

Pharmacological Monitoring

EUTOS for CML



European Treatment and Outcome Study

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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Patient not responding as well as expected

French BLT study

- Trough plasma levels of imatinib were measured in patients with Ph+ CML
- Results from this study indicated
 - Trough plasma levels of imatinib were associated with the likelihood of achieving CCyR and MMR
 - Mean imatinib plasma levels were significantly higher in patients with CCyR (n=56) than in those without (n=12)
 - Mean imatinib trough plasma levels were significantly higher in patients with MMR (n=34) than in those without (n=34)

CCyR, complete cytogenetic response;
MMR, major molecular response

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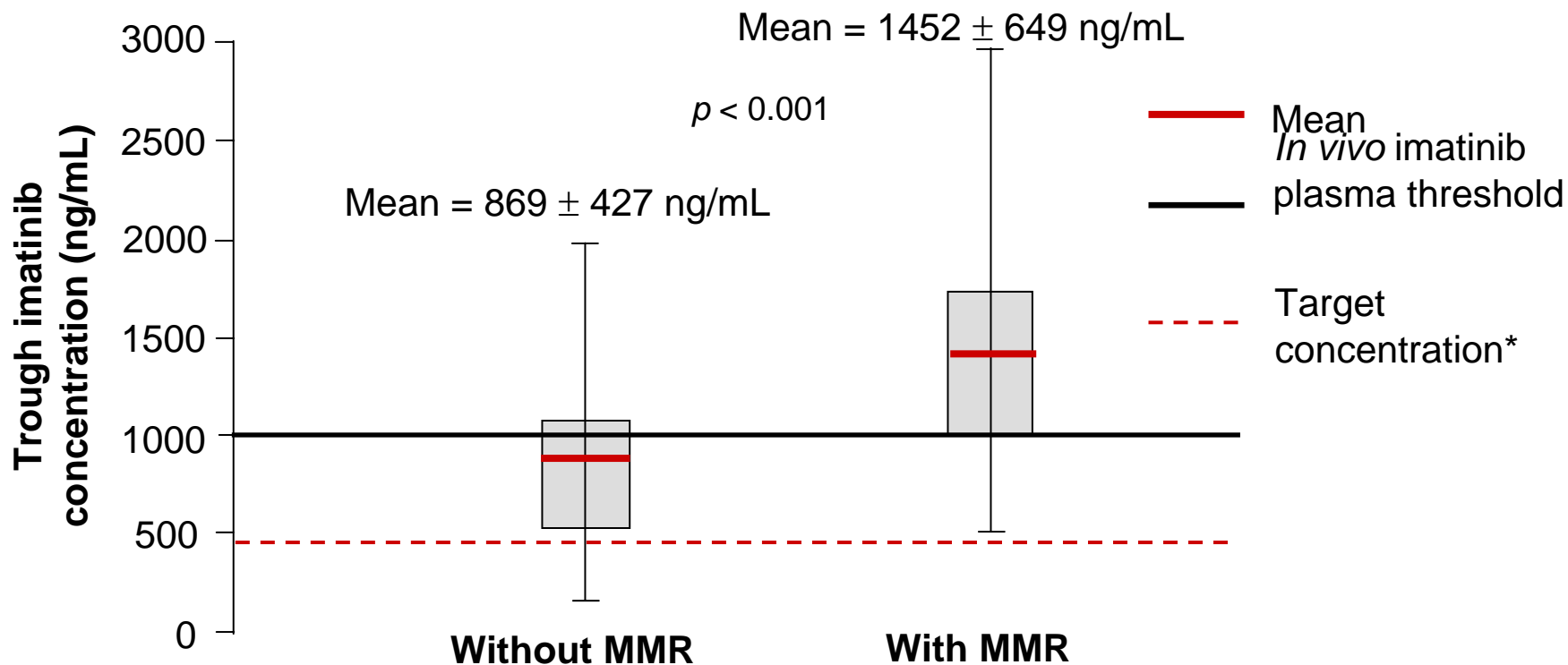


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Picard *et al.* *Blood* 2007;109:3496–3499.

Patient not responding as well as expected

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*.

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

Patient not responding as well as expected

- The study identified a plasma 'threshold' of 1002 ng/mL
- The majority (76%) of patients with MMR had trough plasma levels exceeding the 1002 ng/mL threshold
- The majority (71%) of patients without MMR had trough plasma levels below the threshold

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

Patient not responding as well as expected

Imatinib trough blood levels – correlation with clinical response (Larson *et al.* 2008; IRIS data)

- Study assessed
 - Clinical significance of imatinib plasma concentration, as measured at steady state (day 29 of treatment)
 - How variability in imatinib exposure correlates with responses
- Included 351 (of 553) patients randomized to initial imatinib 400 mg/day in the IRIS trial, with imatinib plasma levels available on day 29 of treatment
- 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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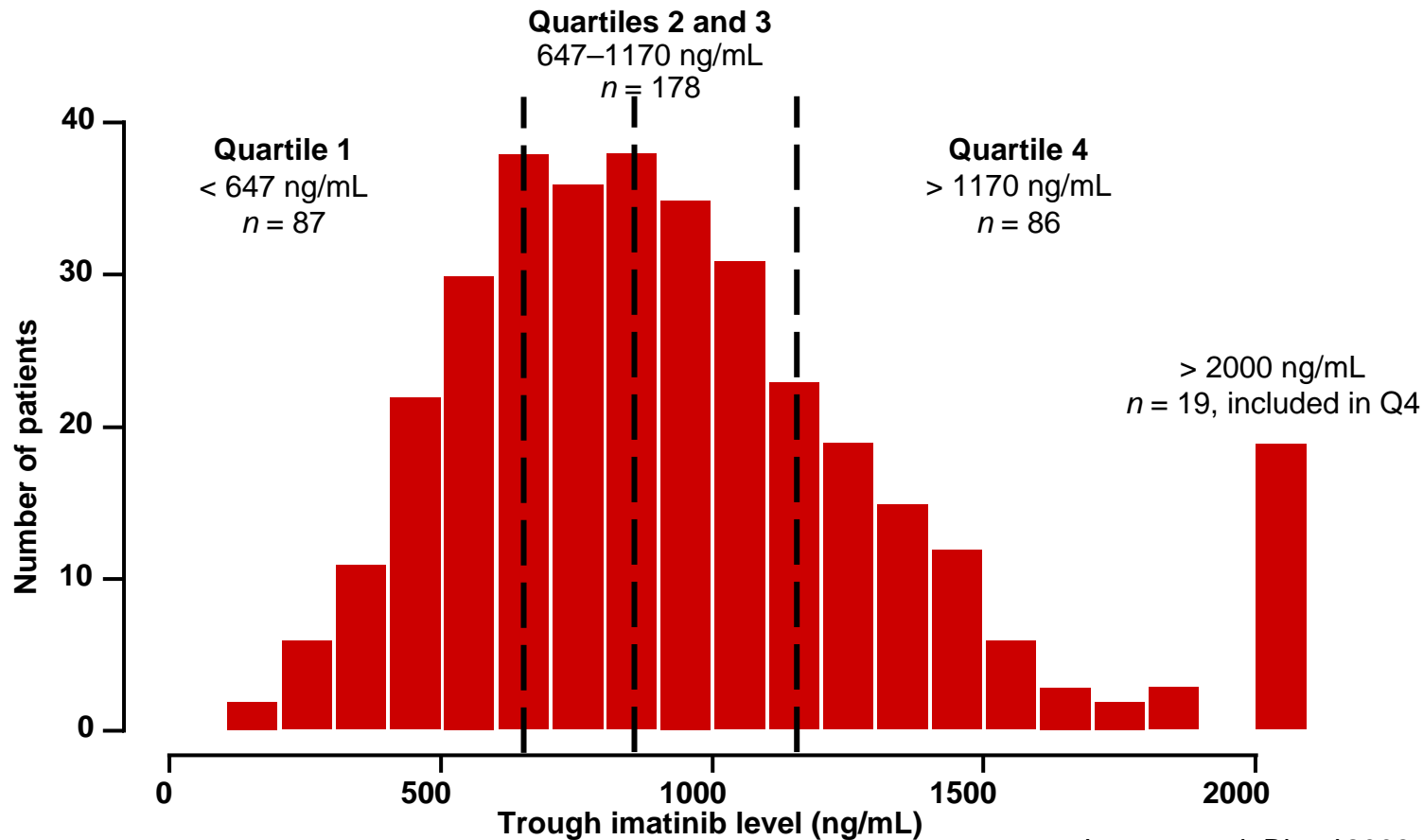


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Larson *et al.* *Blood* 2008;111:4022–8.

Patient not responding as well as expected

Patients were divided into four quartiles according to imatinib blood level

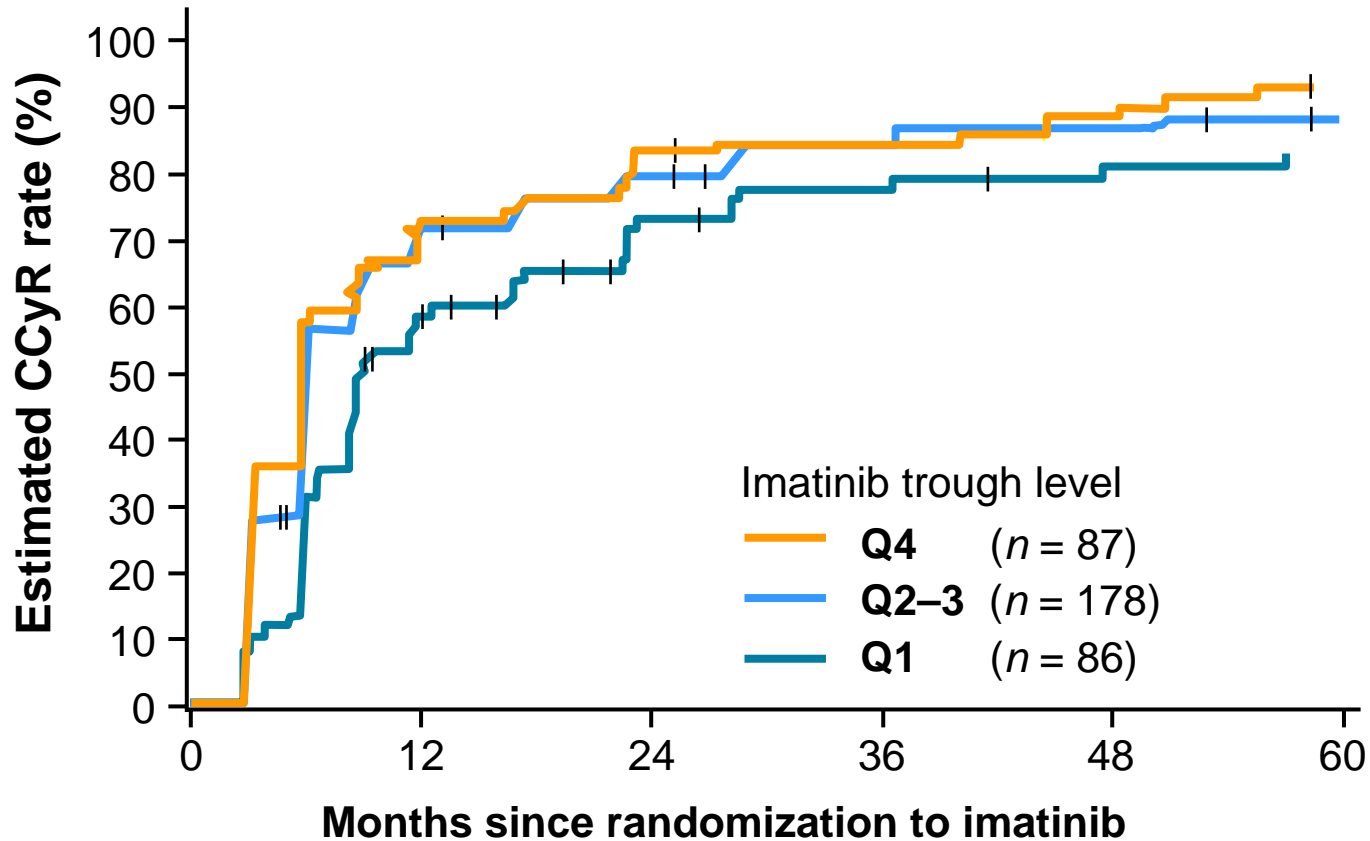


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Larson et al. *Blood* 2008;111:4022–8.

Patient not responding as well as expected

Estimated cumulative CCyR rates according to imatinib trough levels



At 5 years, Q1 vs others, $p = 0.005$, and $p = 0.01$ overall

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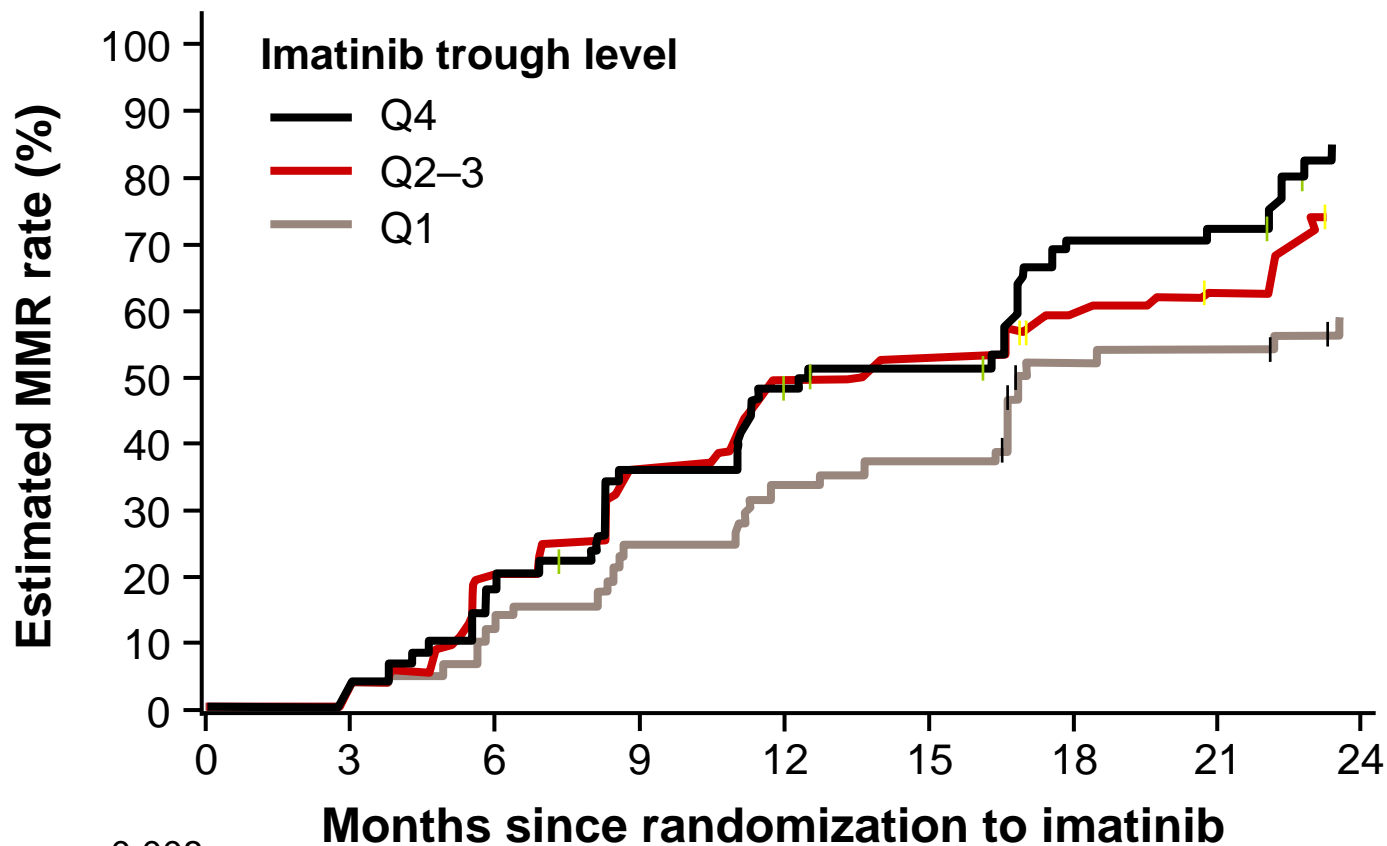
Larson *et al.* *Blood* 2008;111:4022-8.



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Patient not responding as well as expected

Estimated cumulative MMR rates according to imatinib trough levels



Q1 vs others, $p = 0.008$,
and $p = 0.02$ overall

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Larson *et al.* *Blood* 2008;111:4022-8.

Patient not responding as well as expected

- A correlation has been demonstrated between imatinib blood levels and clinical response^{1,2}
- 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.

Blood level testing (BLT)

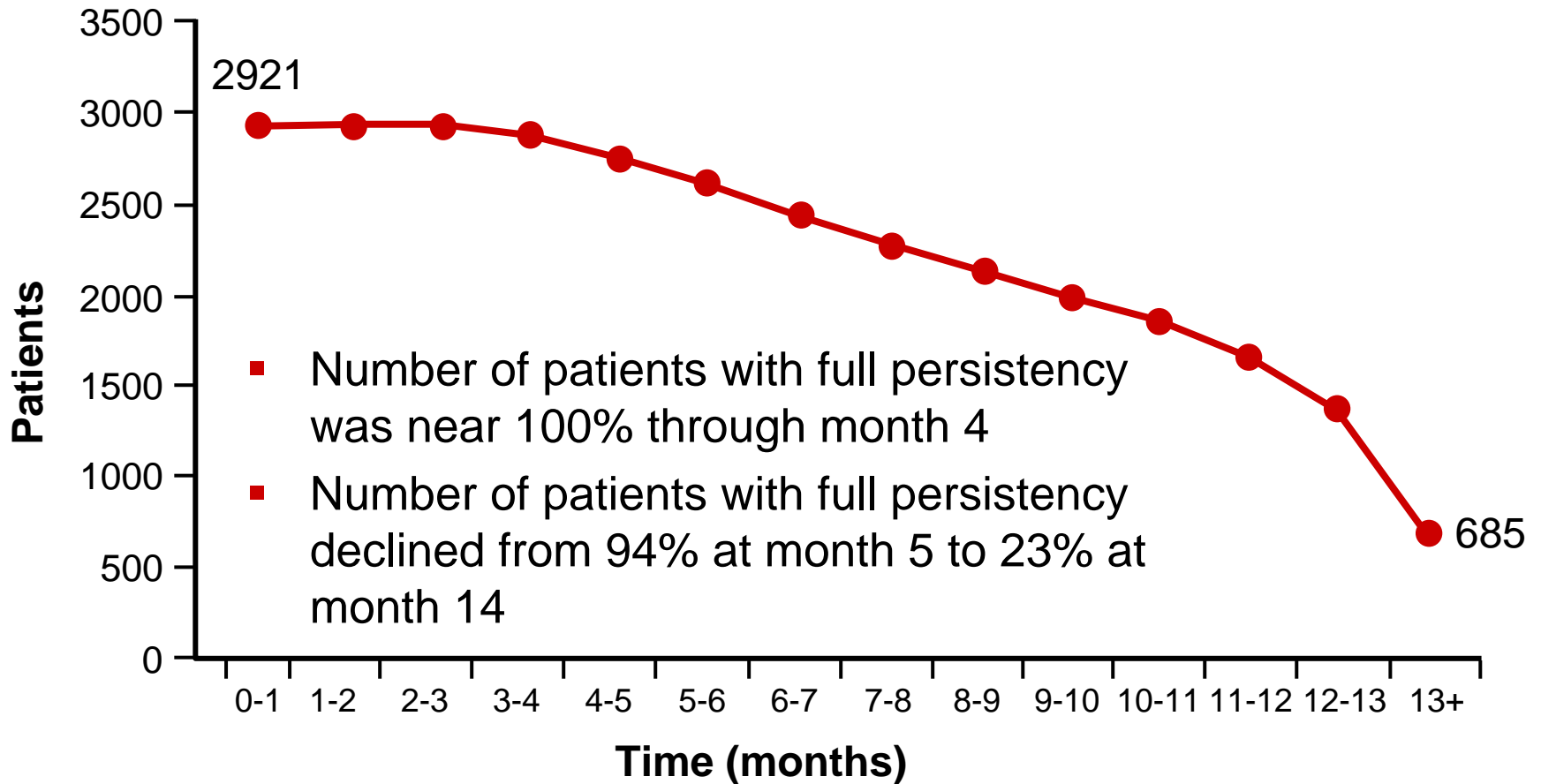
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Suspected poor adherence



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Tsang *et al. J Clin Oncol.* 2006;24:330s. Abstract 6119.



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Blood level testing (BLT)

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Drug–drug interactions

Because imatinib is metabolized by cytochrome P450 (CYP) 3A4 and CYP3A5, substances that inhibit or induce CYP3A4/5 may result in altered metabolism and consequently altered plasma concentrations of imatinib

Aprepitant

Clarithromycin / erythromycin

Cyclosporin

Itraconazole

Pimozide

Grapefruit juice

**CYP3A4/5 inhibitors:
may INCREASE imatinib
plasma concentration**

Barbiturates

Carbamazepine

Dexamethasone

Phenytoin

St John's wort

**CYP3A4/5 inducers:
may DECREASE imatinib
plasma concentration**

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

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Blood level testing (BLT)

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 - **Experiencing side effects that are unusually severe for the prescribed dosage**

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Unusually severe side effects

- High imatinib trough blood levels have been observed in some patients suffering from unusual severe toxicity¹
- Particular adverse events may be linked with high imatinib plasma concentrations²
- Imatinib blood level testing can help decision-making on how to manage patients with unusually severe side effects
- If the imatinib blood concentration is higher than expected, reducing the dose of imatinib may be a logical strategy

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1. Blasdel *et al. Blood* 2007;110:1699.

2. Larson *et al. Blood* 2008;111:4022.

Objectives of the EUTOS for CML Pharmacological Monitoring project

- Expand availability of imatinib BLT to a European level
 - Free of charge at a central facility (Bordeaux University Hospital)
- Establish monitoring facilities in respective countries, using a standardized monitoring protocol
 - Quality control performed by Bordeaux team
- Construct a dosing database to
 - Verify / define the therapeutic threshold (around 1000 ng/mL)

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Pharmacological Monitoring Working Group

- François Guilhot (France)
- François Xavier Mahon (France)
- Peter Schuld – Novartis

- Mathieu Molimard (France) is providing expert technical support

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Easy access to BLT

- A laboratory kit has been created to
 - Facilitate sample submission
 - Ensure all samples arrive in quality and time
- This may be requested from Novartis
- An e-mail address for investigators seeking technical advice has been set up
 - imatinib@chu-bordeaux.fr
 - Mailbox is checked regularly by the Bordeaux team

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Current status (Jan 2009)

- Central facility in Bordeaux is accepting samples from around Europe
- A binder of supporting information has been completed, providing information for physicians wishing to use the central BLT service in Bordeaux
- Control rounds for national laboratories have been initiated, and the first national laboratories have been validated

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Summary

- 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
- Through EUTOS for CML, imatinib BLT is available free of charge at a central facility in Bordeaux
- Quality-controlled national facilities are being established throughout Europe
- Please contact Professor Mahon (Bordeaux) or Dr Schuld (Novartis) for further information

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