Pharmacokinetics and Pharmacodynamics of imatinib in patients with chromic myeloid leukemia for personalized medicine

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The question in cancer chemotherapy

- Who is the right patients?
- How can we select the best drug?
- What is the optimal dosage?

Non small cell lung cancer (NSCLC) and Chronic myeloid leukemia (CML)

All NSCLC → Gefitinib/Erlotinib → 20% Response

EGFR mut^{+} NSCLC → Gefitinib/Erlotinib → 70% Response

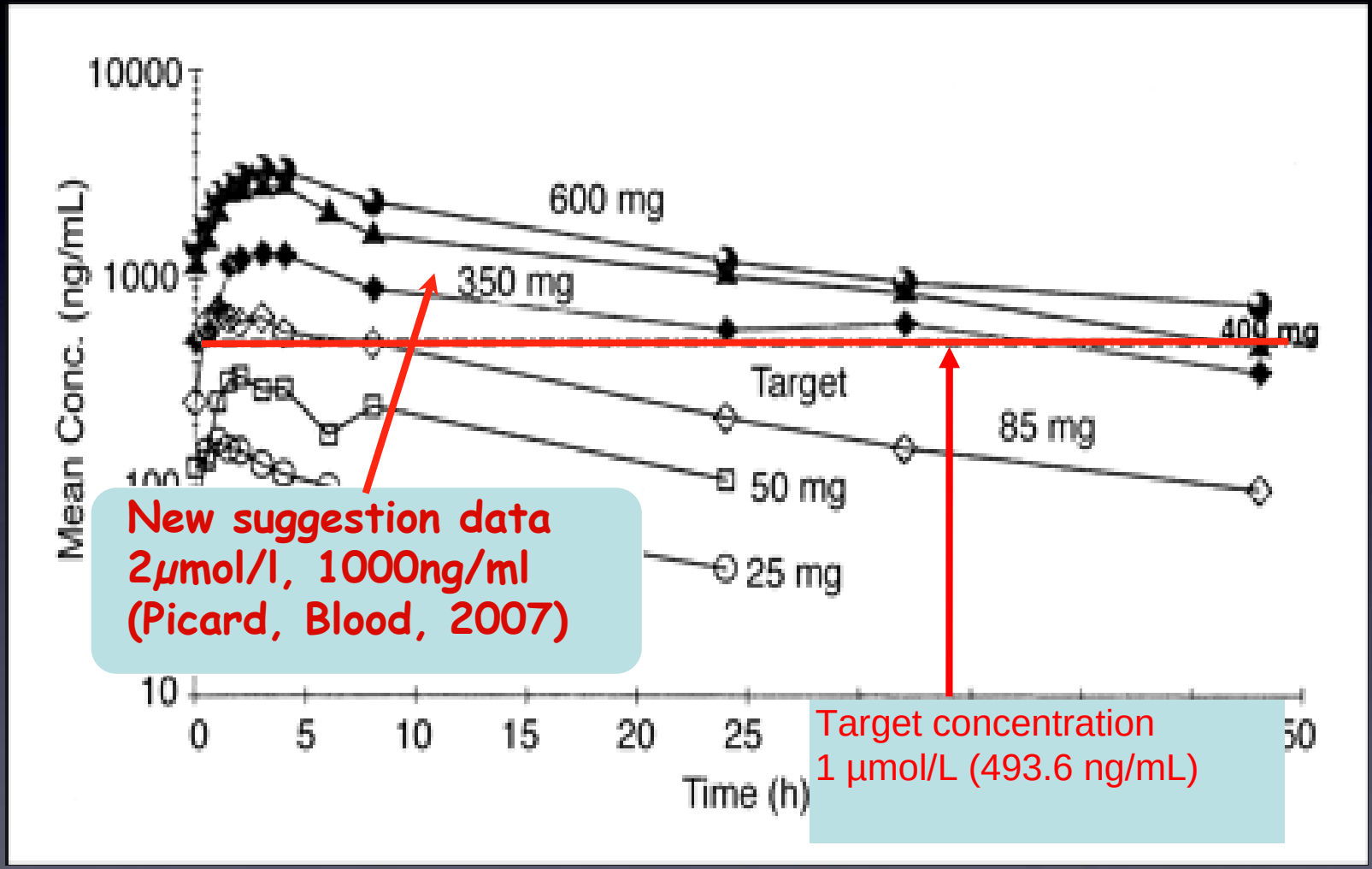
CML → Imatinib → 85% Response

EGFR Exon 19 deletion
EGFR Exon 21 L858R mutation

Philadelphia Chromosome
Bcr-Abl
95% CML patients positive

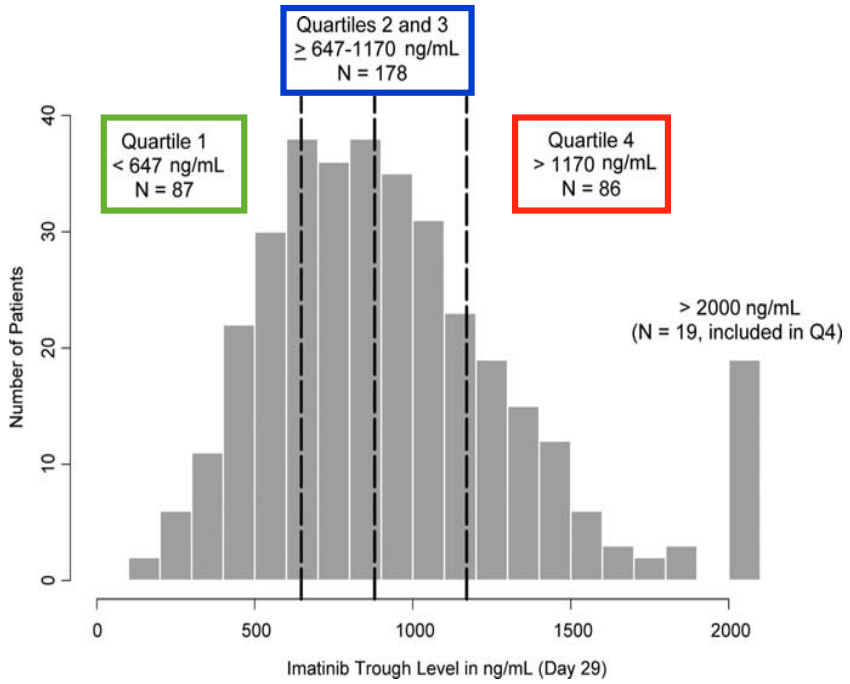
To allow personalized medicine

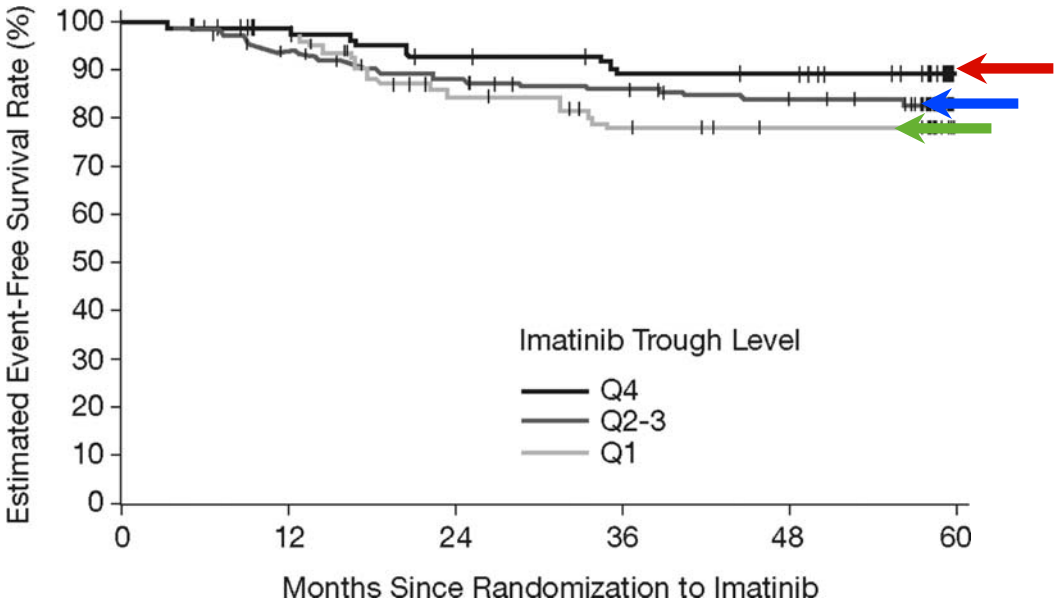
Mean plasma concentrations at day 1 after the oral administration of imatinib



Bin Peng et al, Journal of Clinical Oncology, Vol 22, 2004

Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a sub analysis of the IRIS study





Larson, R. A. et al. Blood 2008;111:4022-4028

Personalized medicine for CML therapy

- Right patient: CML with bcr-abl positive
- Right drug: bcr-abl inhibitor
- Right dosing : 400mg

Physiological and genetic variations cause variable pharmacokinetics and clinical outcome.

The recommended dose of 400 mg/day causes severe adverse effects: myelo-suppression, edema, skin rash

↓

Poor compliance, premature cessation of treatment, failure of therapy

↓

To avoid unfavorable clinical situations, the dose of imatinib is often reduced in clinical practice, although maintaining a low dose of imatinib is not generally recommended.

A reduced dose of 300 mg/day imatinib might be enough to achieve a CCR in some Japanese patients. Weak inverse-correlation was observed between imatinib trough levels and body weight.
(Onishi et al. ASH meeting, 2007)

Korean patients with low BSA benefited from 300 mg/day imatinib.
(Park SJ et al. Acta Hematologica, 2007)

Imatinib dose of 400 mg/day too much for Asian patients with low BSA?

Purpose

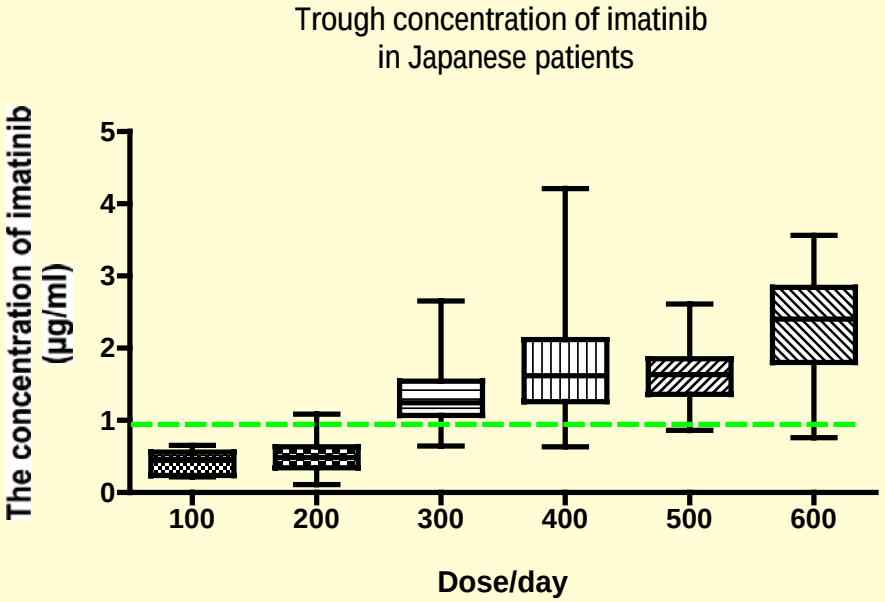
To clarify the relationship of the optimal dose of imatinib with trough levels of imatinib and to investigate covariates of clearance affecting variability of imatinib disposition at the steady-state in CML patients, we measured plasma concentrations of imatinib in Japanese chronic-phase CML patients at several dose.

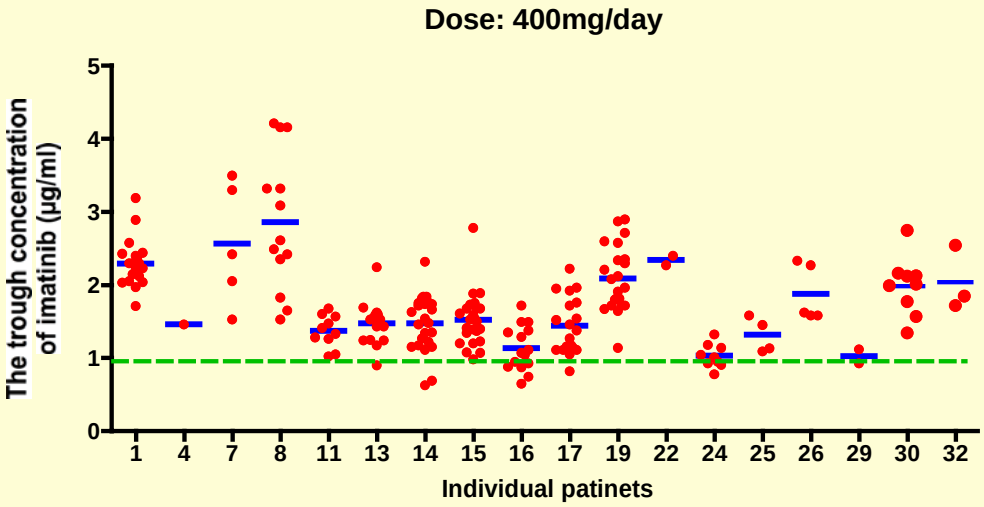
Hamada A, *2008 AACR meeting*, San Diego, 2008
Kawaguchi T and Hamada A, *Int J Hematol*, 2009

Methods

- Plasma concentrations of imatinib at steady state were assessed in patients with chronic-phase CML.
- Patients administered the standard-dose of 400 mg/day.
- In case of severe adverse drug events, imatinib was reduced to 100 to 300 mg/day or discontinued until adverse events were ceased.
- Imatinib dose was escalated up to 800 mg/day if an optimal response was not achieved.
- Dose of imatinib that could achieve a CCR during the observation period was defined as “an optimal dose”.

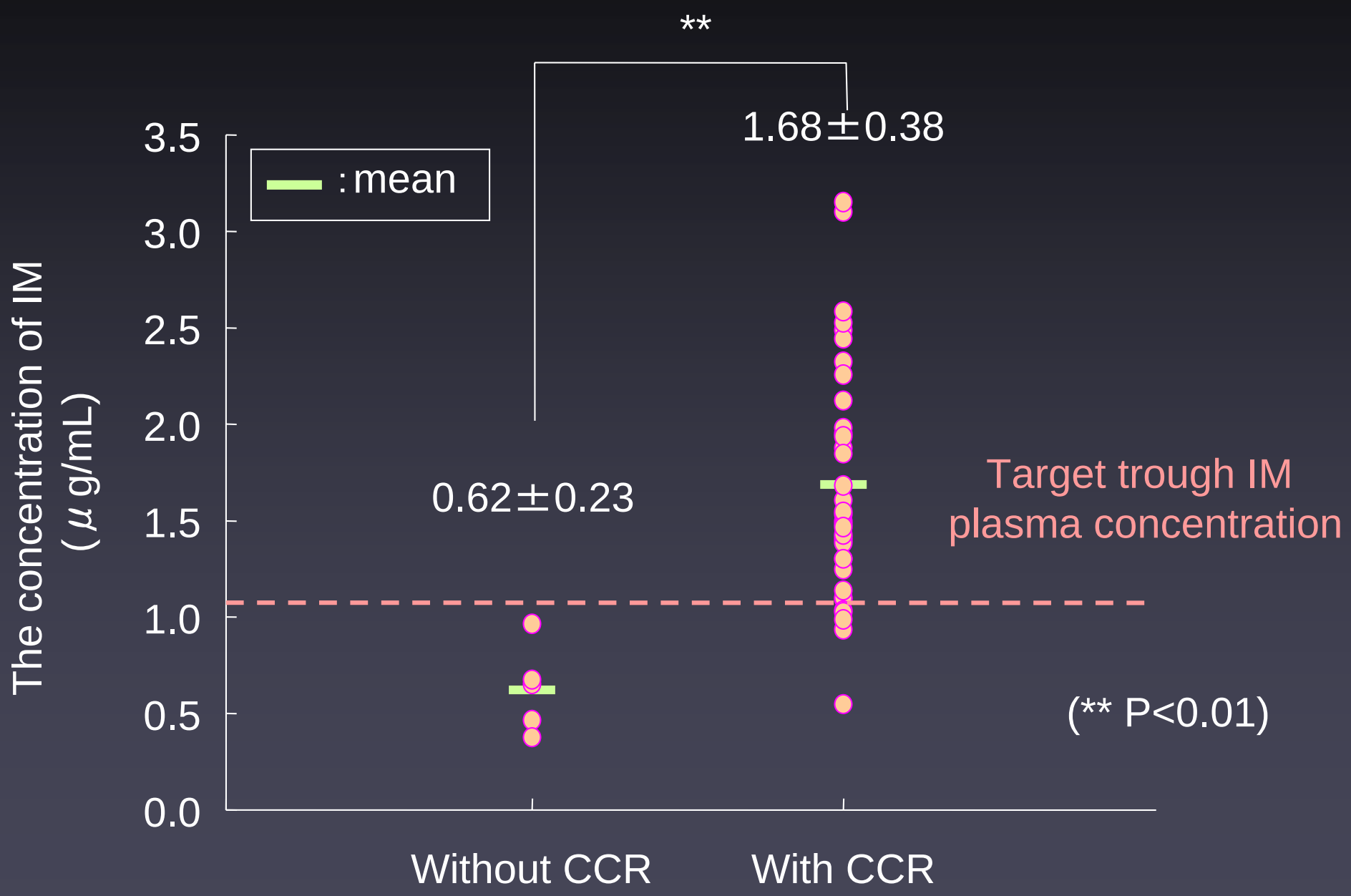
Pharmacokinetic study of imatinib in patients with CML: Kumamoto Univ (n=45)





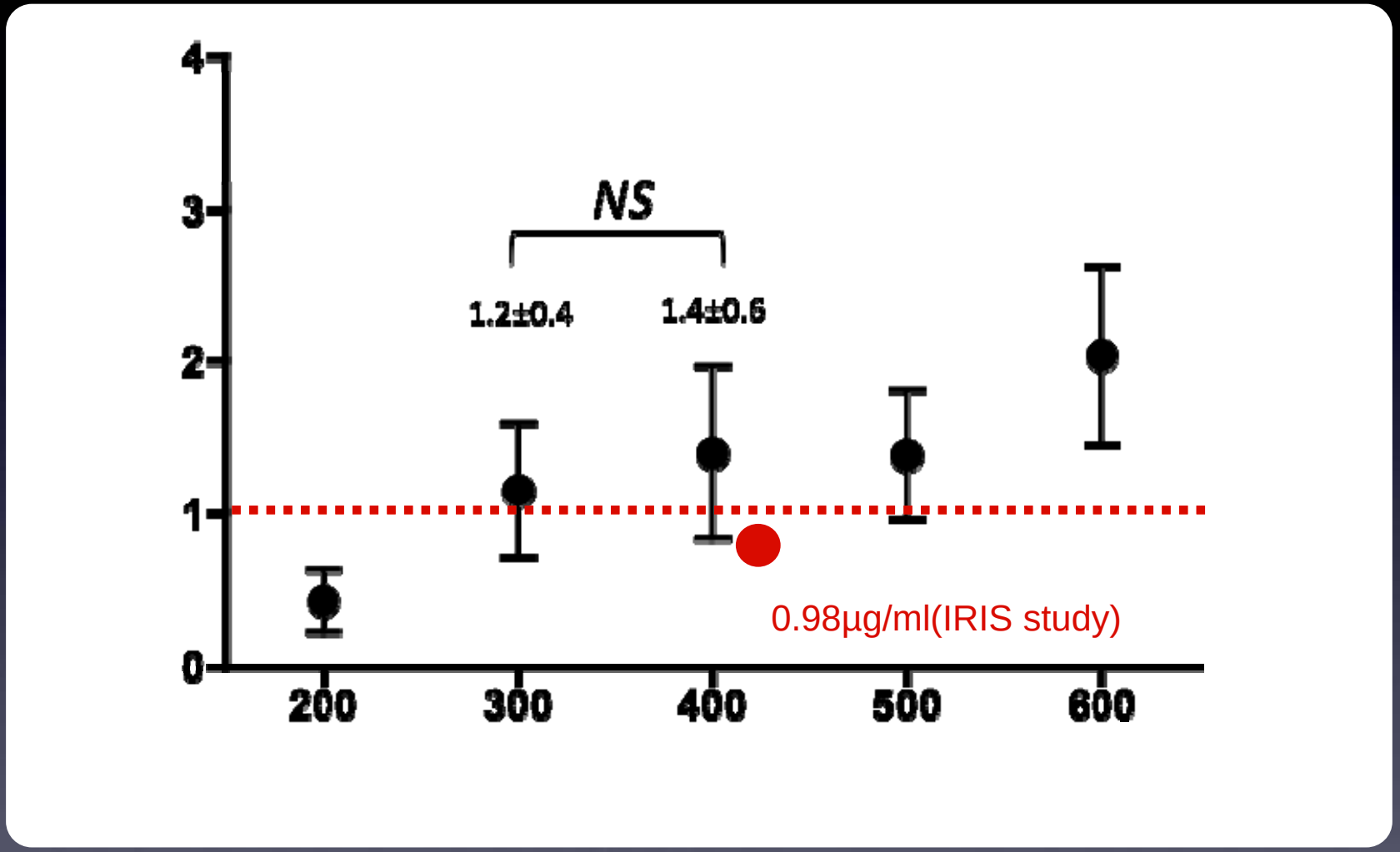
Hamada A, *2008 AACR meeting*, San Diego, 2008
Kawaguchi T and Hamada A, *Int J Hematol*, 2009

Relationship between trough plasma concentration and clinical outcome in Japanese patients



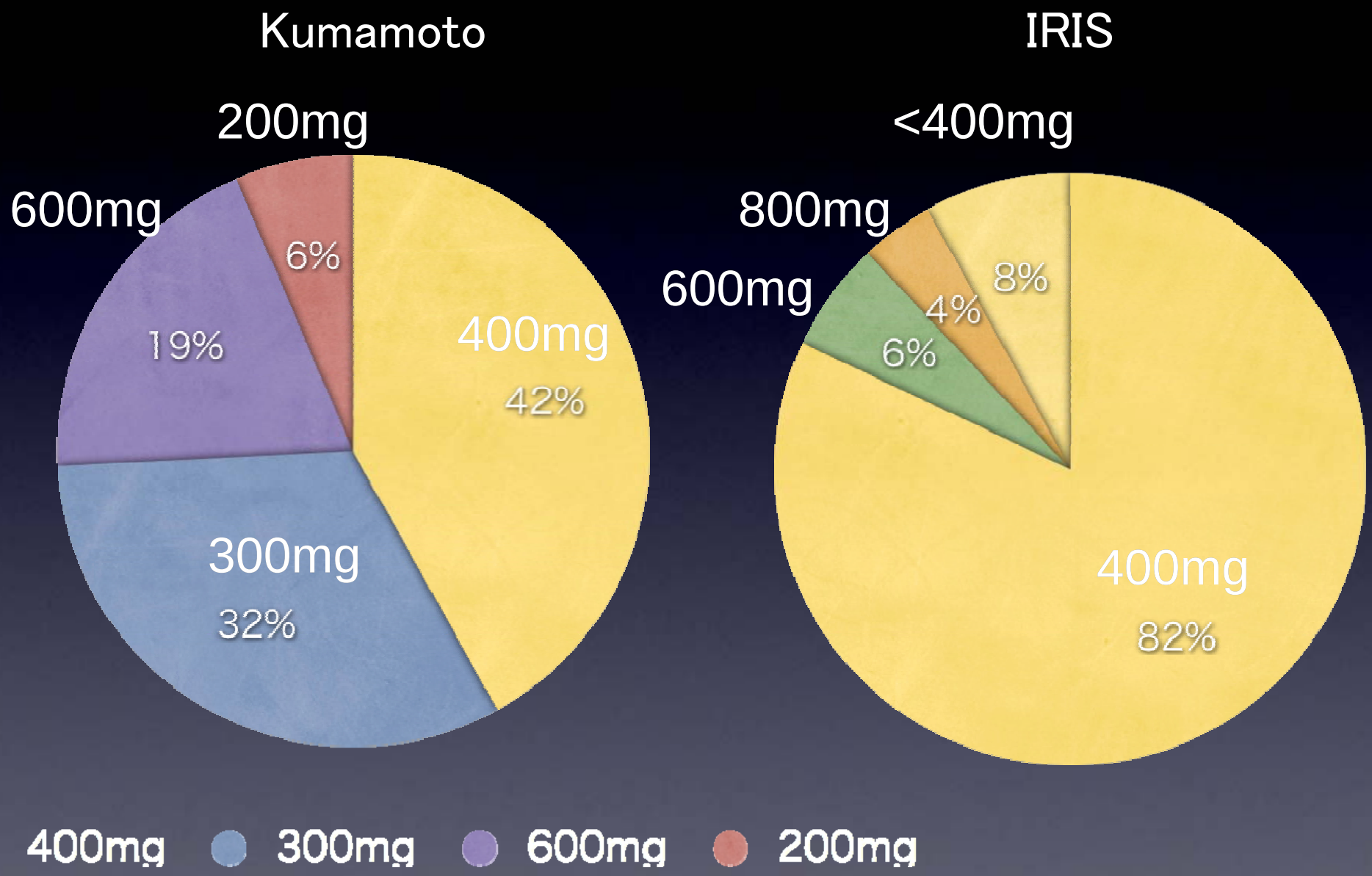
Hamada A, *2008 AACR meeting*, San Diego, 2008

Relationship of trough plasma concentrations of imatinib at steady state with administered dose



Each point represents the mean (SD) plasma imatinib trough concentration

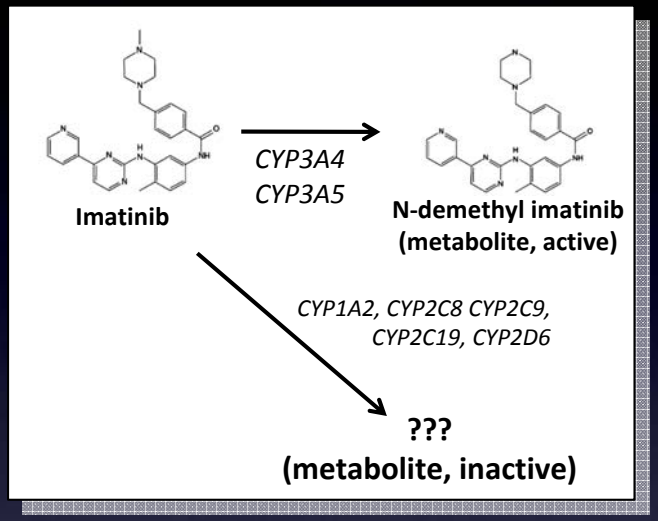
Dosage of imatinib



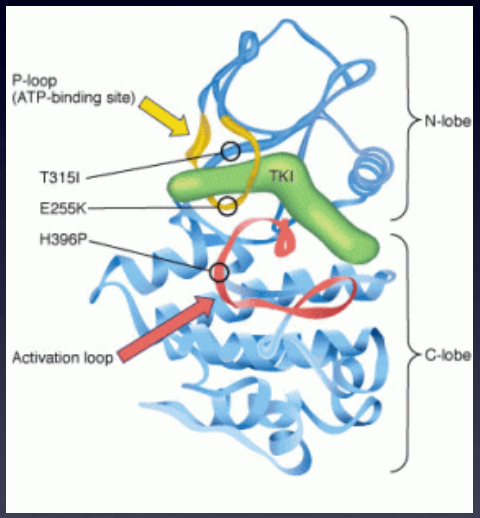
Hamada A, AACR meeting, San Diego, 2008
Kawaguchi T and Hamada A, Int J Hematol, 2009

Future direction for imatinib personalized medicine

Dose

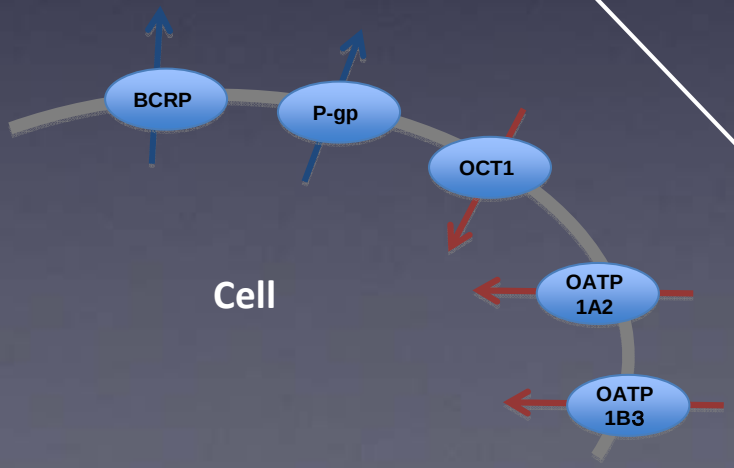


Tumor tissue
Bcr-Abl mutation
Amplification



PK ⟷ PD

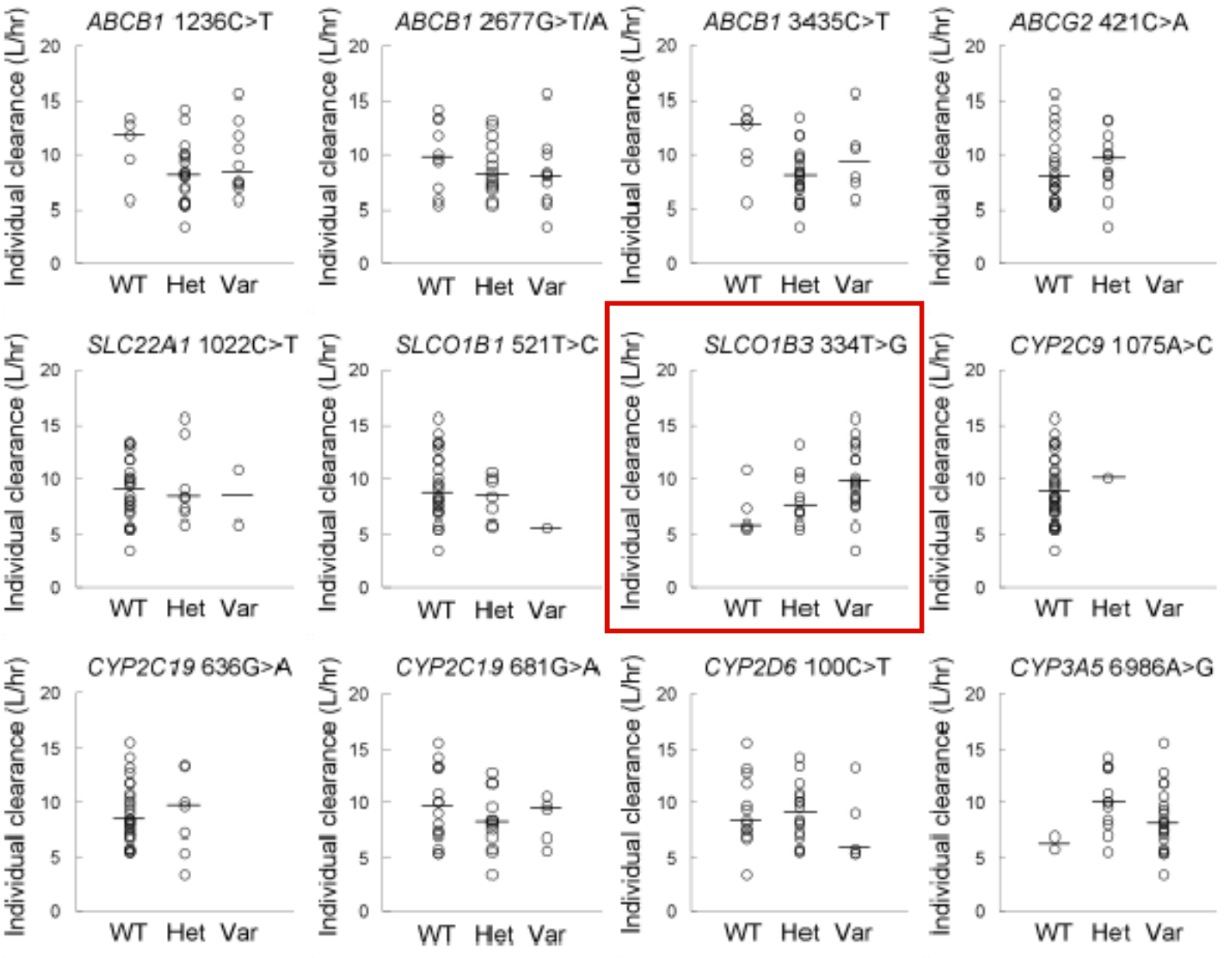
>1.0μg/ml



PG

Clinical effect
Response
Toxicity

Association of individual clearance with targeted genotypes



Each symbol represents an individual patient, and horizontal lines represent median values.
The individual clearance of each patient was estimated by using the Bayesian method in the Basic model.

Yamakawa Y and Hamada A, *Ther Drug Monit(2011)*

Summary-Imatinib

- The standard dose of 400 mg/day imatinib may be too high as an optimal dose for a proportion of patients with chronic phase CML having low BSA
- A reduced dose of 300 mg/day imatinib may be sufficient for the treatment of CML patients with small body size.
- The clearance of imatinib in Japanese patients was smaller than Caucasian patients (8.4 L/hr vs 14 L/hr).
- Clearance of the Final model consisted of age, body surface area, creatinine clearance, and SLCO1B3 genotype.
- To avoid insufficient efficacy at reduced doses, monitoring of plasma imatinib levels is recommended.

Strategy for personalized medicine

PG test for PD

Select patient and drug
Predict sensitive

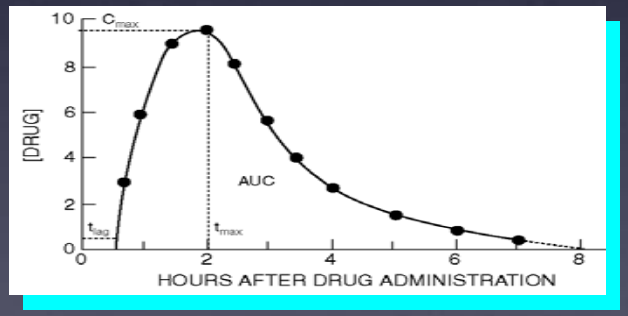
Target molecule
Bcr-Abl mutation, expression

PG test for PK

Select an initial dose

Metabolic enzyme, Transporter
CYP, OATP1B3, ABCB1, ABCG2

Administered Drugs



TDM

PK test for PD

Adjust the optimal dose

Evaluate response/toxicity

Acknowledgments

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