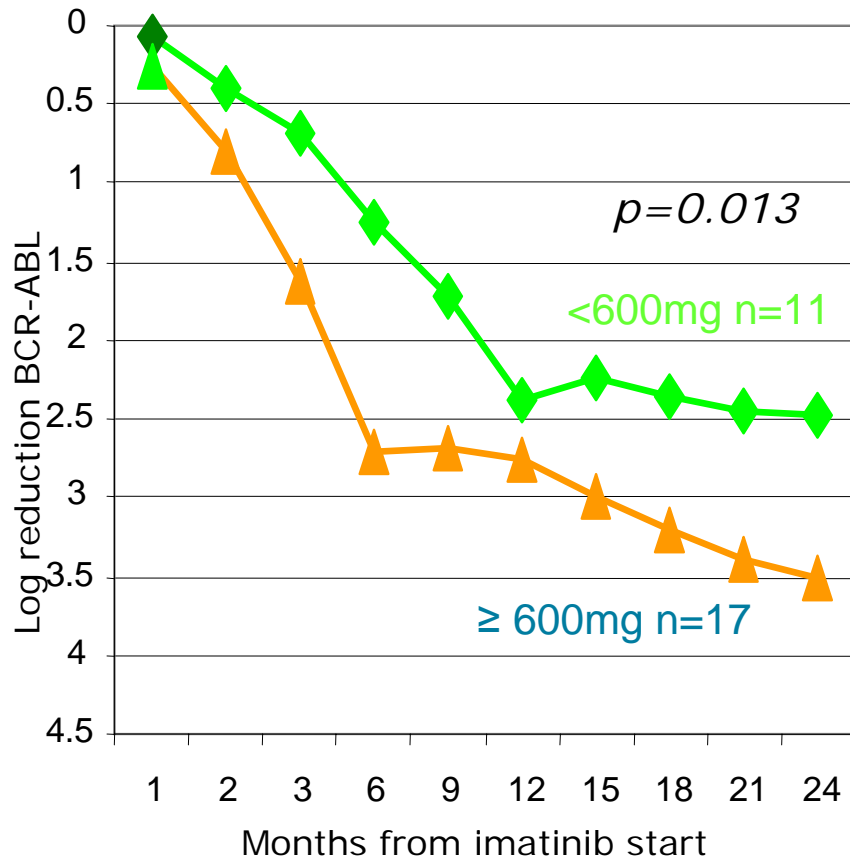


# Complete molecular response in patients with repeated assessments

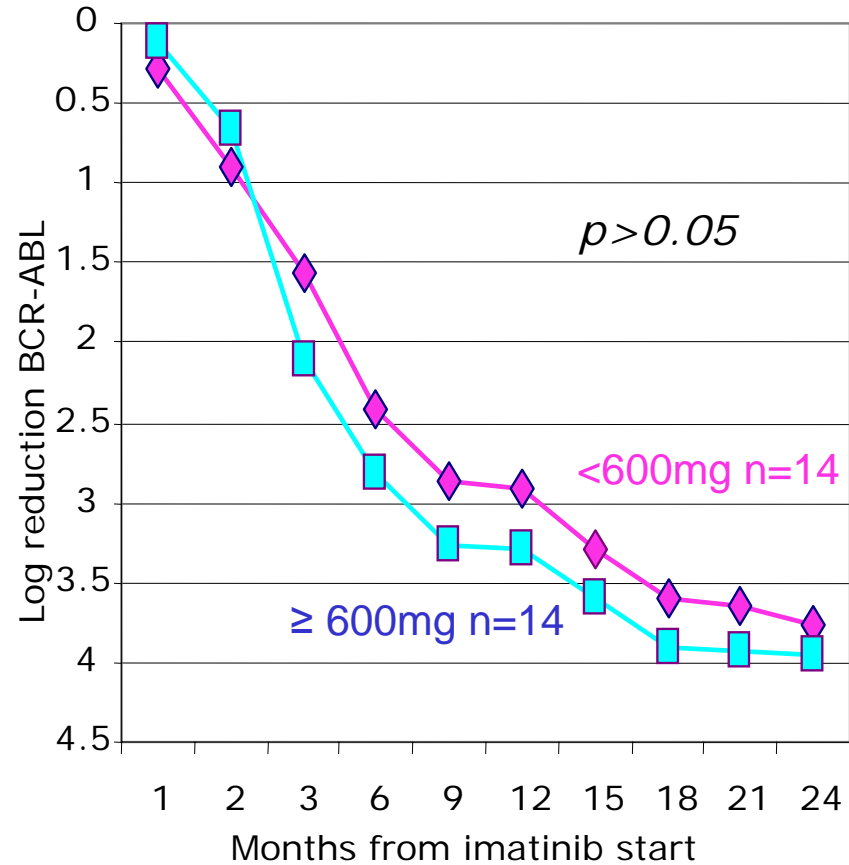


# Effect of Dose by OCT-1 Activity

IM dose-escalation had no effect in high OCT-1 activity patients while patients with low OCT-1 activity achieved satisfactory molecular responses



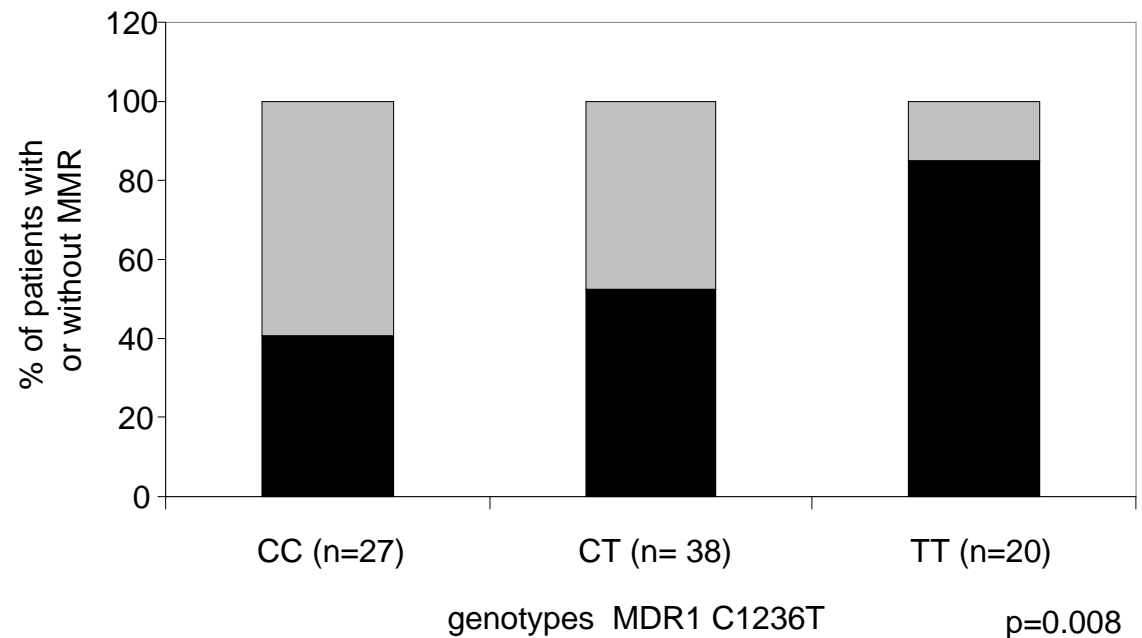
Low OCT-1 Activity



High OCT-1 Activity

# MDR-1 Polymorphisms and Molecular Response

	+1236	+2677	+3435	Frequency (%)	
*1	*1a	C	G	C	40.1
	*1b	C	G	T	11.6
*2	*2a	C	A	C	2.3
	*2b	C	A	T	1.2
*3	T	G	T	5.2	
*4	*4a	T		C	3.5
	*4b	T		T	36



Dulucq S et al. Blood. 2008; 112: 2024-7.

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# Studies on cellular lines

- Cellular lines
  - K562 Sensitive
  - K562 Dox-resistant (overexpresses MDR1)
- 200,000 cells (400 c/μL) in each well (n = 3)
- Imatinib (2 μM) or nilotinib (1 μM)
  - +/- verapamil 5 μg/mL or PSC833 10 μM

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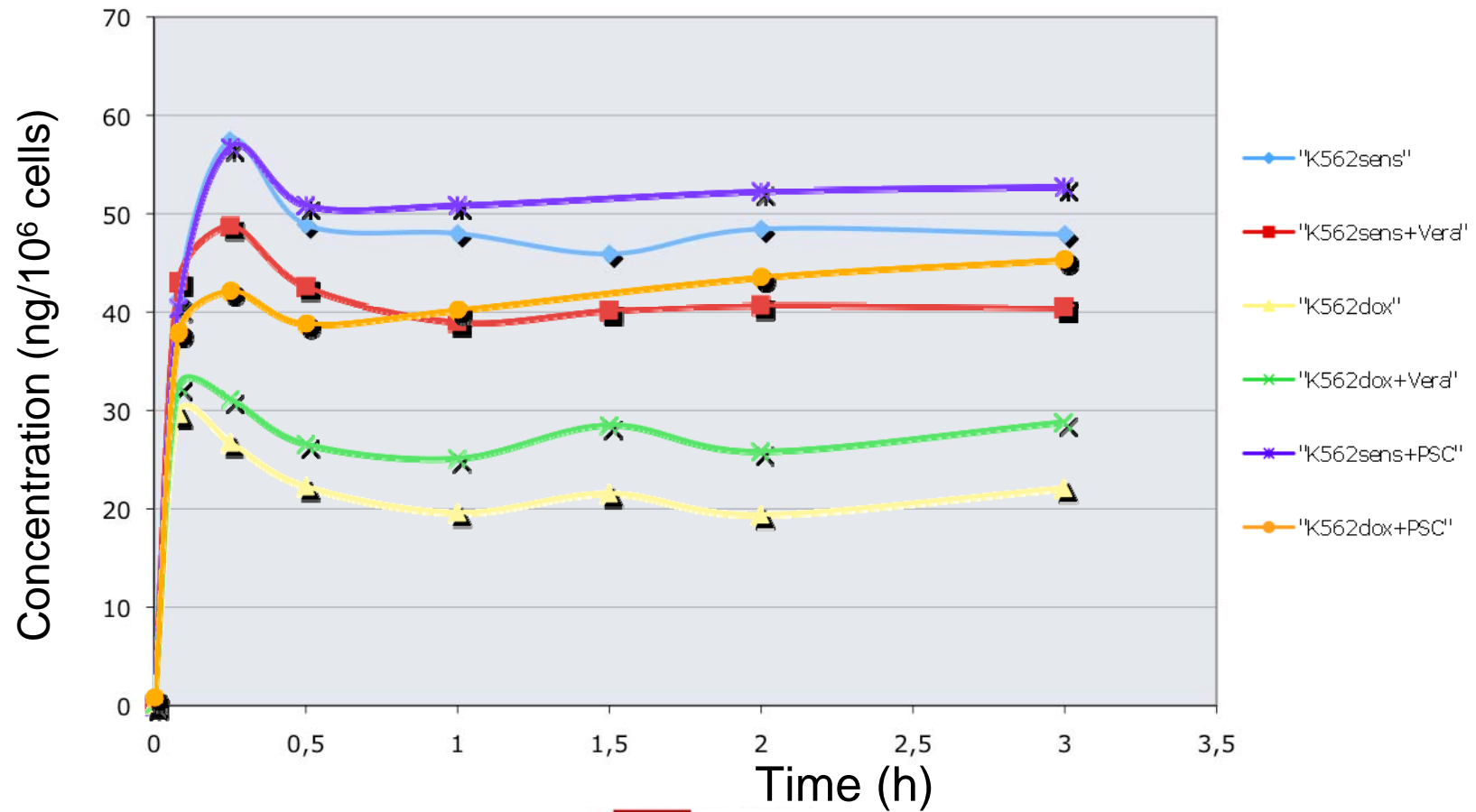


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# Cellular kinetics of imatinib incorporation

Imatinib = 2  $\mu$ M

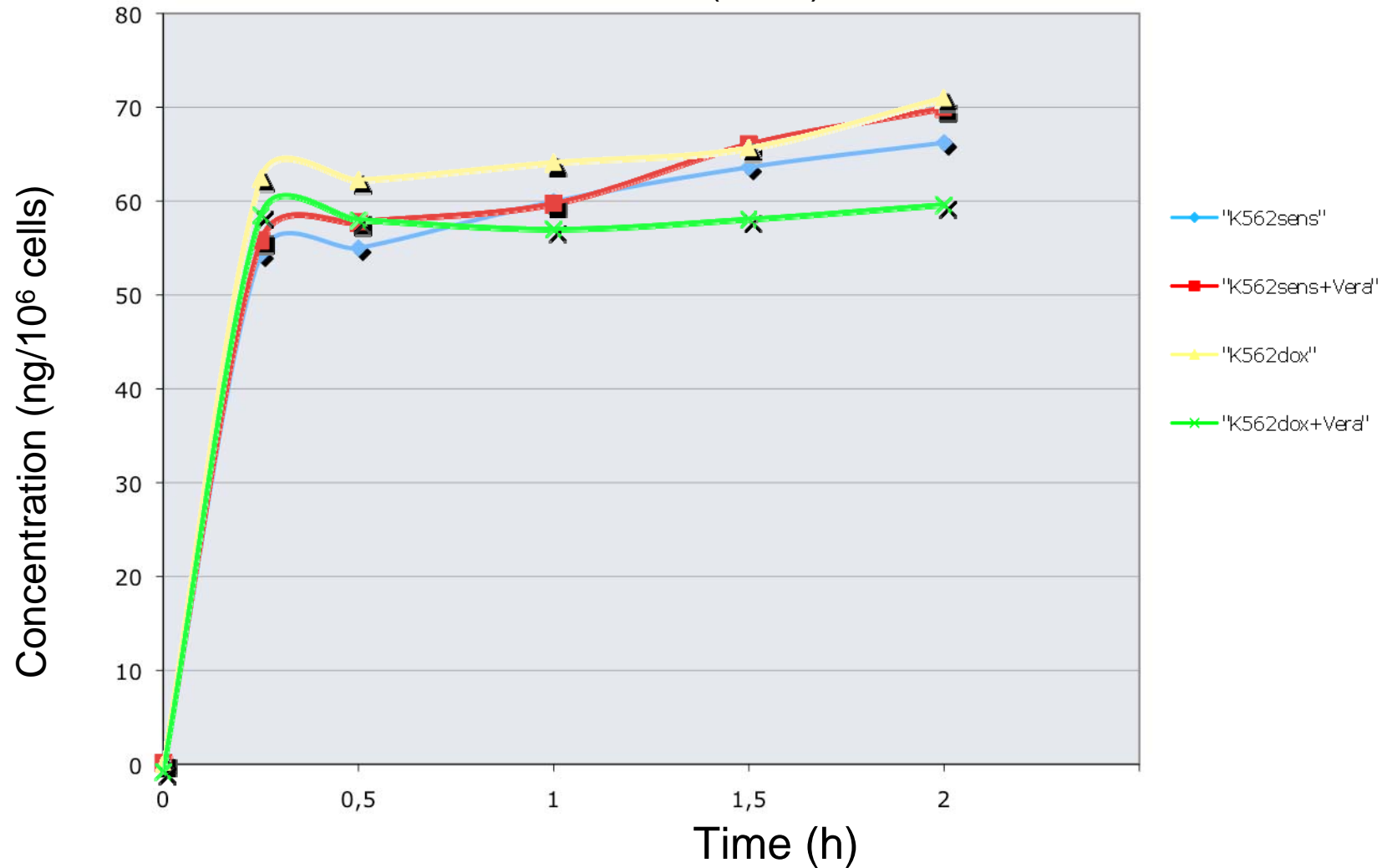
15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h (n = 3)



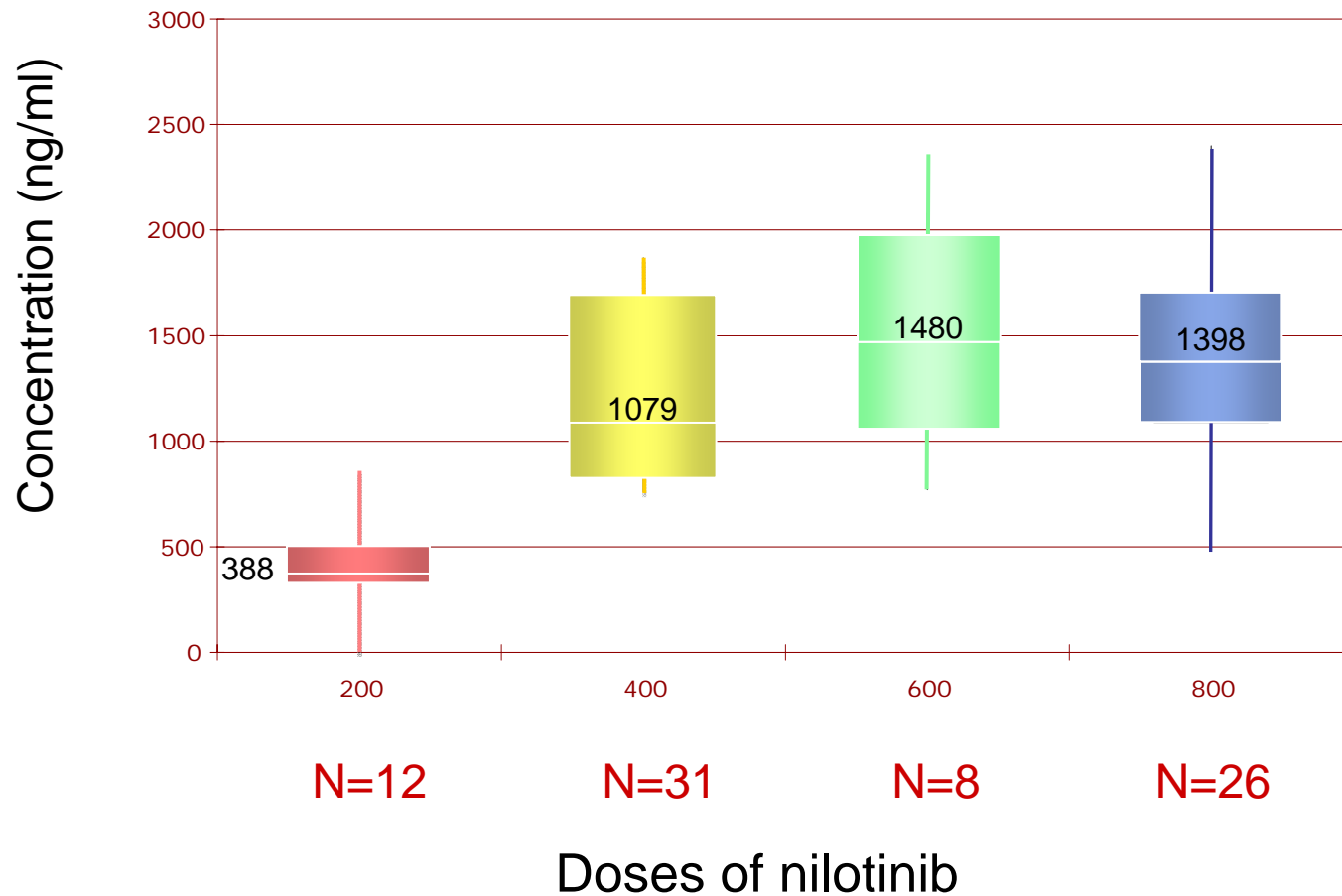
# Cellular kinetics of nilotinib incorporation

Nilotinib = 1  $\mu$ M

15 min, 30 min, 1 h, 1.5 h, 2 h (n = 3)



# Large inter-individual variability of dose–[C] relationships



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From Bordeaux Database

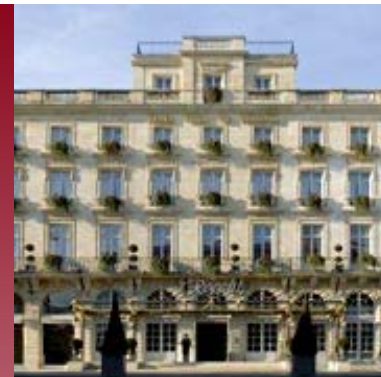
# Summary

- Imatinib is highly effective in treating patients with CML
- However, several studies have demonstrated large inter-patient variability in imatinib trough exposure, possibly leading to inadequate exposure
- Recent data show that achieving an imatinib trough plasma level at or above 1000 ng/mL may be important for achieving improved clinical outcomes
- Imatinib trough blood level testing is a simple and rapid way to determine imatinib exposure
- Plasma concentration testing can alert physicians that imatinib exposure is not within the expected range

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# 11th INTERNATIONAL CONFERENCE ON CHRONIC MYELOID LEUKEMIA

## Biological Basis of Therapy

11-13 September, 2009

Palais des Congrès, Bordeaux - France

Organizers: J.M. Goldman (London), J. Cortes (Houston), T. Hughes (Adelaide), T. Holyoake (Glasgow),  
D. Perrotti (Columbus), J. Reiffers (Bordeaux)

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