PAGE – Montreux – 2018

Meeting Clinicians' and Patients' Needs in the Practice of Therapeutic Monitoring

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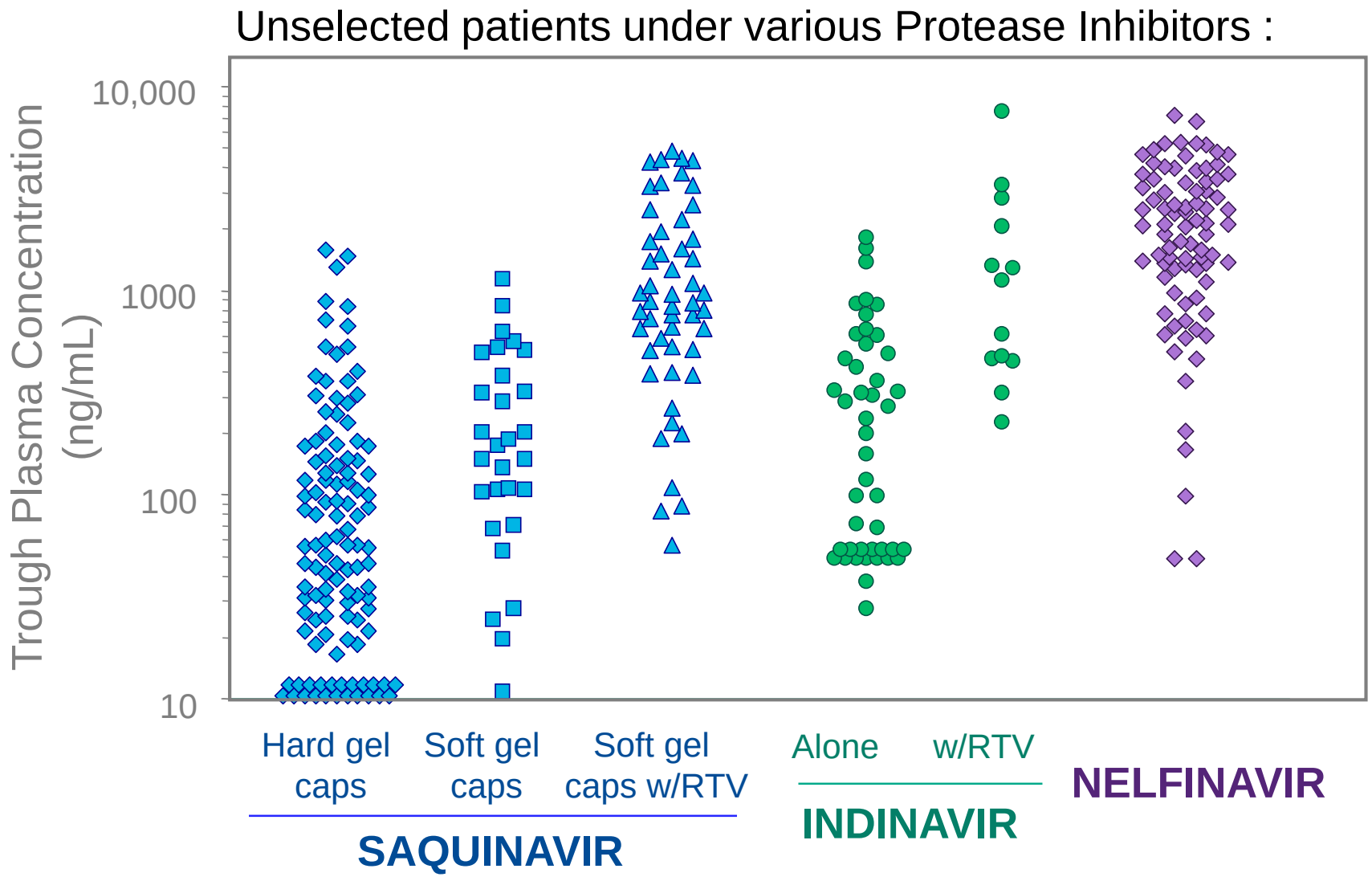
Aims

- To increase awareness of the *implementation gap* that affects Pharmacometrics
- To consider current hurdles against rational treatment individualization through monitoring
- To touch on some prospects that might help patients to better benefit from progress in Pharmacometrics

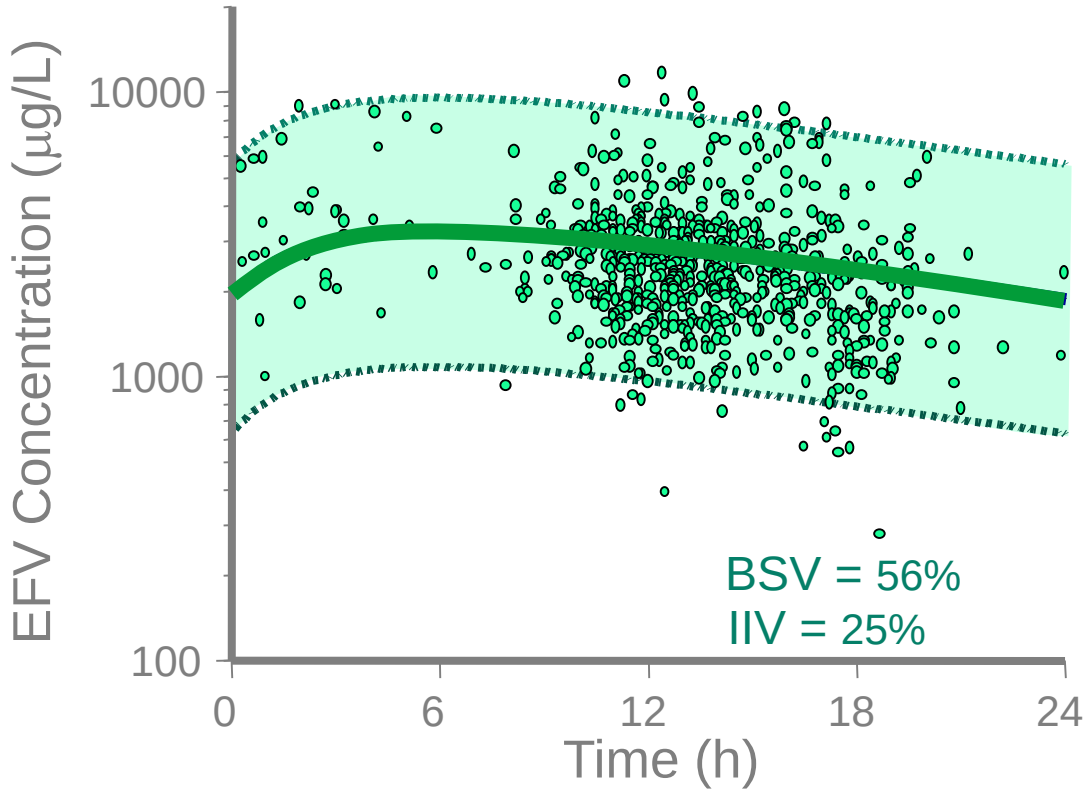
PK Variability of Antiretrovirals: a Deadly Issue



Gibbons ES, Reynolds HE... Back DJ. *The Liverpool therapeutic drug monitoring service – a summary of the service and examples of use in clinical practice* [abstract P259 A]. AIDS 2000, 14(suppl 4):589.

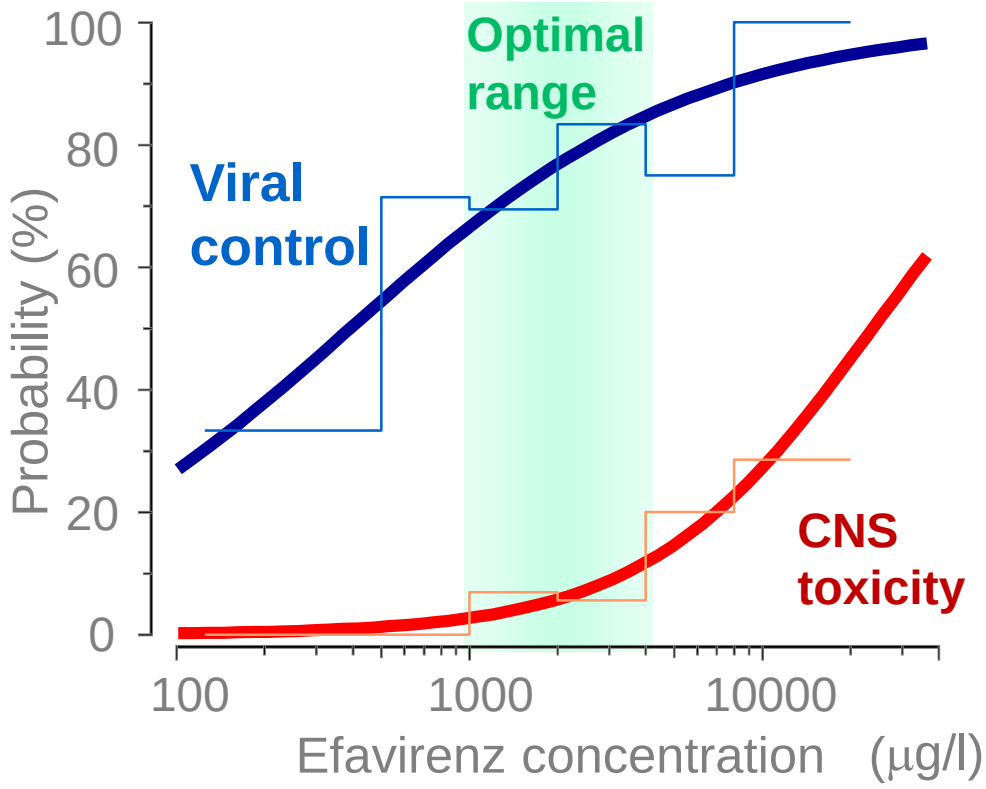
Efavirenz: Still used without Therapeutic Monitoring!

253 unselected patients under
Efavirenz 600 mg q.d. :



C. Csajka & al. *Population pharmacokinetics and effects of efavirenz in patients with human immunodeficiency virus infection*. Clin Pharmacol Ther. 2003;73:20-30

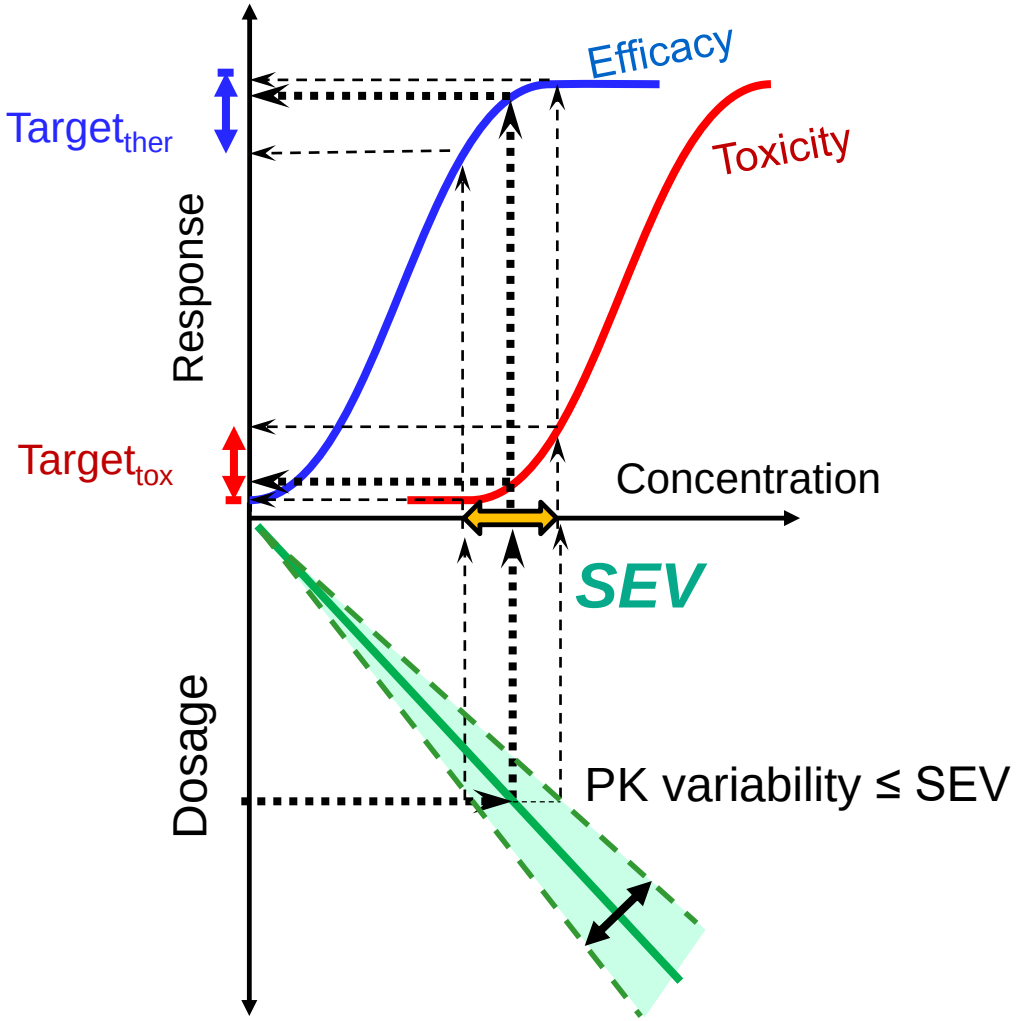
130 unselected patients under
Efavirenz 600 mg q.d. :



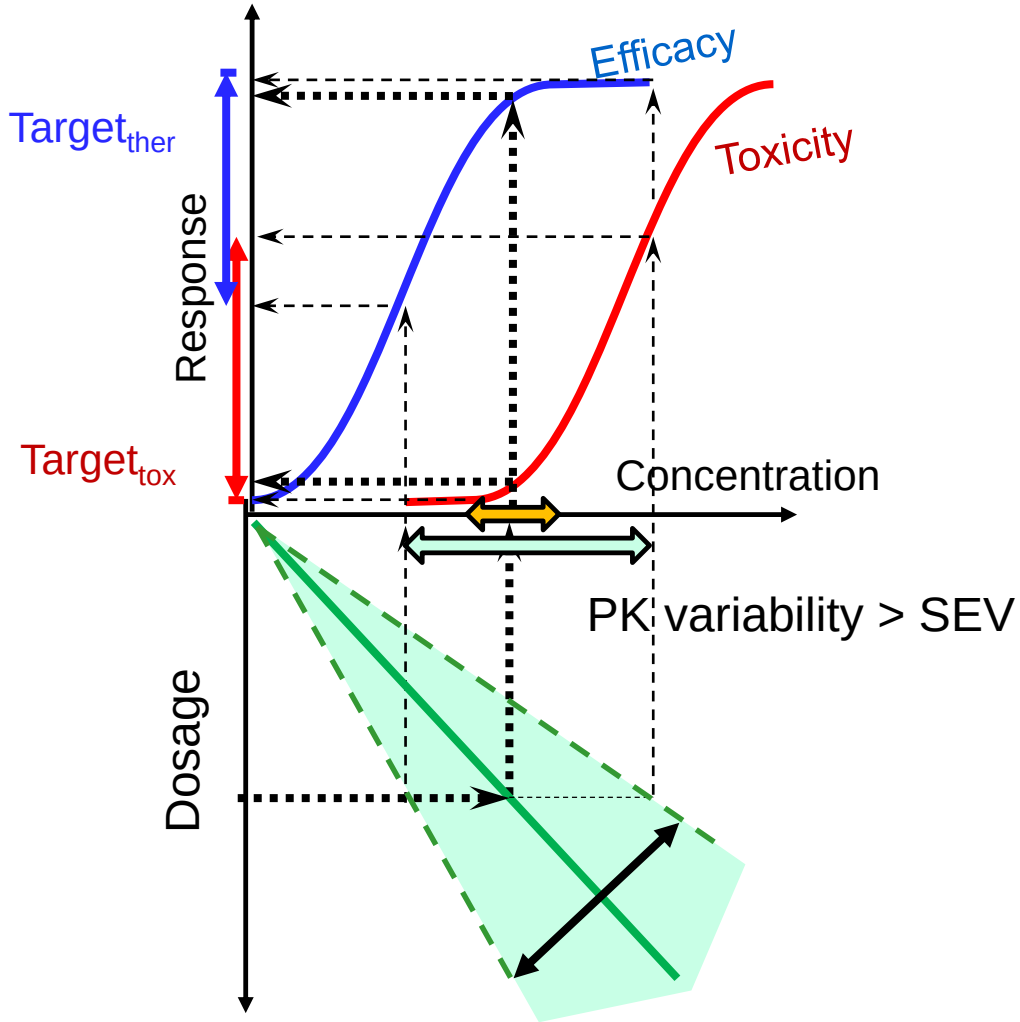
C. Marzolini & al. *Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients*. AIDS 2001, 15:71-75

The criterion of *Safe and Effective Variability*

Standard population or group dosing:

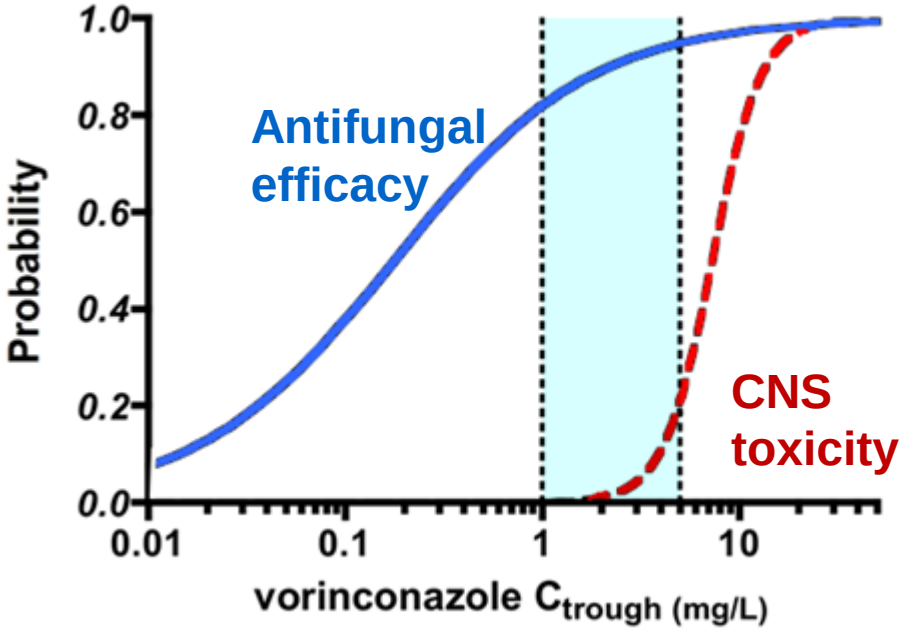


Therapeutic monitoring / Target control intervention:

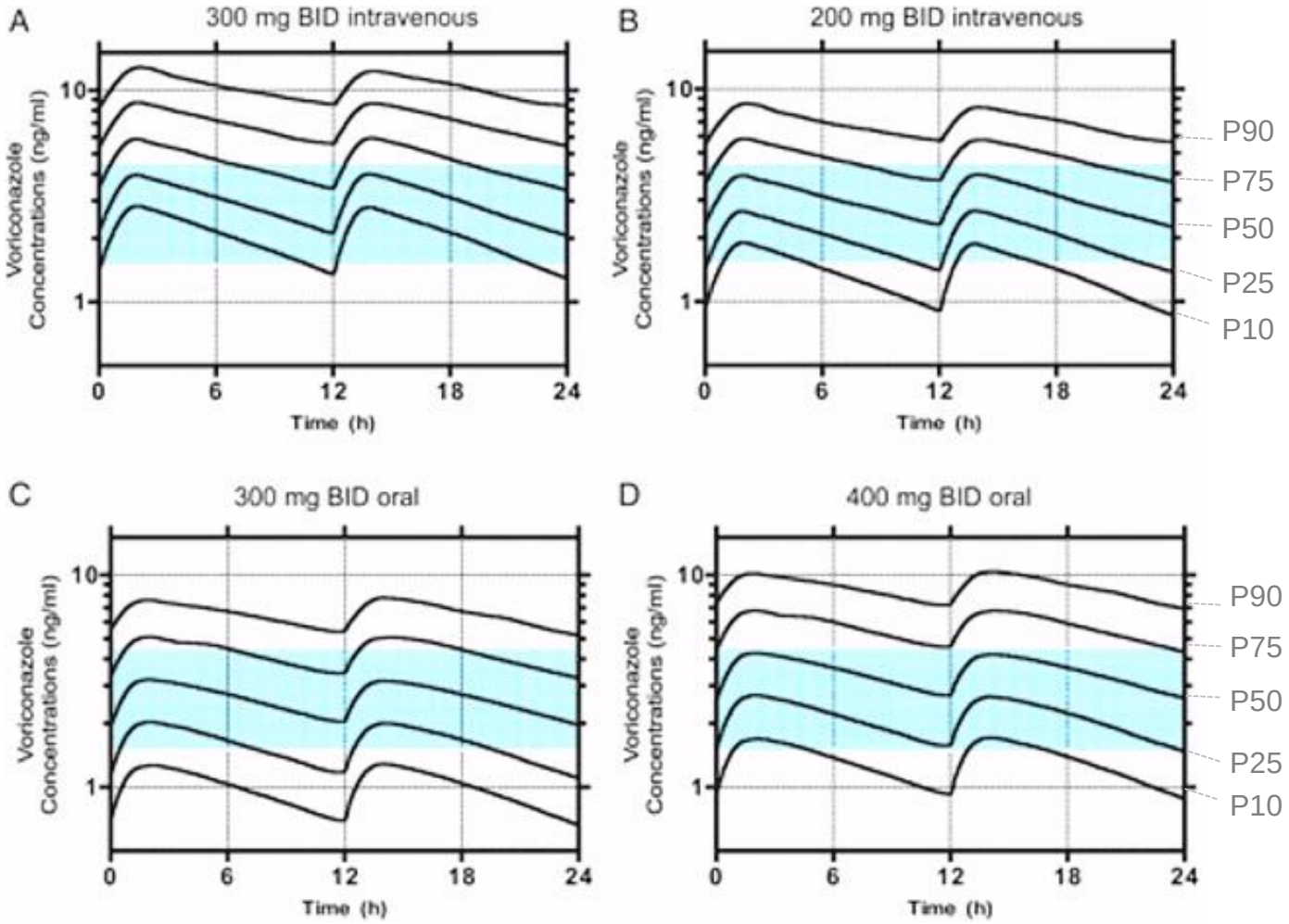


Holford NH, Buclin T. *Safe and effective variability – a criterion for dose individualization.* Ther Drug Monit. 2012;34:565-8

Voriconazole: Suboptimal exposure in ~50%



C. Csajka & al. *Population pharmacokinetics of voriconazole in patients with invasive mycoses*. PAGE meeting 2009



A. Pascual & al. *Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety*. Clin Infect Dis. 2012;55:381-90

Unwilling Drug Compagnies

- Unlike theranostics, therapeutic monitoring based on either concentrations or biomarkers is badly considered.
- Drug candidates that would heavily rely on monitoring are abandoned (despite provocating examples).
- For other candidates, clinical development resolutely ignores the potential benefits of monitoring.
- Very few incentives come from authorities, prescribers or patients.

thebmj

BMJ 2014;349:g4670 doi: 10.1136/bmj.g4670 (Published 23 July 2014)

FEATURE

ANTICOAGULANTS

Dabigatran: how the drug company withheld important analyses

In an investigation by *The BMJ* Deborah Cohen finds that recommendations for use of new generation oral anticoagulants may be flawed because regulators did not see evidence showing that monitoring drug plasma levels could improve safety

Deborah Cohen *investigations editor, The BMJ*

An investigation by *The BMJ* shows how the manufacturers of a blockbuster anticoagulant stroke drug withheld from the regulators important analyses regarding how to use the drug as safely and effectively as possible.

Dabigatran is one of a new generation of oral anticoagulants for stroke prevention in patients with non-valvular atrial fibrillation recently recommended in guidelines from the National Institute for Health and Care Excellence for England and Wales.[1] Guidelines in the US, Europe, and Canada have similarly recommended these drugs, in part because they don't require monitoring of plasma levels or anticoagulant activity and subsequent dose adjustment, unlike older drugs such as warfarin.[2-4]

even after the regulators asked Boehringer to re-examine the trial data for missed events, it is still not clear whether we know how many fatal and life threatening bleeds there were in the trial.[5]

Nevertheless, internal documents show how the company had produced extensive analyses that show how that bleeding risk may be reduced. The company found that if the plasma levels of the drug were measured and the dose was adjusted accordingly major bleeds could be reduced by 30-40%, compared with well controlled warfarin.[5]

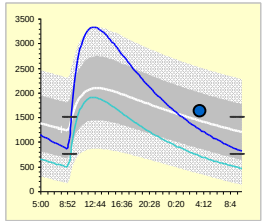
2014

Unwilling Prescribers

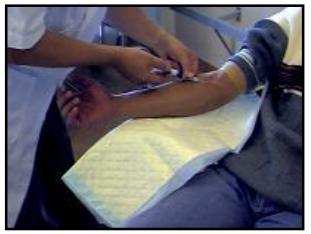
- The feed-back loop of dosage adjustment is complicated and slow.
- Analytical methods demand large, remote central laboratories.
- Standardized samplig time (usually trough) is a problem.
- Interpretation of concentrations or biomarkers results is uneasy.
- Evidence is scarce regarding actual benefit for patients.

Information + Decision

TDM request + clinical data



interpretation + recommendation



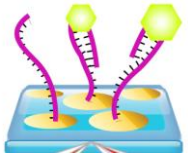
Blood sampling

Analysis

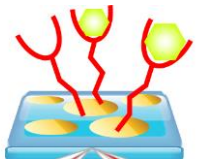
Postage to lab

POCT are coming for Therapeutic Moniroring

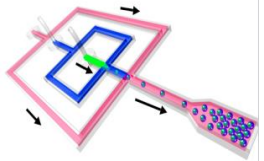
Aptamers :



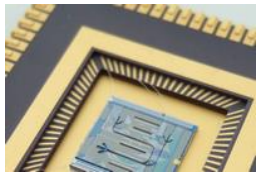
Antibodies:



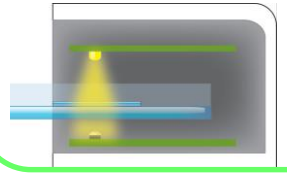
Microfluidics



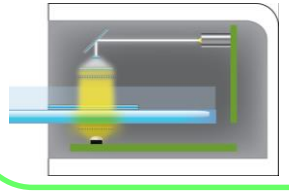
Lab-on-Chip technology



Surface Plasmon Resonance:



Miniaturuzed Fluorescence Polarization:

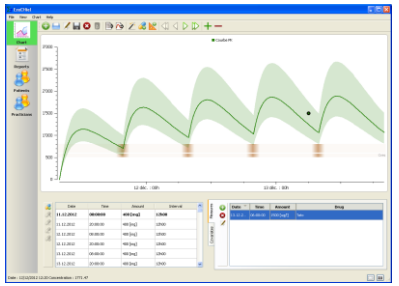


Remote data collection

Central repository for PKPD reference data

Connectivity, privacy

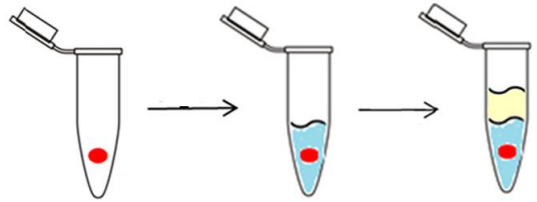
Computer-assisted user-friendly interpretation tools

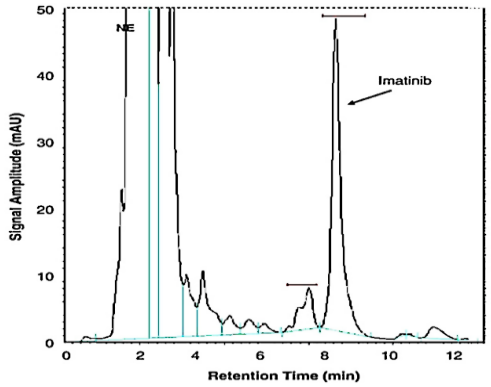


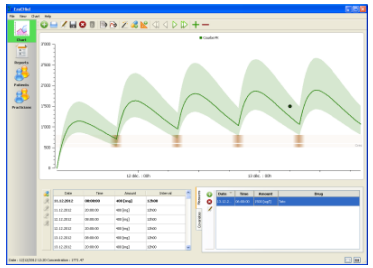
nano-tera.ch

Dry Blood Spots represent an alternative

Minimally invasive sampling





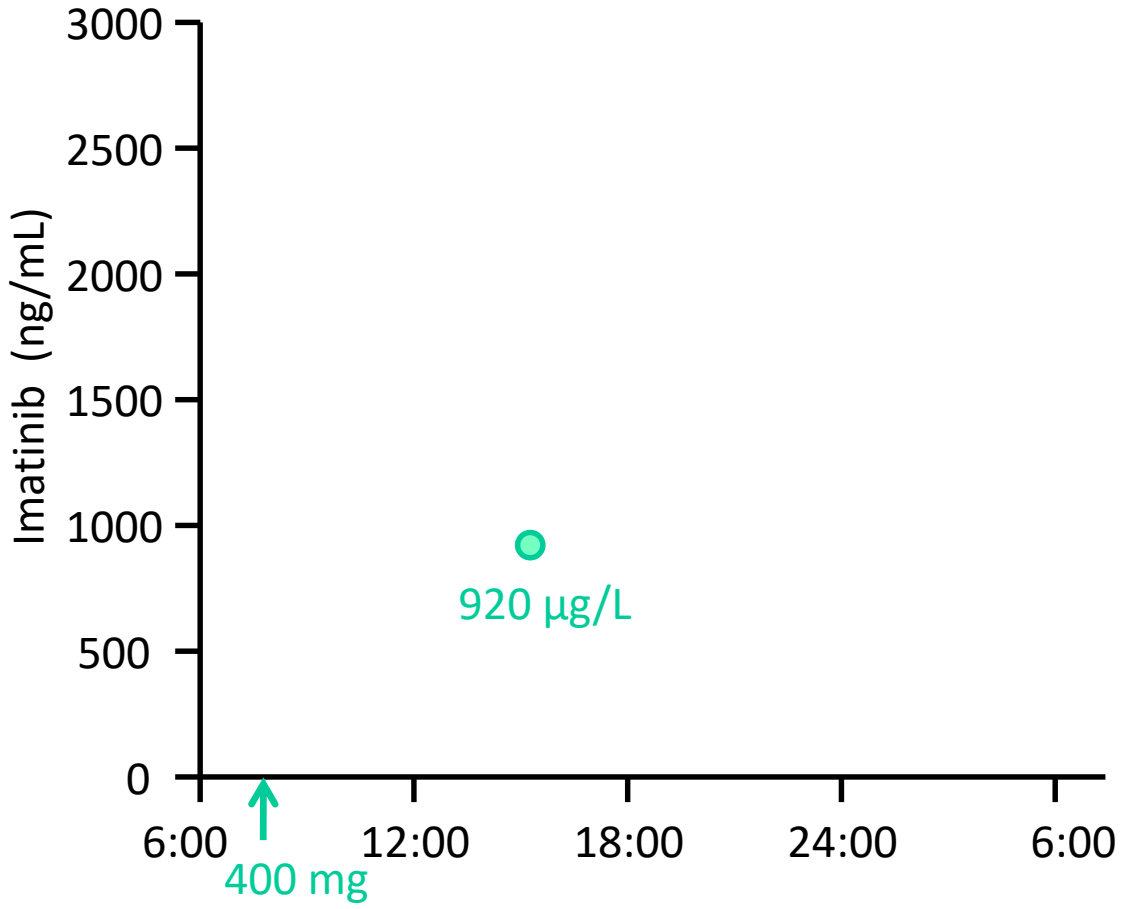


Adjustment instructions

Central analysis and interpretation

Making Therapeutic Monitoring Easy

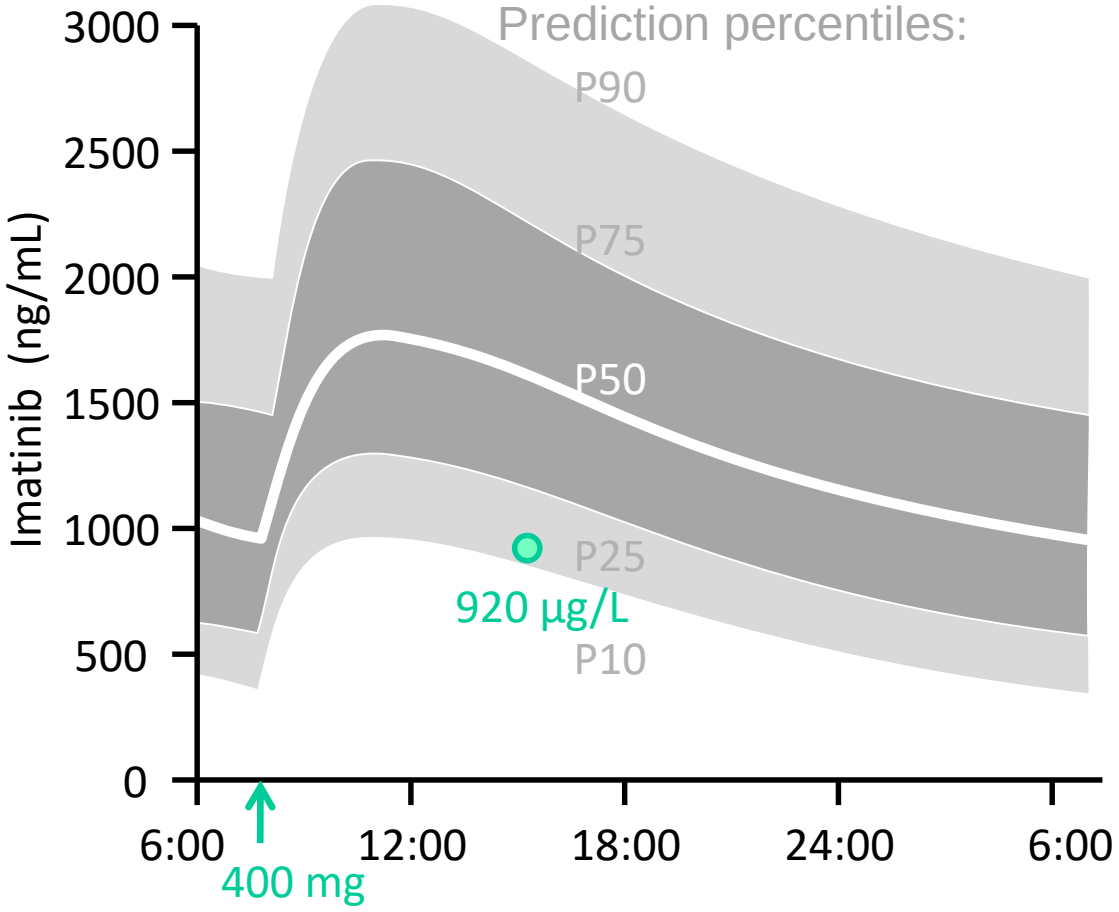
Example: Patient receiving imatinib 400 mg/d for chronic myelogenous leukemia.
Unsatisfactory response → TDM 920 µg/L 8 h post-dose.



Making Therapeutic Monitoring Easy

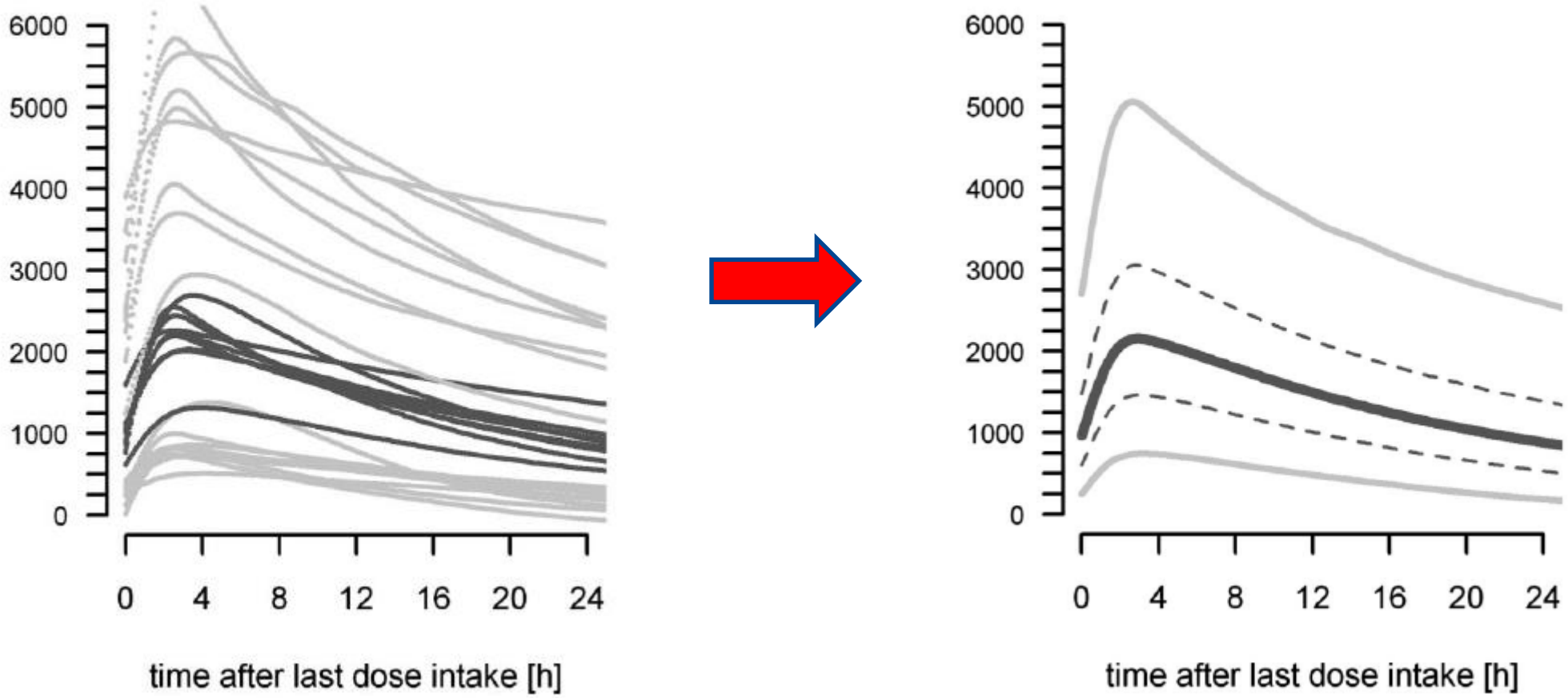
Example: Patient receiving imatinib 400 mg/d for chronic myelogenous leukemia. Unsatisfactory response → TDM 920 µg/L 8 h post-dose.

1 **Is this concentration "normal"?**
consdering drug dosage and patient's characteristics



Normality or Expectedness relies on Pop-PK

Single study or Systematic Review and Meta-Analysis of studies



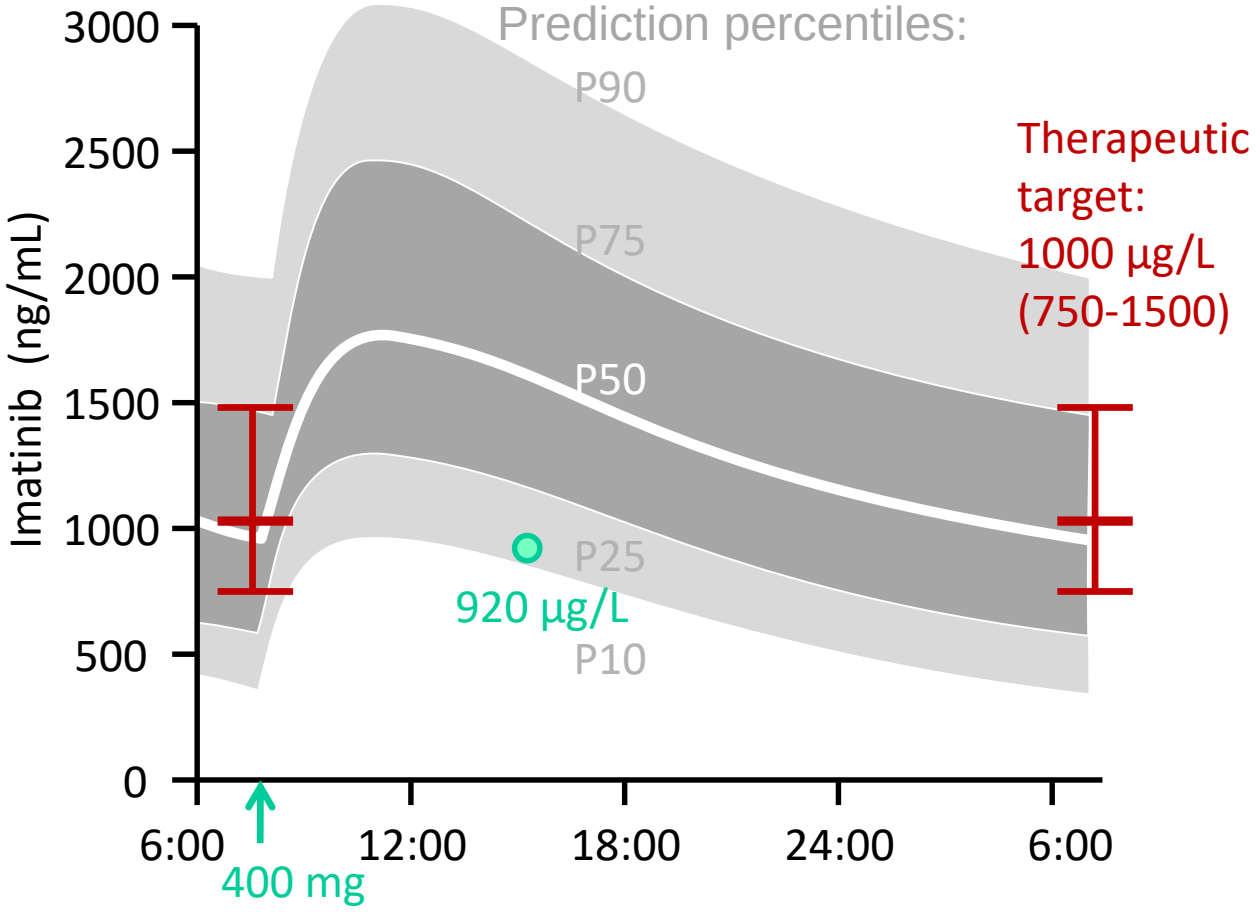
Gotta V, Buclin T, Csajka C, Widmer N. *Systematic review of population pharmacokinetic analyses of imatinib and relationships with treatment outcomes*. Ther Drug Monit. 2013;35:150-67.

Making Therapeutic Monitoring Easy

Example: Patient receiving imatinib 400 mg/d for chronic myelogenous leukemia. Unsatisfactory response → TDM 920 µg/L 8 h post-dose.

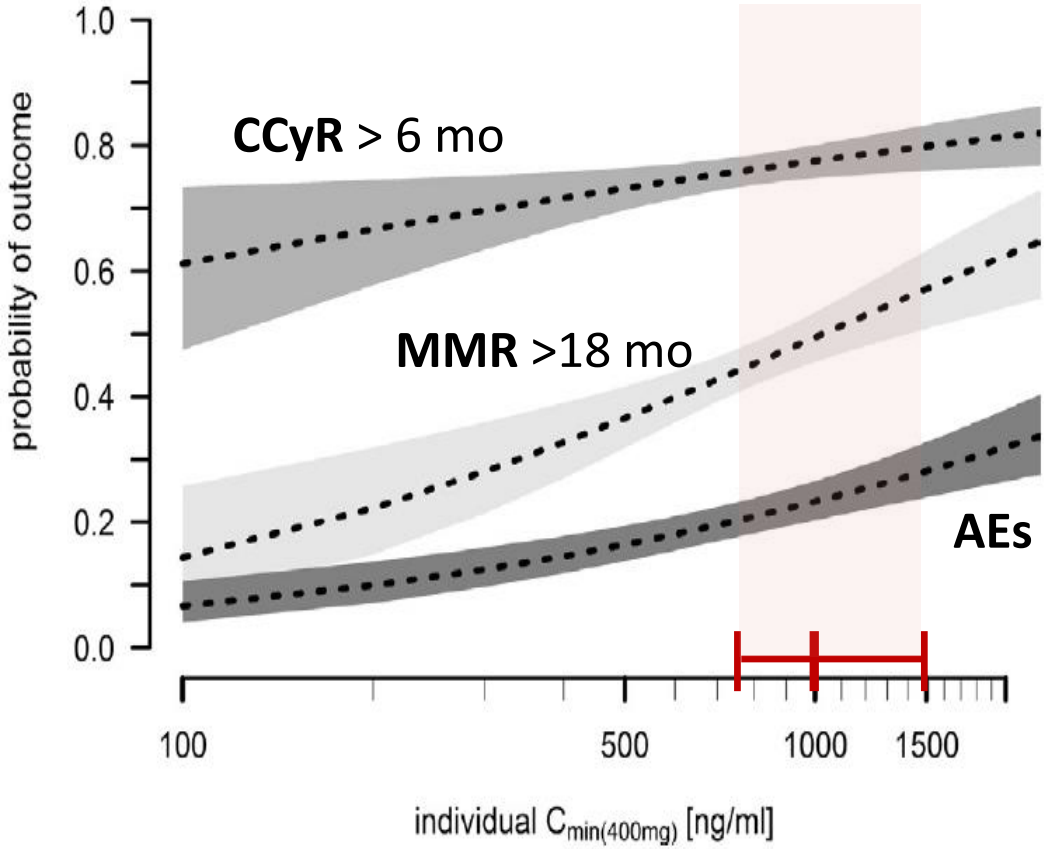
1 **Is this concentration "normal"?**

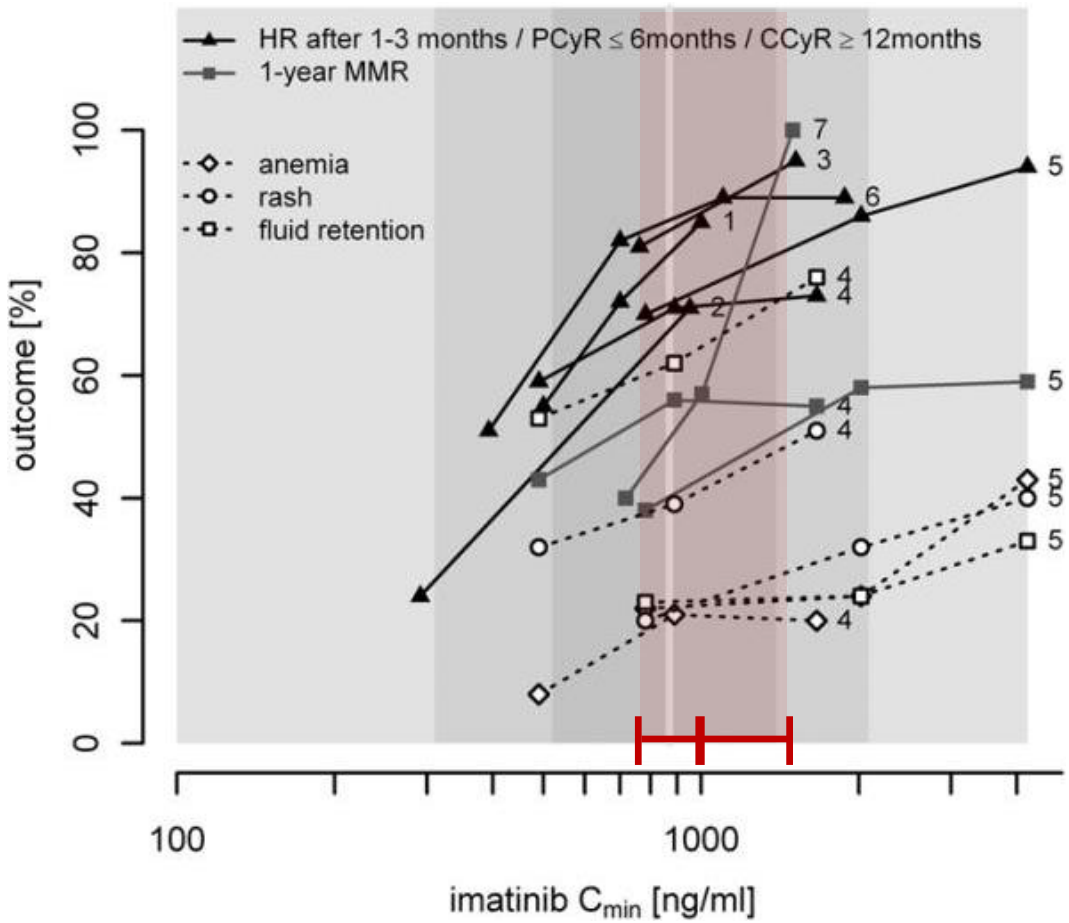
2 **Is this concentration "good"?**
for patient's condition and well-being



Suitability or Appropriateness relies on Pop-PKPD

Single study or Meta-Analysis of studies





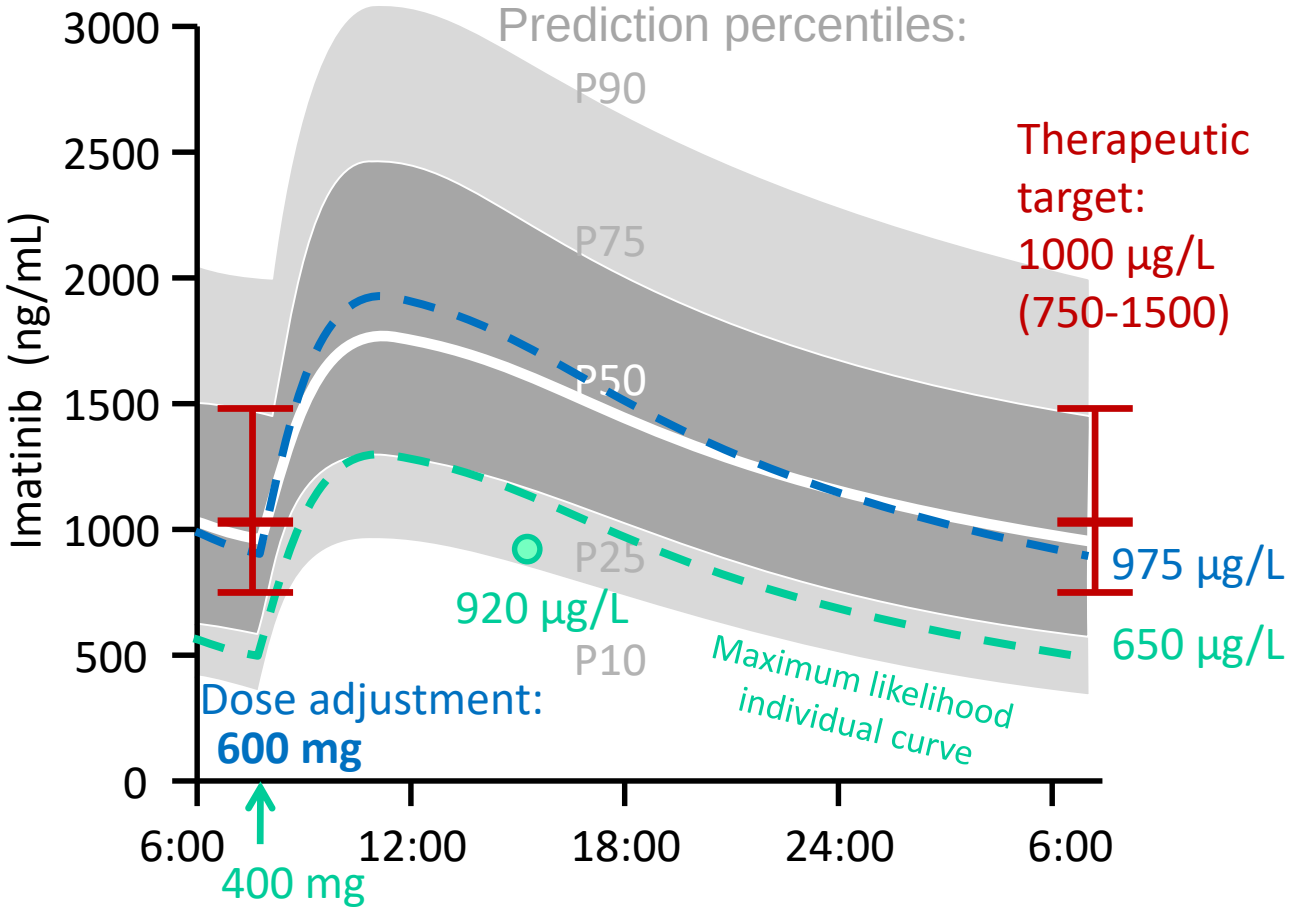
Suitable therapeutic target

Gotta V & al. *Large-scale imatinib dose-concentration-effect study in CML patients under routine care conditions.* Leuk Res. 2014;38:764-72.

Making Therapeutic Monitoring Easy

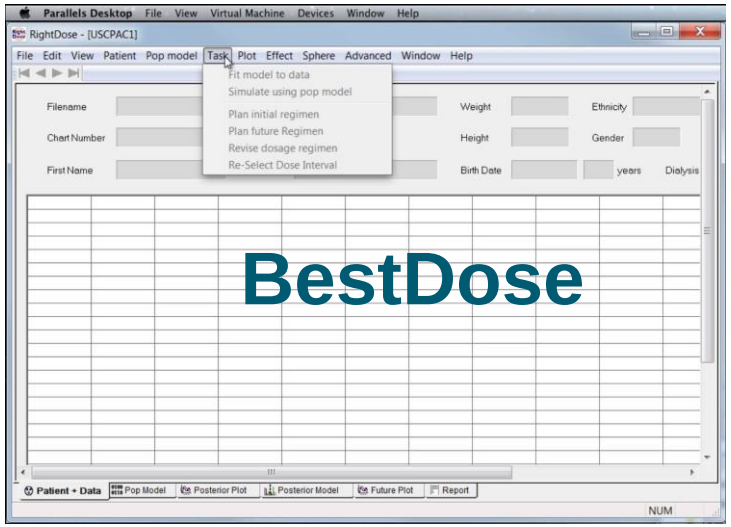
Example: Patient receiving imatinib 400 mg/d for chronic myelogenous leukemia. Unsatisfactory response → TDM 920 µg/L 8 h post-dose.

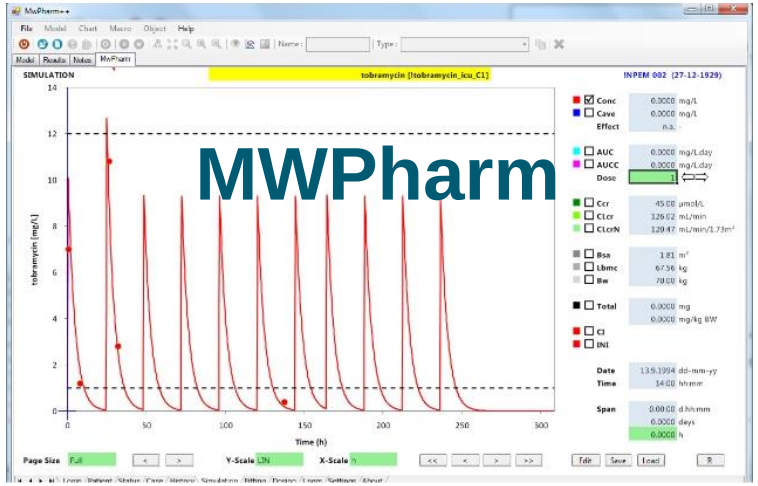
1. **Is this concentration "normal"?**
2. **Is this concentration "good"?**
3. **How to reach optimal exposure?**
   through dosage and follow up decisions

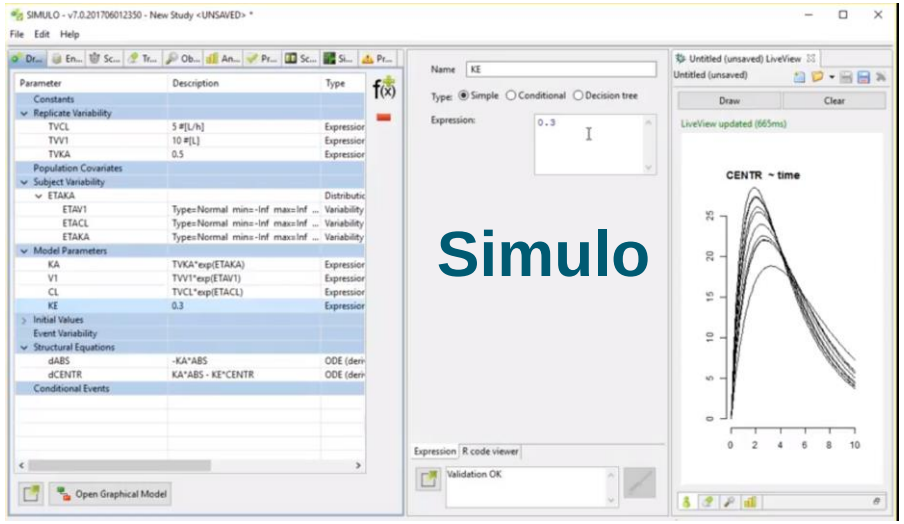


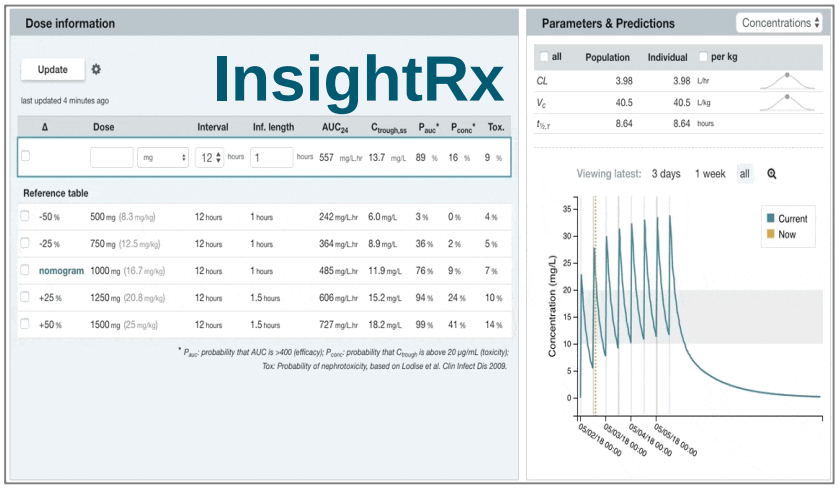
Decision Support relies on Bayesian Adaptation

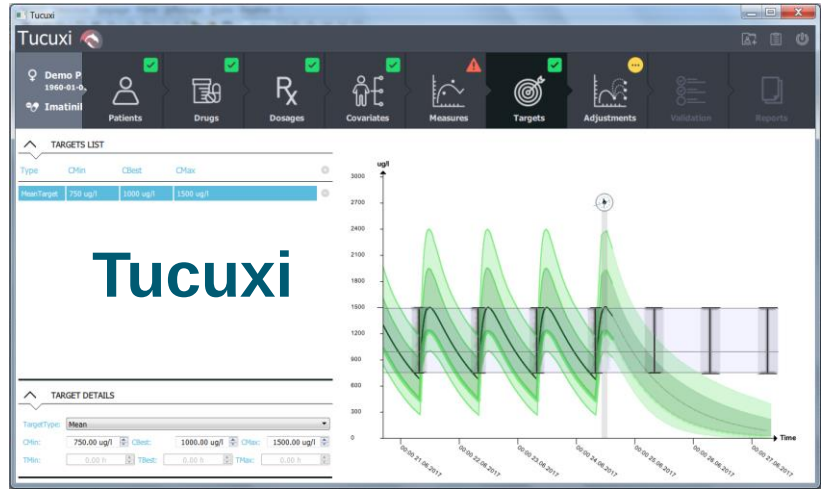
Computer tools have been made available!











etc.

Evidence remains largely to be produced

Cancer Chemother Pharmacol
DOI 10.1007/s00280-014-2599-1

CLINICAL TRIAL REPORT

Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial

V. Gotta · N. Widmer · L. A. Decosterd · Y. Chalandon · D. Heim · M. Gregor · R. Benz · L. Leoncini-Franscini · G. M. Baerlocher · M. A. Duchosal · C. Csajka · T. Buclin

Received: 24 July 2014 / Accepted: 22 September 2014

Abstract
Purpose This study assessed whether a cycle of "routine" therapeutic drug monitoring (TDM) for imatinib dosage individualization, targeting an imatinib trough plasma concentration (C_{min}) of 1,000 ng/ml (tolerance: 750–1,500 ng/ml), could improve clinical outcomes in chronic myelogenous leukemia (CML) patients, compared with TDM use only in case of problems ("rescue" TDM).
Methods Imatinib concentration monitoring evaluation was a multicenter randomized controlled trial including adult patients in chronic or accelerated phase CML receiving imatinib since less than 5 years. Patients were allocated 1:1 to "routine TDM" or "rescue TDM." The primary endpoint was a combined outcome (failure- and toxicity-free survival with continuation on imatinib) over 1-year follow-up, analyzed in intention-to-treat (ISRCTN31181395).
Results Among 56 patients (55 evaluable), 14/27 (52 %) receiving "routine TDM" remained event-free versus 16/28 (57 %) "rescue TDM" controls ($P = 0.69$). In the "routine TDM" arm, dosage recommendations were correctly adopted in 14 patients (median C_{min}: 895 ng/ml), who had fewer unfavorable events (28 %) than the 13 not receiving the advised dosage (77 %; $P = 0.03$; median C_{min}: 648 ng/ml).
Conclusions This first target concentration intervention trial could not formally demonstrate a benefit of "routine TDM" because of small patient number and surprisingly limited prescriber's adherence to dosage recommendations.

Abstract (oral presentation) at 11th Conference of the European Association for Clinical Pharmacology and Therapeutics (EACPT), August 28–31, 2013, Geneva, Switzerland.

Electronic supplementary material The online version of this article (doi:10.1007/s00280-014-2599-1) contains supplementary material, which is available to authorized users.

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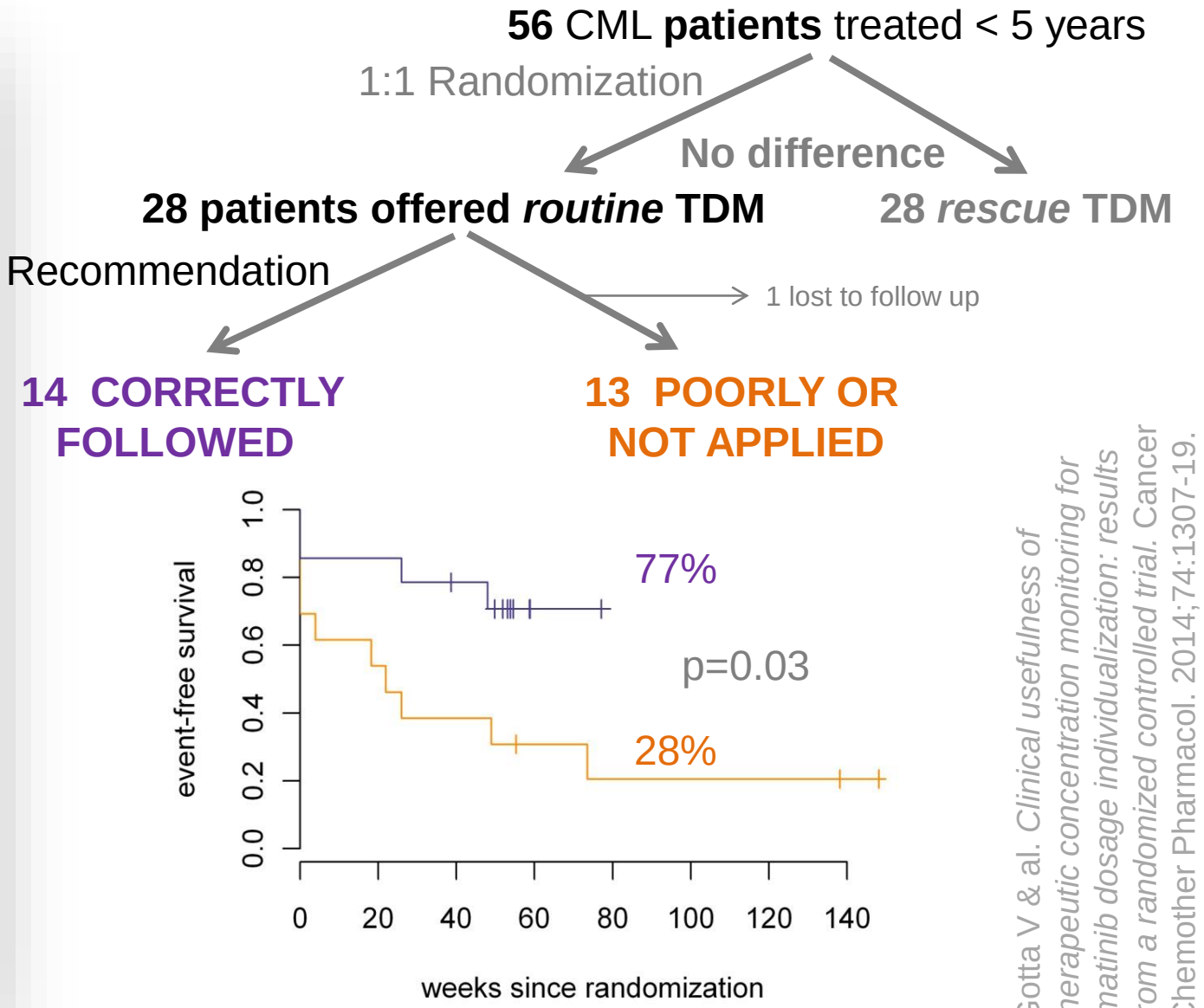
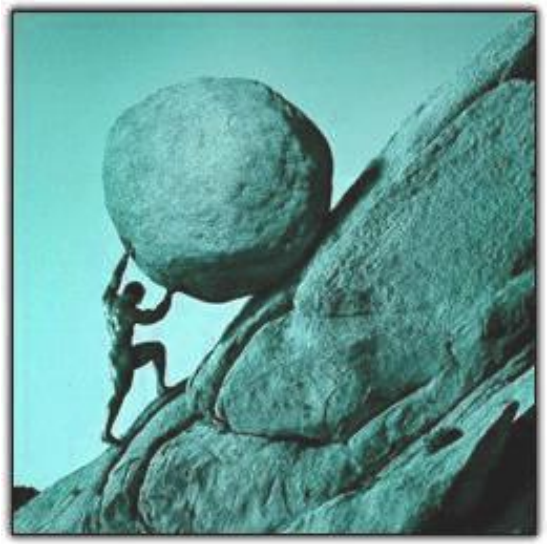


Gotta V & al. *Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial.* Cancer Chemother Pharmacol. 2014;74:1307-19.

38 Small molecule STIs now approved by EMA



Drug	Trade name	Company	EMA	Indications
Imatinib	Gleevec, Glivec	Novartis	2001	Chronic myelogenous leukaemia, Acute lymphoblastic leukemia Phi+, GIST
Erlotinib	Tarceva	Roche, Genentech	2005	Non-small cell lung cancer, Pancreatic cancer, etc.
Sorafenib	Nexavar	Bayer, Onyx	2006	Renal cell carcinoma, Hepatocellular carcinoma, Differentiated thyroid carcinoma
Sunitinib	Sutent	Pfizer, Sugen	2006	Renal cell carcinoma, GI stromal tumour, Pancreatic neuroendocrine tumour
Dasatinib	Sprycel	BMS	2006	Chronic myelogenous leukaemia, Acute lymphoblastic leukemia Phi+ (2nd line)
Temsirolimus	Torisel	Wyeth	2007	Renal cell carcinoma, Uterine cancer
Lapatinib	Tykerb	GSK	2008	Breast cancer HER2-positive
Nilotinib	Tasigna	Novartis	2009	Chronic myelogenous leukaemia (2nd line)
Gefitinib	Iressa	AstraZeneca	2009	Non-small cell lung cancer with EGFR mutation
Everolimus	Afinitor, Votubia	Novartis	2009	Breast, kidney, neuroendocrine cancers,sarcomas,Waldenström
Pazopanib	Votrient	GSK	2010	Renal cell carcinoma, soft tissue sarcoma
Vandetanib	Caprelsa	AstraZeneca	2012	Medullary thyroid cancer
Vemurafenib	Zelboraf	Roche	2012	Melanoma with B-RAF mutation
Ruxolitinib	Jakavi	Novartis, Incyte	2012	Myelofibrosis
Axitinib	Inlyta	Pfizer	2012	Renal cell carcinoma (2nd line)
Crizotinib	Xalkori	Pfizer	2012	Kinase-positive non-small cell lung cancer
Bosutinib	Bosulif	Pfizer	2013	Chronic myelogenous leukaemia, Acute lymphoblastic leukemia
Ponatinib	Iclusig	Ariad	2013	Chronic myelogenous leukaemia, Acute lymphoblastic leukaemia Phi+ (2nd line)
Dabrafenib	Tafinlar	GSK	2013	Melanoma with B-RAF mutation
Regorafenib	Stivarga	Bayer	2013	Colorectal cancer, Gastrointestinal stromal tumour
Afatinib	Gilotrif	Boehringer Ing.	2013	Non-small cell lung cancer
Ibrutinib	Imbruvica	Janssen	2014	Chronic Lymphocytic leukemia, Mantle cell lymphoma
Sonidegib	Odomzo	Sun	2015	Basal cell carcinoma
Panobinostat	Farydak	Novartis	2015	Multiple myeloma
Carfilzomib	Kyprolis	Amgen	2015	Multiple myeloma
Cobimetinib	Cotellic	Roche	2015	Melanoma BRAF V600+
Osimertinib	Tagrisso	AstraZeneca	2016	Non-small-cell lung cancer EGFR T790M+
Lenvatinib	Kisplyx	Eisai	2016	Renal cell carcinoma
Cabozantinib	Cometriq	Exelixis	2016	Metastatic thyroid cancer
Cabozantinib	Cabometyx	Ipsen	2016	Renal cell carcinoma
Palbociclib	Ibrance	Pfizer	2016	Breast cancer ER+ HER2-
Ixazomib	Ninlaro	Takeda	2016	Multiple myeloma
Venetoclax	Venclyxto	AbbVie	2016	Chronic lymphocytic leukaemia with 17p deletion or TP53 mutation
Alectinib	Alecensa	Roche	2017	Non-small cell lung cancer ALK+
Ribociclib	Kisqali	Novartis	2017	Breast cancer ER+ HER2-
Tivozanib	Fotivda	Aveo	2017	Renal cell carcinoma
Midostaurin	Rydapt	Novartis	2017	Acute myeloid leukemia, mastocytosis
Niraparib	Zejula	Tesaro	2017	Ovarian cancer

Authorities are to Convert!

Please go and fill in the **ISoP Response Form** to insist on the importance of **assessing PKPD variability** and of systematically **evaluating the potential merits of therapeutic monitoring**, based on either concentrations or biomarkers!

Conclusions

- Pharmacometrics bring about key components for the advocated *precision medicine*
- Technological advances will shape and foster new forms of therapeutic monitoring
- Pharmacometricians have a definite responsibility in bridging the implementation gap