TDM and Dose Optimization of Immunosuppressive and Oncolytic Agents

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Conflicts of interest

My personal and professional background
Erik van Maarseveen

1979: Birth
2005: Pharmacy Degree
2010: C
2011: H   oratory UMCU
2014: P
2015: T   culty)
2016: C
2017 D   tee IATDMCT
2018 E

Resear
- inspir
- pharmacokinetics, immunosuppressants & bio-based therapies
- clinical immunopharmacology
- practical drug use/administration problems
- innovations in clinical pharmacy (transitional care, laboratory)
- transplantation: solid organs and hematopoetic cells
- >50 Pubmed-indexed publications

Utrecht

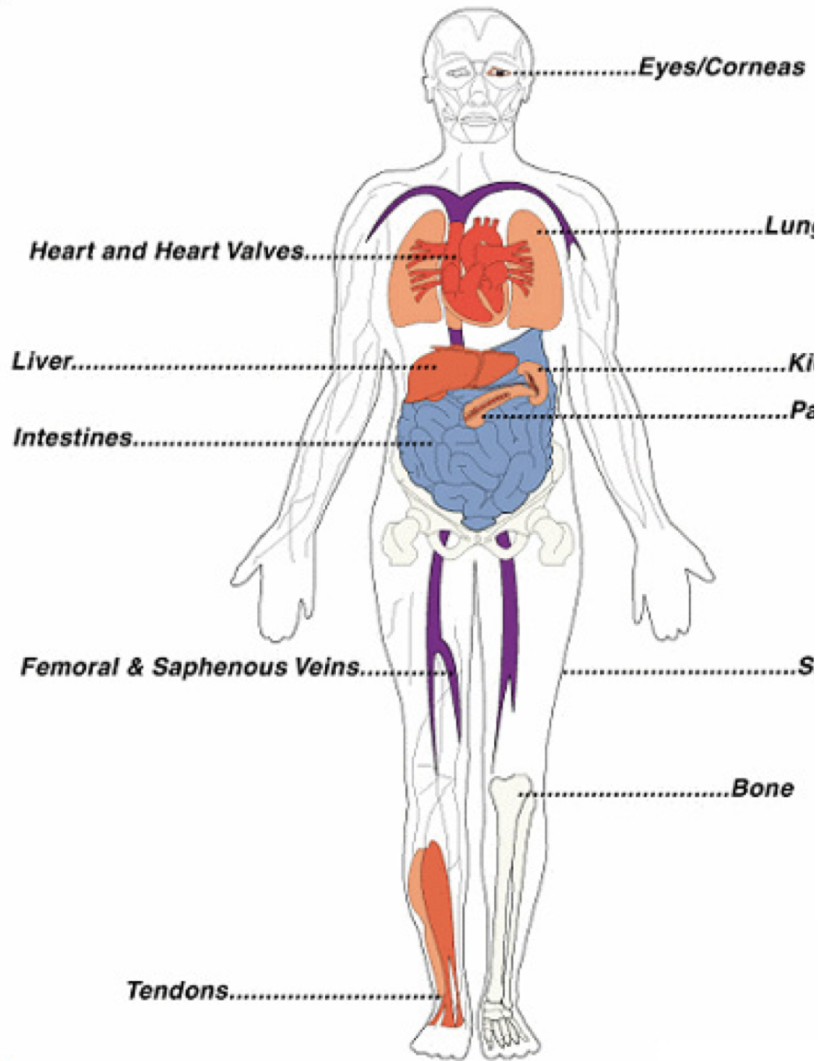# Connecting Pharmacy/Pharmacology and Clinic
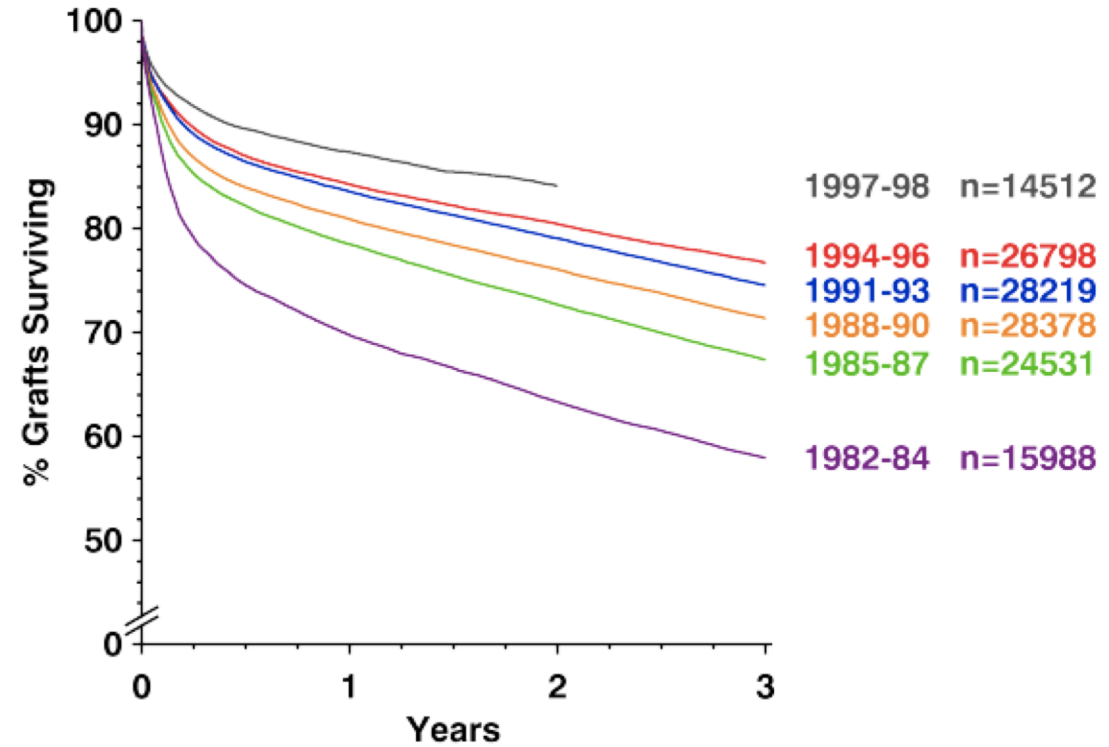
Basis of Therapeutic Drug Monitoring

- Therapeutic drug monitoring (TDM) is advised for drugs
  - With narrow therapeutic window
  - With concentration-effects (PK-PD) relationship, but efficacy sometimes difficult to quantify
  - With high interpatient variability (PK, PG, drug interactions..)
  - Needing strong long term compliance. Pharmacoeconomy
  - Possible confusion between SE and pathology

- Immunosuppressants and oncolytics belong to drugs taking advantage of TDM or personalized dosing

P Wallemacq. Clin Chem Lab Med, 42,1204-11, 2004

Transplantation & Immunosuppressants

First Cadaver Kidney Transplants

1997-98   n=14512
1994-96   n=26798
1991-93   n=28219
1988-90   n=28378
1985-87   n=24531
1982-84   n=15988

Precision or Personalized Medicine in transplantation and oncology
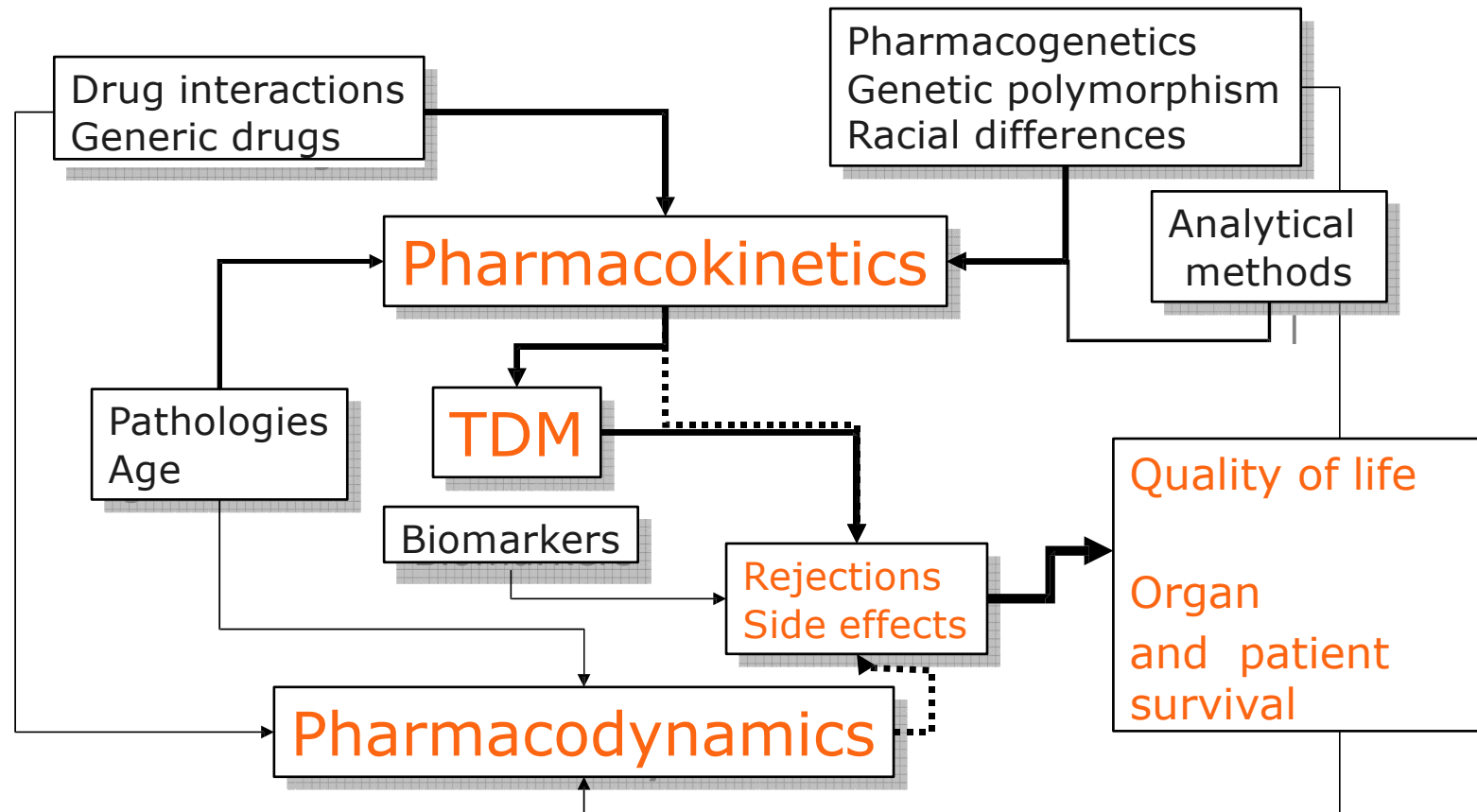
Variability of the Pharmacokinetics

Variability of the pharmacokinetics

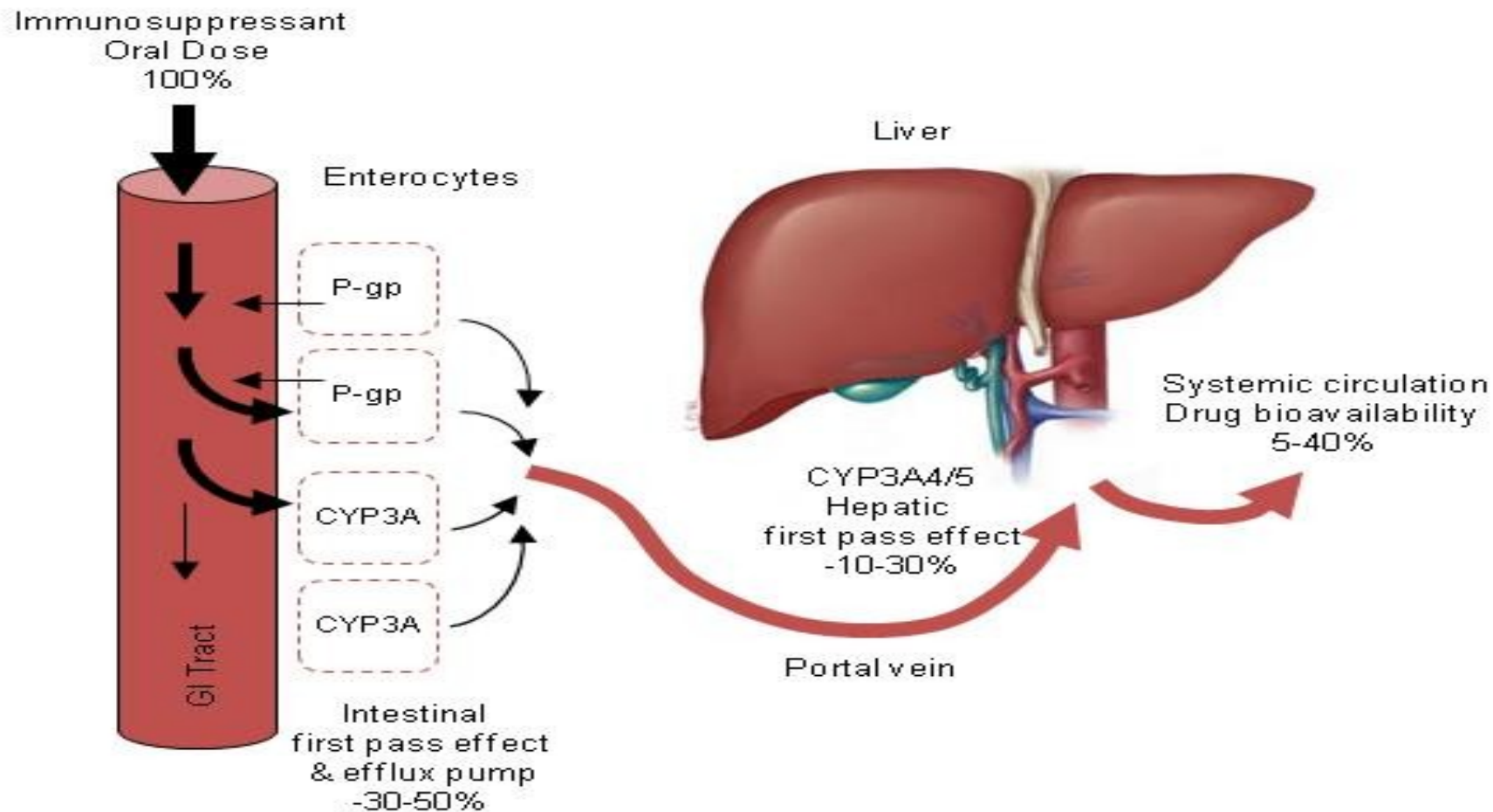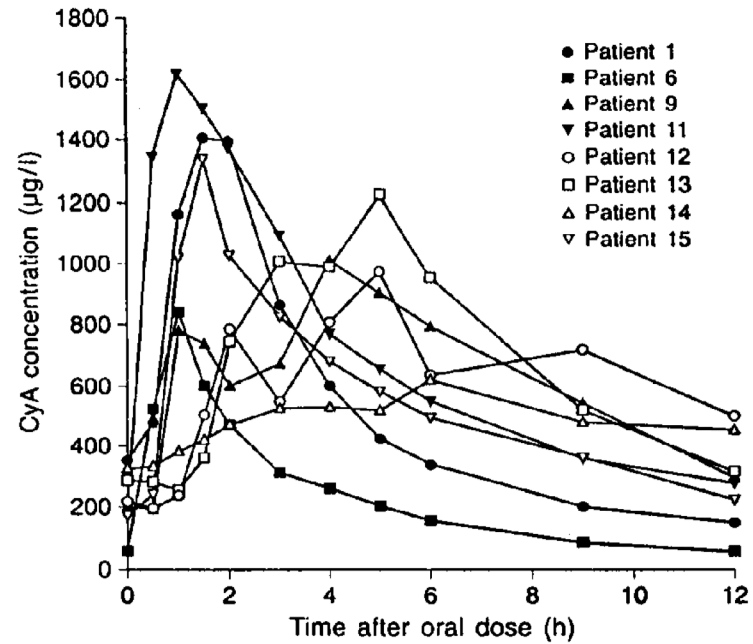Fig. 1 Cyclosporin concentrations versus time profiles ($n = 8$) obtained after Neoral administration at steady state Pk_3 with the monoclonal whole blood FPIA method

Variability of the pharmacokinetics

- CsA, TAC, Siro and Evero are highly lipophilic agents characterized by variable level of absorption
- They are metabolized by CYP3A subfamily enzymes and are substrate of P-glycoprotein
  - subject of **interactions and ontogeny**
  - characterized by **genetic polymorphism**
- Substrates for many drug-drug (food) interactions
- Chronic diarrhea
- As a consequence: large intra- and interpatients variability in the blood levels
- Need to predict AUC and/or drug concentration at the target site

Drug interactions

Drugs that may increase tacrolimus blood concentrations

Calcium Channel Blockers	Antifungal Agents	Macrolide Antibiotics
diltiazem	clotrimazole	clarithromycin
nicardipine	fluconazole	erythromycin
nifedipine	itraconazole	troleandomycin
verapamil	ketocon azole	
	voricon azole	

Gastrointestinal Prokinetic Agents		
	bromocriptine	
		nefazodone
cisapride		
metoclopramide	chloramphenicol	lansoprazole
	cimetidine	omeprazole
	cyclosporine	protease
	danazol	inhibitors ethinyl
Drink	methylprednis	estradiol
	olone	
	magnesium-aluminum-hydroxide	
grapefruit juice	fluoroquinolones	

Drugs that may decrease tacrolimus blood concentrations

Anticonvulsants	Antimicrobials
carbamazepine	rifabutin
phenobarbital	caspofungin
phenytoin	rifampin

Herbal Preparations	Other Drugs
St. John's Wort	sirolimus

These tables are not all inclusive

DDI Tacrolimus and Ritonavir in HIV-infected RTx patients

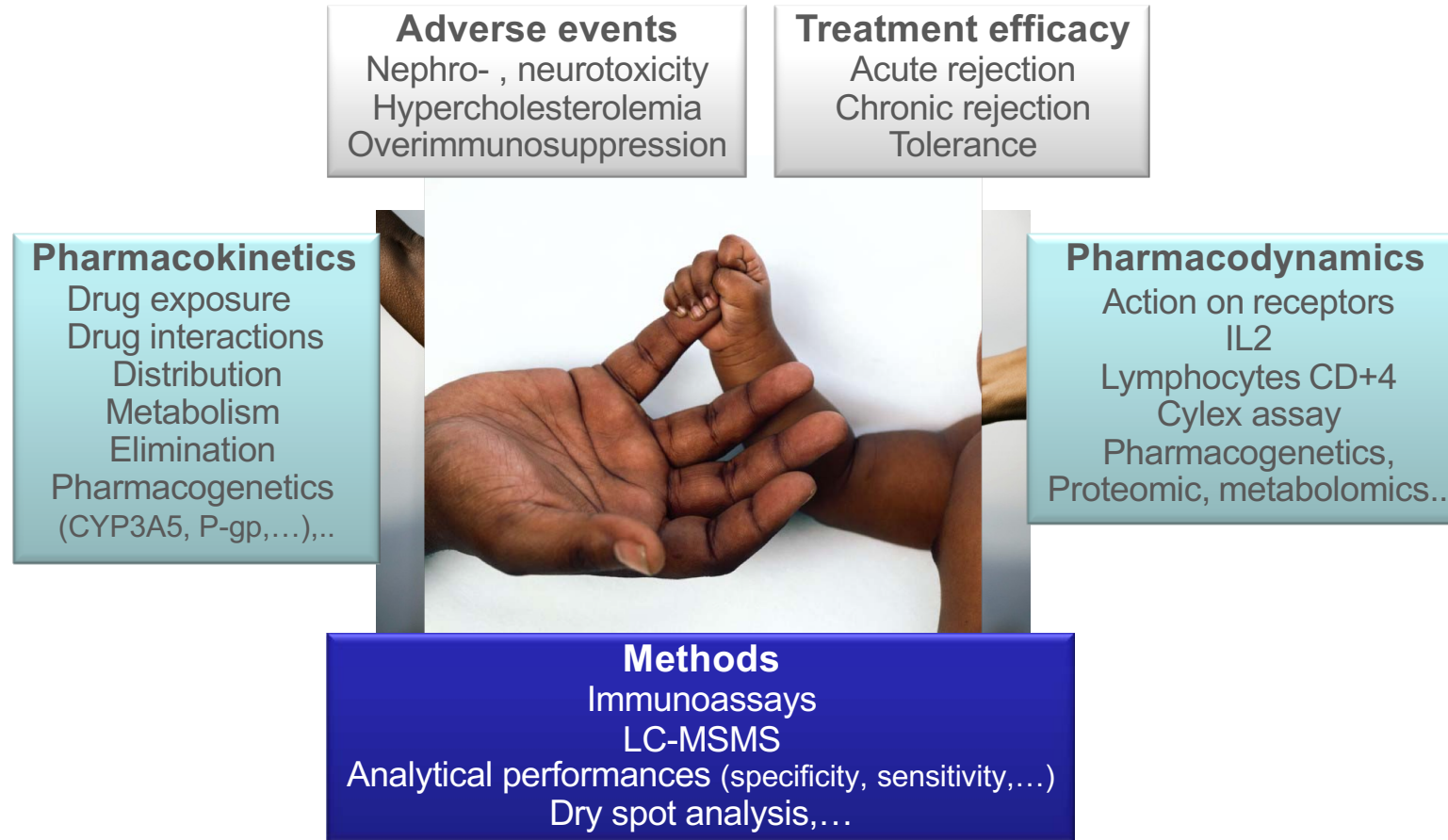*Crommelin and van Maarseveen, Transplantation 2013*
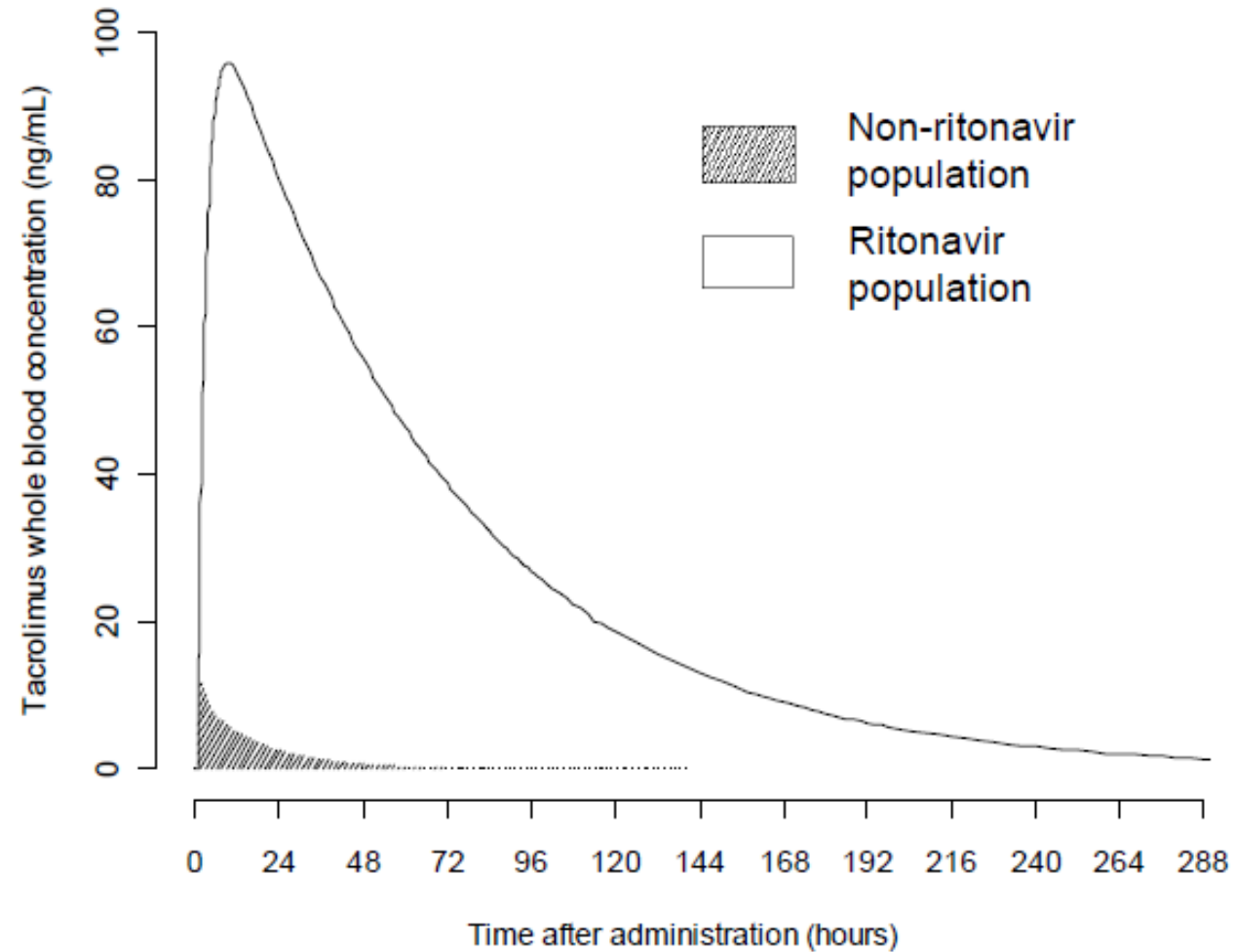
Immunosuppressants:
Drugs used to prevent organ rejection

- Steroids (no TDM) anti-inflammatory, rejection or maintenance
- Antibodies (no TDM) induction or rejection therapy
  - Anti-IL2 receptor (anti-CD25, e.g. Daclizumab, Basiliximab), anti-CD3
  - ATG or ALG
- Azathioprine (no TDM but need check TPMT activity), maintenance
- Calcineurin inhibitors
  - Cylosporine (TDM required), maintenance
  - Tacrolimus (TDM required), maintenance
- Mycophenolate mofetil/sodium (TDM recommended), maintenance
- mTOR inhibitors
  - Sirolimus/everolimus (TDM required), maintenance
- …

Several possible combinations

How individualize Tx drug treatment

Adverse events
Nephro- , neurotoxicity
Hypercholesterolemia
Overimmunosuppression

Treatment efficacy
Acute rejection
Chronic rejection
Tolerance

Pharmacokinetics
Drug exposure
Drug interactions
Distribution
Metabolism
Elimination
Pharmacogenetics
(CYP3A5, P-gp,…),..

Pharmacodynamics
Action on receptors
IL2
Lymphocytes CD+4
Cylex assay
Pharmacogenetics,
Proteomic, metabolomics..

Methods
Immunoassays
LC-MSMS
Analytical performances (specificity, sensitivity,…)
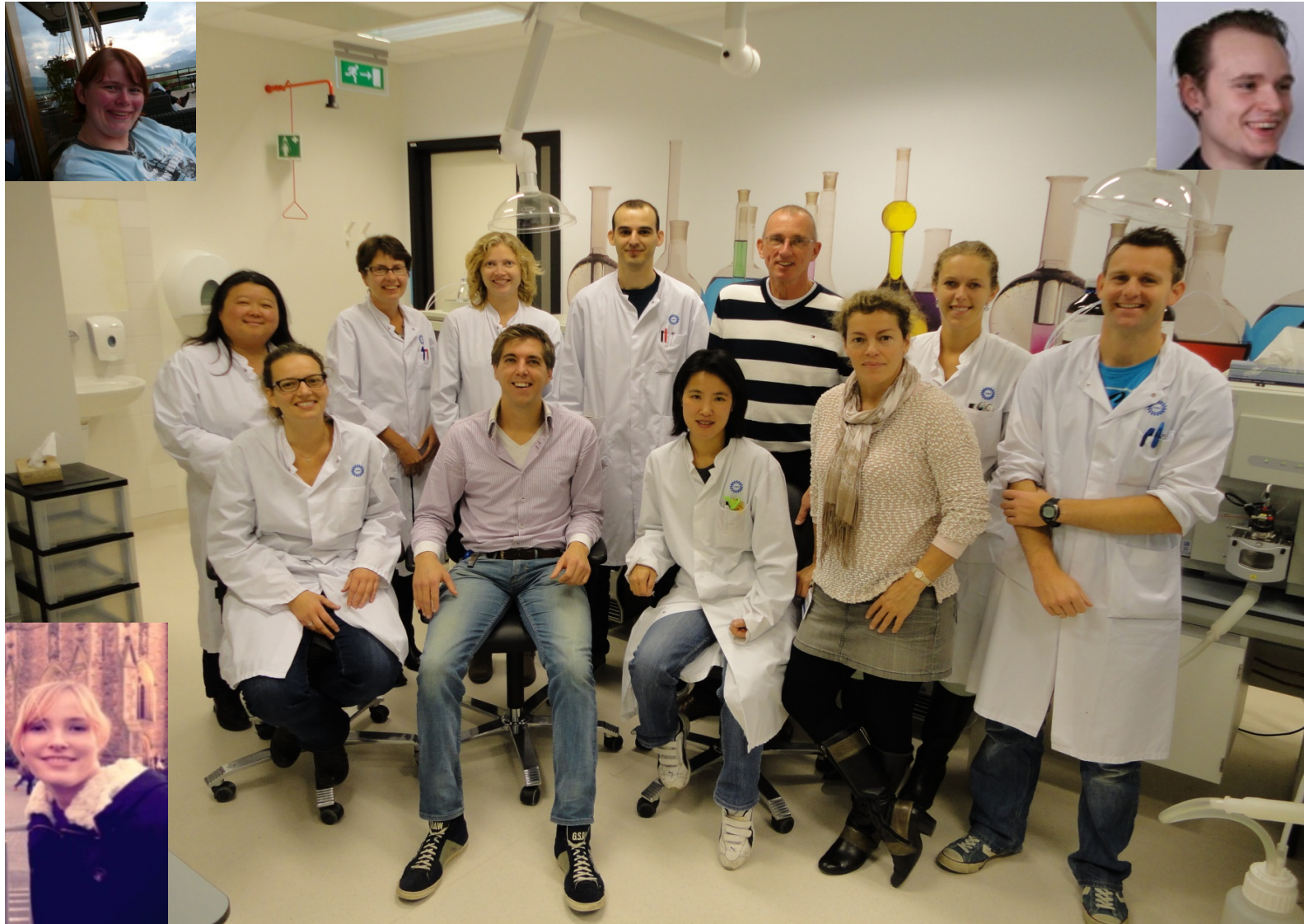Dry spot analysis,…

Precision Medicine & LCMSMS
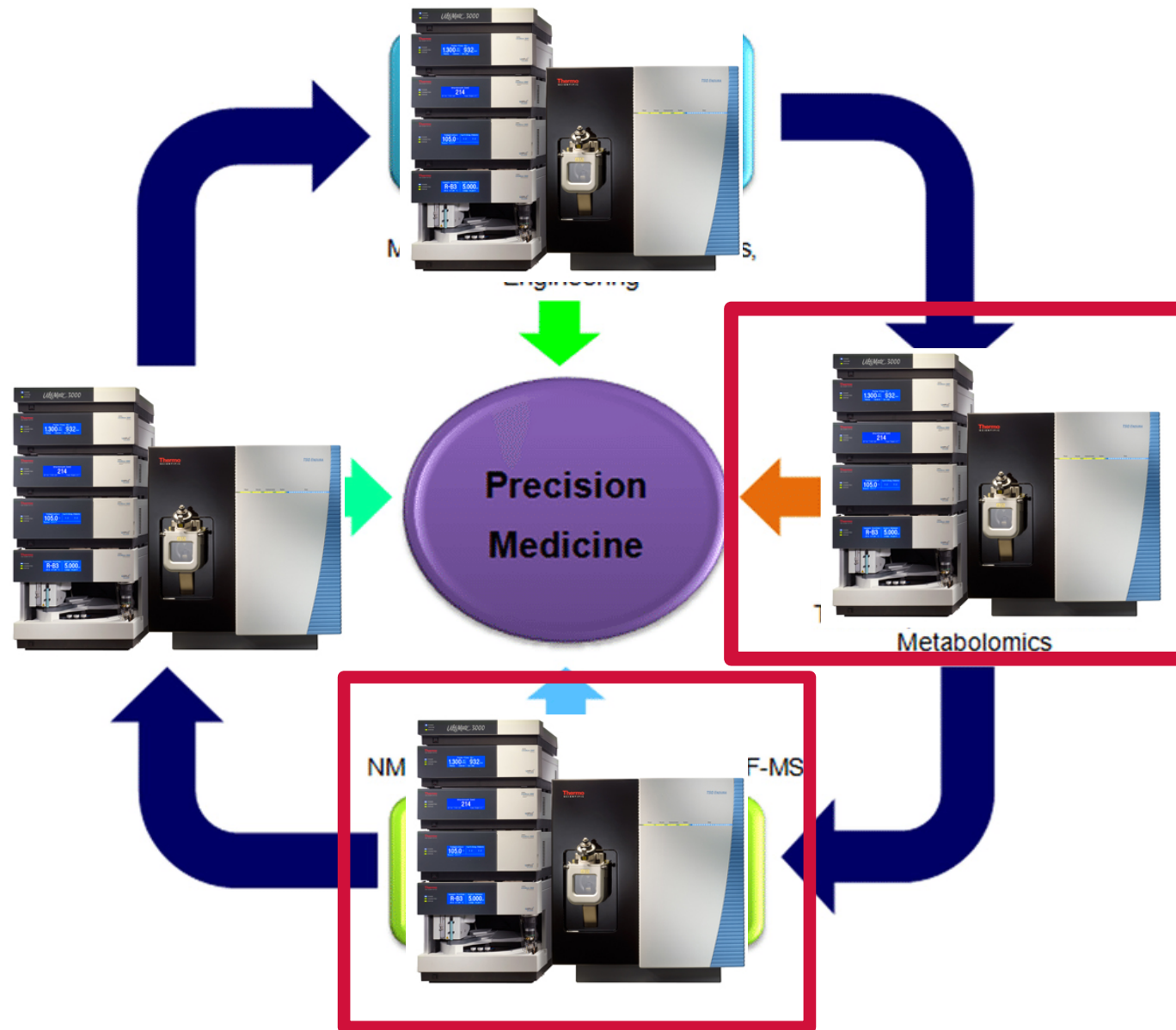
LCMS @ UMC Utrecht pharmacology lab

LCMS team @ UMC Utrecht

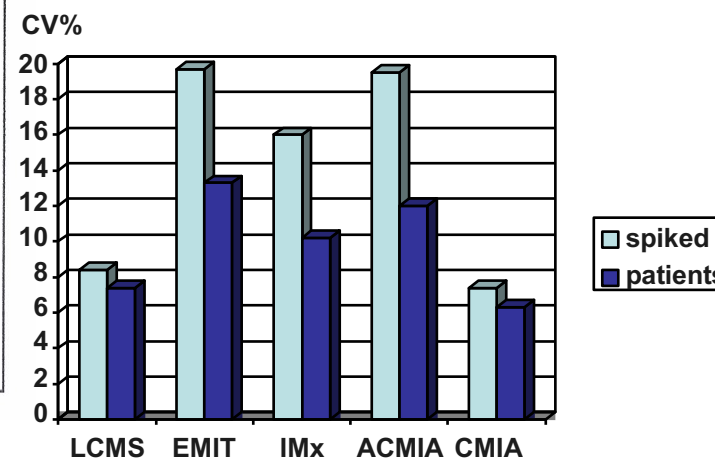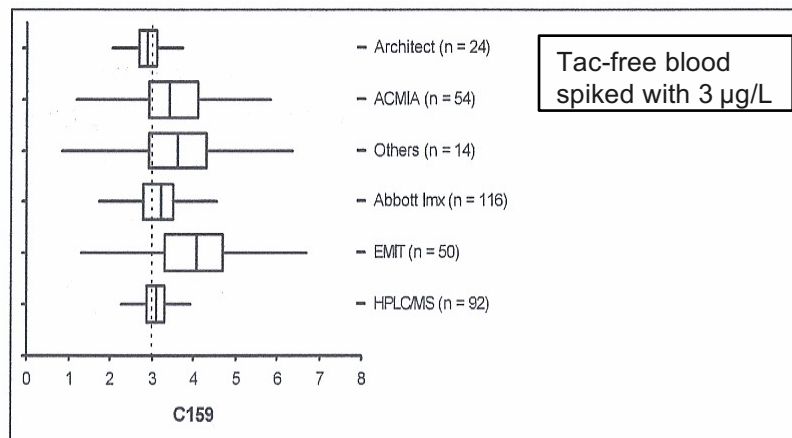# Skilled lab technicians

Tacrolimus International Proficiency Testing Scheme

March –August 2008: precision data
  Improvement of the LC-MS(MS)
  Good results of the CMIA

August 2008

Tac-free blood spiked with 3 µg/L

- Architect (n = 24)
- ACMIA (n = 54)
- Others (n = 14)
- Abbott Imx (n = 116)
- EMIT (n = 50)
- HPLC/MS (n = 92)

C159

CV%

spiked
patients

LCMS EMIT IMx ACMIA CMIA

Laboratory challenges

- Since early 21st Century, with the tremendous progress in computer sciences and technologies, <u>new biomarkers and techniques appear every year</u>…
- With progress in life expectation and in medicine, the global "<u>costs of health" became a real challenge</u> for the Society
- During last decade, business has undergone fundamental changes as the world economy became more global with growing competition, <u>affecting also clinical chemistry</u>

As a consequence, a real gap exists currently between what is technically possible and available financial resources

KNOWLEDGE @ WHARTON

Search

TOPICS ▾   REGIONS ▾   RESEARCH   K@W RADIO   MORE ▾   ABOUT ▾

INNOVATION

From Startup to Meltdown: The Unraveling of Theranos

Jul 17, 2018

North America   Books, Business Ethics, Business Radio, Podcasts

Role of Immunosuppressive drugs TDM

- Expected future progress will most likely consider <u>patients quality of life</u>: new challenge for TDM!
  - Reduction of side effects, rejection episodes
  - Reduction of number of drugs intake
  - Reduction of hospital stay…

- <u>TDM is not only a drug concentration assay</u> !
  - It should be considered as a tool for individualized therapy
  - It should be based on
    - Analytical expertise
    - Clinical pharmacokinetics including pharmacogenetics
    - Pharmacodynamics

Therapeutic drug monitoring:

- development of new strategies

- Since the years '80, permanent search for an optimal marker of efficacy/toxicity e.g.:
  - plasma, **whole blood**, free vs **total** fraction
  - bioassay (MLC, radio-receptor assay, calcineurin pentamer assay…),
  - sampling time: **trough**, C_2, peak, full AUC, abbreviated **AUC**, …

- No other strategy has shown reproduced superiority to routine C_0 monitoring for predicting transplant organ rejection

9
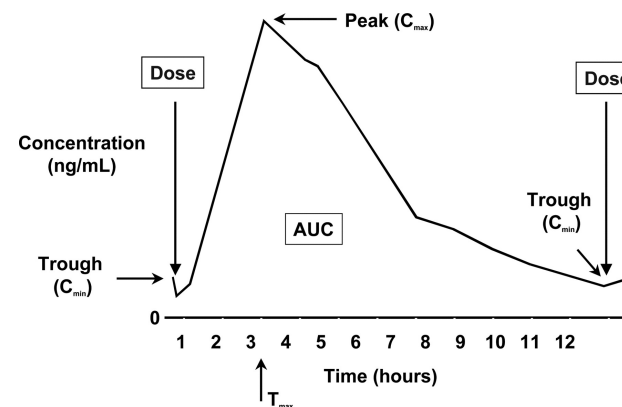
Suggested therapeutic ranges

Trough level	Time	Kidney	Liver	Heart or lung
Cyclosporine C_0 (C2) (ng/mL)	Initiation maintenance	150-250 (>1200) 75-150 (800)	250-350 (>1000) 100-200 (600)	250-350 150-250
Tacrolimus (ng/mL)	Initiation Maintenance Minimization	10-15 5-10 3-7	10-20 5-10 -	15-20 5-10 -
MPA (µg/mL)	Initiation Maintenance	1.3-3.5 (CsA) or 1.7-4.0 (Tac) Target AUC 30-60 µg.h/mL		
Sirolimus (ng/mL)	Initiation Maintenance	5-15		
Everolimus (ng/mL)	Initiation Maintenance	5-15 3-8		

Complementary possible approaches

- Pharmacokinetics
  - Improve AUC prediction: by Pop PK, Bayesian estimates, abbreviate AUC,…
  - Determine or predict drug concentration in target tissues (biopsies, lymphocytes,…)
  - Implement pharmacogenetics for early dosage optimisation
- Pharmacodynamic markers
  - Identify markers
  - Standardize methods
- Analytical
  - Improve robustness and standardisation
 - Improve sensitivity and specificity

How better predict AUC?

- Tacrolimus AUC_{0-12} (full or abbreviated: 5-12 samples)
  - Probably the best estimate for exposure but difficult to obtain
    Undre N et al. Transplant Proc,31,296-8,1999
    Uchida K et al. Transplant Proc,34,1736-7,2002….
- Limited Sampling Strategies (*Ting LSL et al. TDM,28,419-30,2006*)
  - Most studies proposed LSS using sampling within 4h (C_2, C_4) or (C_1, C_4, C_8) with multiple regression analysis
  - promising results obtained, but need proper validation before clinical use
- Influence of covariates on AUC_{0-12}
  - Various performances
    Staatz CE et al. Liver Transplant,9,130-7,2003
- Pop PK and AUC_{0-12} Bayesian estimation using LSS
  - Need accurate PK model
    Saint-Marcoux F, Clin Pharmacokinet,44,1317-28,2005

Unpredictability of the drug concentration at the target site

- Target sites are the Lymphocytes or indirectly (surrogate m.)
  - Transplant tissues (liver biopsies,…)
  - Peripheral Blood Mononuclear Cells (PBMC)
- Absence of clear relationship between blood concentration and tissue or Lymphocytes concentration
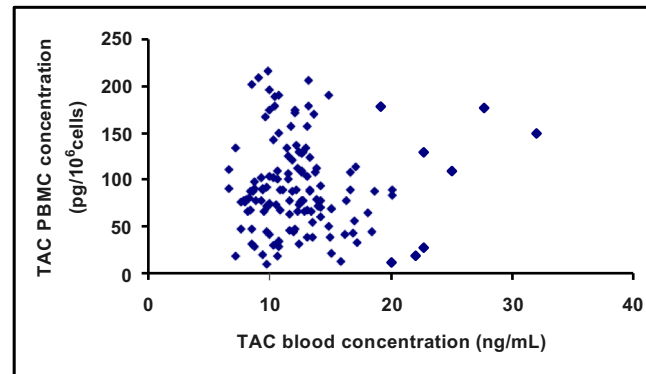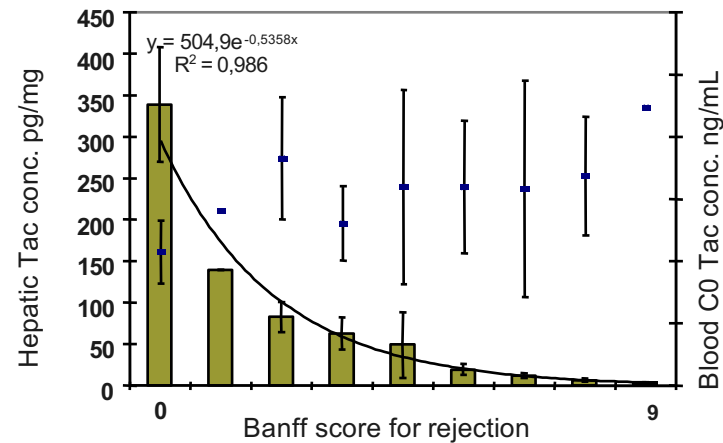

Capron A et al. TDM 2008

Tacrolimus concentration in liver biopsies
Relationship with histologic rejection score

- Choice of alternative biological matrix
  - Better correlation between Tac tissue levels (hepatic biopsies) and score for rejection than with whole blood

Capron A et al. TDM 29, 240-8,2007

Clinical impact of genetic polymorphism

- Kidney Transpl expressor: 2.3 fold difference in dose requirement
  - Proposed guidelines: different prospective loading Tac dose based on CYP3A5 GP: 0.15 vs 0.075mg/kg/12h (in expr vs non-expr)
    Haufroid V et al. Am J Transplant 6,2706-13,2006

- Liver Transpl pop: need to consider both donor and recipient

- No incidence of CYP3A5 expression on acute rejection,
  - Most likely due to TDM action during the 1st week
    Hesselinck DA et al, Pharmacogenet Genomics.18, 339-48, 2008

- Lack of studies analysing the incidence of the prospective loading dose based on GP, on acute rejection rate

Immunosuppressants:
Conclusions and general perspectives

- TDM: major support to patient management
  - Compliance and side effects prevention (less clear for efficacy)
  - New TDM challenge: quality of life
- Keep aware of causes of variability
  - Pharmacogenetics (CYP3A5 expressors need higher doses)
  - Chronic diarrhea alters P-gp and causes increased Tac levels
  - Paediatrics (higher dosage requirements)
  - Drug interactions, liver function,…
- TDM should not anymore be considered as a simple blood concentration numerical result!!
  - It should include all complementary approaches helping tailoring individually optimal drug dosage (PK, PG, PD...)

Part 2
Cancer and Chemotherapy
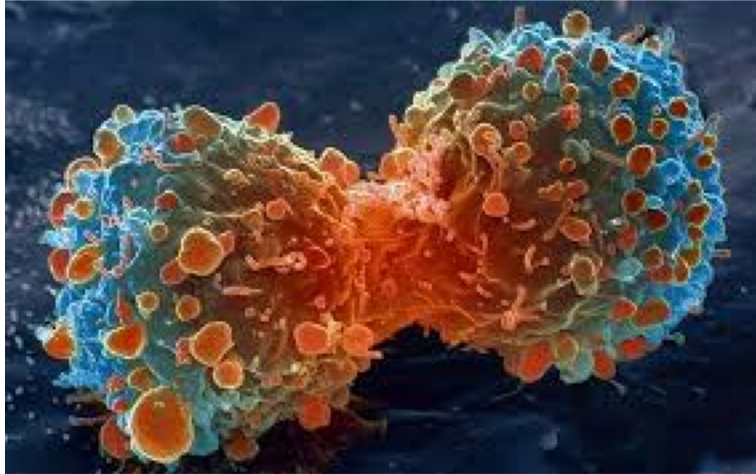
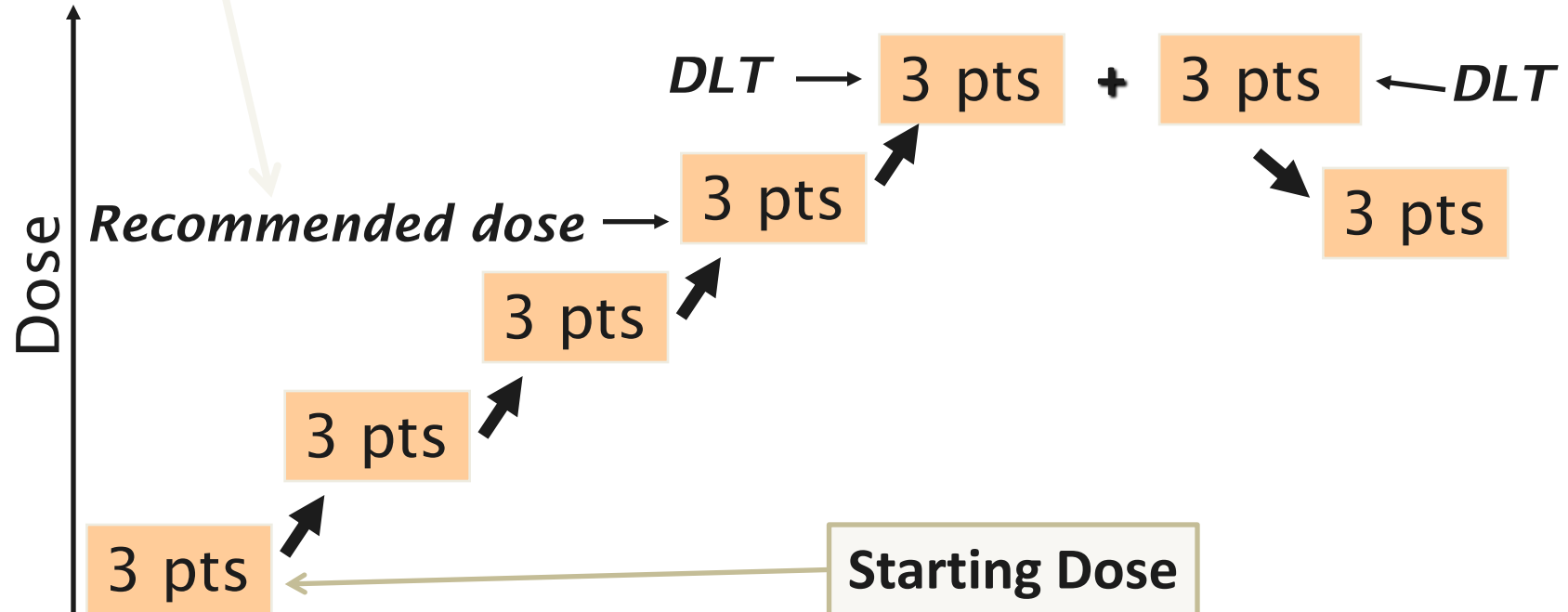# Monitoring Chemotherapy Drug Levels

- Chemotherapeutic drugs are not routinely monitored, with a few exceptions
  - (e.g. methotrexate, busulfan)
  - Traditional administration is dose according to body surface area
  - Measure clinical response (or toxicity); choose next steps; repeat

- Opportunities:
  - 5FU, paclitaxel, imatinib

Maximum Tolerated Dose

At this level, 50 to 66% of patients are not receiving MTD

DLT = 1 or more patients w/grade 3 or 4 toxicity

DLT → 3 pts **+** 3 pts ← DLT

3 pts

Recommended dose → 3 pts

3 pts

3 pts

3 pts → **Starting Dose**

Seymour et al. *Cancer Chemother Pharmacol*. 47 (2001) 2.
Eisenhaur et al. *J Clin Oncol*. 18 (2000) 684.
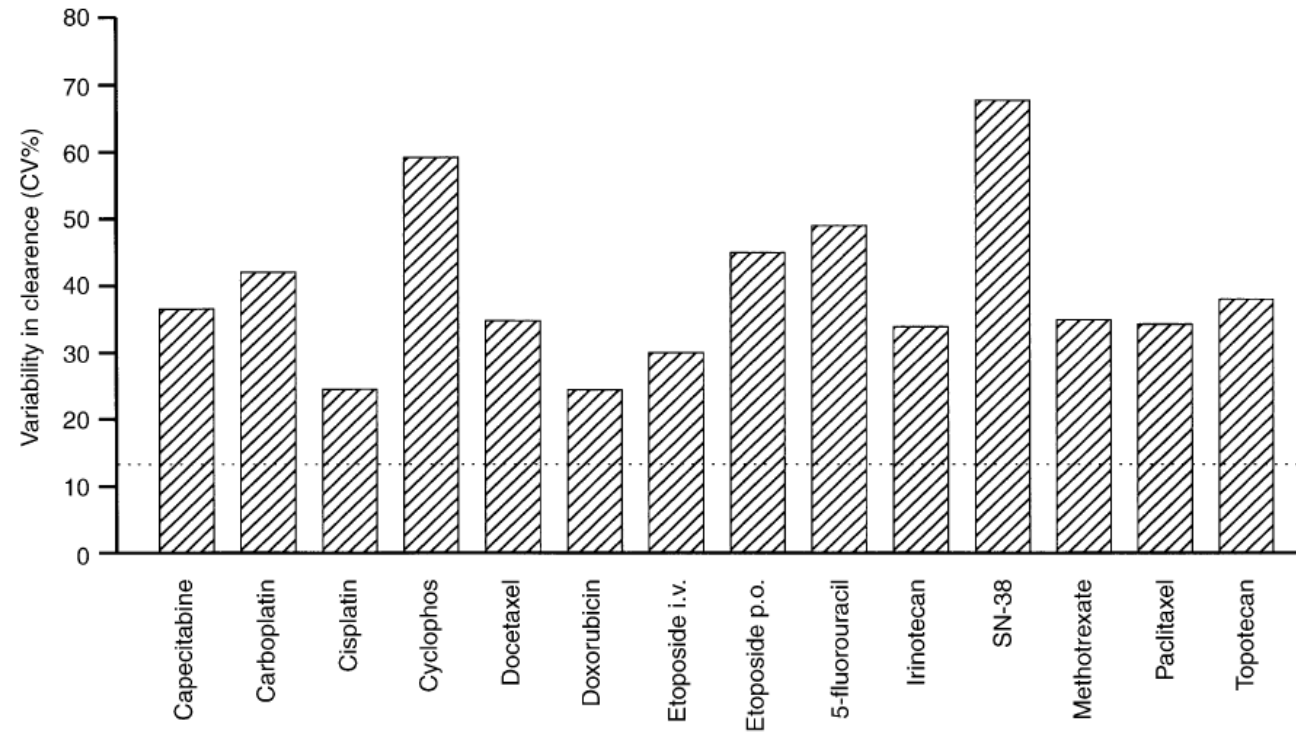
PK Variability in Cancer Chemotherapy

Fig. 1. Variability in the plasma clearance of commonly used anticancer drugs with data expressed as the coefficient of variation (%CV). The dotted line indicates the %CV in body surface area (BSA) in a group of 2355 patients treated at the Rotterdam Cancer Institute (mean (standard deviation (SD)), 1.855 (0.225) m^2). i.v., intravenous; cyclophos, cyclophosphamide; p.o., orally.

A. Felici et al. / European Journal of Cancer 38 (2002) 1677–1684

5-Fluorouracil

Colorectal Cancer

- Gamelin et al. 1998: Prospective multicenter trial with 152 patents with metastatic colorectal cancer
  - Leucovorin followed by 8 hour continuous infusion of 5-FU
- Target range: 2000 to 3000 µg/mL at steady state
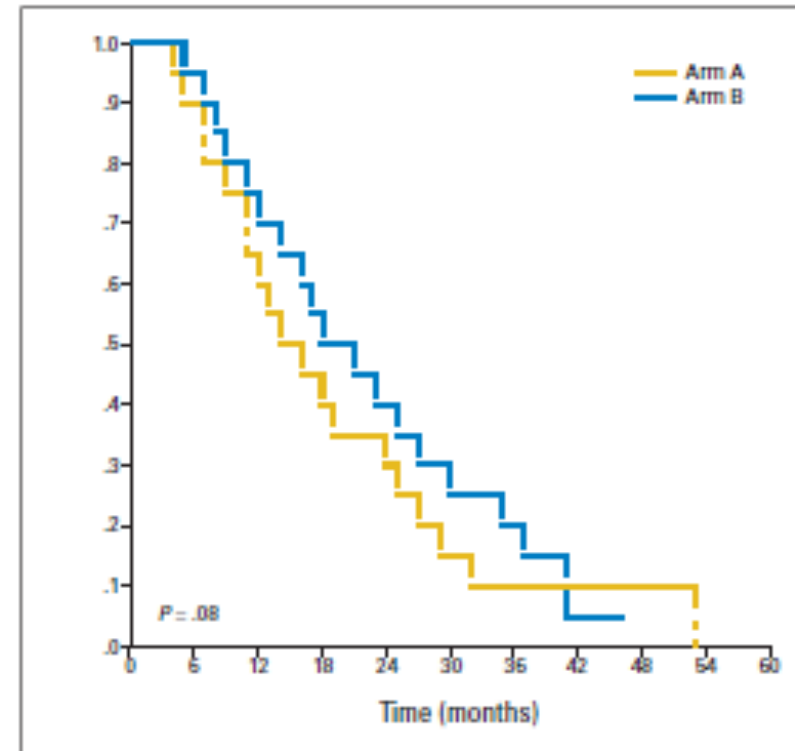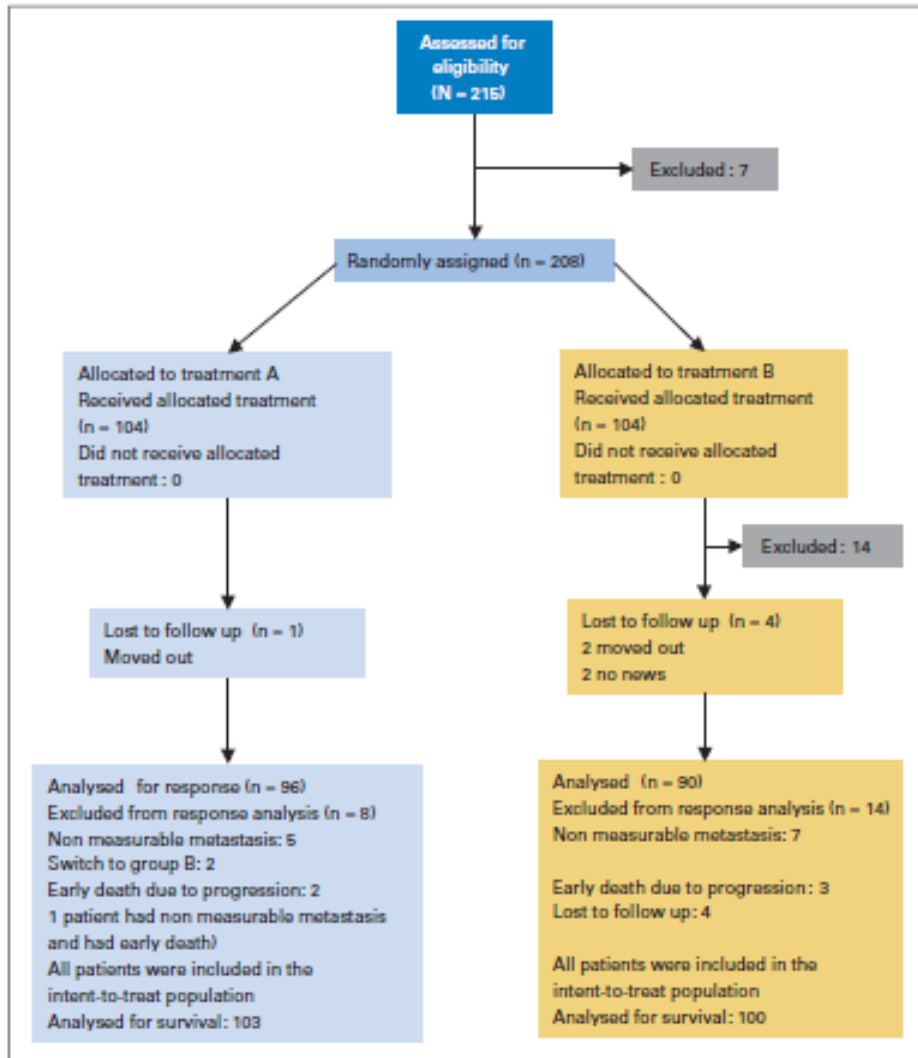
J Clin Oncol (1998) 16:1470-78

5-Fluorouracil (Adrucil)

Fig 2. Survival curve comparison: standard arm (arm A) versus pharmacokinetically guided, fluorouracil dose–adjusted arm (arm B).

Gamelin et al. *J Clin Oncol*. 26 (2008) 2099.

Gamelin Results

- Based on blood levels, 9% required lower doses while 81% required higher doses
- Often good responders had plasma levels increase over time and therefore needed reduced doses to avoid toxicity
- Correlation between acute toxicity and levels >3000 µg/mL was highly significant (P= .0001)

Paclitaxel

Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC)[†]

M. Joerger[1]*, J. von Pawel[2], S. Kraff[3], J. R. Fischer[4], W. Eberhardt[5], T. C. Gauler[6], L. Mueller[7], N. Reinmuth[8], M. Reck[8], M. Kimmich[9], F. Mayer[10], H.-G. Kopp[11], D. M. Behringer[12], Y.-D. Ko[13], R. A. Hilger[14], M. Roessler[15,16], C. Kloft[17], A. Henrich[17], B. Moritz[15,16], M. C. Miller[18], S. J. Salamone[18] & U. Jaehde[3]

Cycle 1

Patient gender and age

Patient age [y]	Dose women [mg/m^2]	Dose men [mg/m^2]
<46	185	200
46–50	180	195
51–55	175	190
56–60	170	185
61–65	160	175
>65	150	165

Cycles 2–6

Patient BSA, age, gender, bilirubin
Paclitaxel concentration

Paclitaxel population PK model

Estimation of individual $T_{C>0.05}$

| Neutropenia 0–2 in previous cycle		Neutropenia 3 in previous cycle		Neutropenia 4 in previous cycle	
$T_{C>0.05}$	Dose	$T_{C>0.05}$	Dose	$T_{C>0.05}$	Dose
>50	−30%	>50	−30%	>50	−40%
41–50	−25%	41–50	−25%	41–50	−30%
31–41	−20%	31–41	−20%	31–41	−25%
26–31	0%	<31	0%	<31	−20%
20–26	+10%				
10–20	+20%				
<10	+30%				

Figure 1. Dosing algorithm for patients in the experimental study arm B. BSA, body surface area; y, years; $T_{C>0.05}$, time over a paclitaxel plasma concentration of 0.05 µmol/l. First-cycle paclitaxel dose is guided by patient gender and age, while next-cycle paclitaxel dosing is guided by previous-cycle categorical neutropenia and $T_{C>0.05}$.
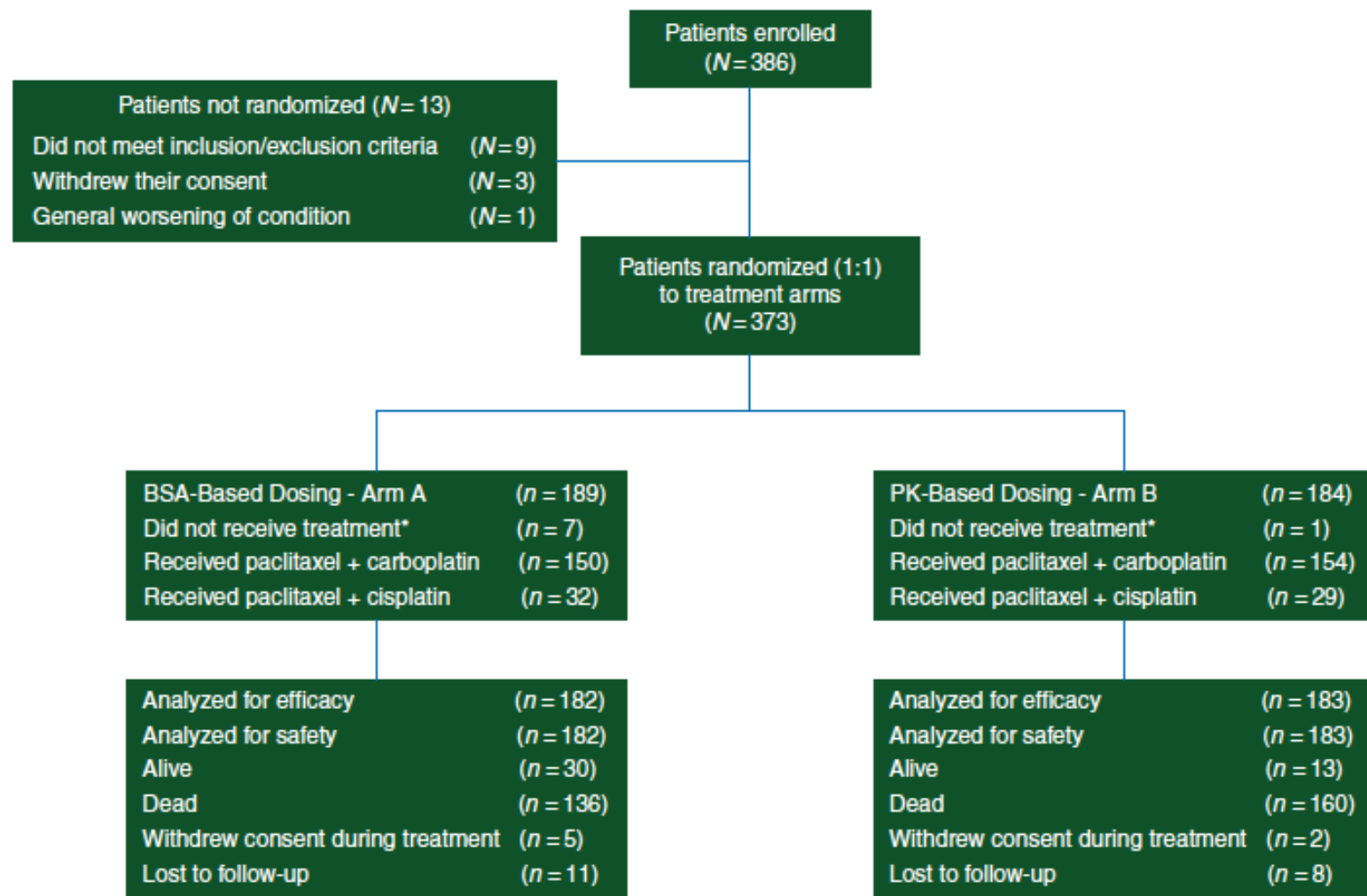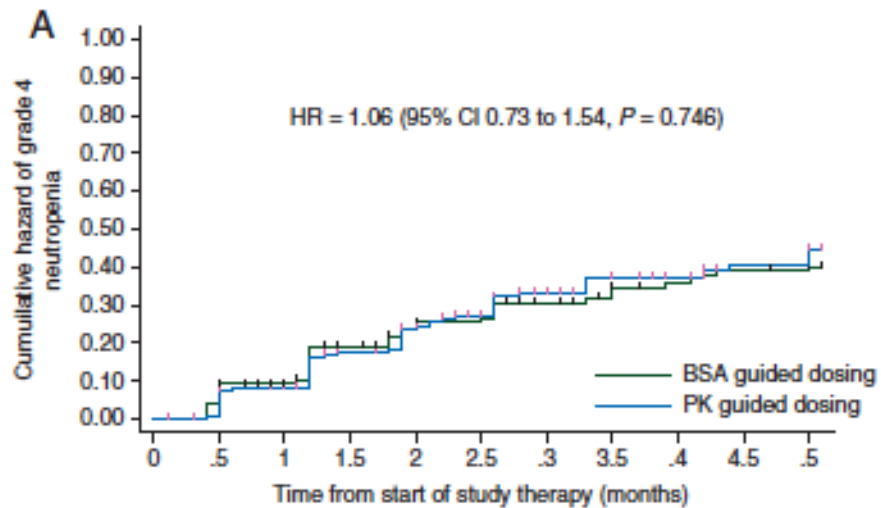
Figure 2. Disposition of patients. BSA, body surface area; PK, pharmacokinetic. *These patients were randomized but did not receive any study treatment due to rapid deterioration of their general health status, why they were not included into the efficacy or safety analysis.
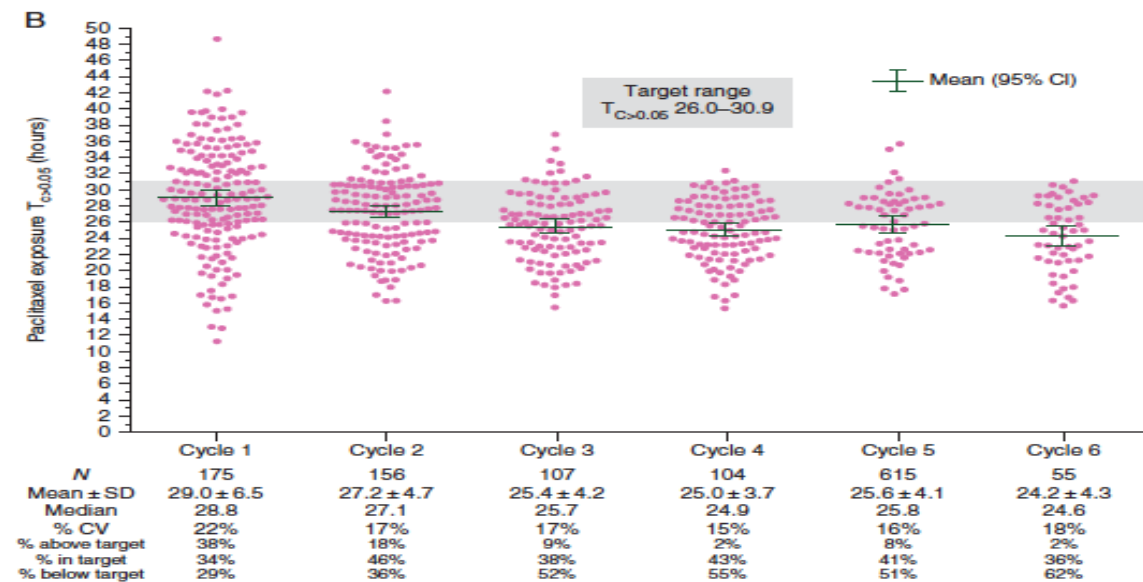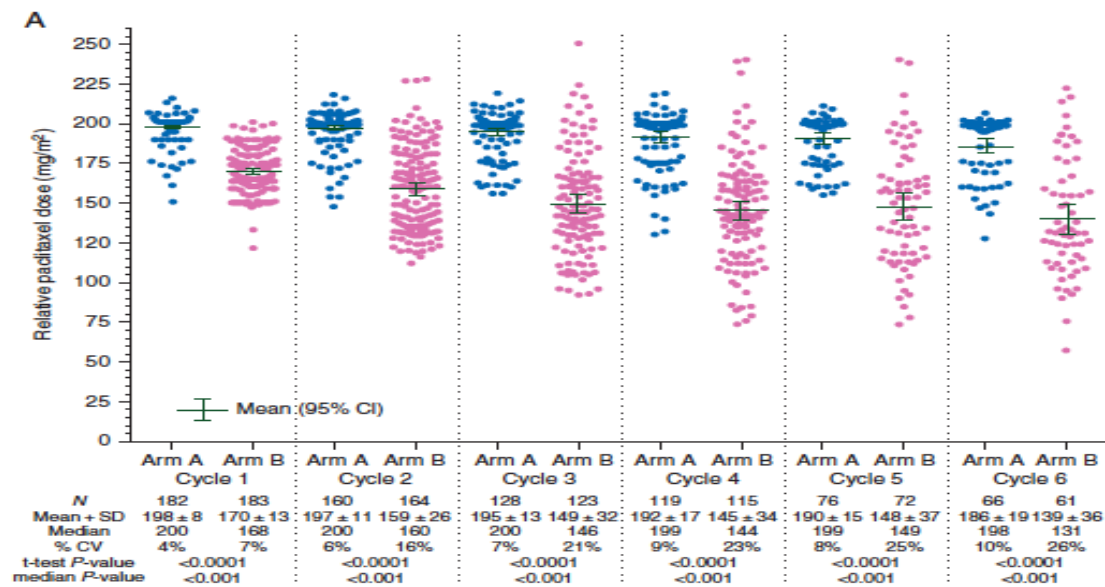
Figure 3. Paclitaxel relative dose and pharmacology. (A) Comparison of relative paclitaxel dose (mg/m²) over treatment cycles and per treatment arm. A significantly lower dose of paclitaxel was observed in study arm B compared with arm A over all treatment cycles. (B) Paclitaxel exposure ($T_{C>0.05}$) in the experimental treatment arm B over all six treatment cycles ($T_{C>0.05}$ target range between 26.0 and 30.9 h).

A

Cumulative hazard of grade 4 neutropenia

HR = 1.06 (95% CI 0.73 to 1.54, $P = 0.746$)

1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00

BSA guided dosing
PK guided dosing

0   .5   1   1.5   2   2.5   .3   3.5   .4   4.5   .5

Time from start of study therapy (months)

No at risk

BSA 182	172	155	134	122	119	107	103	97	87	86
PK 183	177	160	137	124	115	104	86	91	84	84

B

Cumulative hazard of grade 2–4 neuropathy

BSA guided dosing
PK guided dosing

1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0

HR=0.59 (95% CI 0.43 to 0.80, $P = 0.001$)

0   .5   1   1.5   2   2.5   3   3.5   4   4.5   5   5.5   6   6.5   7   7.5   8   8.5   9   9.5   10

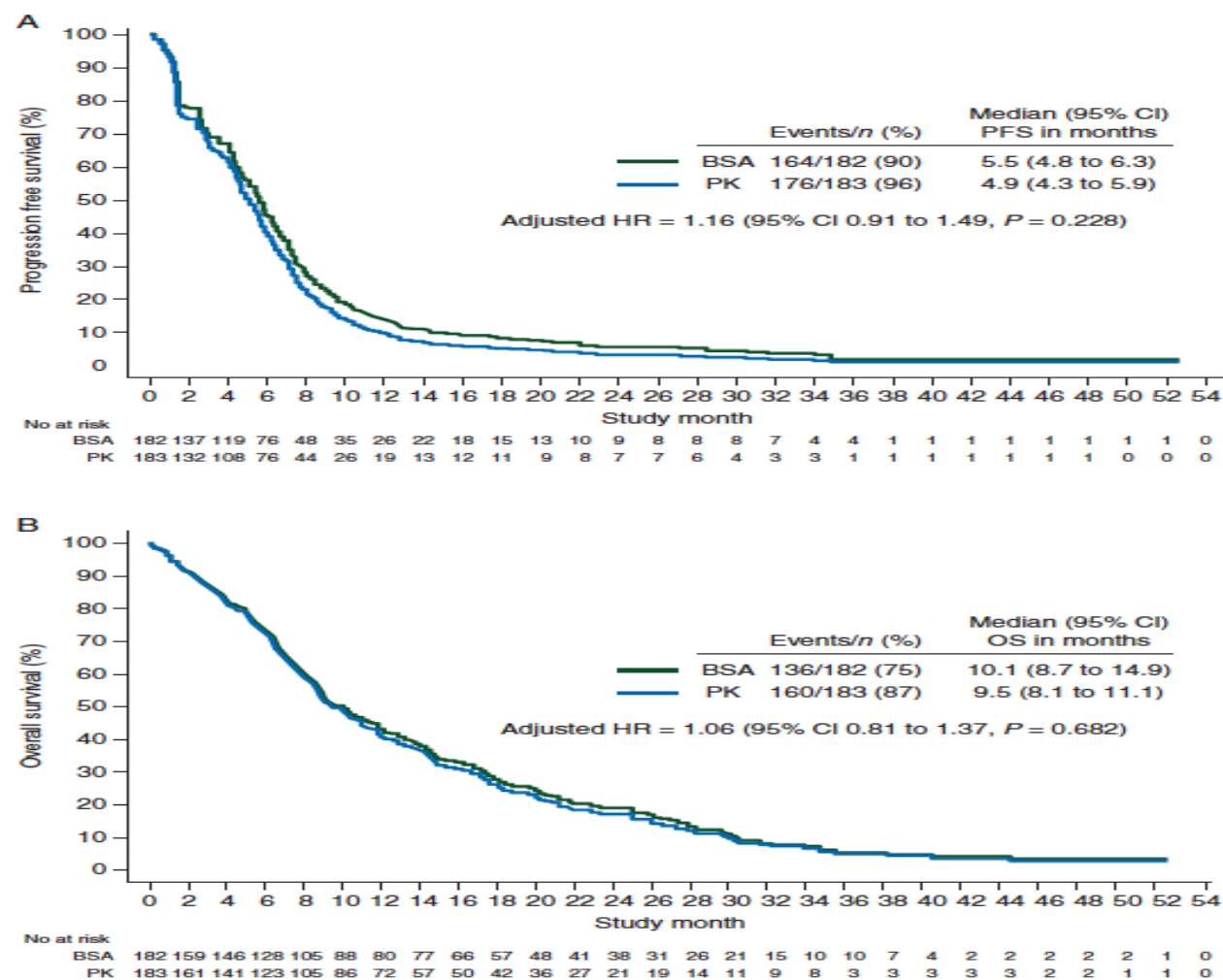Time from start of study therapy (months)
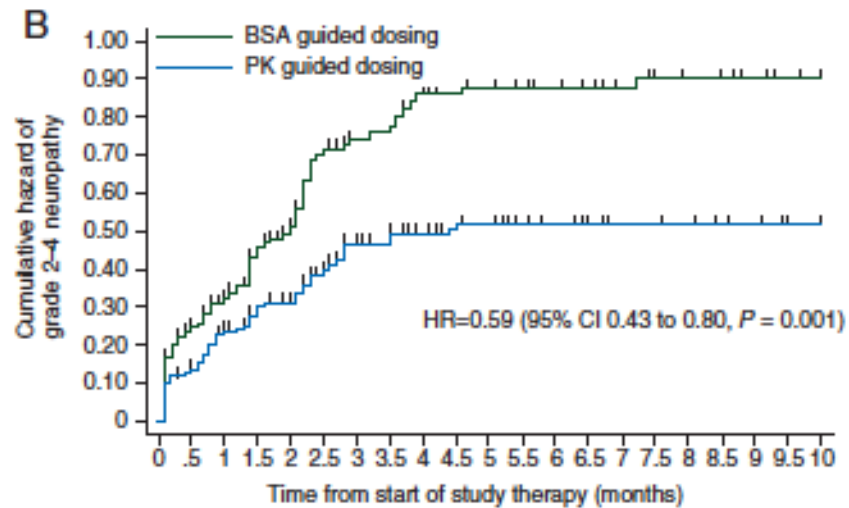
No at risk

BSA 182 139 122 102 90 71 64 63 56 51 49 47 45 43 39 37 35 35 30 28 27
PK   183 155 138 123 115 102 90 87 80 75 73 67 64 61 56 56 55 51 50 48 47

No difference in efficacy

Figure 5. (A) Progression-free survival (PFS) and (B) overall survival (OS) for patients receiving body surface area-based versus pharmacokinetically guided dosing of paclitaxel (patients included in the efficacy analyses). HR, hazard ratio; BSA, body surface area; CI, confidence interval; PK; pharmacokinetically.

Study Arm	Decrease	No Change	Increase
Standard (Arm A)	33 / 130 (25%)	95 / 130 (73%)	2 / 130 (2%)
PK-Guided (Arm B)	85 / 138 (62%)	30 / 138 (22%)	23 / 138 (17%)

ASCO Abstract #8501: Joerger et al.

Study Conclusions

- PK-guided dosing of 3-weekly paclitaxel results in clinically relevant reduction of neuropathy compared to standard dosing

- Lower paclitaxel dosing had no negative effect on clinical outcome

- TDM = promising approach given the inability to prevent or treat chemotherapy induced neuropathy by other means
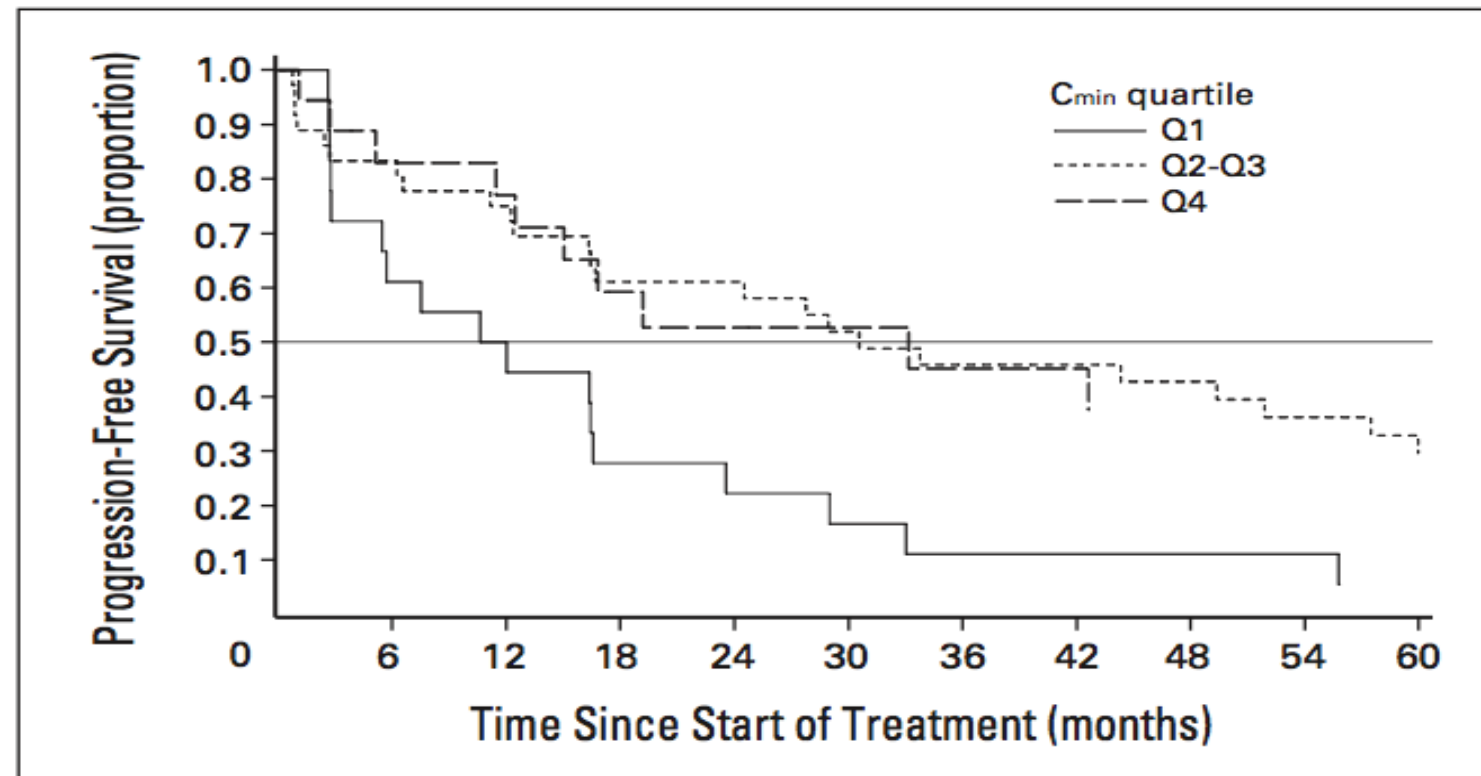
ASCO Abstract #8501: Joerger et al.

Imatinib

TDM of Imatinib

Imatinib Plasma Levels Are Correlated With Clinical Benefit
in Patients With Unresectable/Metastatic Gastrointestinal
Stromal Tumors

From the Ludwig Center, Dana-Farber/
Harvard Cancer Center, and Harvard
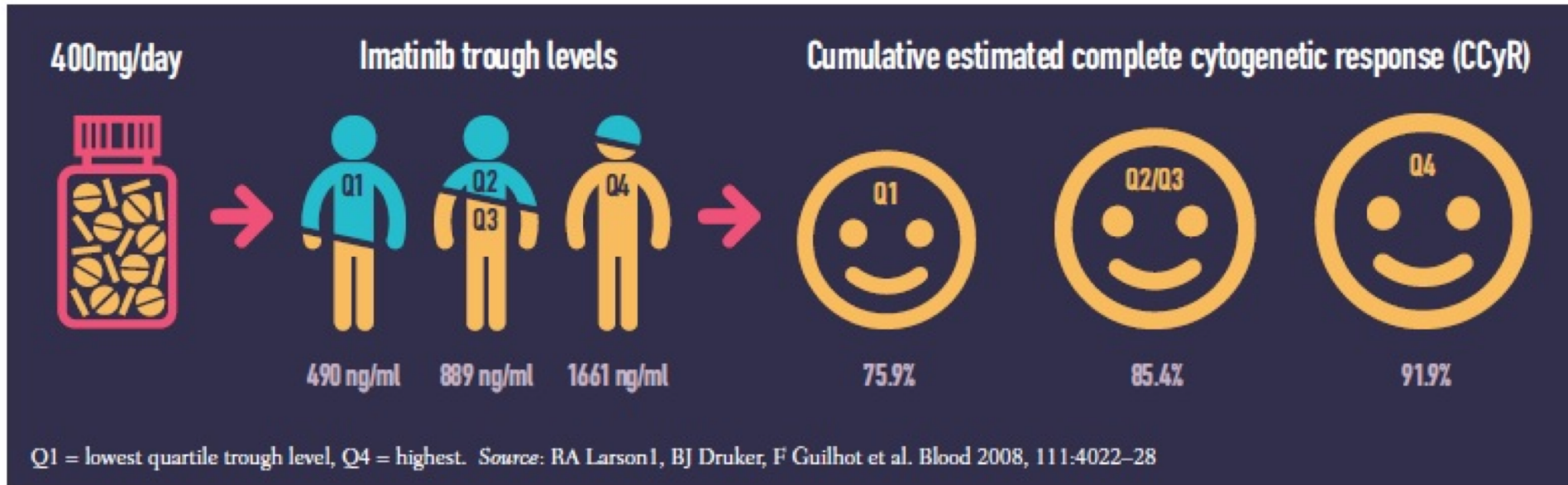Medical School, Boston, MA; Oncology

George D. Demetri, Yanfeng Wang, Elisabeth Wehrle, Amy Racine, Zariana Nikolova, Charles D. Blanke,
Heikki Joensuu, and Margaret von Mehren

Fig 3. Time to progression by imatinib day 29 trough level (C_{min}) quartile (Q).

TDM of Imatinib

400mg/day

Imatinib trough levels

Cumulative estimated complete cytogenetic response (CCyR)

Q1	Q2/Q3	Q4
490 ng/ml	889 ng/ml	1661 ng/ml
75.9%	85.4%	91.9%

Q1 = lowest quartile trough level, Q4 = highest. *Source*: RA Larson1, BJ Druker, F Guilhot et al. Blood 2008, 111:4022–28

Take Home Message
Comprehensive Approach to Precision Medicine