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Clinical cases on dose adjustments based on TDM of immunosuppressives and oncolytic agents

Hematopoetic Cell Transplantation as an example

Dr. Erik van Maarseveen
Clinical pharmacist, clinical pharmacologist, PharmD, PhD
UMC Utrecht, Dept. of Clinical Pharmacy

EAHP Seminar Warsaw, October 2018

Conflicts of interest

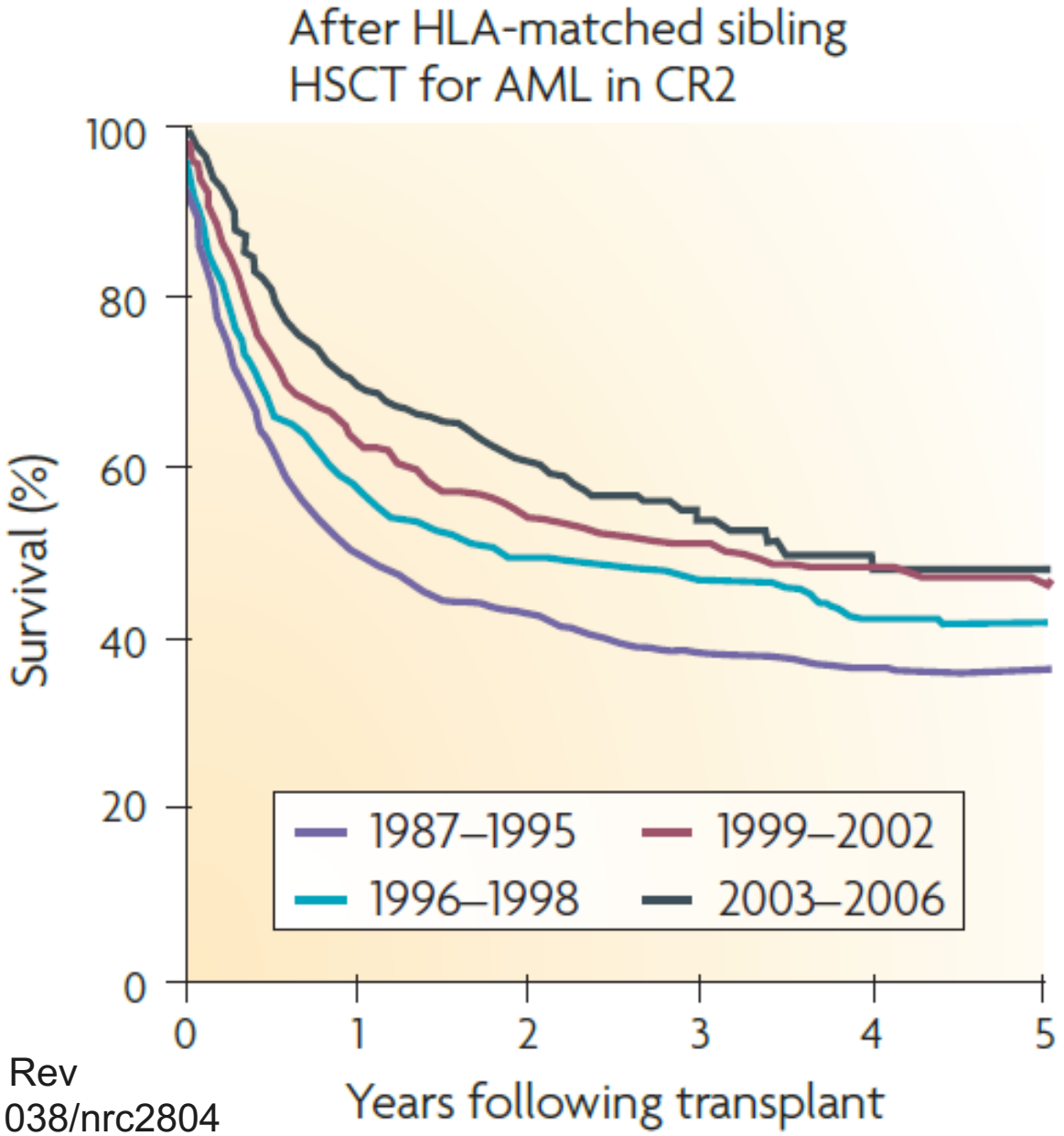
none


Wilhelmina Kinderziekenhuis
vóór kinderen tégen kanker
prinses MÁXIMA
centrum voor kinderoncologie
UMC Utrecht

This is Luuk and he wants to become a soccer player

- In 2016 Luuk was diagnosed with acute lymphoblastic leukemia
- He needed a hematopoetic cell transplantation (HCT)

HCT survival over the past decades

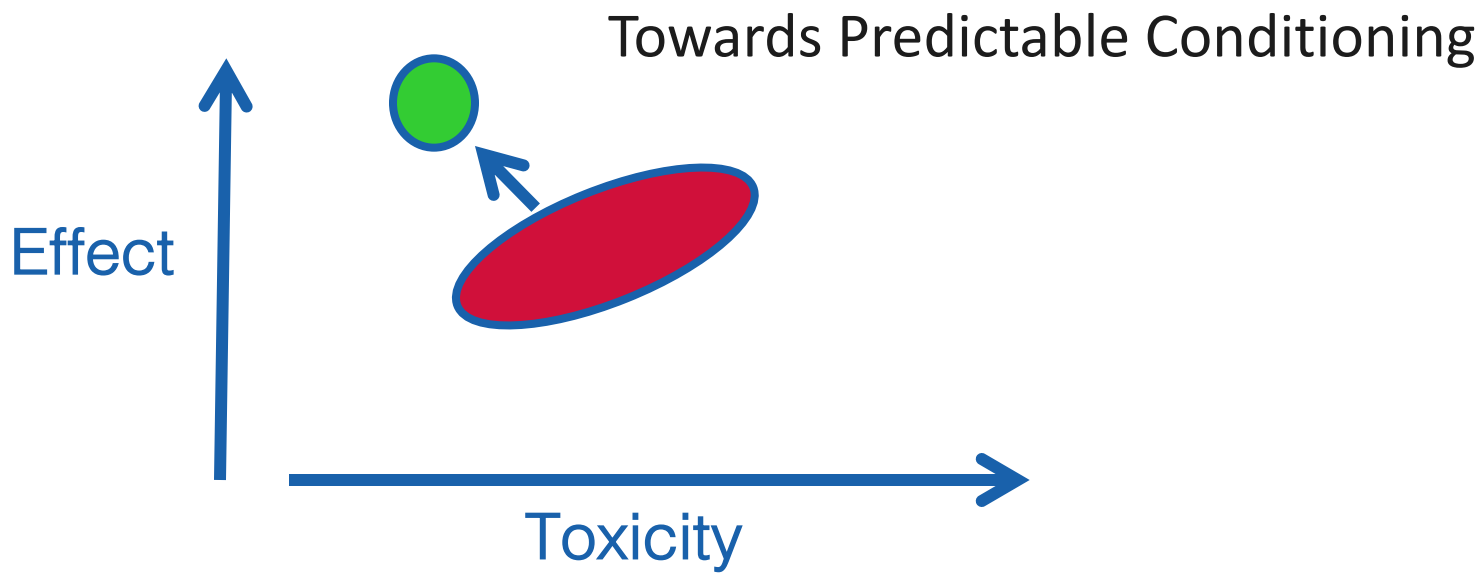


Jenq RR et al. Nature Rev Cancer, 2010;doi:10.1038/nrc2804

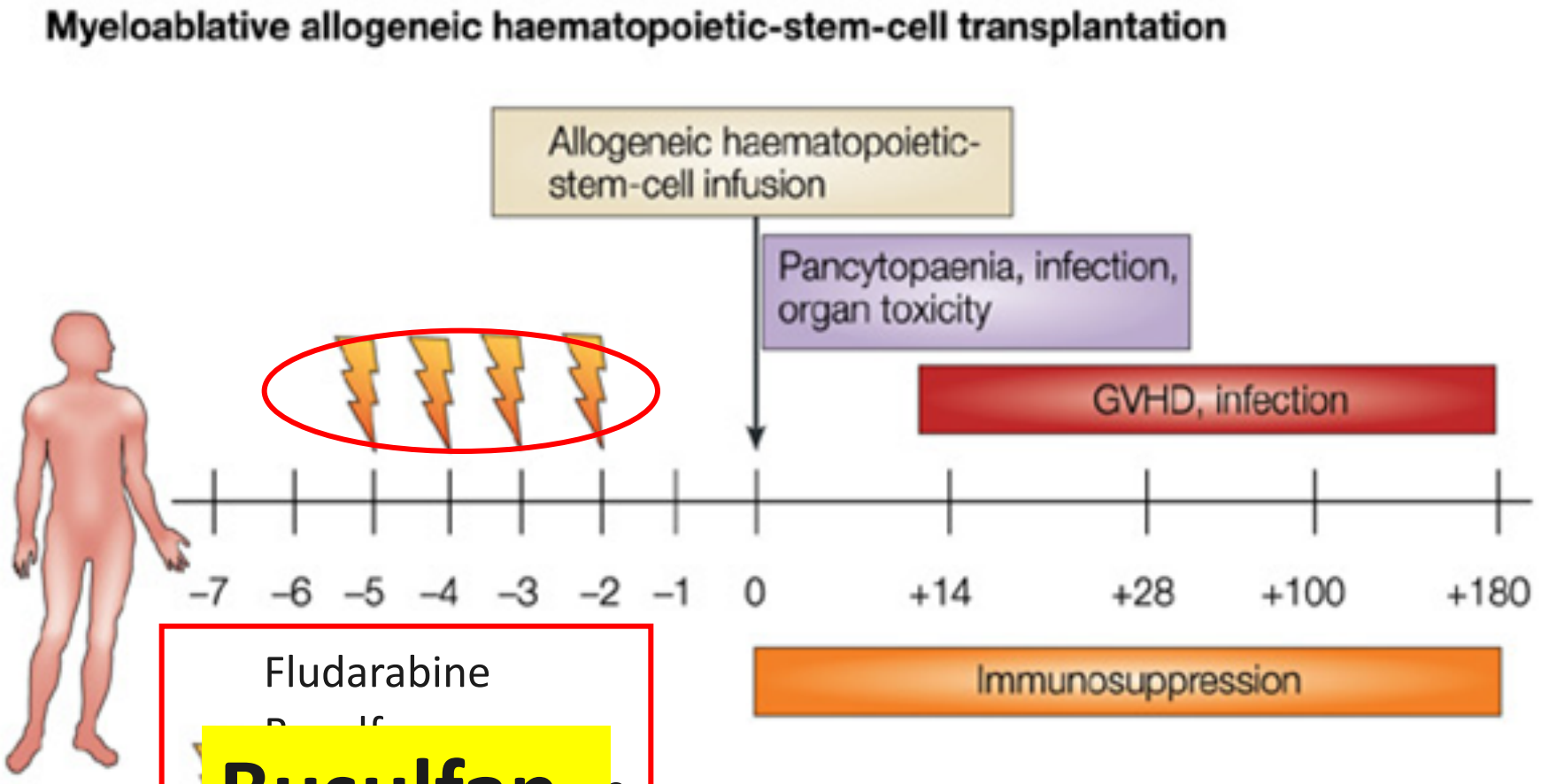
Challenges in HCT for upcoming years

1. **Reducing the toxicity of HCT**
    1. Short term toxicity: viral reactivation, GvHD; TRM
    2. Long term toxicity

2. **Better disease control**
    1. Lower risk of relapse



Conditioning prior to HCT



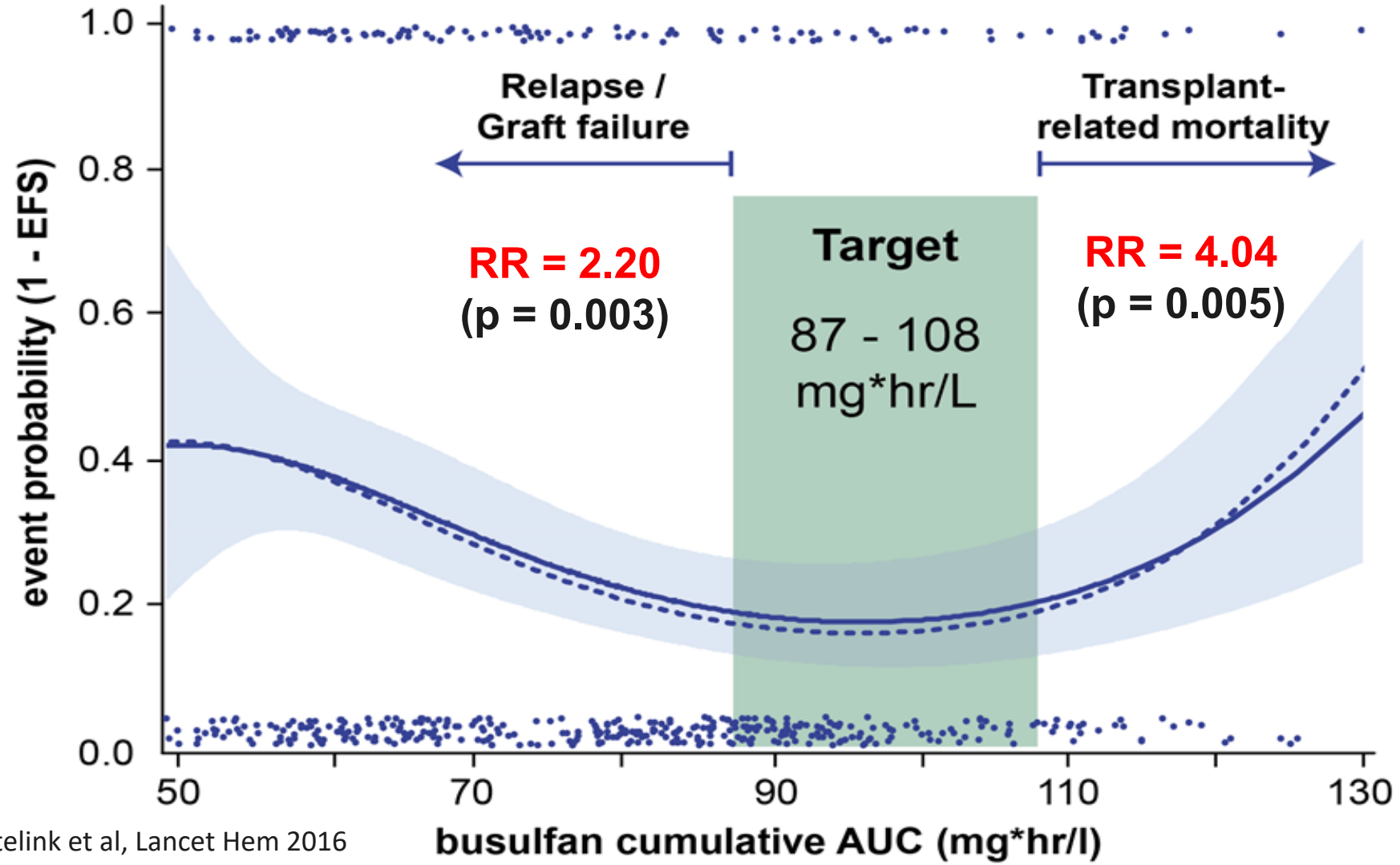
Bleakley & Riddell. Nature Reviews Cancer 4. 2004

Window of opportunity for Busulfan (BU) TDM?

1. Narrow window (exposure-effect relationships)
2. High between-patient variability in pharmacokinetics
3. Low within-patient variability in pharmacokinetics
4. Lack of a dose-effect relationship
5. Availability of appropriate bioanalytical assay including timely results
6. Effect can not readily be assessed by clinical observation or biomarkers

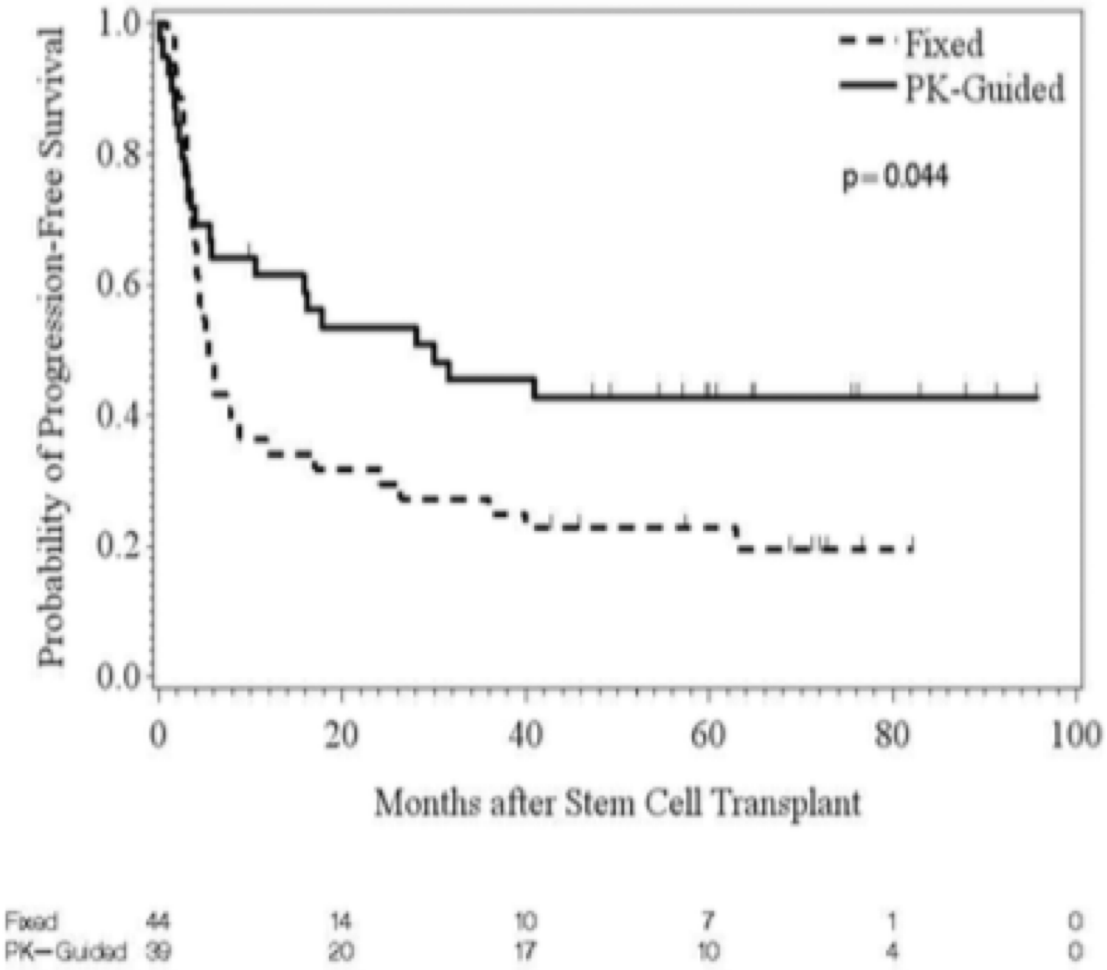
Aarnoutse, TDM 2003

Exposure-effect relationships (1 of 5)
Event-free survival (EFS) and Bu-AUC in children



Bartelink et al, Lancet Hem 2016

Evidence from an RCT in MDS/AML adults



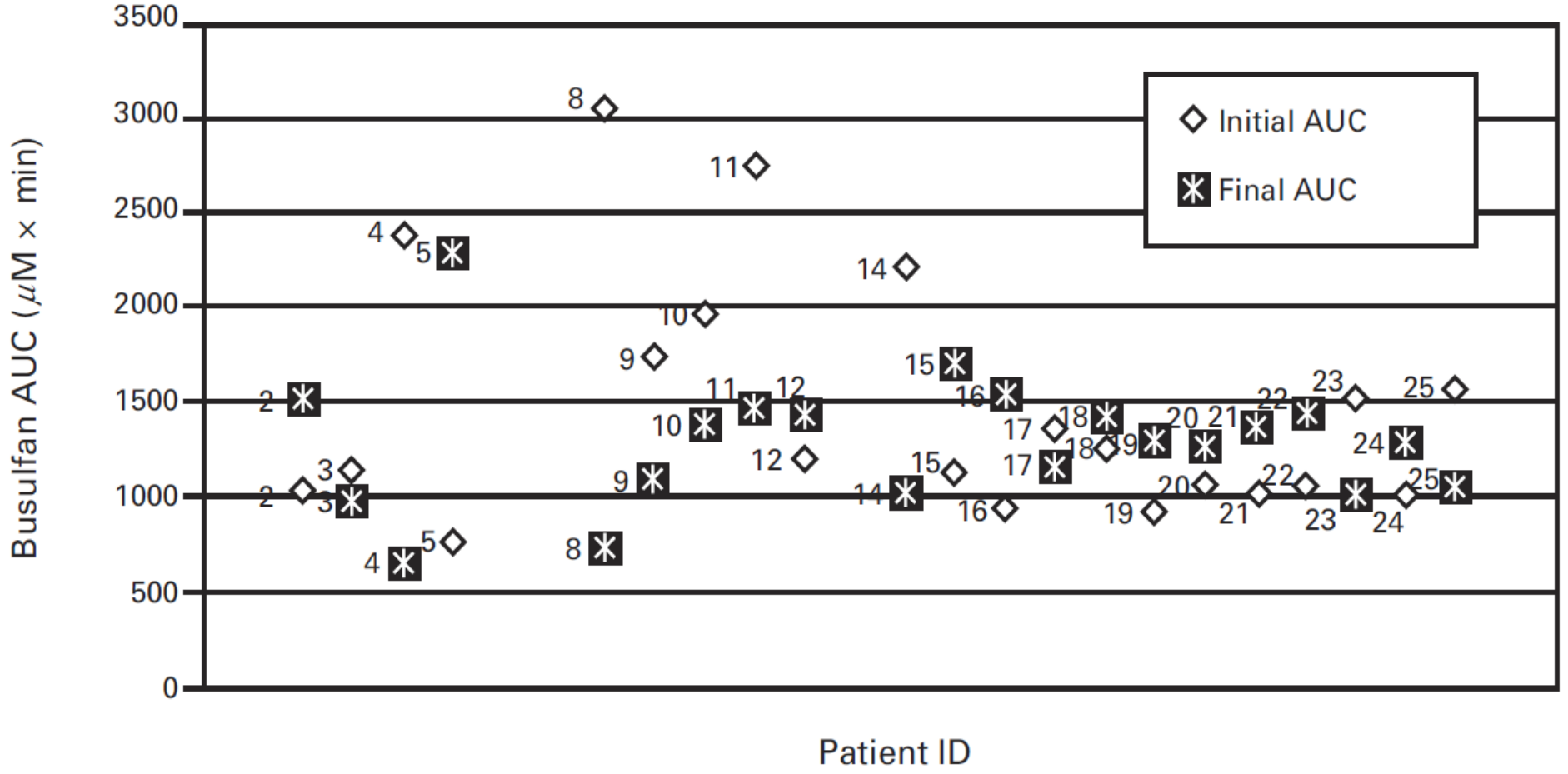
Andersson B. et al., BMT 2017

FDA label and EMA labels for BU

Therapeutic drug monitoring and dose adjustment following the first dose of BUSULFEX is recommended.

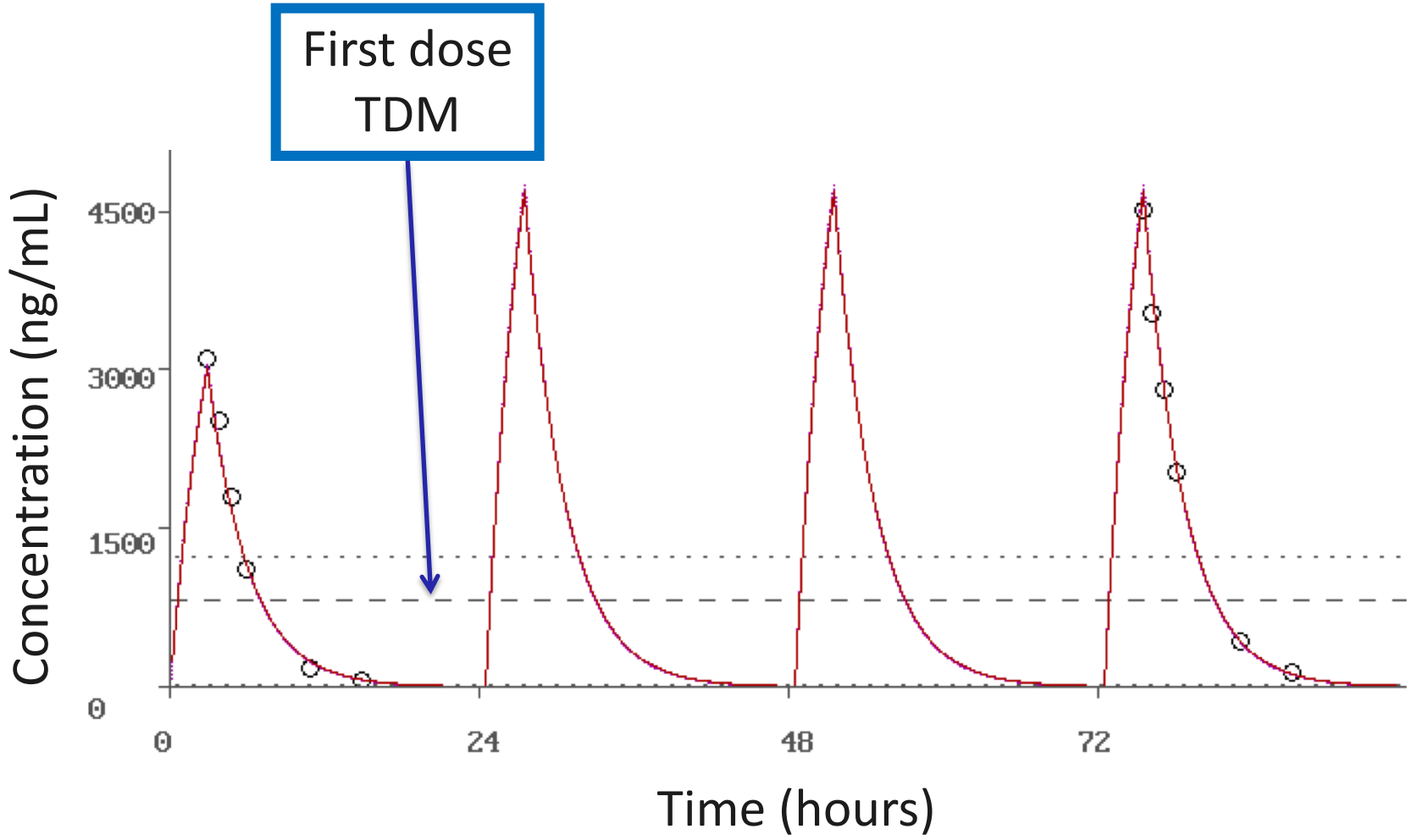
Within-patient PK variability (2 of 5)

Oral formulation

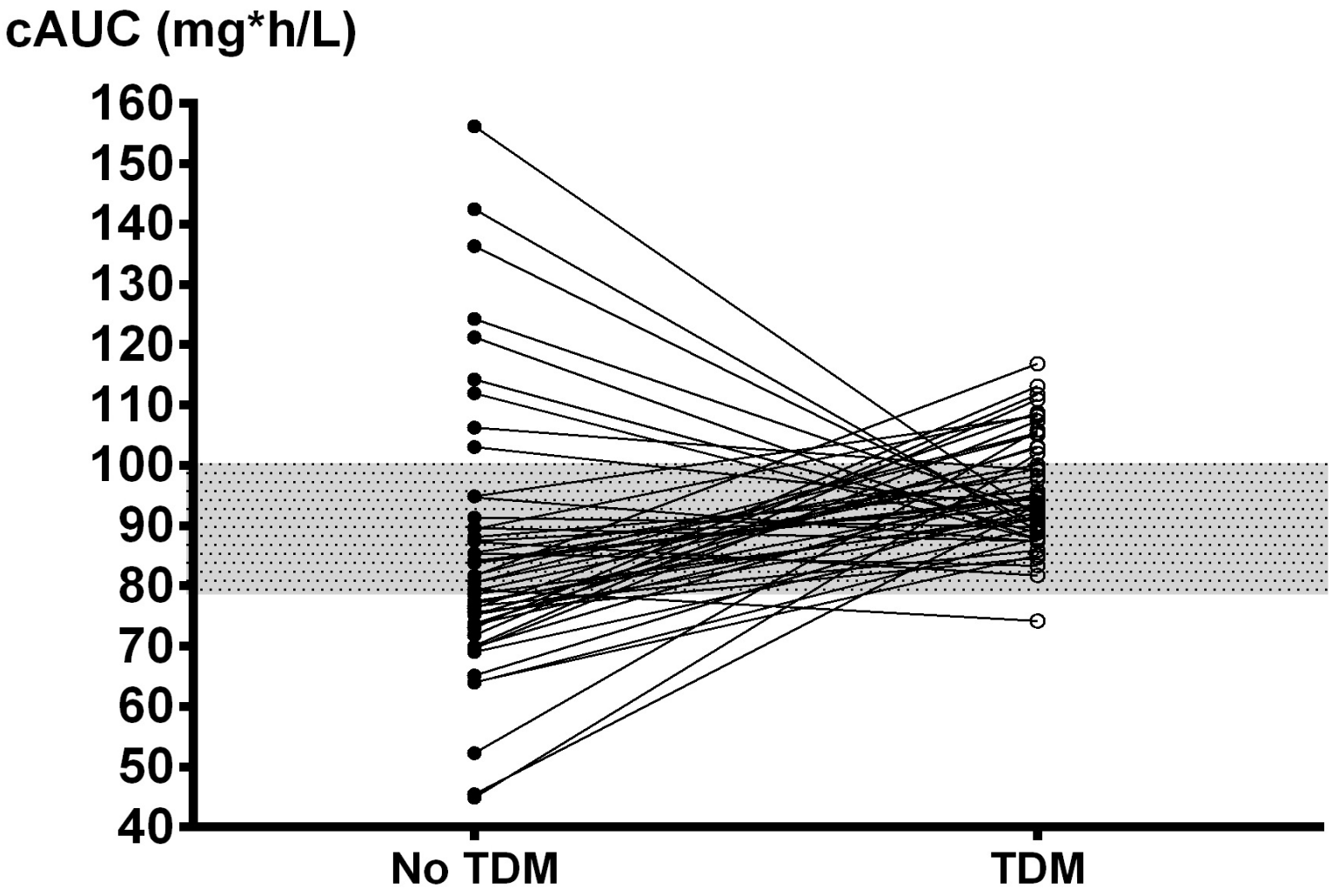


Tran H et al. Bone Marrow Transpl, 2000;26:463

Within-patient PK variability (3 of 5)
Intravenous formulation

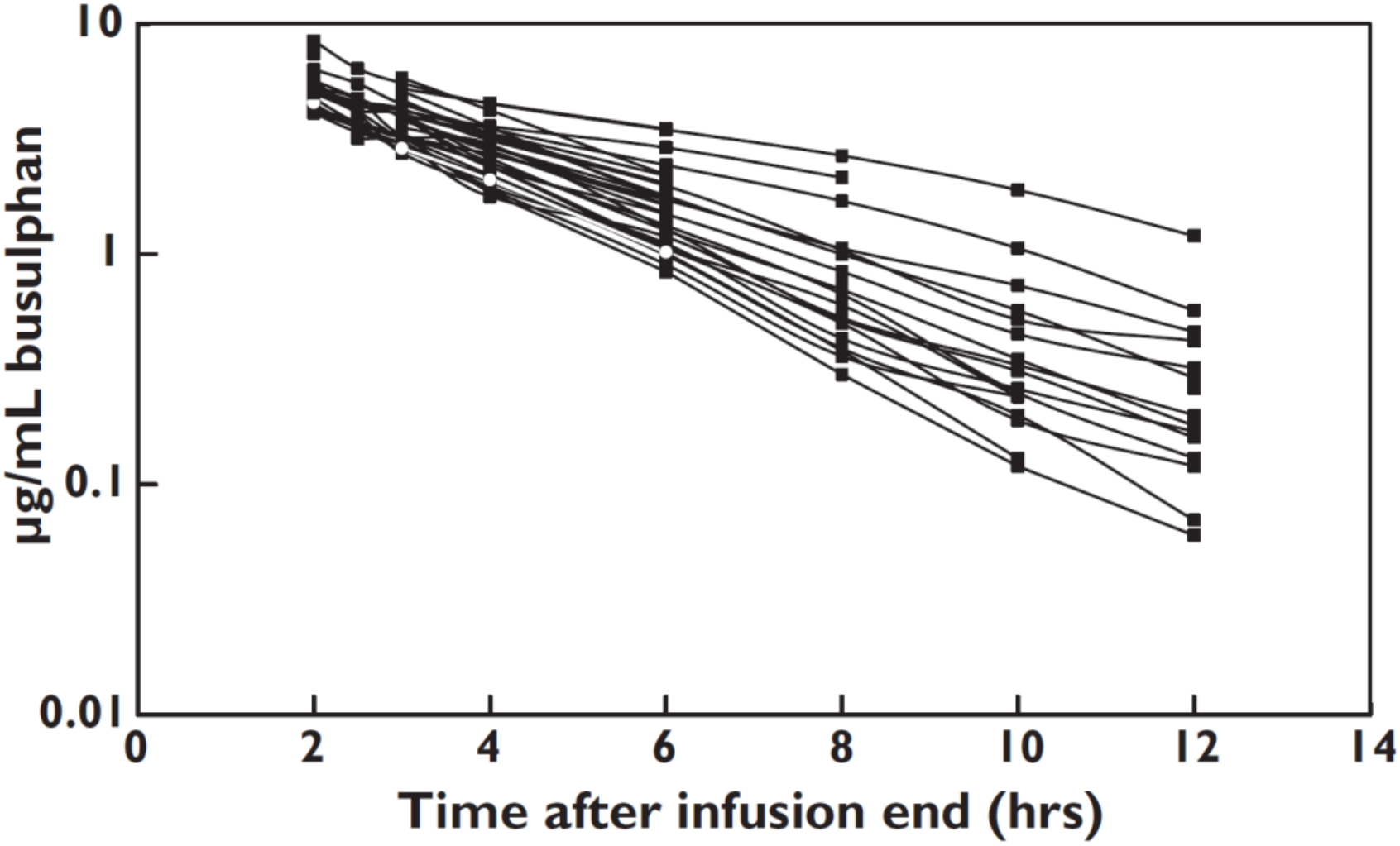


Within-patient PK variability
Intravenous formulation



Langenhorst et al, manuscript in preparation

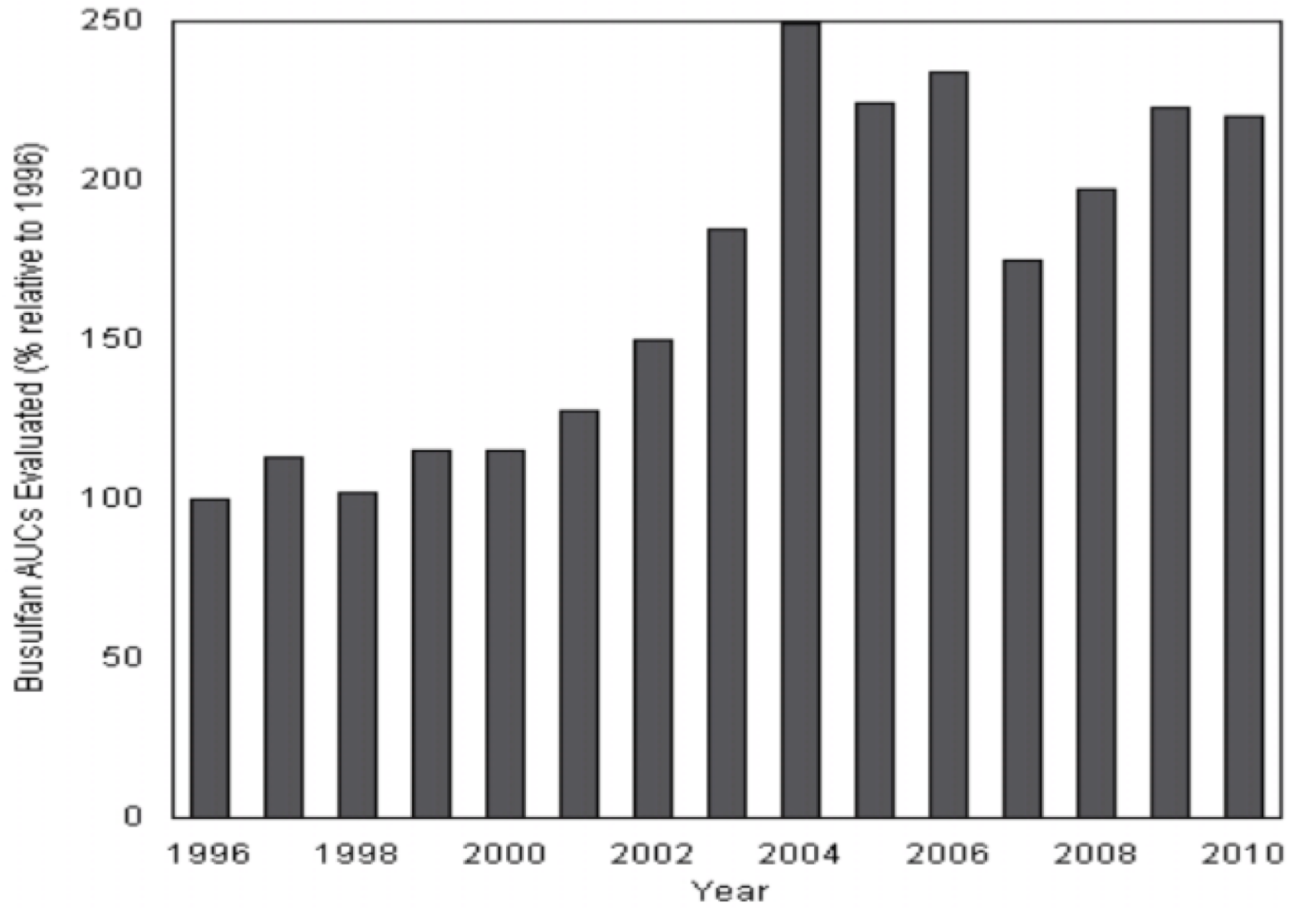
Between-patient PK variability (4 of 5)



Nath C et al. Br J Clin Pharmacol, 2008;66:50

Assay availability (5 of 5)

Supplemental Figure 1. Increasing use of busulfan therapeutic drug monitoring. IV busulfan was FDA approved on February 4th, 1999.



Slide at courtesy of Jeannine McCune


North Sea
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Leeds
Manchester
Sheffield
UNITED KINGDOM
Birmingham
NETHERLANDS
Hamburg
Berlin
The Hague
Amsterdam
Rotterdam
London
Düsseldorf
Cologne
BELGIUM
Brussels
Lille
GERMANY
English Channel
Prague
Frankfurt
TAIWAN
Luxembourg
Mannheim
Paris
Stuttgart
Vienna
Munich
Zürich
SWITZERLAND
Vaduz
AUSTRIA
Atlantic Ocean
Bern
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Florence
Monaco
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Window of opportunity for Busulfan TDM?

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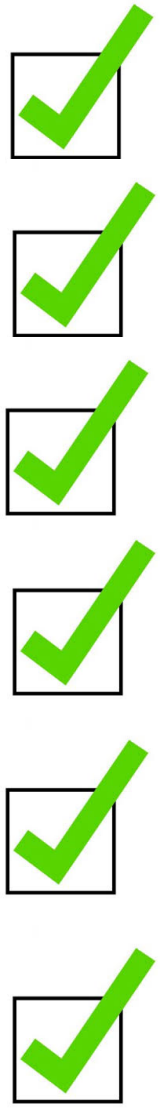


Aarnoutse, TDM 2003

Current discrepancies in BU within EU and beyond

1. Dosing nomograms
   - Once vs. multiple daily dosing

2. Assay quality and availability

3. Exposure target definition
   - Population & conditioning regimen
   - Exposure units

4. Method of exposure estimation

A Survey by the Complications and Quality of Life Working Party of the EBMT

Use of Busulfan in Conditioning for Allogeneic Hematopoietic Stem Cell Transplantation in Adults:

Tapani Ruutu, Steffie van der Werf, Anja van Biezen, Janne Backman, Arnon Nagler, Silvia Montoto, Mohamad Mohty, Dietger Niederwieser, Claudia Langebrake, Zinaida Peric, Rafael F Duarte and Grzegorz Basak

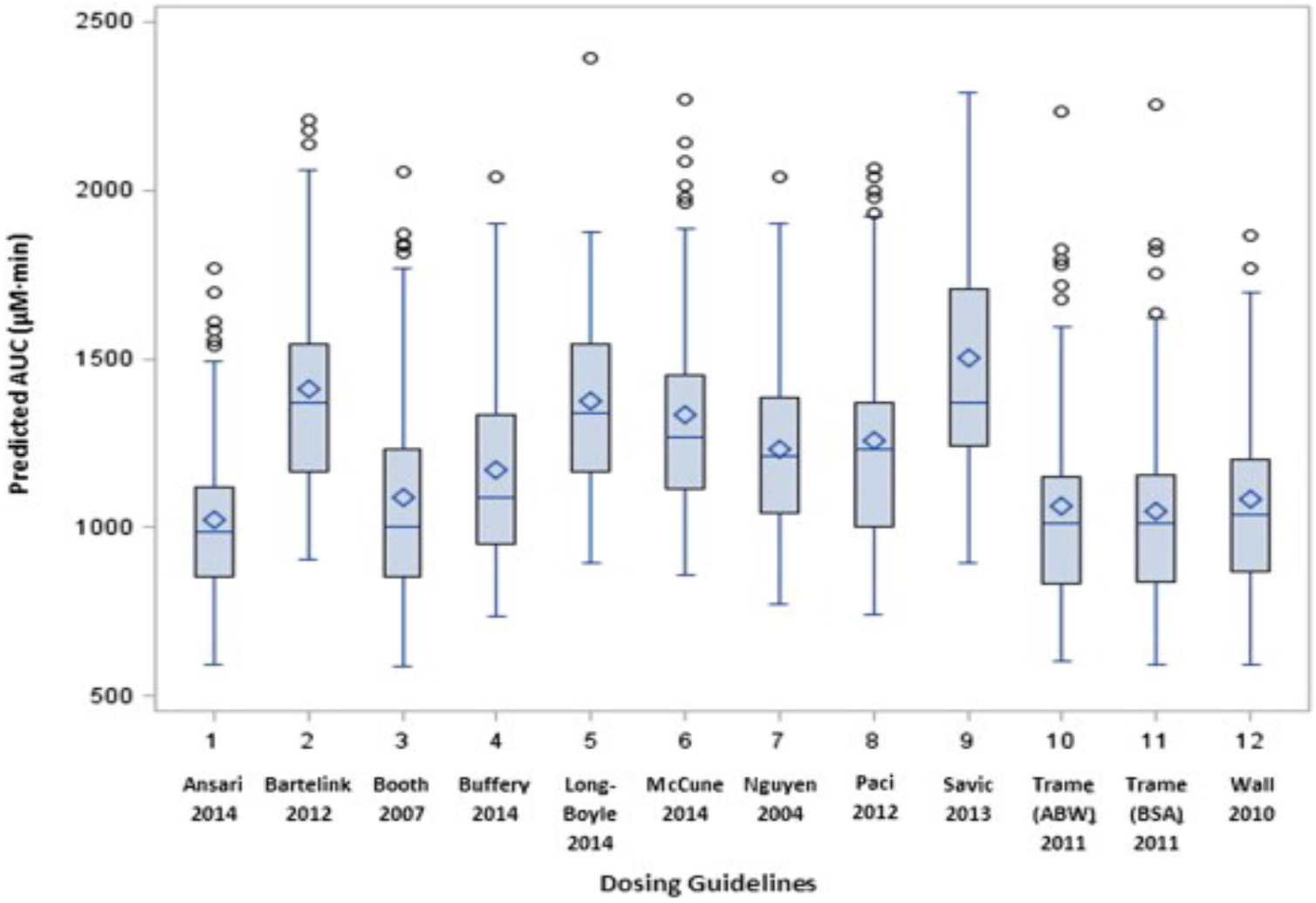
Ruutu et al., abstract presented at ASH 2017, Dec 1-4, San Diego, CA

A Survey by the Complications and Quality of Life Working Party of the EBMT

Inclusions

- Centers: 109 (28 % of EBMT registry) sent their report.
  - 105 used BU conditioning.
- Indications:
  - AML (99)
  - MDS (87)
  - CML (75)
  - ALL (56)
  - lymphoma (26)
  - thalassemia and other hemoglobinopathies (22)
  - CLL (17)
  - MPD (6)

Dosing nomograms (1 of 4)



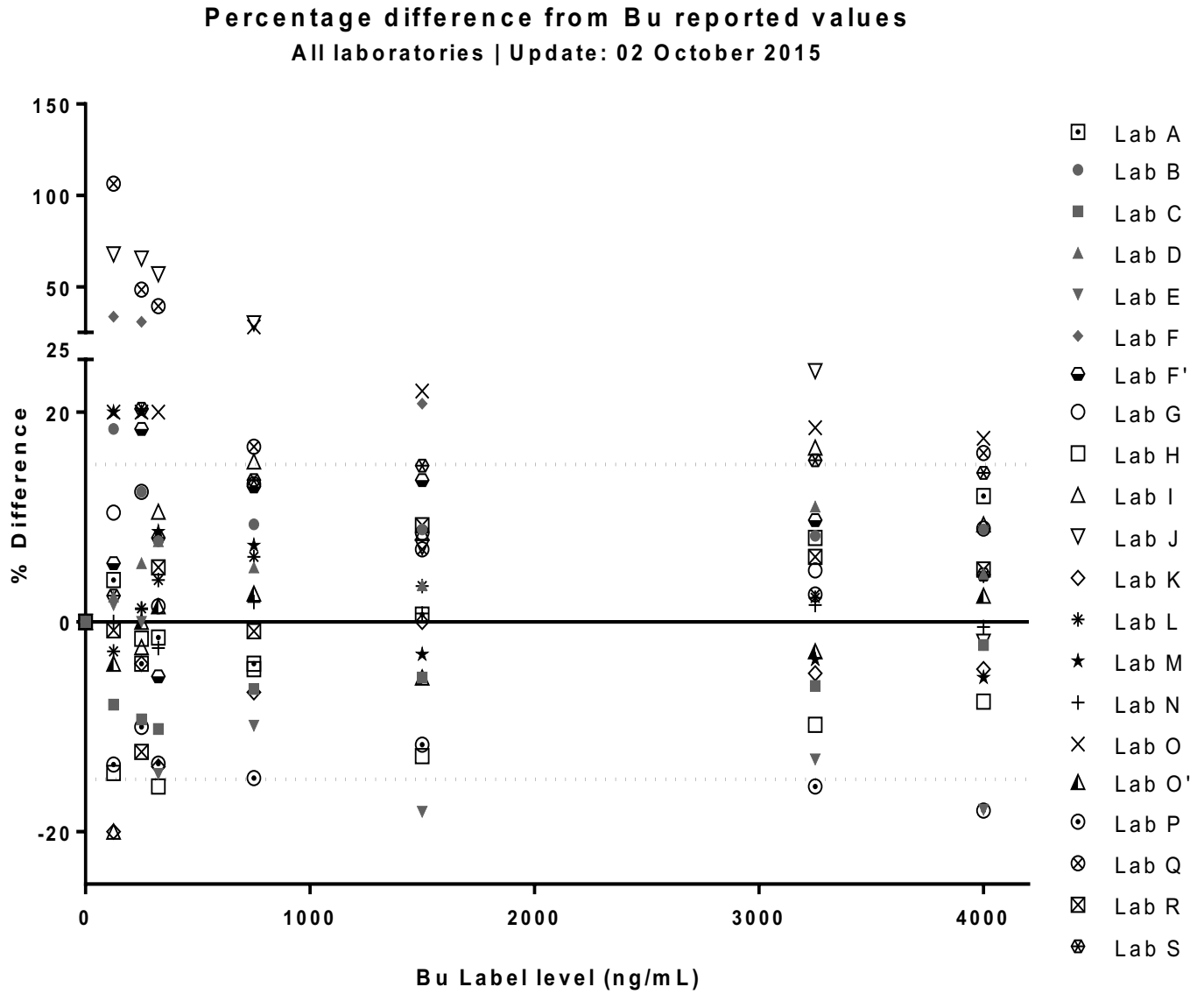
Slide provided at the courtesy of Lee Depuis (SickKids, Toronto, Canada)

A Survey by the Complications and Quality of Life Working Party of the EBMT

DOSING

- Eleven centers gave full dose busulfan orally and 94 i.v.
- In i.v. administration, the number of daily doses was one in 46 centers, four in 42 centers, and two in 4 centers.
- Twenty-seven centers reported having alternative busulfan administration schedules depending on the disease.
- In obese patients was based on actual body weight (12 centers, ideal body weight (15), AIBW-25 (ideal body weight + 0.25 x (actual body weight – ideal body weight)) (46) and AIBW-40 (10)

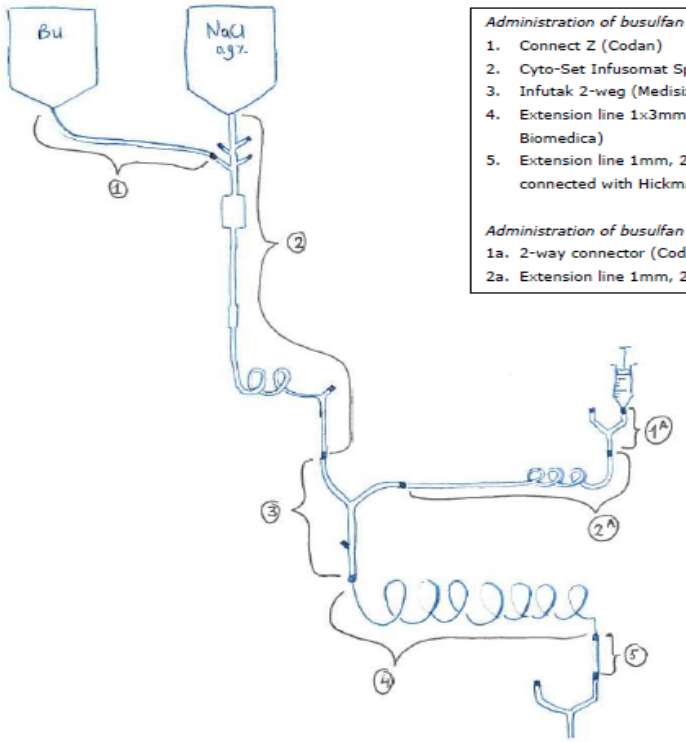
Assay Quality and Availability (2 of 4)



UMC Utrecht % Difference
1.3
0
3.4
-2.8
2.3
4.4
4.0
6.2

The infusion matters…..

APPENDIX I: infusion system busulfan

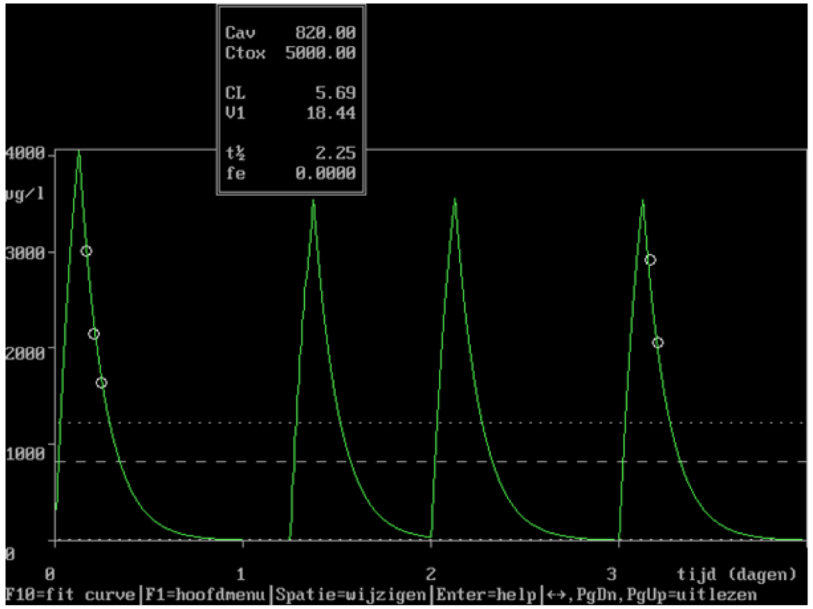


Administration of busulfan in infusion bag:

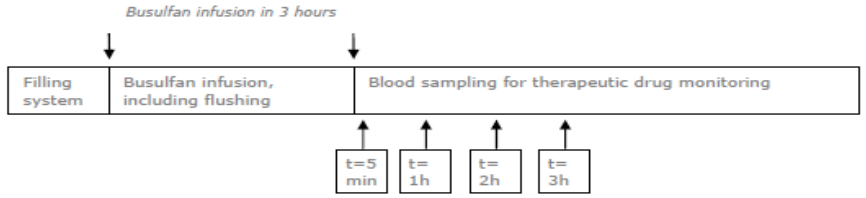
1. Connect Z (Codan)
2. Cyto-Set Infusomat Space (B. Braun)
3. Infutak 2-weg (Medisize)
4. Extension line 1x3mm, 700cm (Dialex Biomedica)
5. Extension line 1mm, 25cm (Cair), connected with Hickman catheter

Administration of busulfan in syringe:

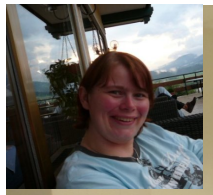
1a. 2-way connector (Codan)
2a. Extension line 1mm, 200cm (Cair)

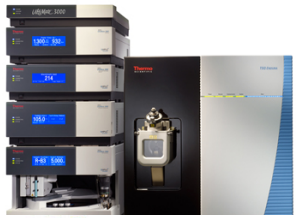


APPENDIX II: schedule of busulfan administration and blood sampling



LCMS team & facility



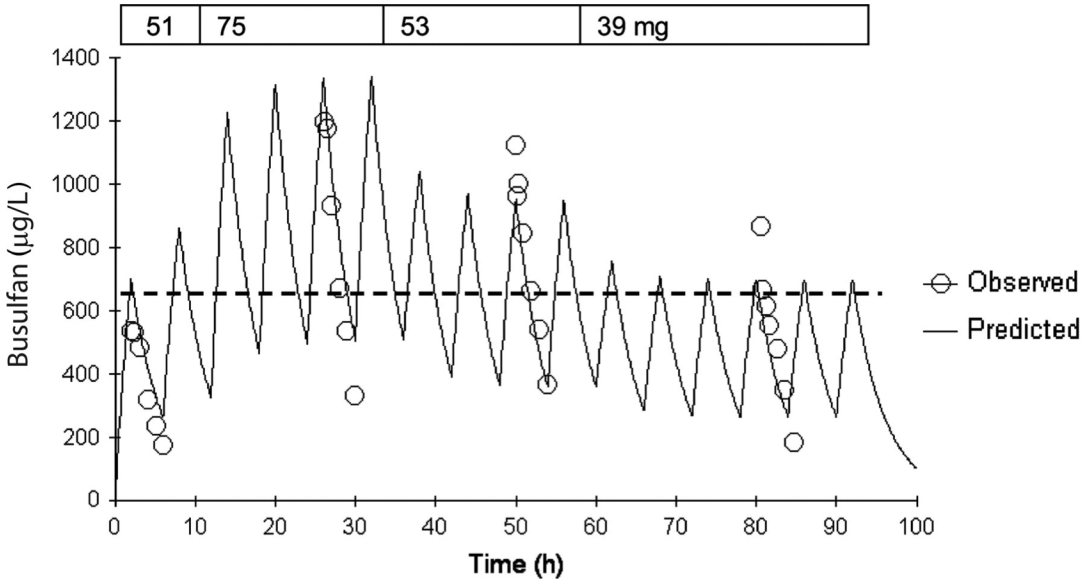


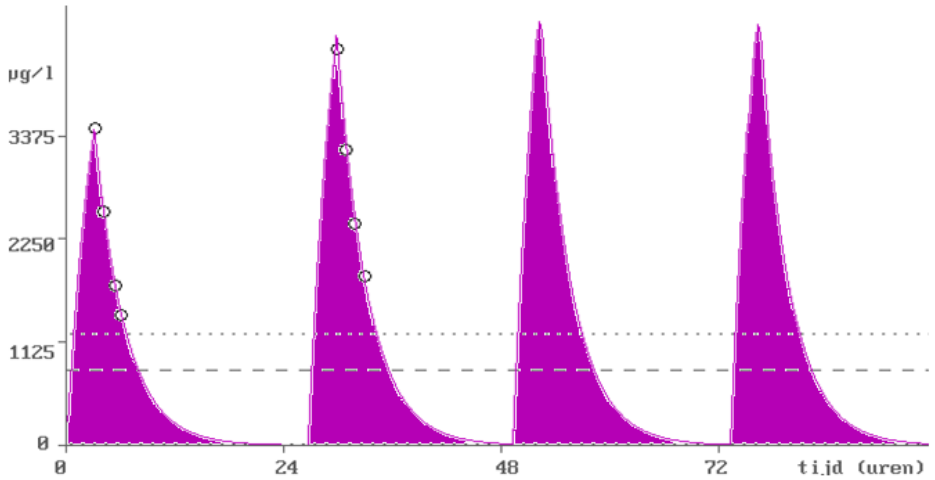
A Survey by the Complications and Quality of Life Working Party of the EBMT

PK availability and Assays

- Overall, 17 of the 105 centers used PK measurements to adjust busulfan doses. Busulfan concentration was measured using liquid chromatography (+ mass spectrometry in 8 centers).

Exposure target definition: Css vs AUC (3 of 4)





Johnson-Davis, et al. "Which dose of busulfan is best?" *Clinical Chemistry 2010*
Langenhorst et al., to be submitted

Exposure targets and units: Can you the Math?

Table 2
BU AUC to CSS Equivalency Table

AUC	AUC	CSS *	AUC†	AUC
µMolar × min Q6H dosing	µMolar × min daily dosing	ng/ mL	mg/L × h Q6H dosing	mg/L × h daily dosing
877	3508	600	3.60	14.4
900	3800	650	3.90	15.6
1125	4500	770	4.62	18.5
1316	5262	900	5.40	21.6
1500	6000	1026	6.16	24.6

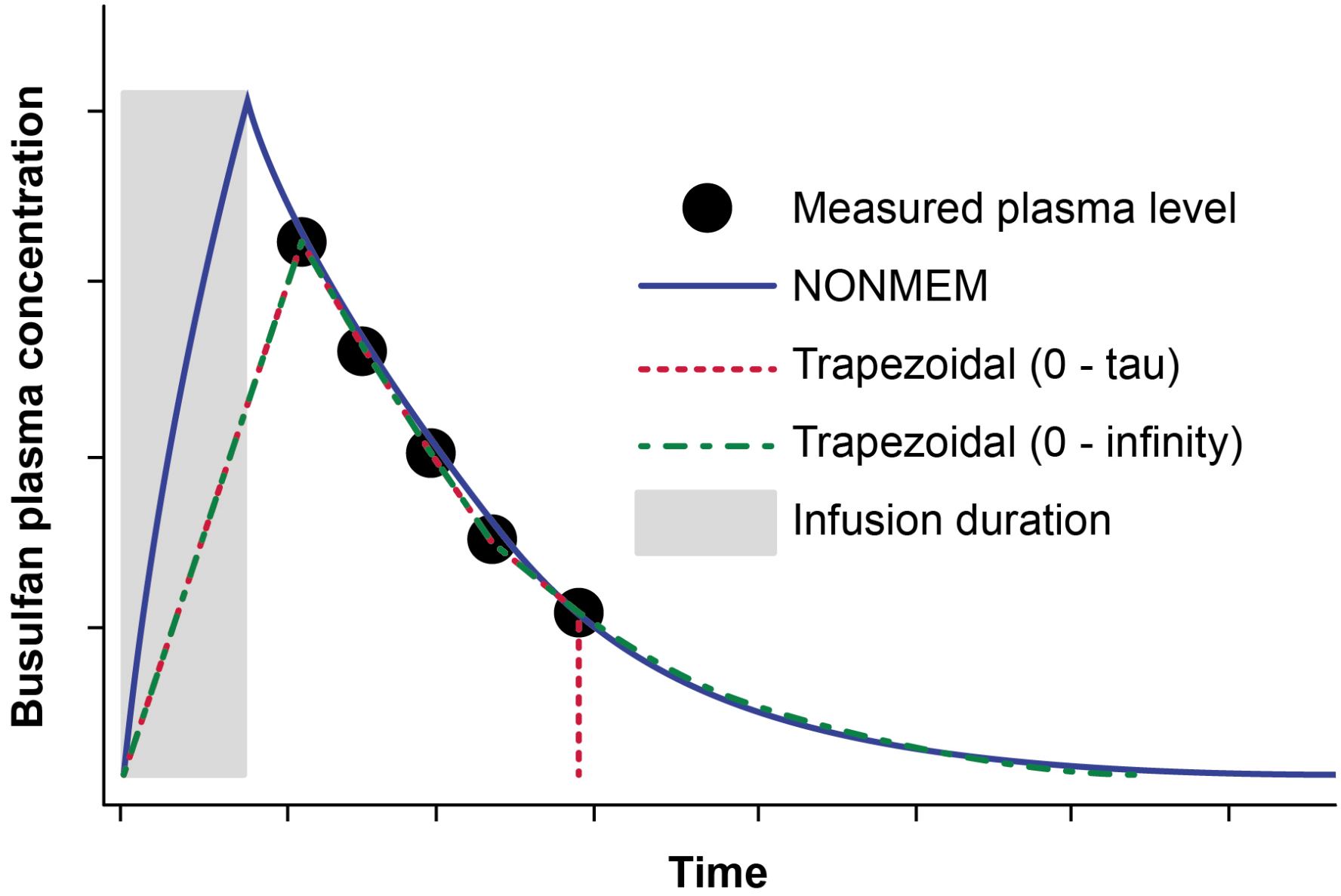
All BU plasma exposures are presented in this manuscript using the units within the original manuscript and, if needed, converted to BU concentration at steady state (CSS). The technical appendix and equations 1 to 3 in FAQ5 explain how to convert between the various BU exposure units.

* CSS = AUC divided by the dosing frequency.

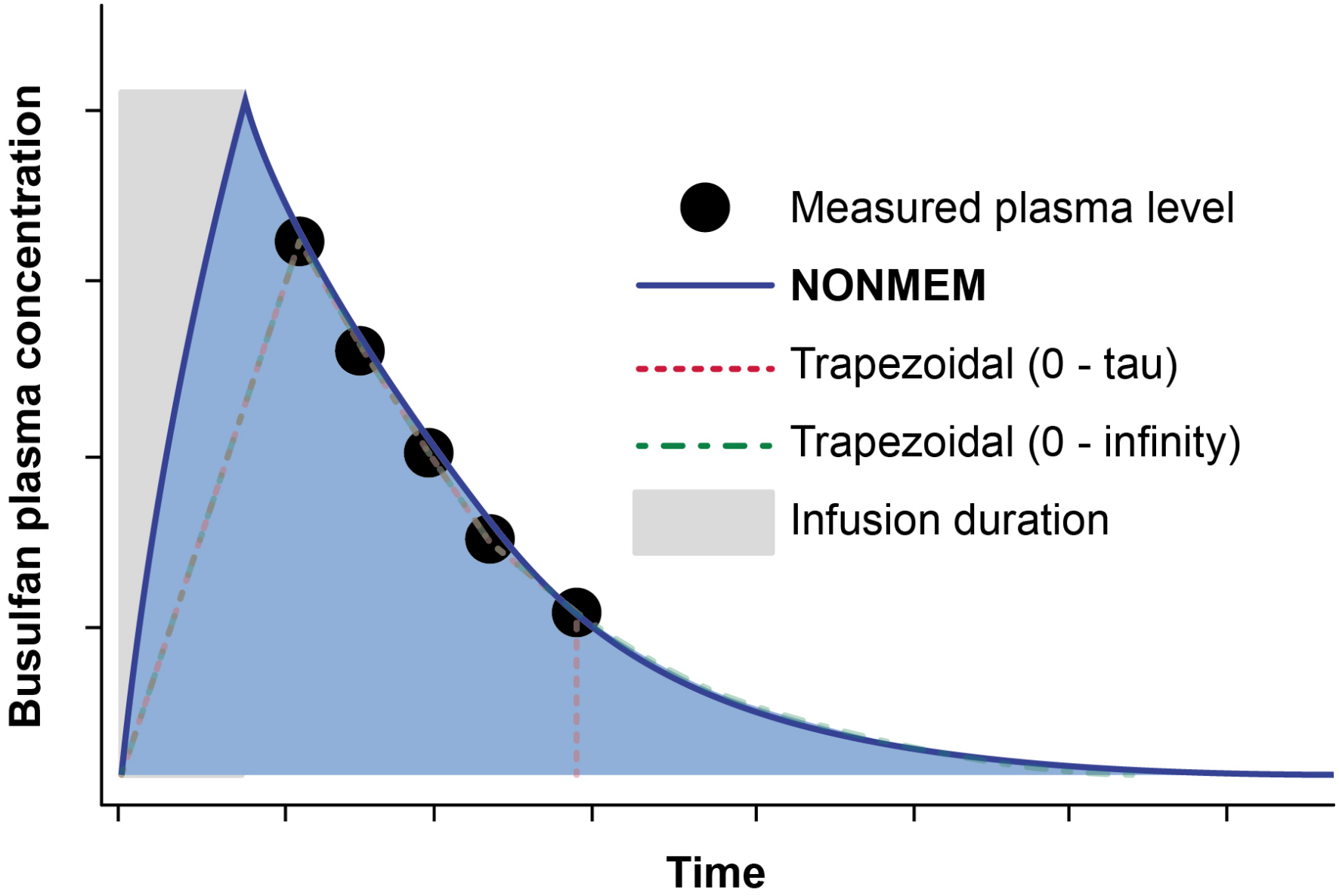
† When the AUC is expressed in micromolar (micromoles/L) units, then the BU molecular weight (246.3 g/mol) must be used to calculate the AUC in mg/L units.

Palmer J, McCune JS et al, BBMT 2016

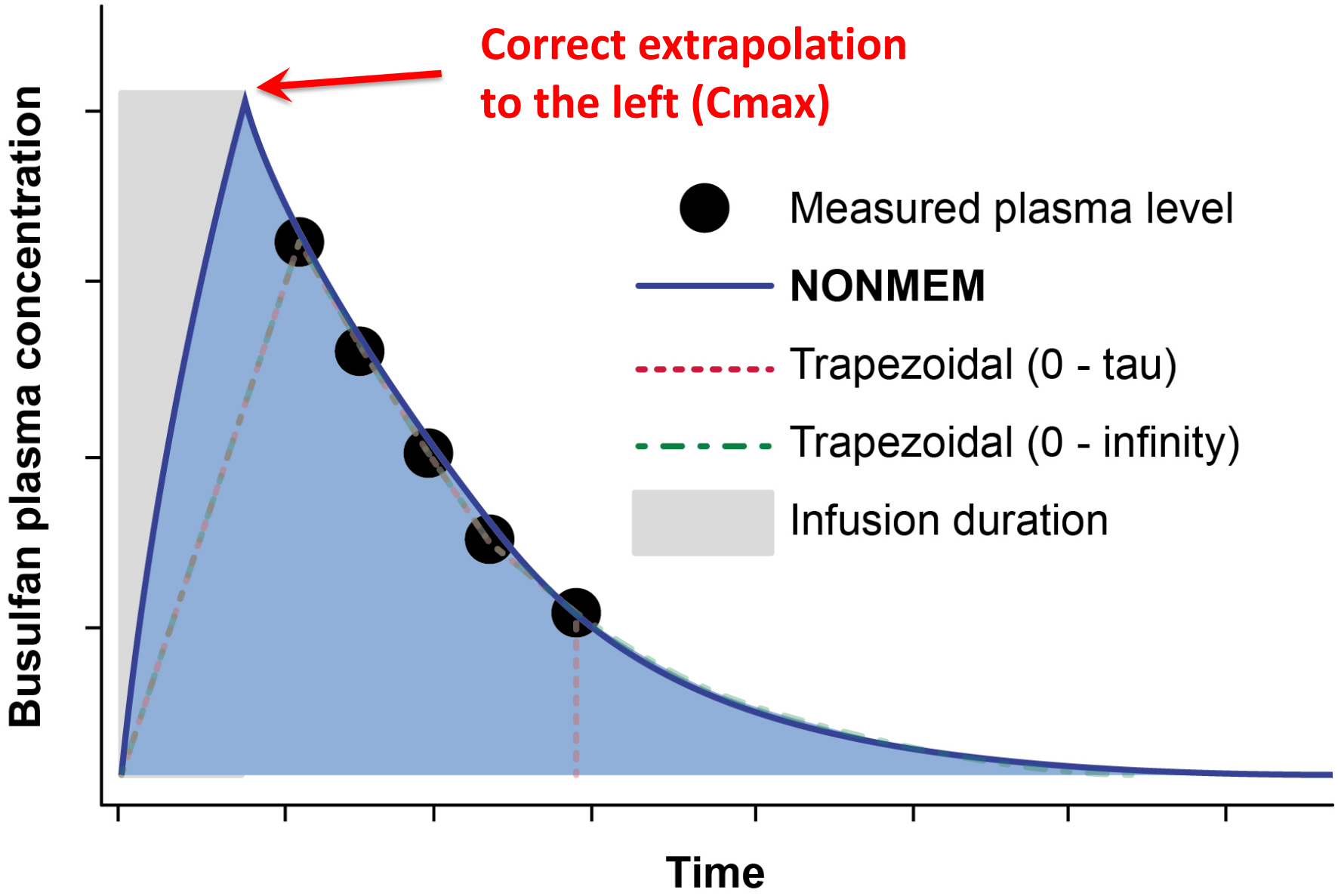
Method of BU exposure estimation (4 of 4)



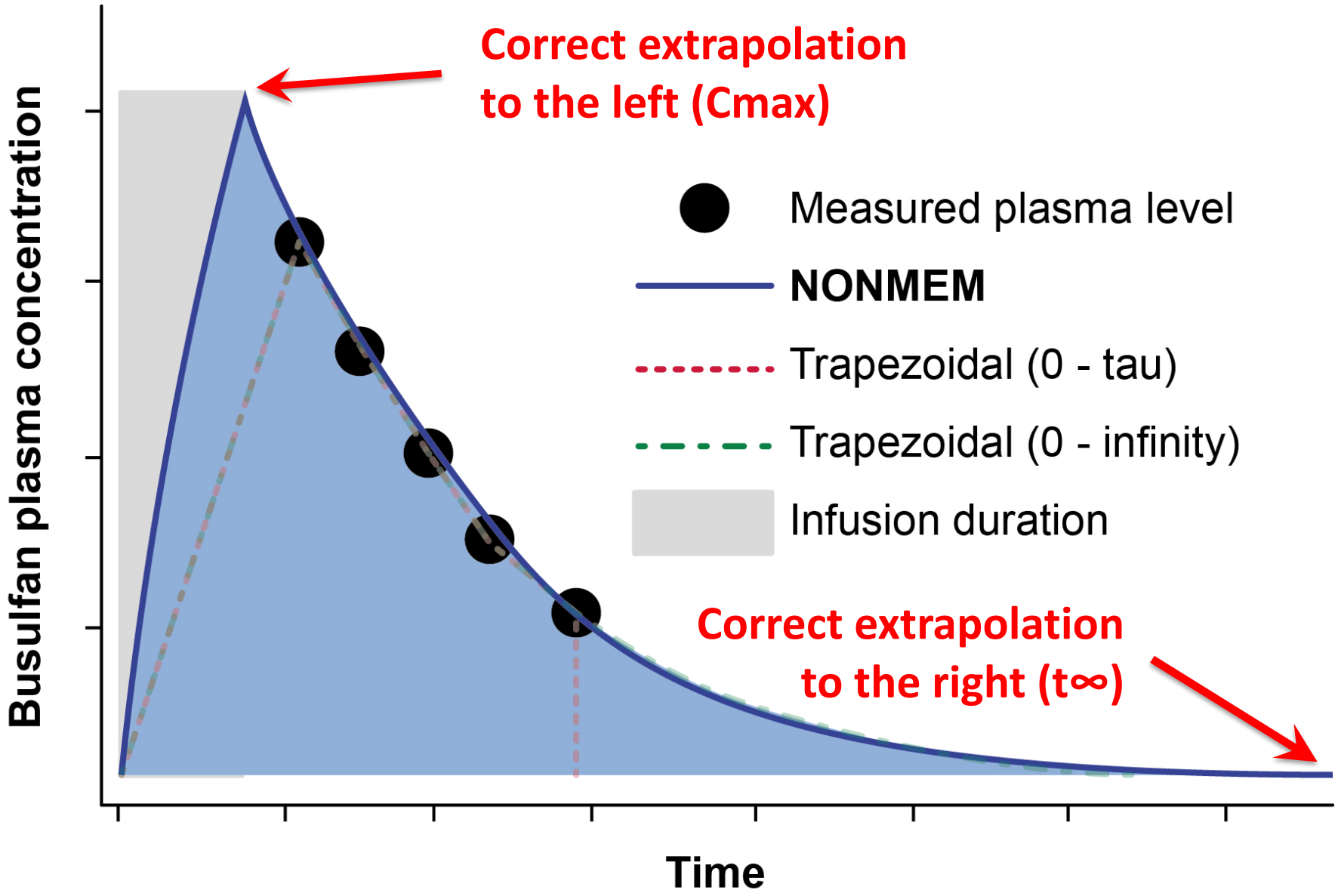
BU AUC estimation method



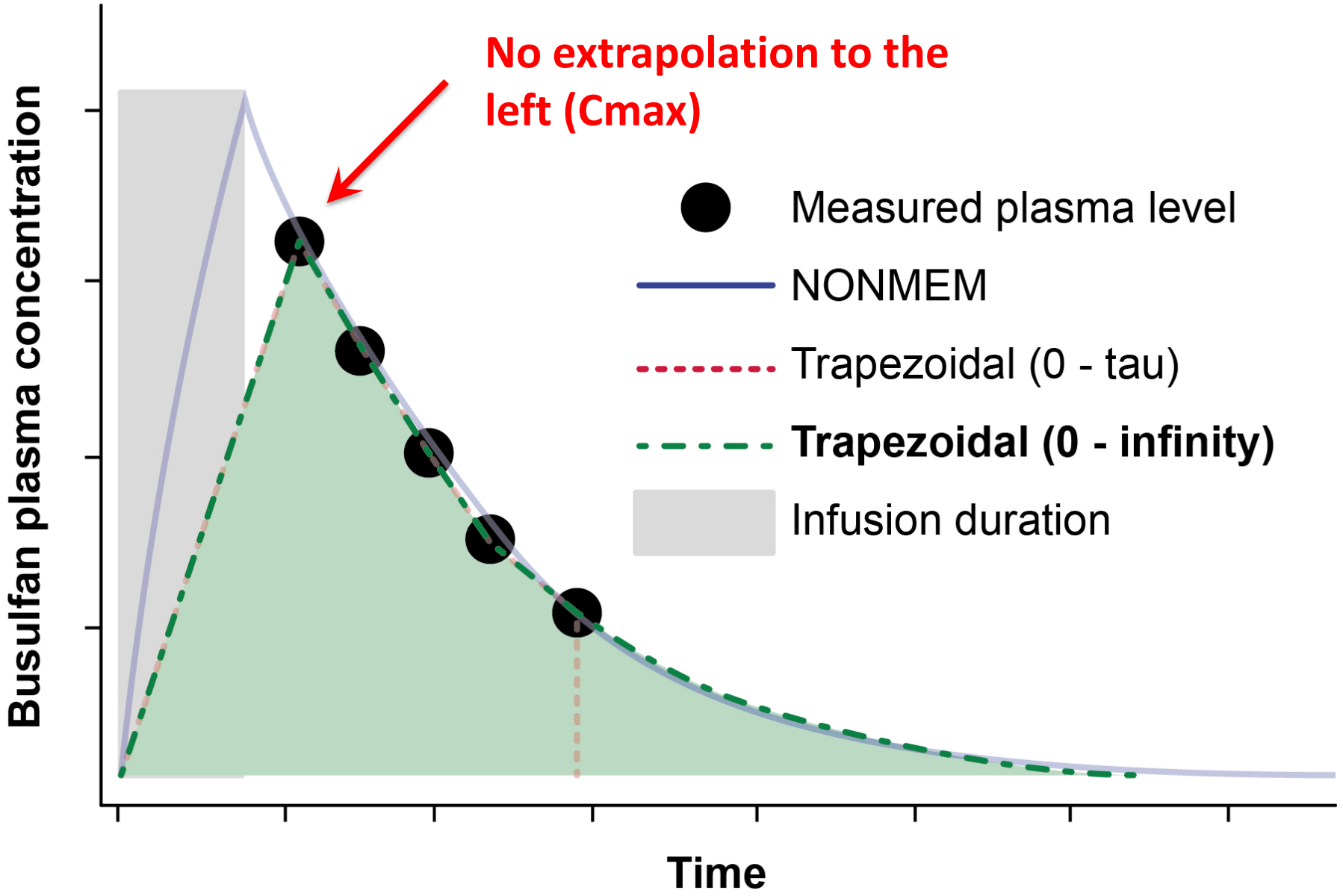
BU AUC estimation method



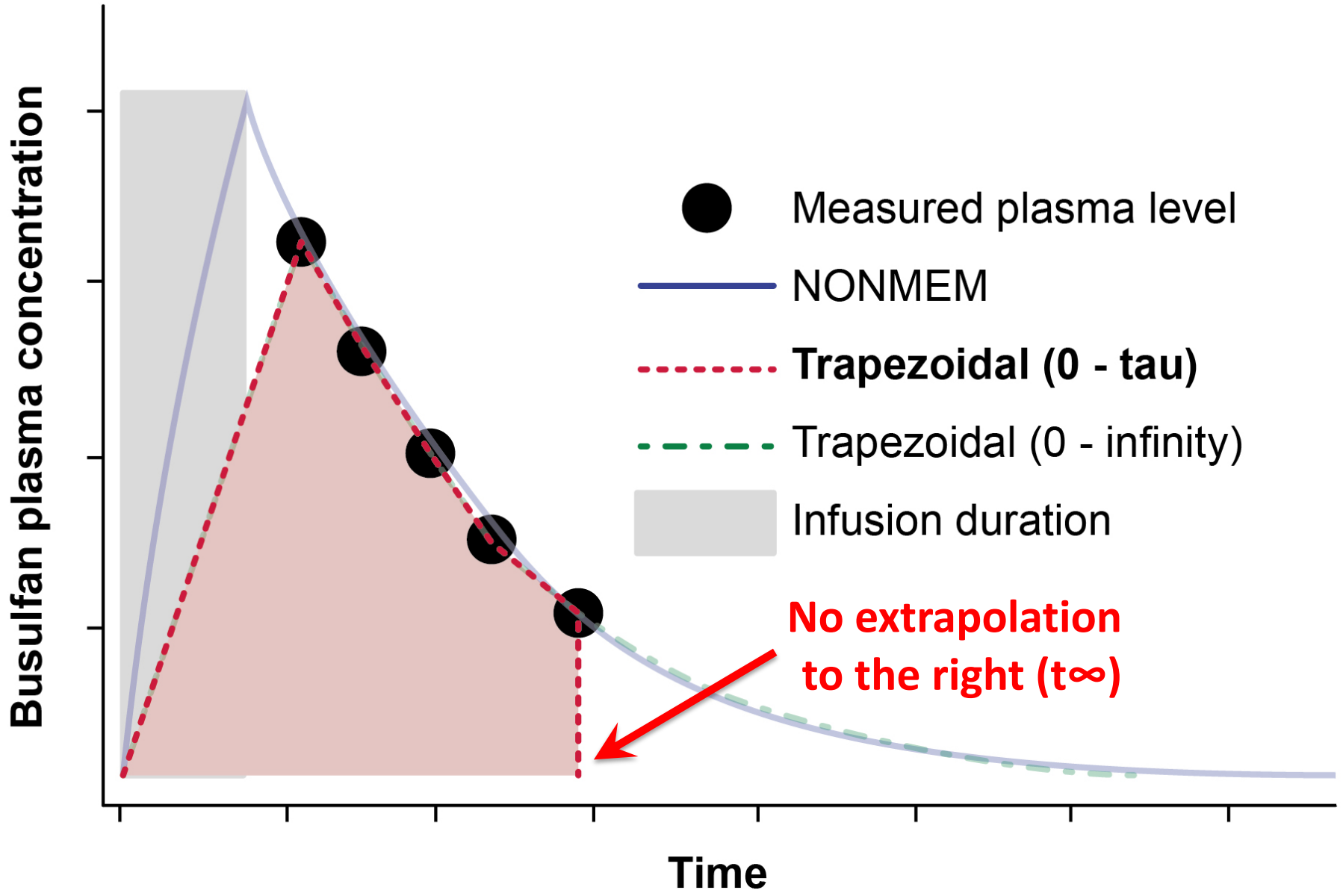
BU AUC estimation method



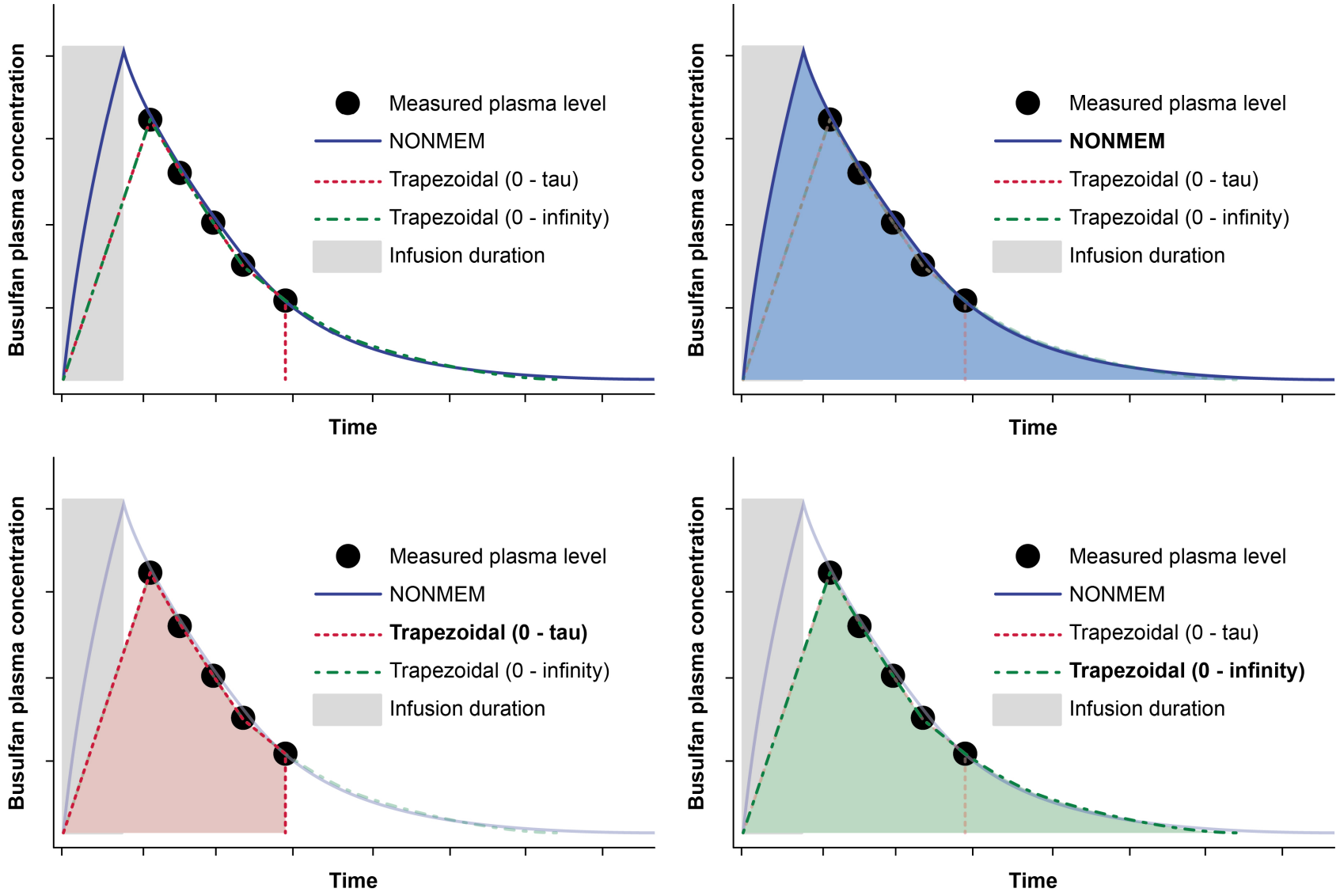
BU AUC estimation method



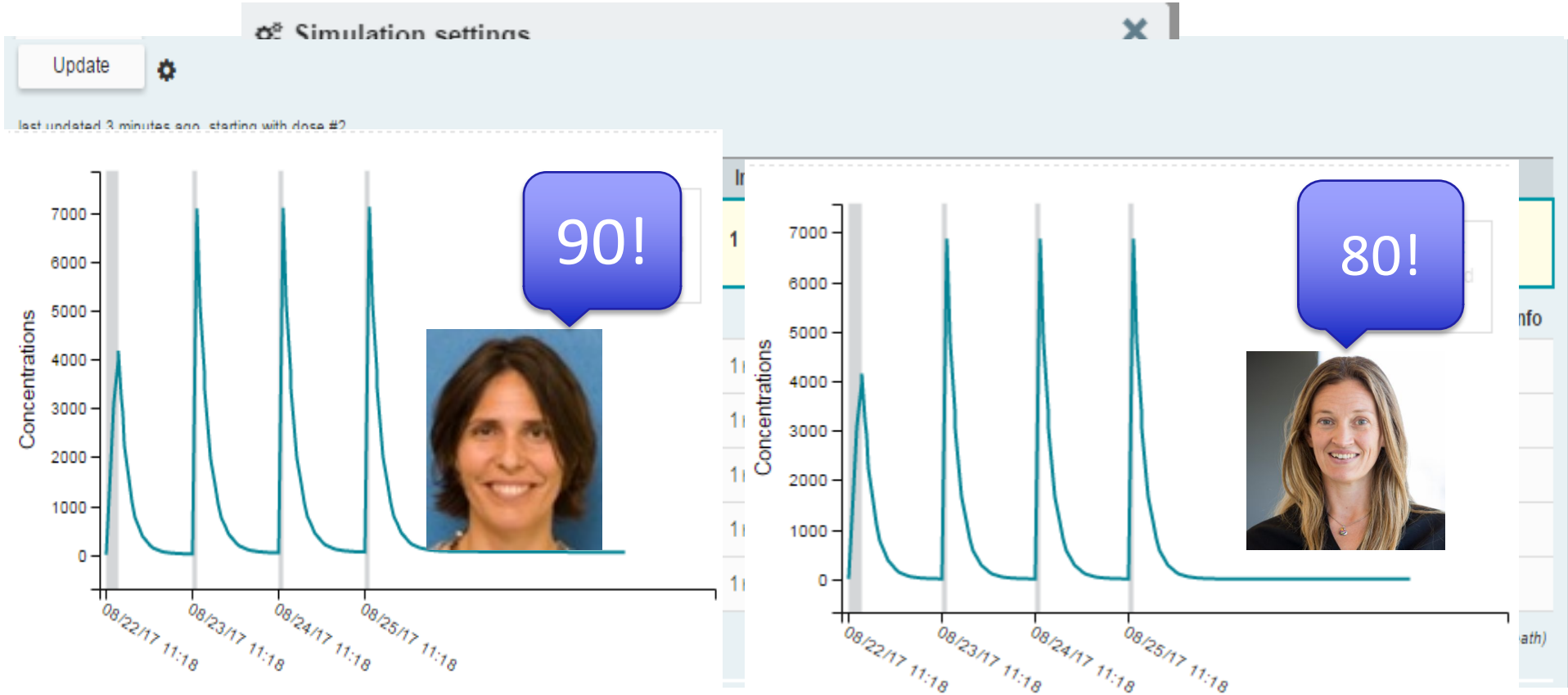
BU AUC estimation method



BU AUC estimation method

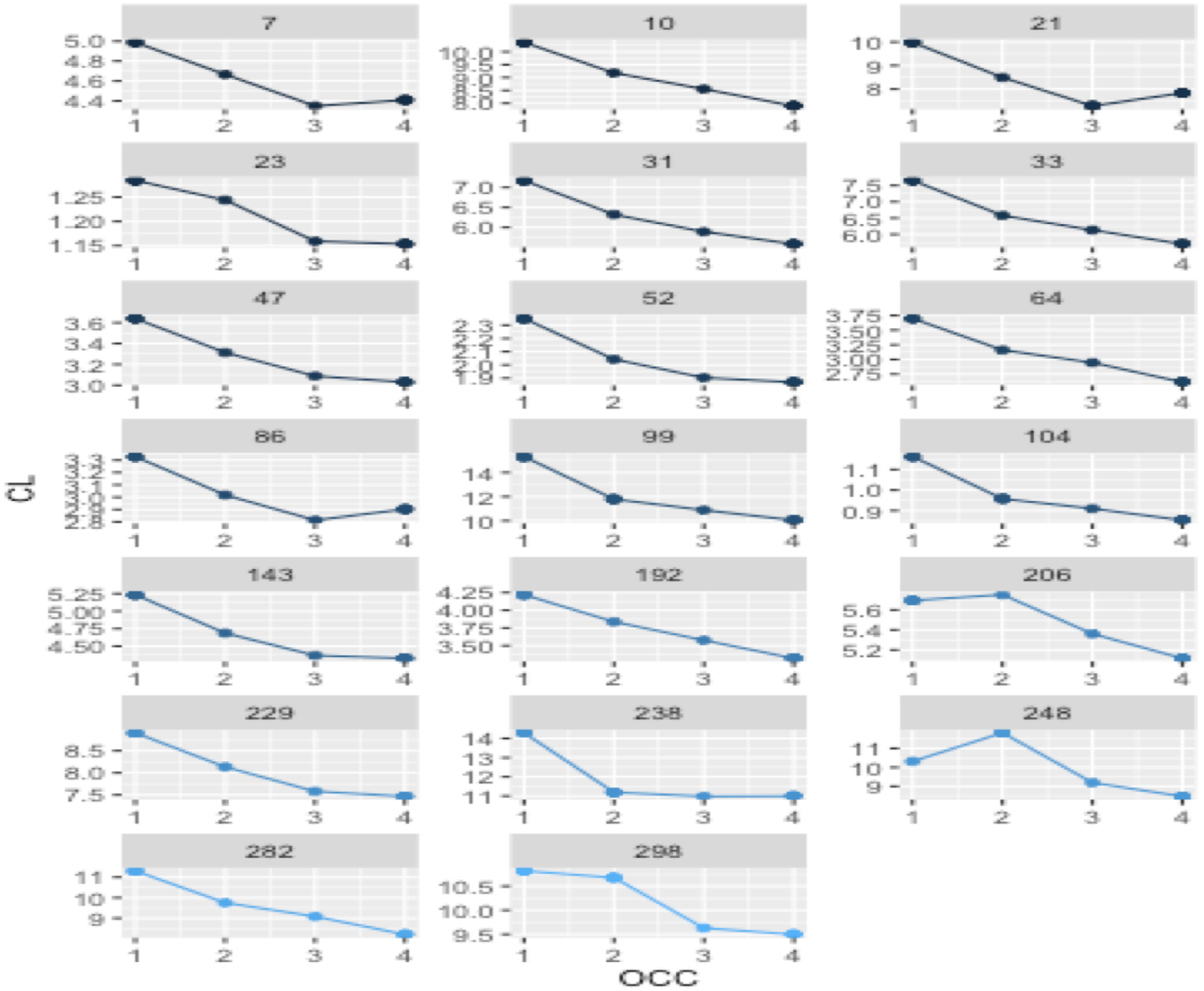


And finally, the PPK Model and fitting procedures do matter!



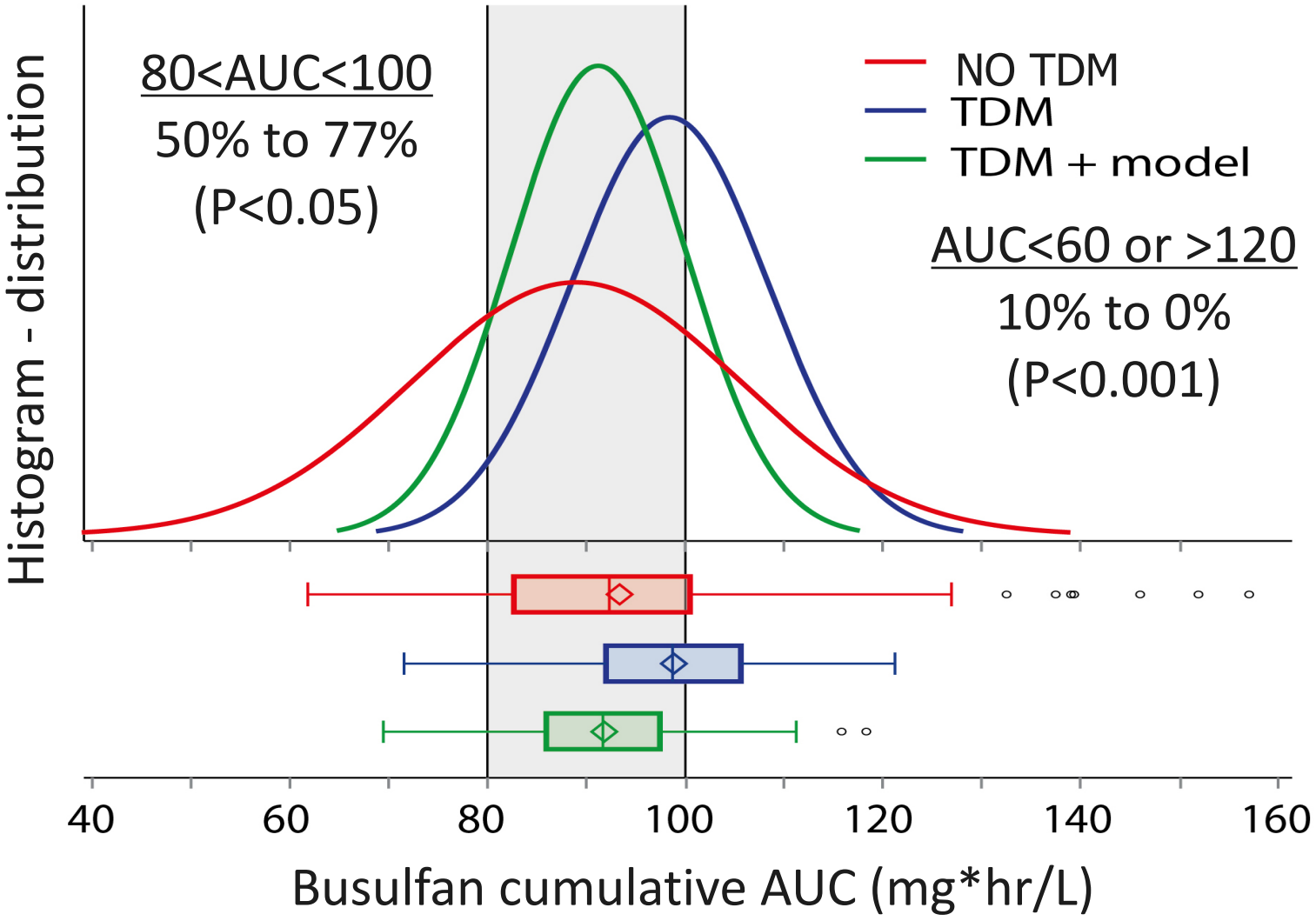
Insight RX

Explanation: a drop in busulfan clearance over time within-patient



Langenhorst et al., manuscript in preparation

Drop in busulfan clearance over time within-patient



Langenhorst et al., manuscript in preparation

Busulfan and Paracetamol drug-drug interaction

	BU Cl (L/h)		Multivariate	
	Day 1	Day 4	Δ	P
Paracetamol				
none	8.52	8.37	+1.3%	ref
during Bu course	7.01	6.64	-2.9%	0.392
prior to Bu	9.52	8.46	-7.8%	0.025
Clobazam	8.40	7.66	-4.6%	ref
other/none	6.67	6.72	+4.3%	0.044

Langenhorst et al., manuscript in preparation

A Survey by the Complications and Quality of Life Working Party of the EBMT

AUC calculation

- The details of the sampling for PK measurements as well as the method of AUC calculation varied.

A Survey by the Complications and Quality of Life Working Party of the EBMT

Conclusions and recommendations

- There is marked variation between centers in the details of busulfan administration for aHCT conditioning
- The clinical impact of this variation remains uncertain.
- The present results are useful in the production of recommendations toward a more standardized use of busulfan.

BU Harmonization Project

- Initiated and coordinated by Jeannine McCune (Duarte, CA, former Seattle Cancer Center)

- A global initiative
  - USA, EU, ASIA, AUS

- Goal: a consistent assessment of PK-directed busulfan dosing by different HCT centers (Project 1) and ONE busulfan exposure unit (Project 2)

Project 1: Quantitation & Dose Adjustment

- Led by Rosa Yeh of Seattle and Erik van Maarseveen of Utrecht & the KKGT, the Dutch organization which stands for Association for Quality Assessment in Therapeutic Drug Monitoring and Clinical Toxicology.

- Quantitation & PK-directed dosing calculations and interpretation and a treatment advice to the physician.

- Fee-for-service charge paid by each participating lab

KKGT contact details:
http://kkgt.nl/?lang=en,
info@kkgt.nl

Project 2: Harmonize busulfan exposure unit

- Led by Lee Dupuis (Toronto, CA) & Jim Ritchie (Atlanta, GA)

- Predominant units of measuring busulfan exposure:
  - Css (ng/ml)
  - AUC (micromolar × min, North American units)
  - AUC (ng × hr/ml, European units)

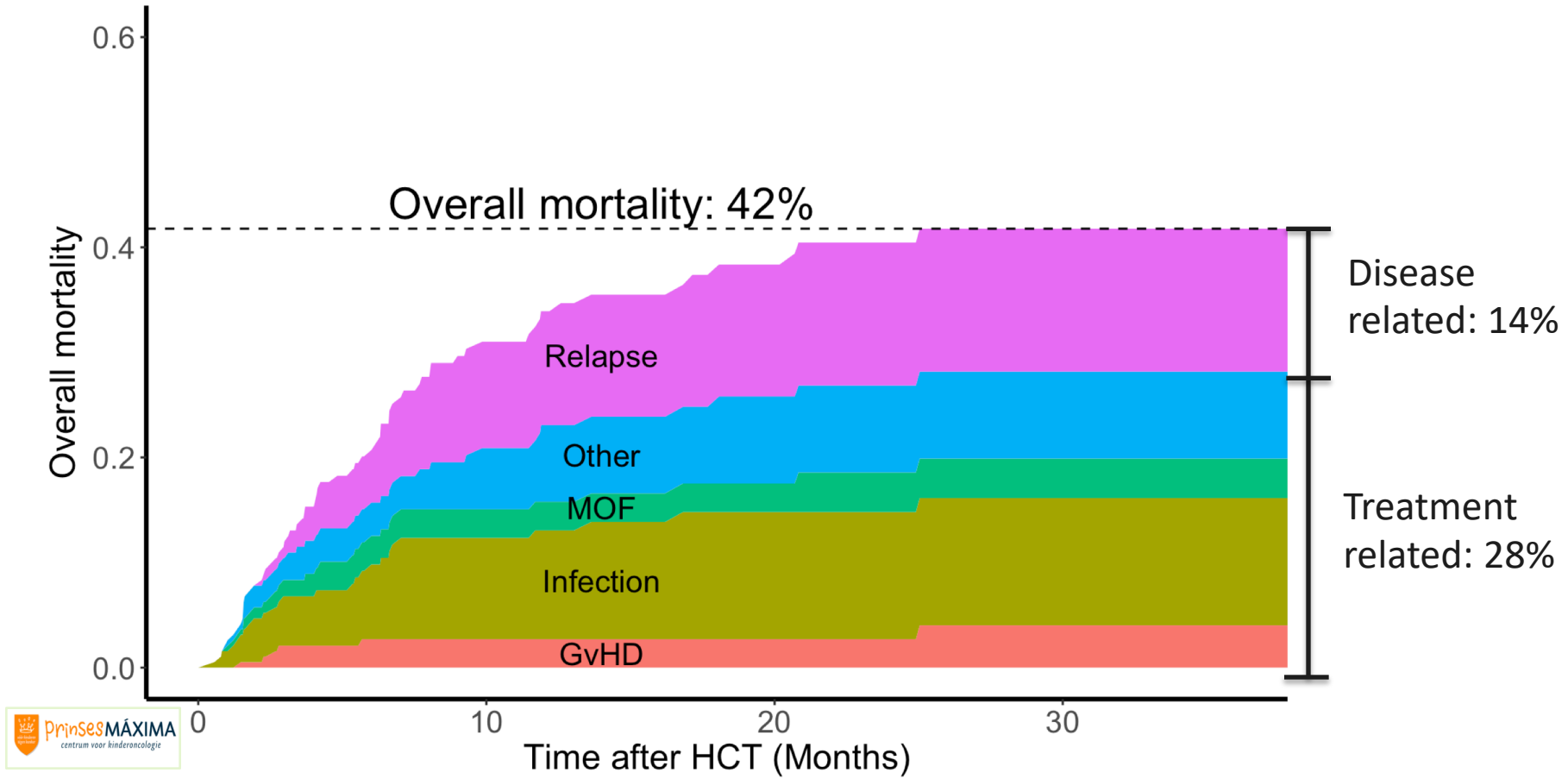
- Minimize the chance of errors by avoiding calculations

- With the ultimate goal to harmonize BU exposure target

Busulfan: Conclusions & Recommendations

- Many discrepancies in current practices of personalized dosing of BU exist within the EU and beyond.
- Personalized dosing of BU can improve clinical outcomes
  - other conditioning agents: ATG, fludarabine, clofabine, melfalan (test dose) and treosulfan
- Harmonization of personalized dosing of BU through international collaboration is key!
- Pharmacists can play a more active role in personalized dosing of BU

Clinical need: current HCT prospectives



ATG-FluBu as Standard Conditioning

Lympho-depletion	Bone marrow depletion	HCT

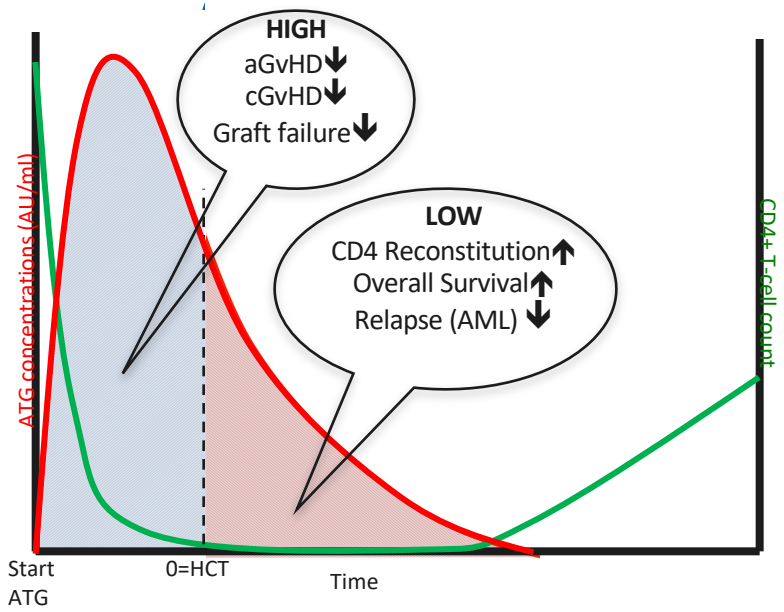
✓ **ATG:** targeted

✓ **Busulfan:** targeted

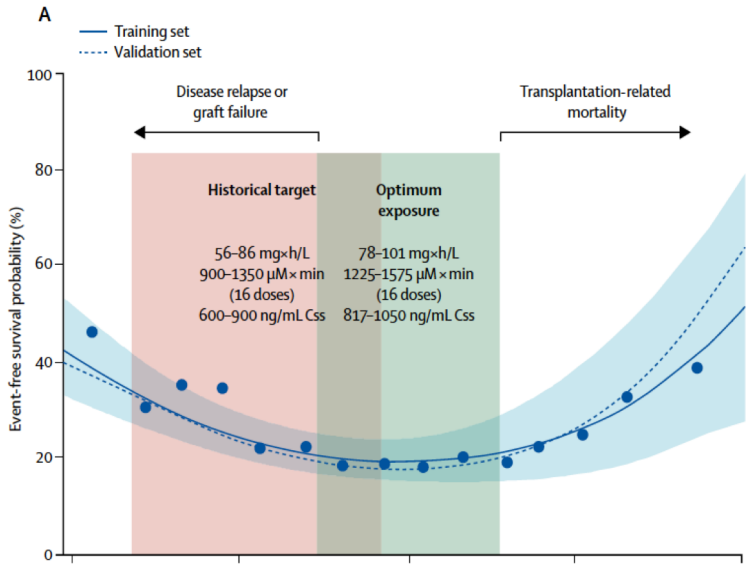
✕ **Fludarabine?**
- ❖ **160 mg/m2**

Day: -9 -8 -7 -6 -5 -4 -3 -2 -1 0

Previous results: ATG & Busulfan (Peds + Adults)



Peds : Admiraal et al., **Lancet Hematology 2015**
& Adults: Admiraal et al., **Lancet Hematology 2017**
ATG pre- and post-HCT exposure related to outcomes



Peds: Bartelink et al: **Lancet Hematology 2016**
Busulfan cumulative exposure related to outcomes

ATG-FluBu as Standard Conditioning

Lympho-depletion	Bone marrow depletion	HCT

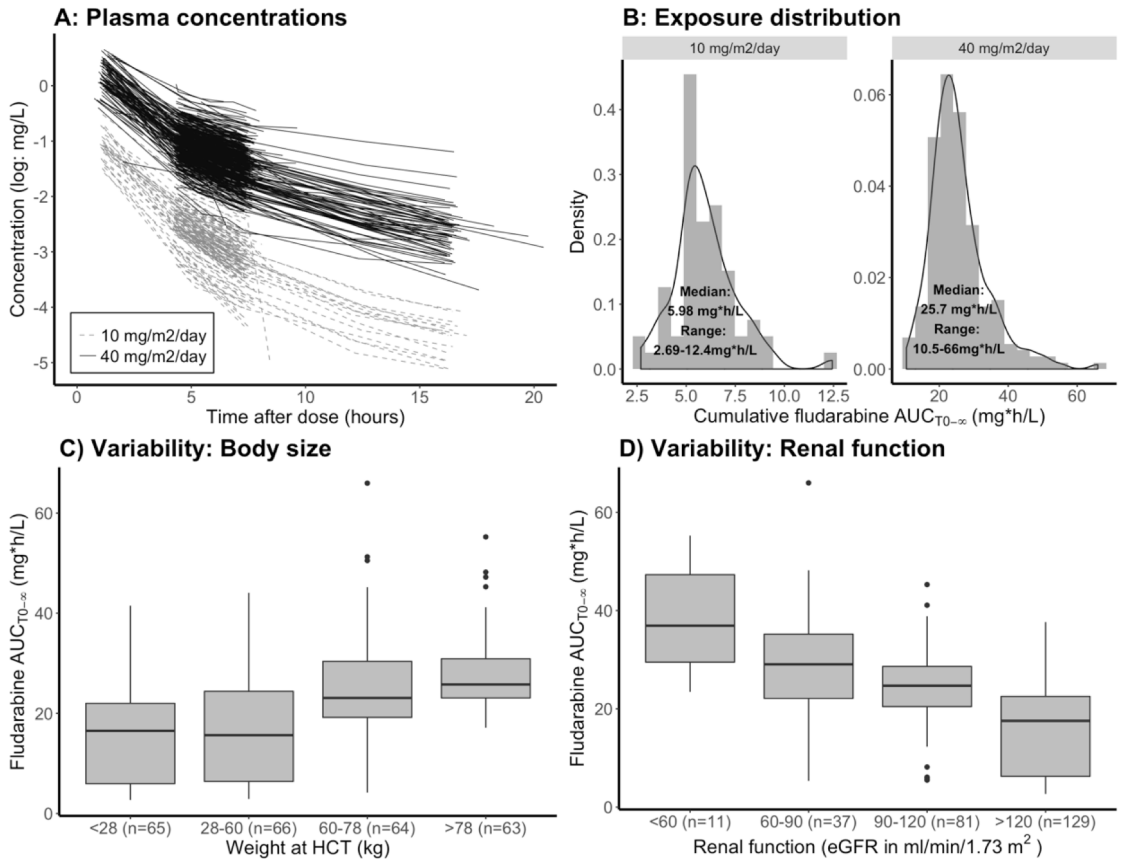
✓ **ATG:** targeted

✓ **Busulfan:** targeted

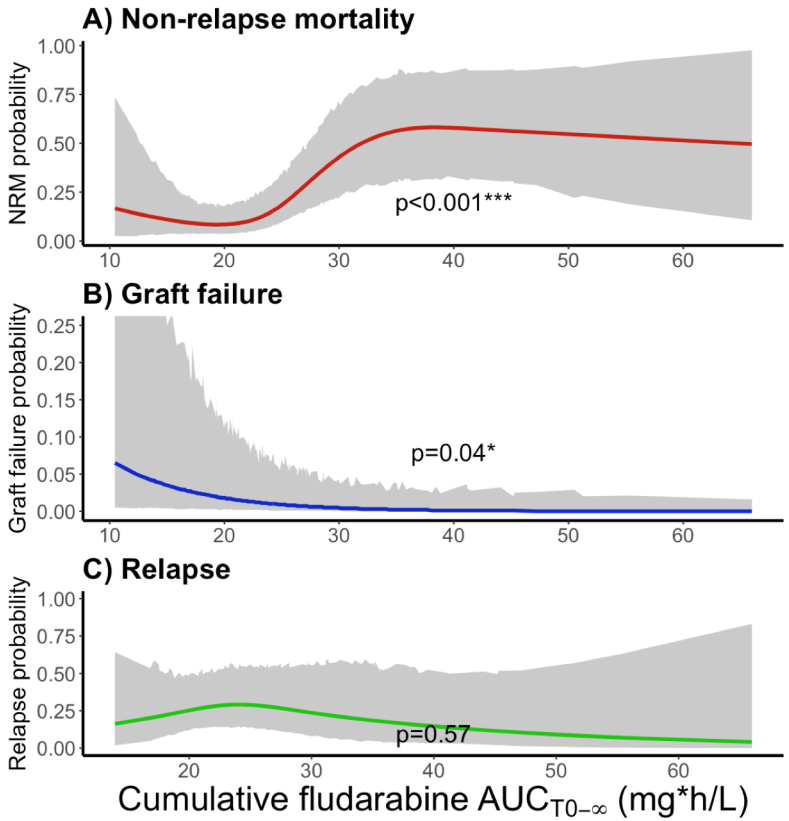
✕ **Fludarabine?**
- ❖ **160 mg/m2**

Day: -9 -8 -7 -6 -5 -4 -3 -2 -1 0

Fludarabine PK and its determinants



Relationships between PK and treatment outcome (PD)



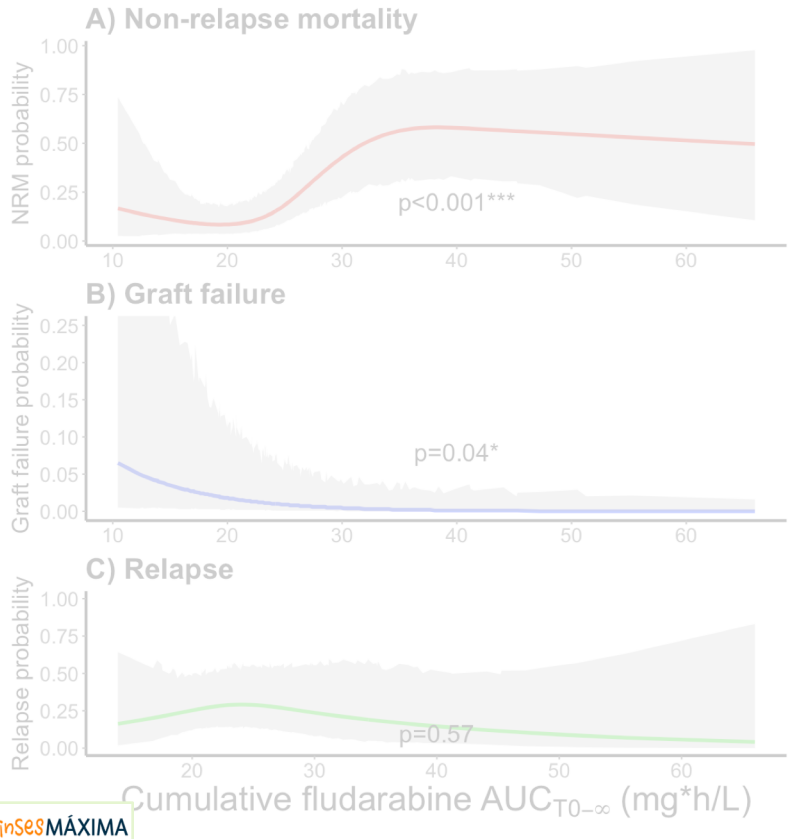
Increased NRM at AUC>20 mg*h/L

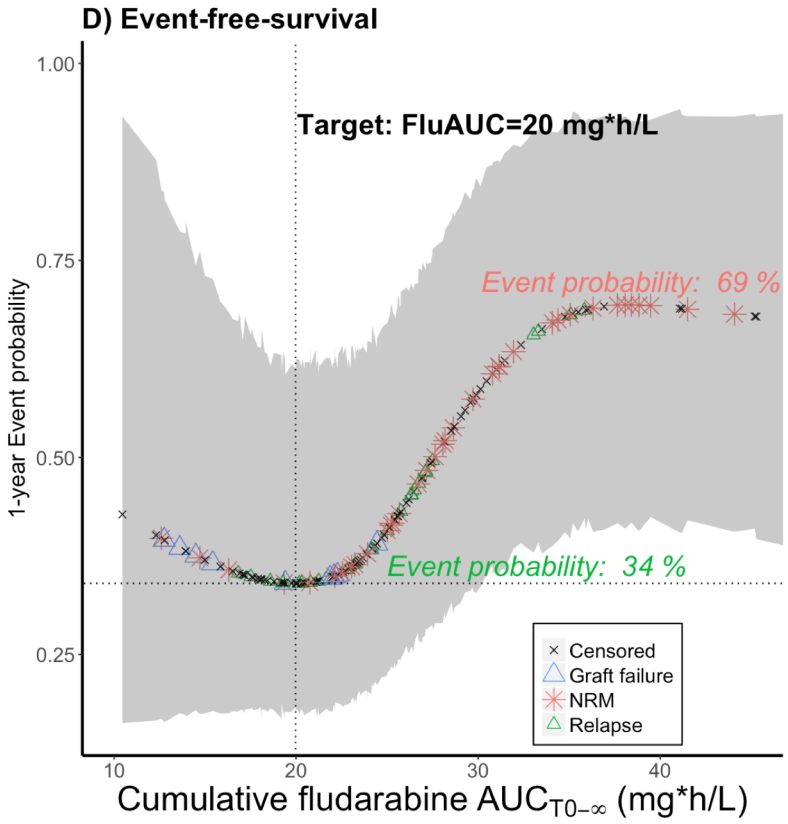
Lower AUC -> More graft failures

No relationship with relapse

Langenhorst et al., submitted

Effect of fludarabine exposure on events





Langenhorst et al., submitted

Aims

- To perform a prospective clinical trial simulation testing the effect of a personalized dosing algorithm and TDM.

- The primary aim of simulations was to evaluate the expected survival gain of alternative dosing based on either the developed PK-model or therapeutic drug monitoring (TDM).

Development of optimal dosing strategy

Current protocol:

160 mg/m2 regardless of age/indication/renal function

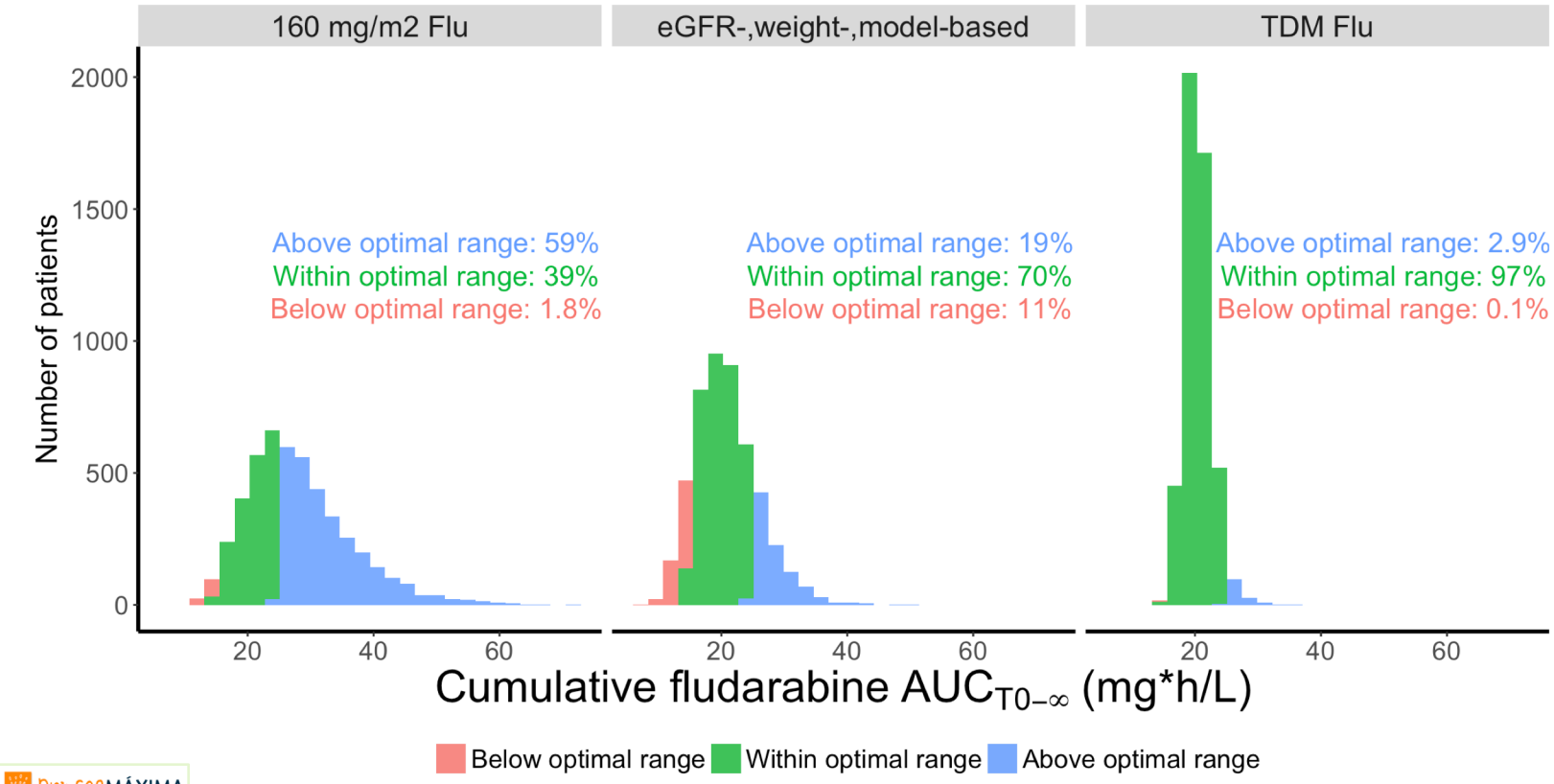
eGFR and body weight based dosing:

Taget AUC = 20, dosing based on eGFR and body weight according to PK model

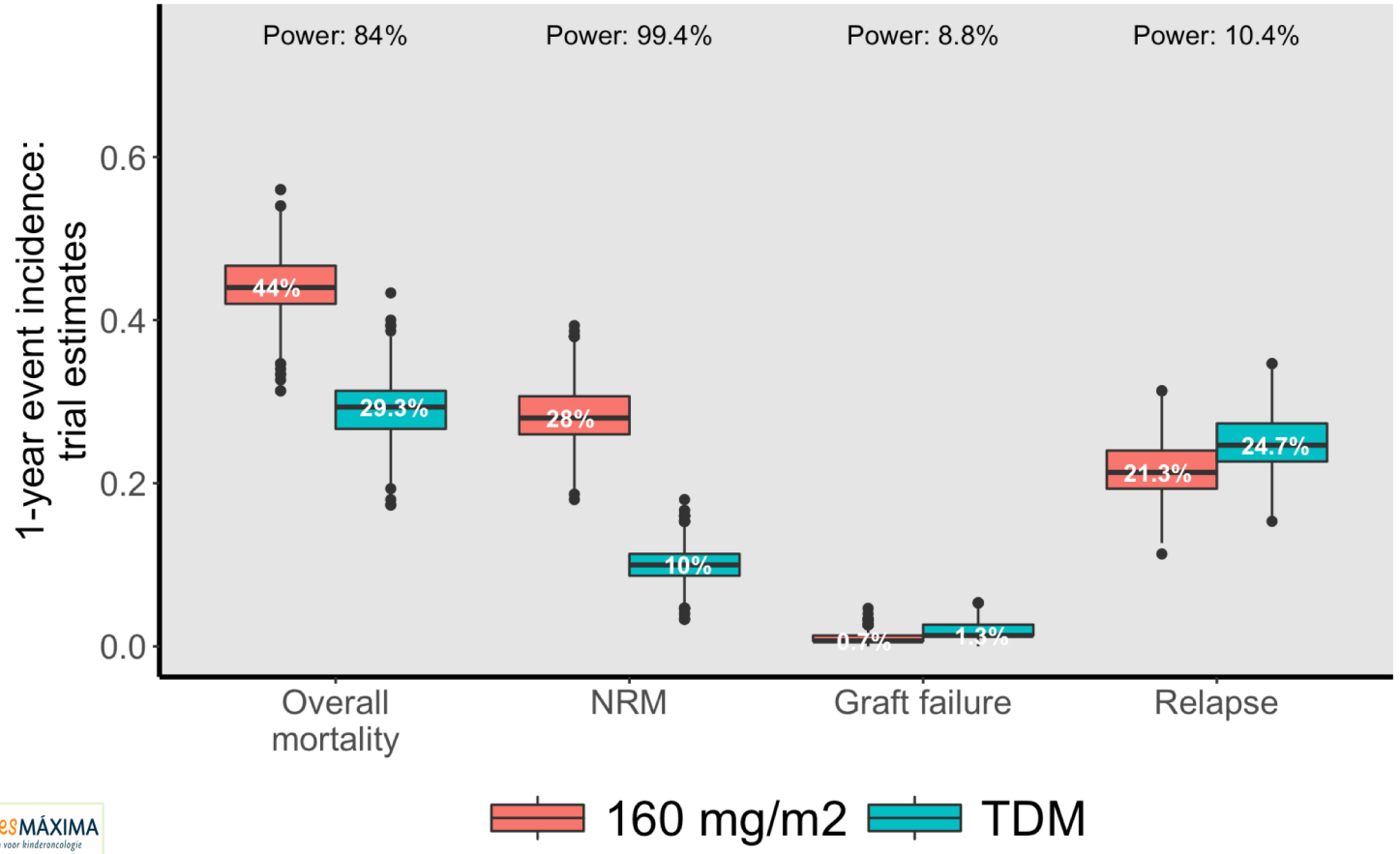
TDM based:

Target AUC = 20, collect blood samples on day 1, measure Flu exposure and adjust dose on day 2-4.

Development of optimal dosing strategy (simulation)



Trial design (OS as endpoint, 150 patients/arm) simulation



Sensitivity analysis: testing uncertainty of assumptions

- Account for possible **failure of TDM** during the trial:
  - Arbitrary 90% success-rate of TDM
  - Remaining 10% get model-based dosing

- Take into account the **uncertainty** in the **fludarabine~event** relationship:
  - What if NRM probability for high exposures (>20 mg*h/L) is 10% lower than predicted
  - What if graft failure probability for low exposures (<20 mg*h/L) is 10% higher than predicted

Sensitivity analysis: results

	OS-trial (N=150 per arm)		**NRM-trial (N=75 per arm)**	
	Original power	Adjusted power	Original power	Adjusted power
TDM uncertainty	84%	81%	82%	79%
Model uncertainty: lower NRM effect		75%		81%
Model uncertainty: higher Graft failure effect		72%		83%

Conclusion and discussion

- To achieve sufficient power for a trial setting, a TDM intervention is recommended as individualized dosing arm with an expected overall survival probability increase from 56% to 71%.
- Overall survival as an end-point best reflects the overall benefit in patients receiving fludarabine as part of pre-HCT conditioning with BuFlu(+ATG)
  - NRM necessitates half the patients for similar power as it is less sensitive to survival model uncertainties
- Trial simulation platforms allow for simulation of various end-points (i.e. separate events, cumulative events, overall survival)
- Multicenter RCT of Flu TDM has IRB-approval and inclusion will start end of 2018.

This is Luuk in 2018; he is still here after HCT with Busulfan TDM, and we of course hope that he will win Holland the World Cup in 2030

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KWF KANKER BESTRIJDING

prinsesMÁXIMA centrum voor kinderoncologie

ZonMw

4th Edition Masterclass Immunopharmacology in HCT, June 27-29, 2018 @Utrecht, NL
contact: e.m.vanmaarseveen@umcutrecht.nl

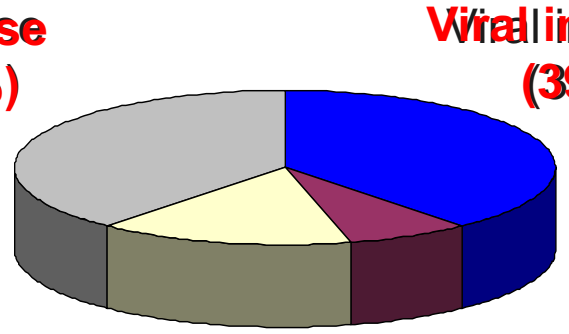
Vrienden Wilhelmina Kinderziekenhuis

BACK-UP

Introduction: hematopoietic cell transplantation (HCT)

- Replacing bone marrow + immune system
- Underlying disease:
  - Malignancy (leukemia, lymphoma)
  - Immune deficiency
  - Benign disorders (metabolic, hematological)
- Overall mortality ≈ 30%

Adaptive immune system
T-cells



Kennedy-Nasser et al, BBMT

From dose to effect: Pharmacokinetics en Pharmacodynamics

Pharmaco kinetics

Body size (weight)
Organ function
Maturation (neonates)
Drug characteristics (lipophilicity)
Pharmacogenomics
Target concentration (antibodies)
Critical illness
Compliance

Pharmaco dynamics

Receptor density
Receptor occupancy
Kill rate (antibiotics, chemo)

Dose is often a poor descriptor of response

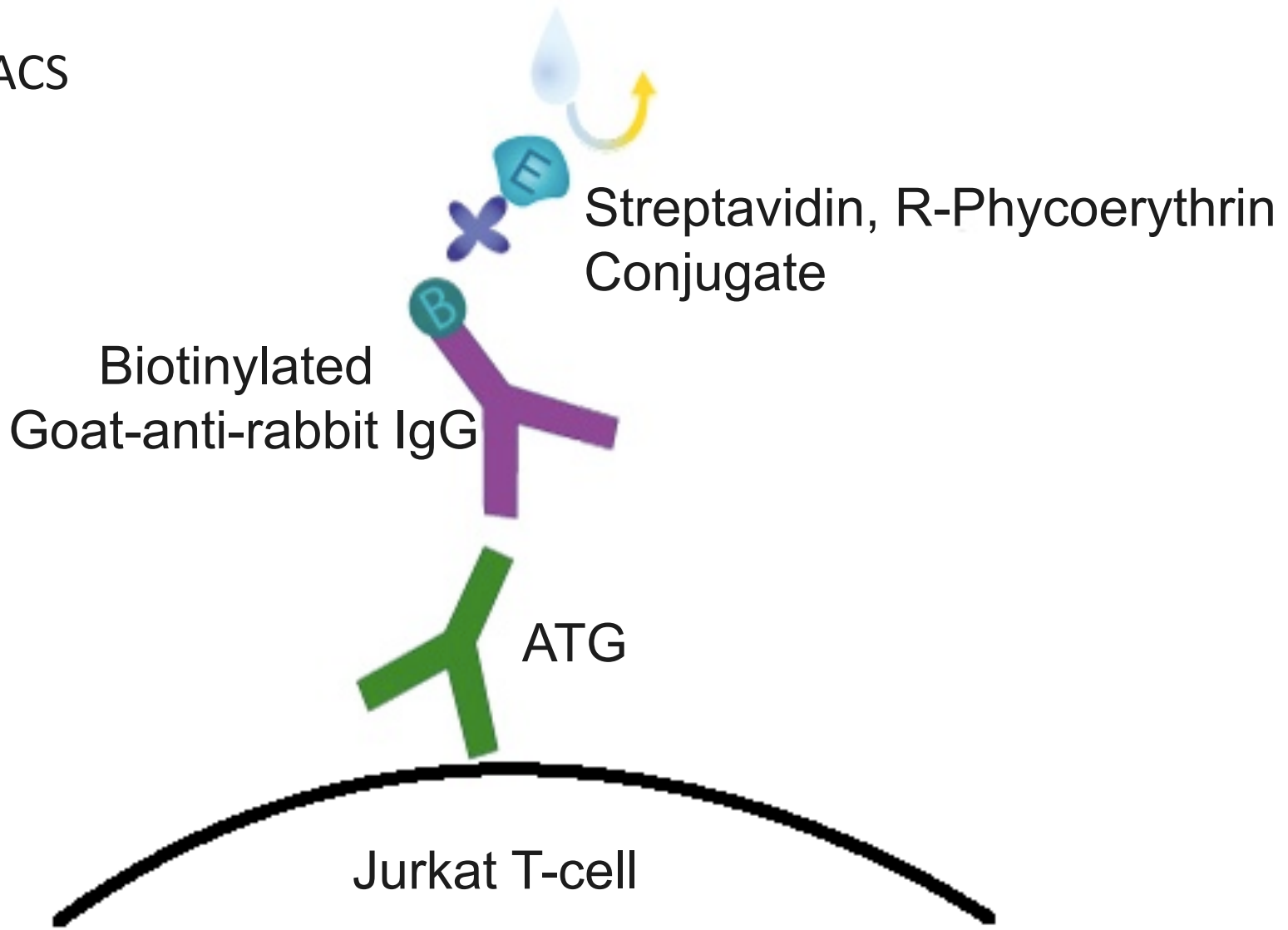
Introduction: ATG pharmacology

- ATG (Anti-thymocyte globulin)
  - Thymoglobulin®, Sanofi
  - Polyclonal IgG antibody
  - *In-vivo* lymphodepletion
  - Long half-life of 7-14 days
  - Main toxicity: Delayed immune reconstitution

- Total ATG
  - Active + “inactive” ATG
  - ELISA
- **Active ATG (~9%)**
  - Fraction rabbit IgG capable of binding to human targets
  - FACS-based cellular assay

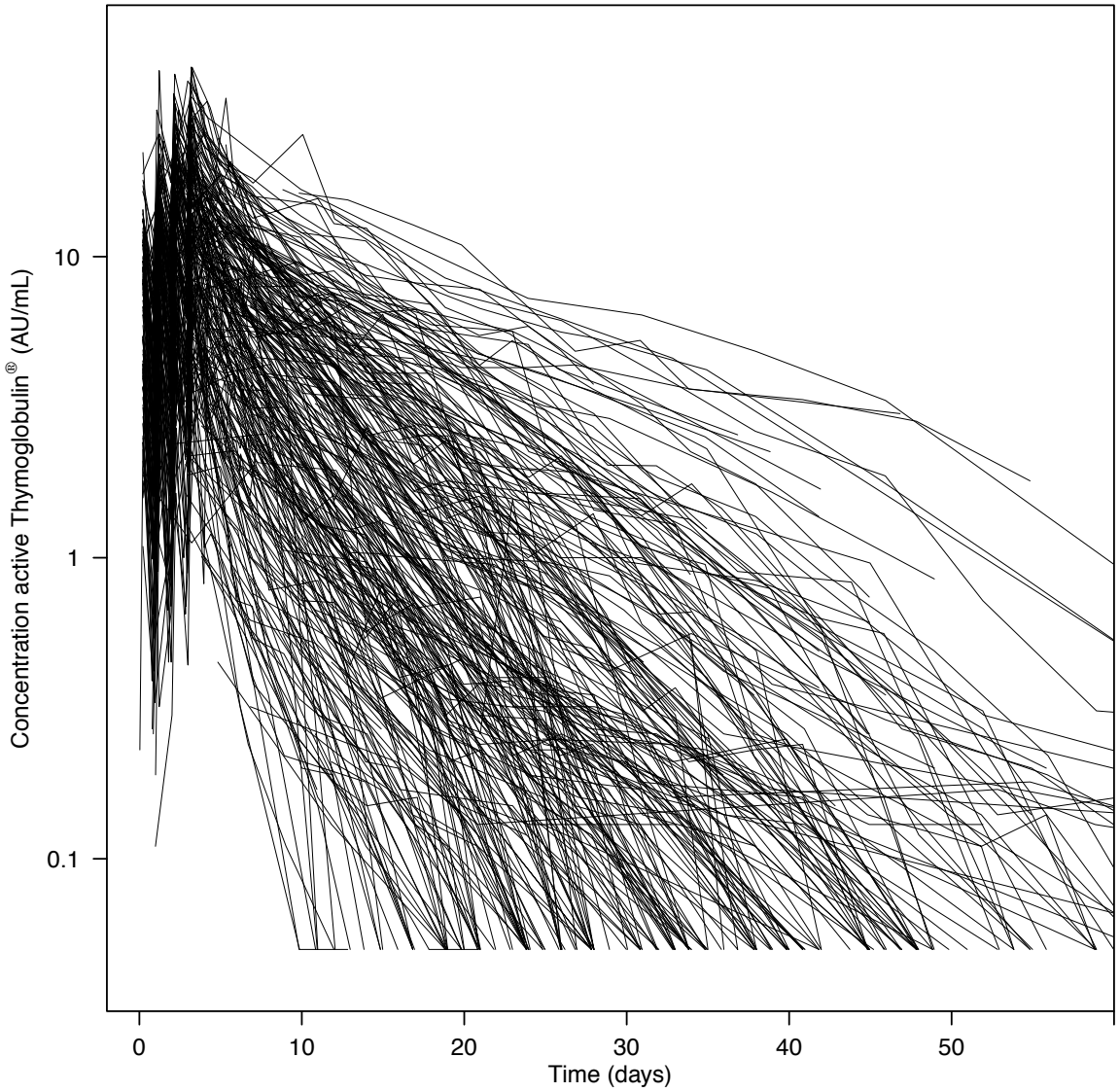
Assay for active ATG

- FACS



Variability in ATG PK: n= 267 children

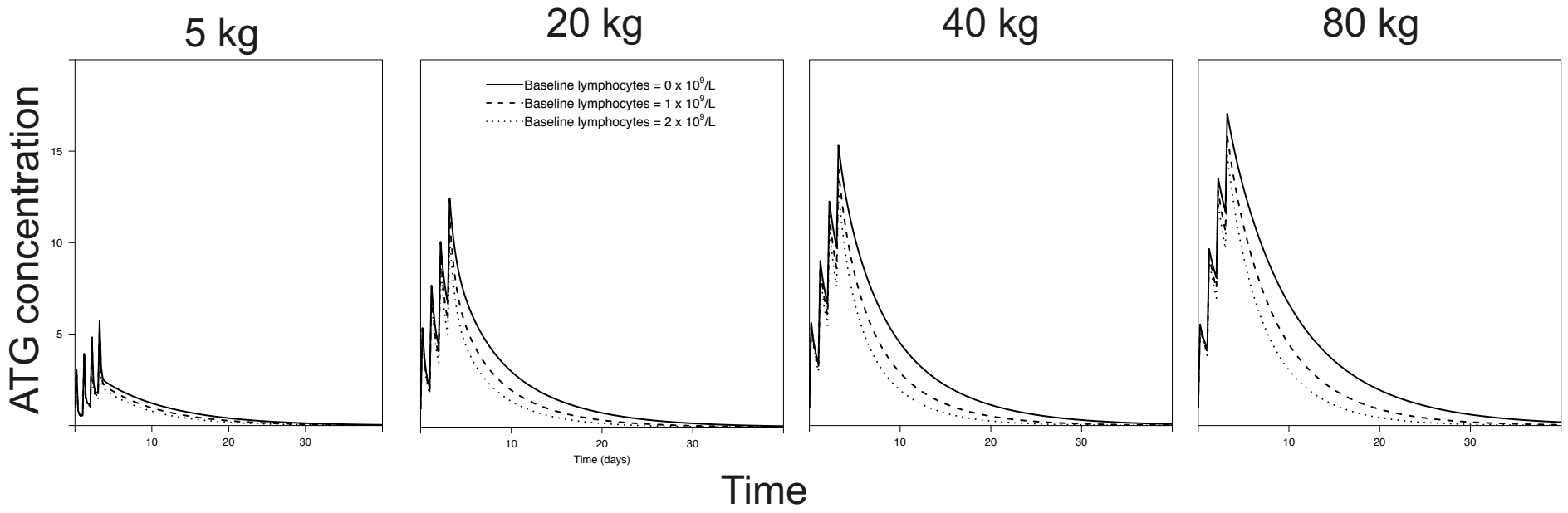
94% of patients received 10 mg/kg



Population PK model: Simulations

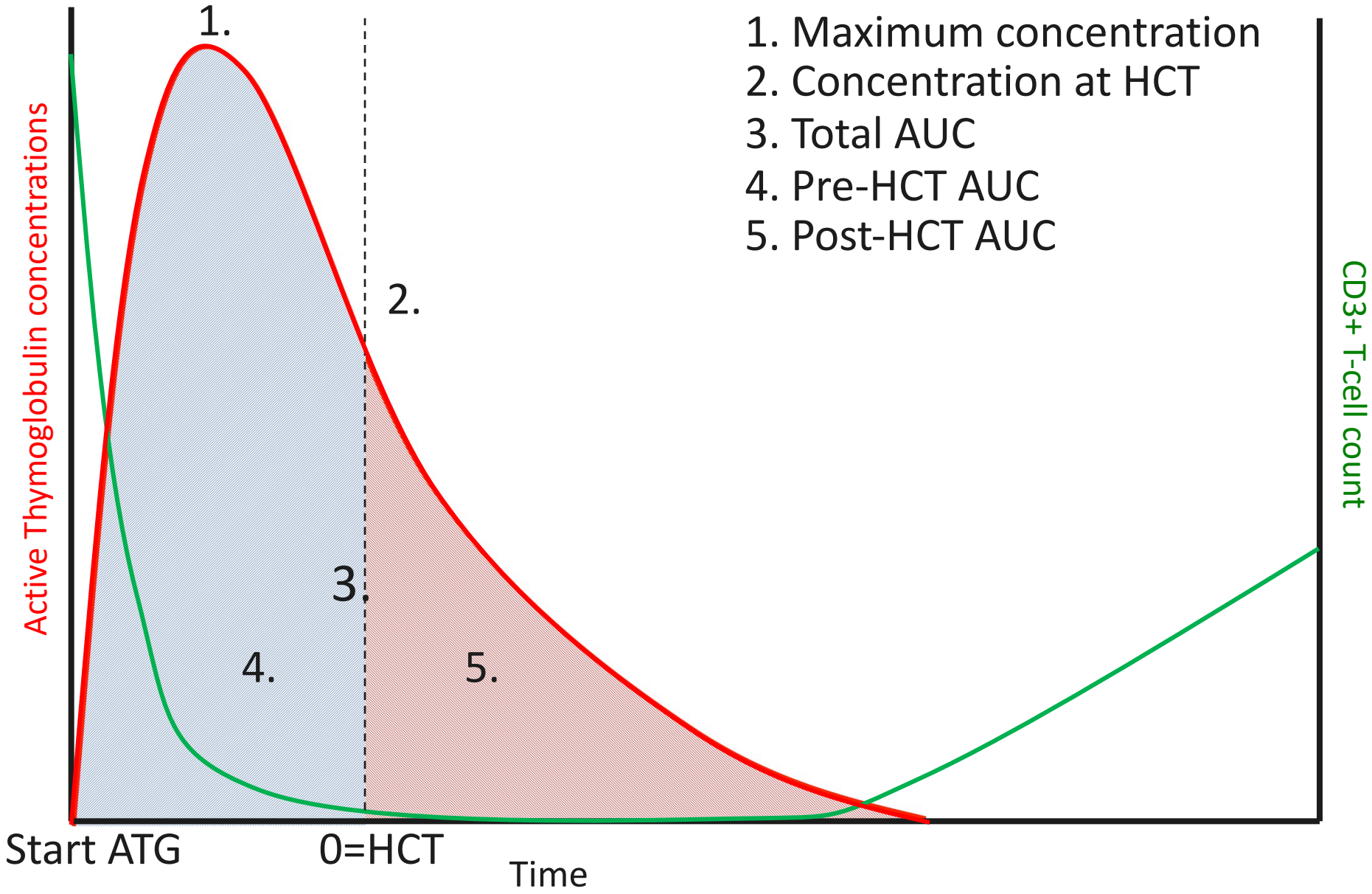
- Exposure (pre and post) varies based on **body weight** and **absolute lymphocyte counts** as well as the timing

What happens with same dose (10mg/kg) for all?



Admiraal et al, Clin. Pharmacokinetics 2014

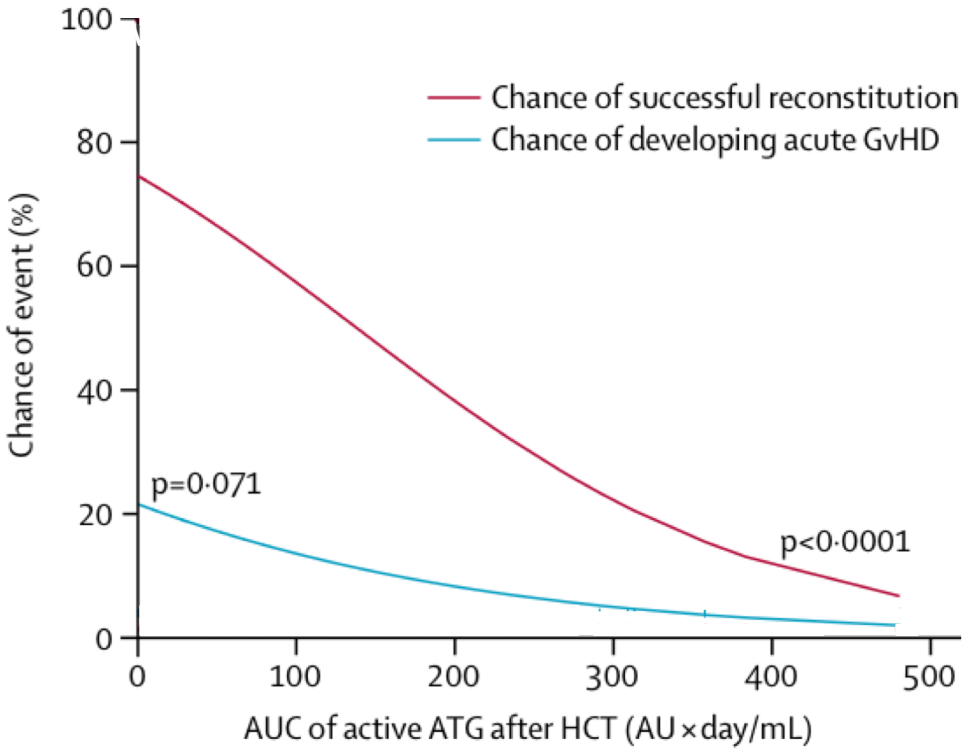
PK-endpoints



1. Maximum concentration
2. Concentration at HCT
3. Total AUC
4. Pre-HCT AUC
5. Post-HCT AUC

Active-ATG exposure after HCT vs IR, GvHD and OS according to IR (n=251 children)

Logistic regression
aGvHD and IR vs post-HCT AUC



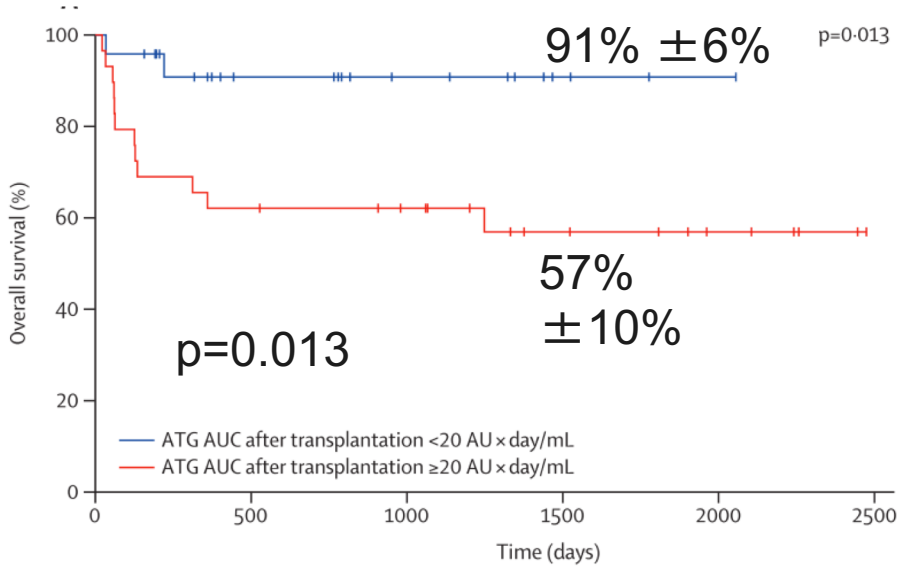
OS according to CD4 IR

Admiraal et al, Lancet Haematology 2015

Post-HCT AUC predicts survival chances; cut-off dependent on cell source

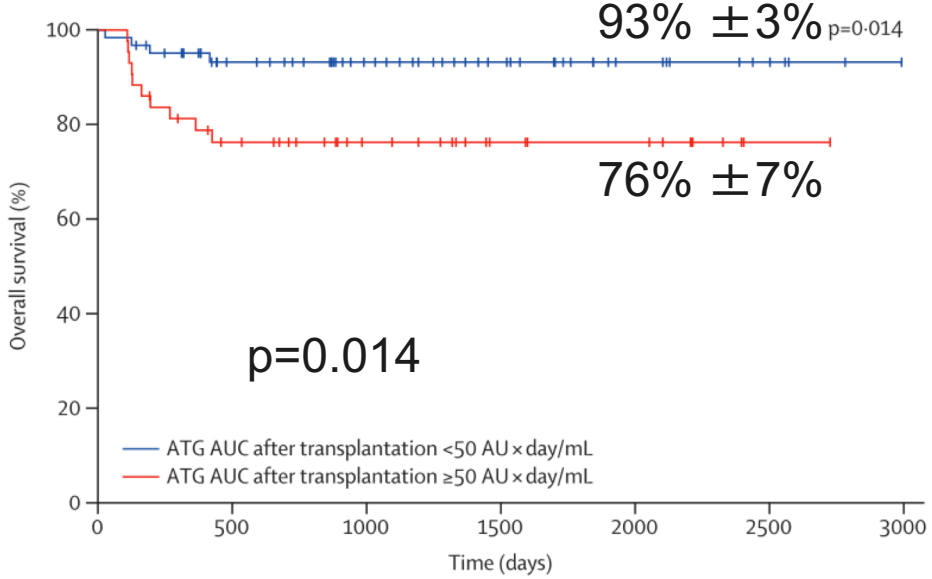
Cordblood

Post-HCT AUC <> **20** AU*day/mL

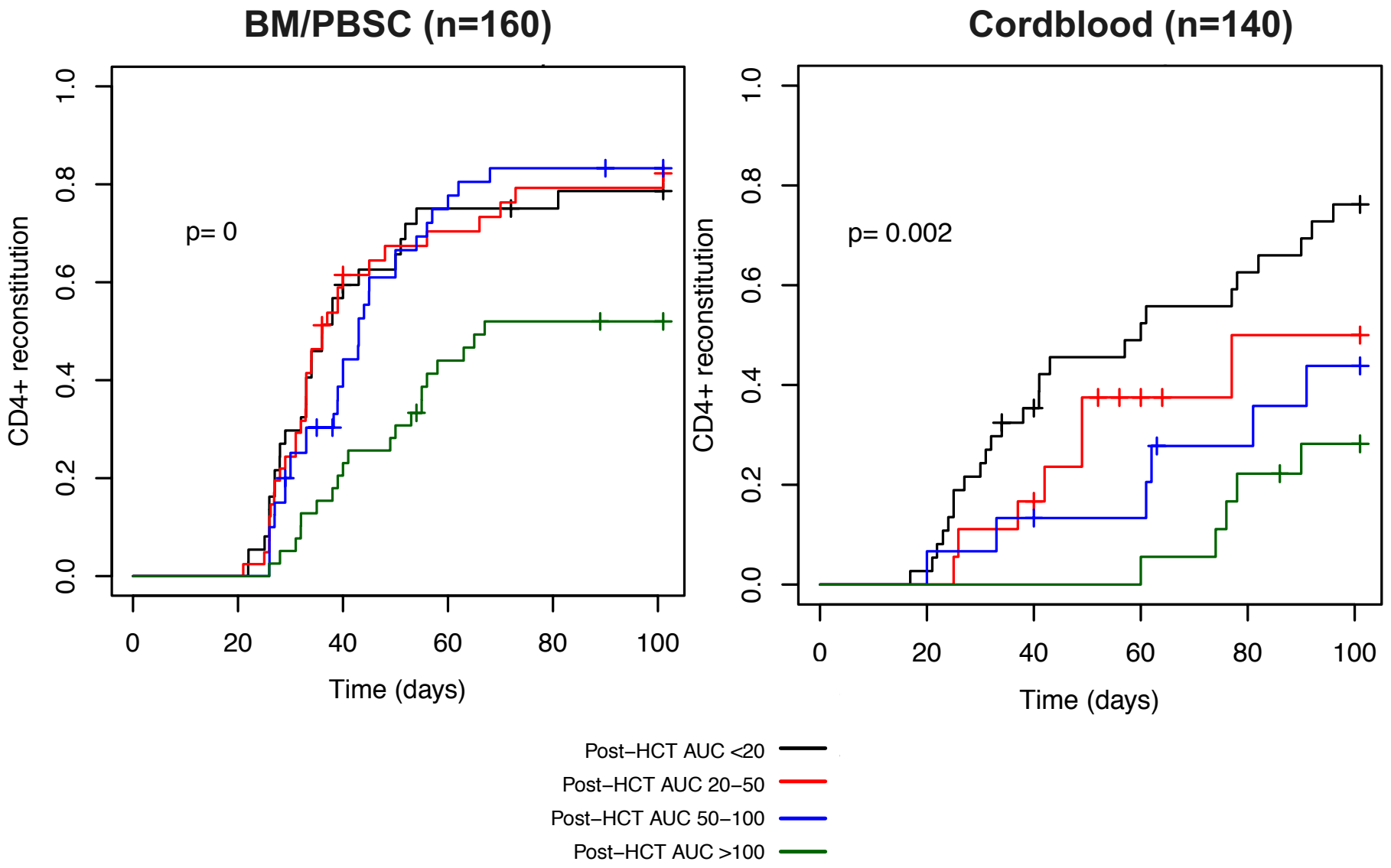


Bone Marrow/PBSC

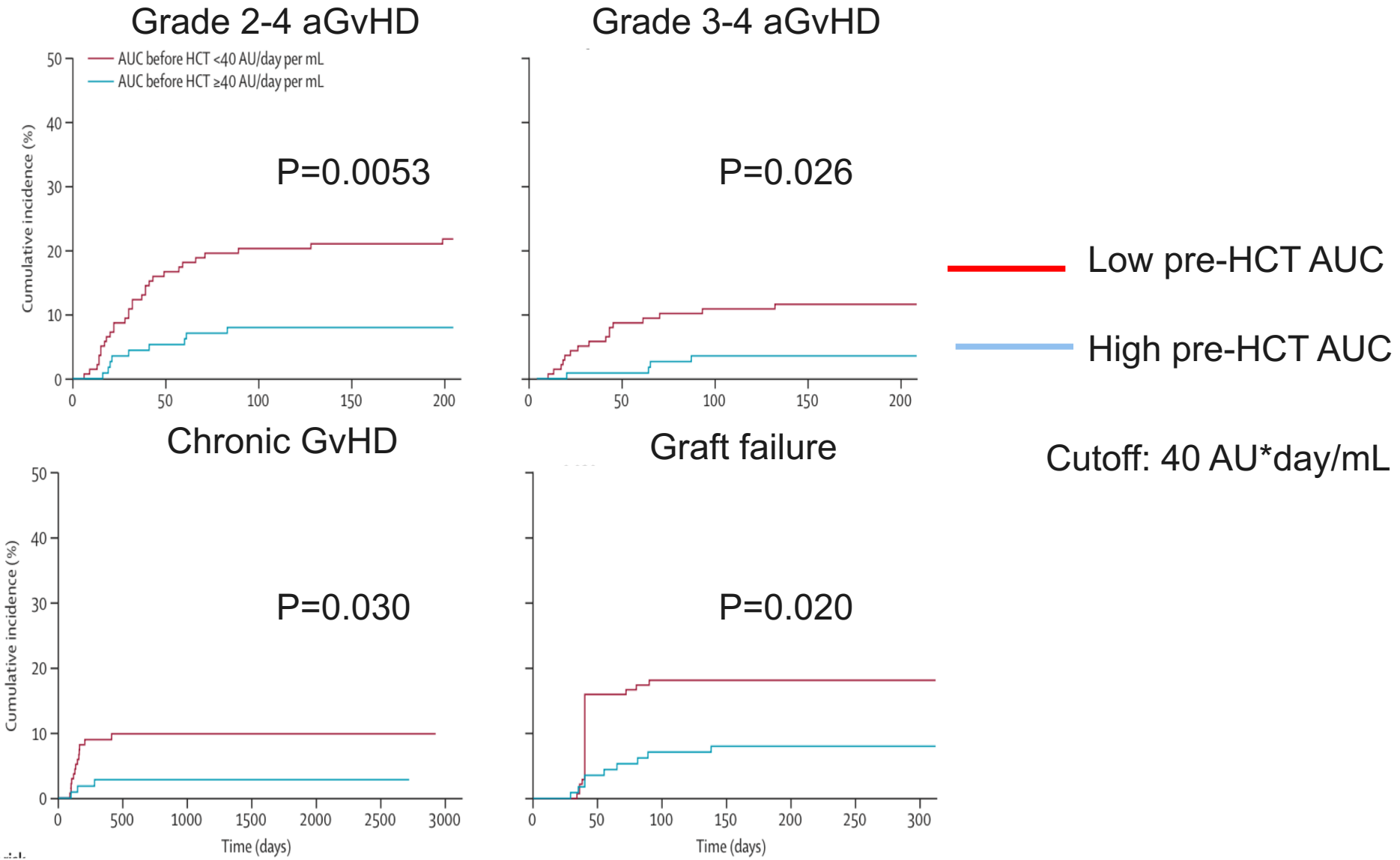
Post-HCT AUC <> **50** AU*day/mL



Influence of post-HCT AUC differs according to cell source

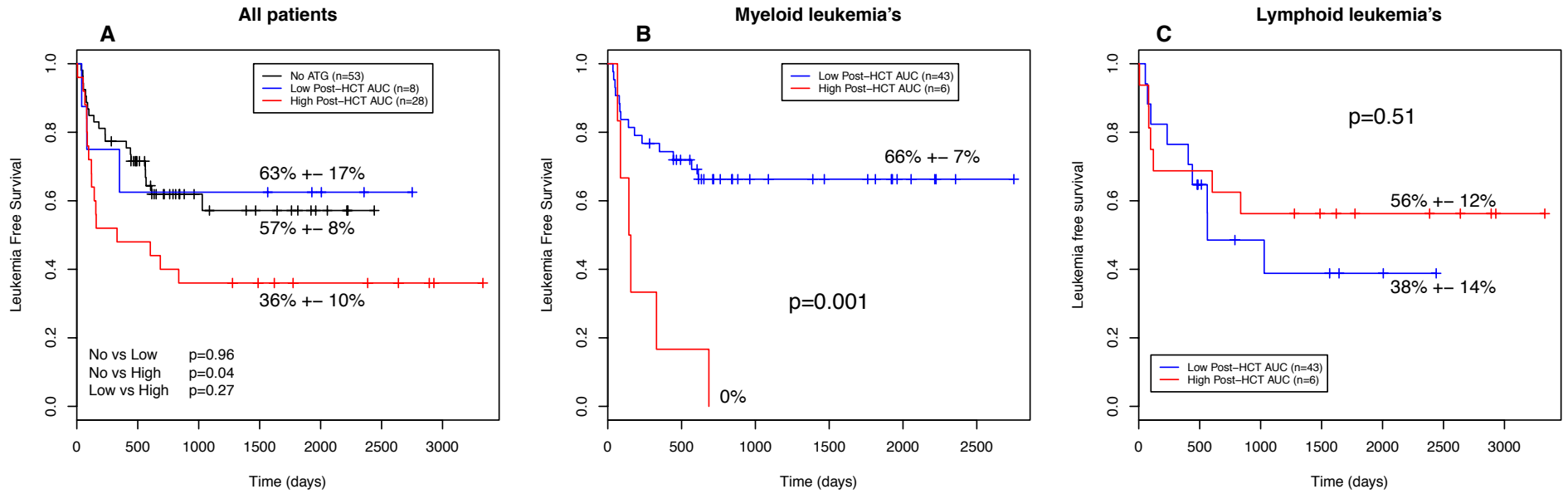


Pre-HCT AUC important for effect: predicts GvHD and graft failure



Relapse after cordblood transplantation: IR especially important in AML (n=90)

Leukemia free survival according to post-HCT ATG exposure



Admiraal et al, BBMT 2015

Validation of results in all UMCU cords
Comparable results (n=127)

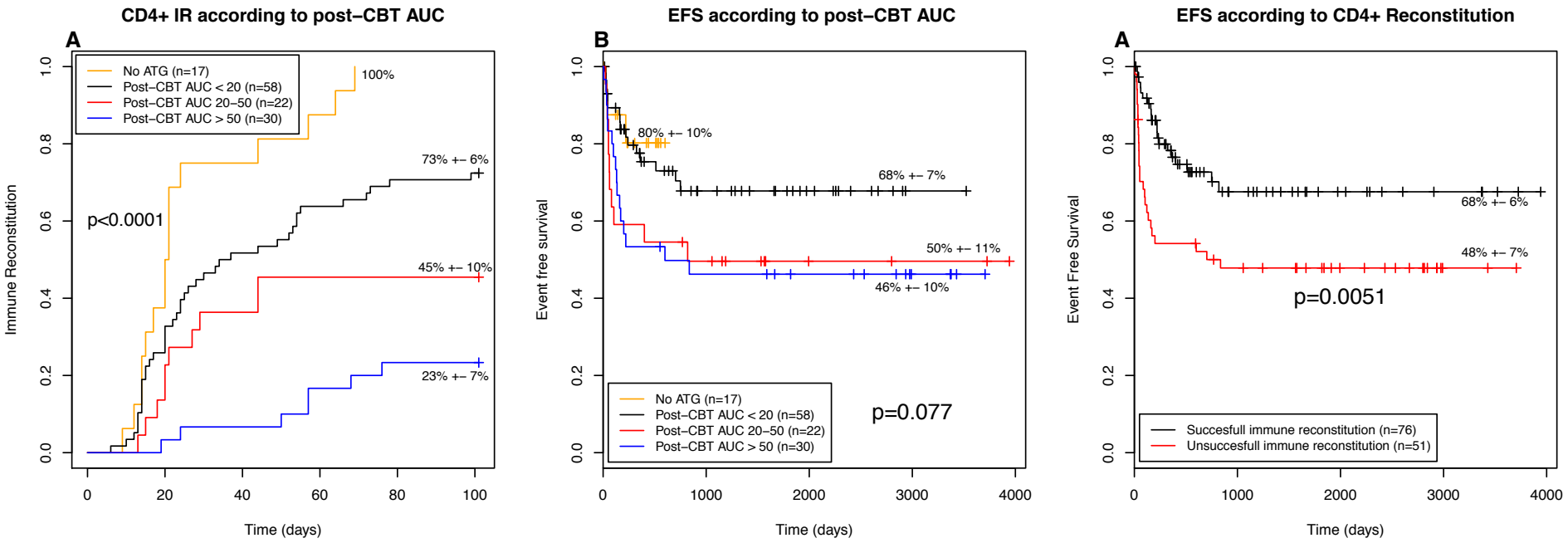


Figure 1. Panel A: Cumulative incidence of CD4+ immune reconstitution according to post–CBT ATG exposure. Panel B: Event Free Survival according to post–CBT ATG exposure. Panel C: Event Free Survival according to successful CD4+ Immune Reconstitution

Admiraal et al, submitted

ATG exposure predicts survival in adults (n=146)

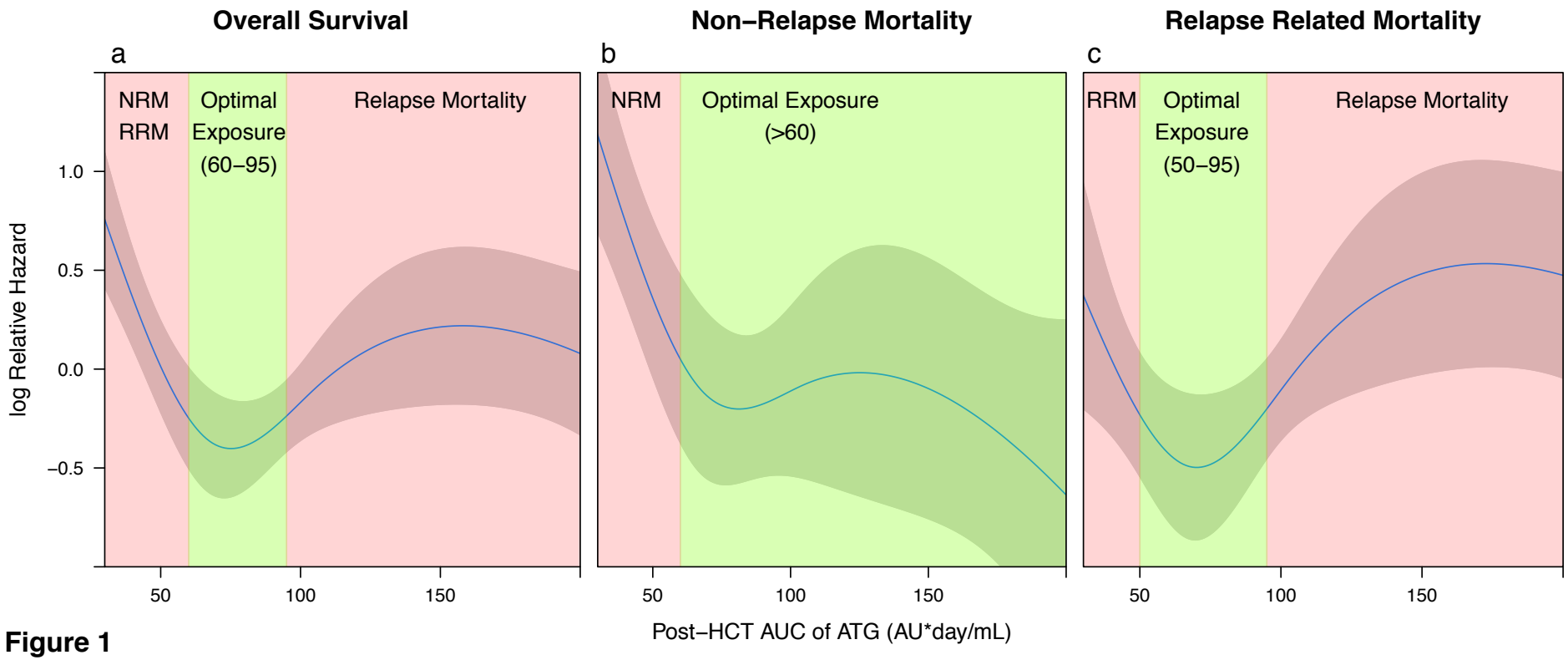
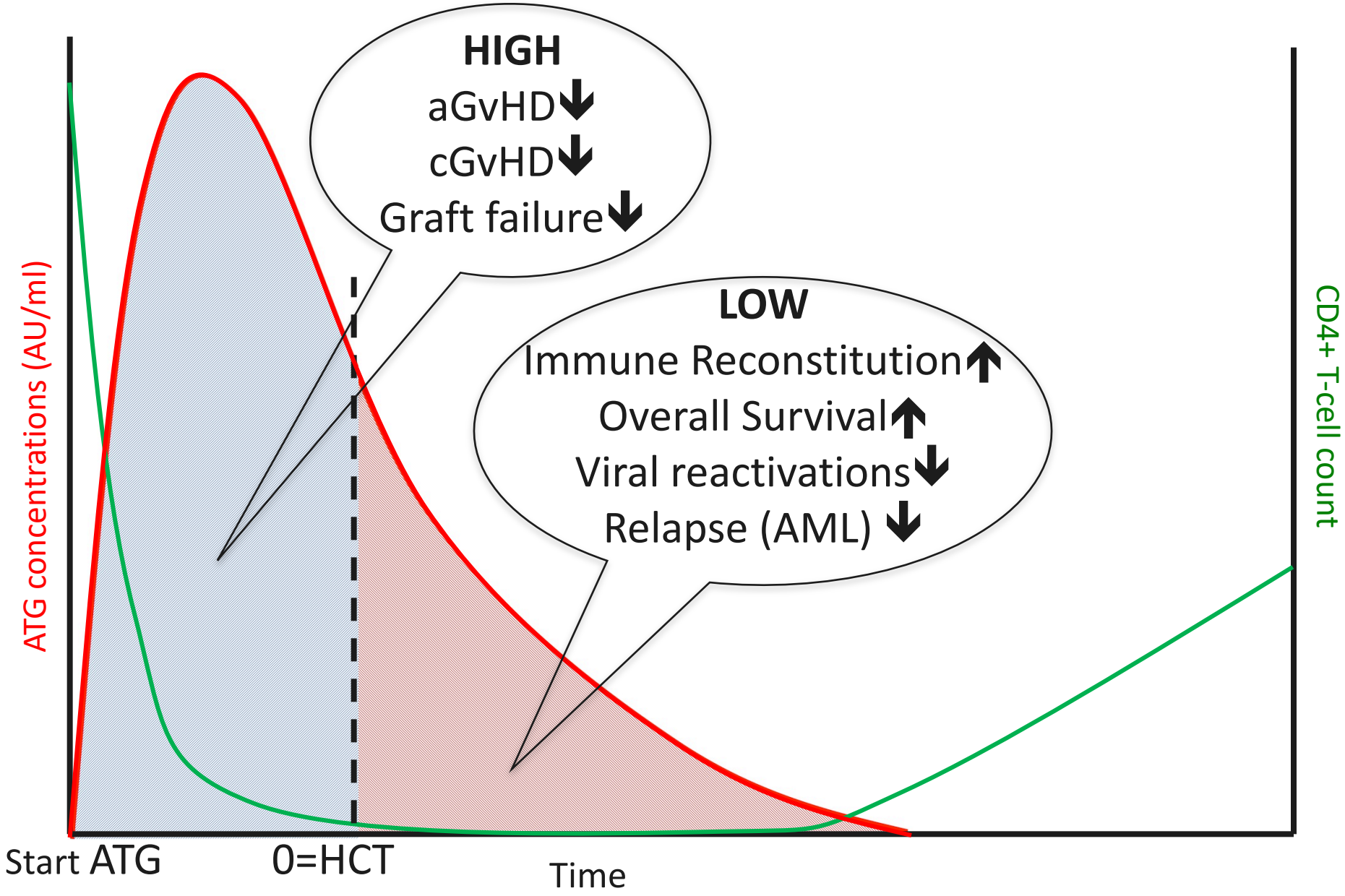
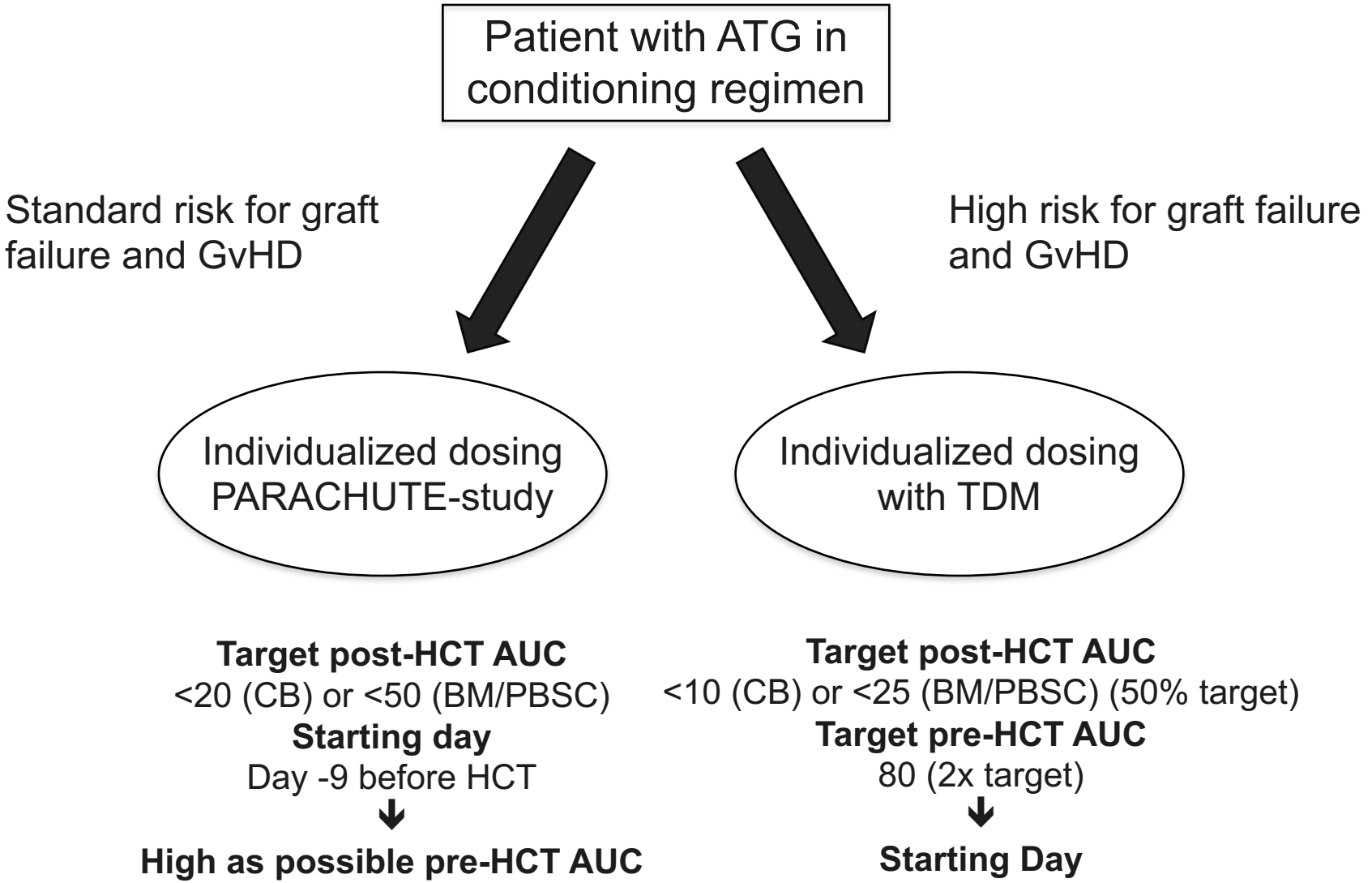


Figure 1

Summary: ATG pharmacodynamics

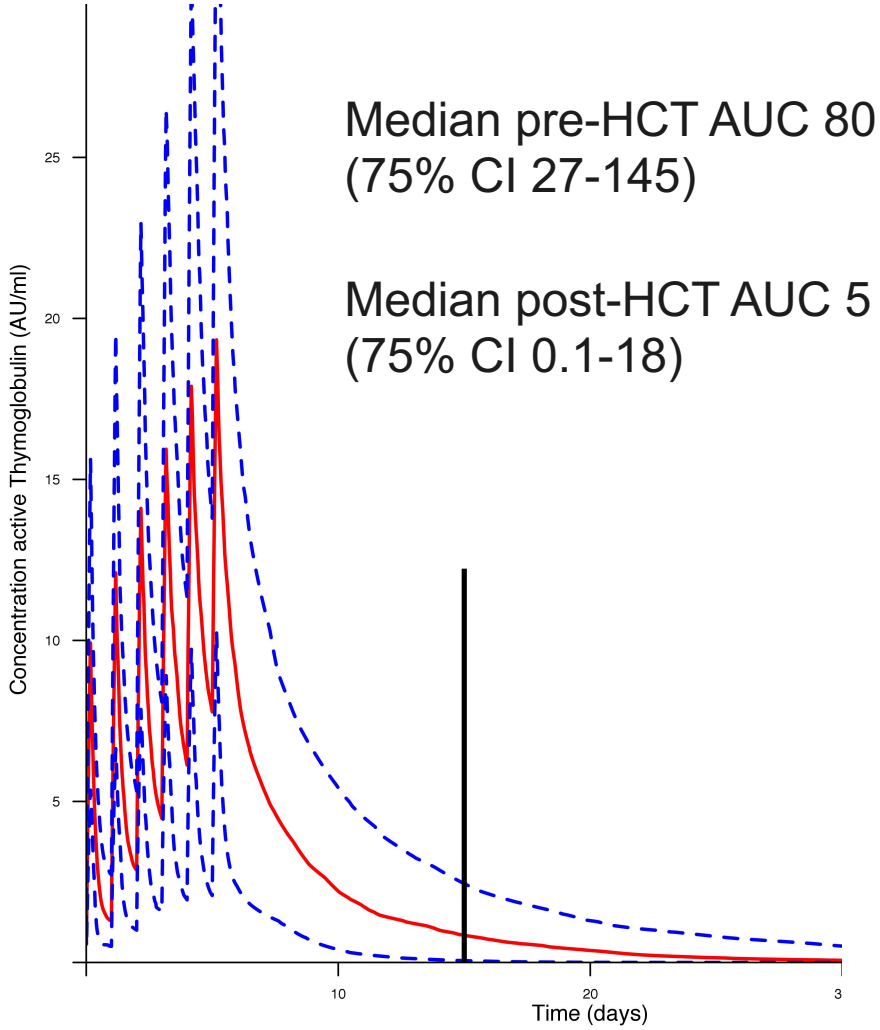


Approach to ATG Dosing in UMC Utrecht



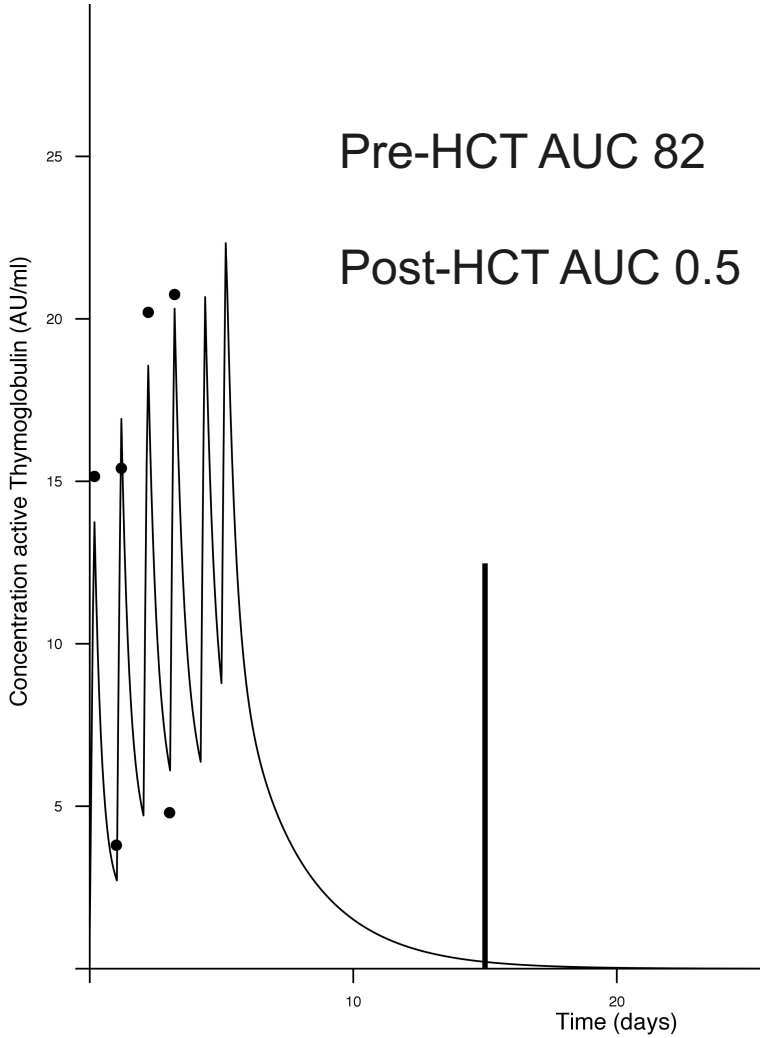
Example of TDM

10-month old boy, chronic granulomatous disease, high lymphocyte count
6x5 mg/kg Thymoglobulin, starting day -15: **30 mg/kg ATG**



Median pre-HCT AUC 80
(75% CI 27-145)

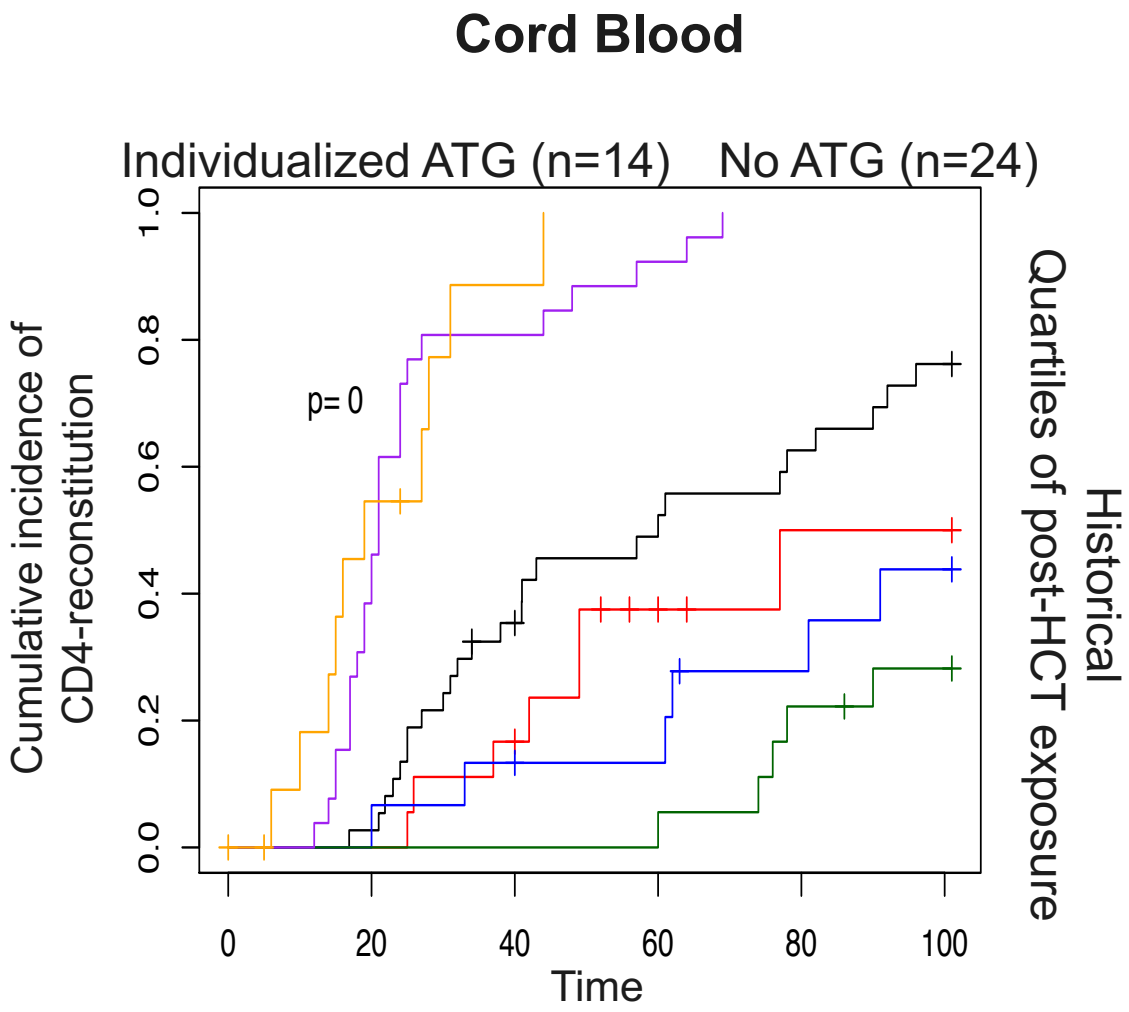
Median post-HCT AUC 5
(75% CI 0.1-18)



Pre-HCT AUC 82

Post-HCT AUC 0.5

CD4 IR following individualized ATG is improved and comparable to NO ATG



Perspectives: PARACHUTE trial

- Prospective validation of individualized ATG dosing/timing
- Interventional, phase II clinical trial
- Simon 2-stage approach (safety phase, efficacy phase)

- Primary endpoint: CD4+ immune reconstitution
- Secondary endpoints:
  - Survival
  - GvHD
  - Rejection
  - Validation of PK-model
- Results compared with historical cohort
  - Standard dose ATG

Study interventions

- Dosing based on body weight, lymphocyte count and stem cell source
- Dose varies from:
  - 2 mg/kg (older children, low lymphocyte counts, cordblood)
  - 10 mg/kg (younger children, high lymphocyte counts)
- Starting day -9
- Dose reduction in cordblood when compared to BM

- Blood sampling for ATG concentrations

Conclusions

- Dosing of ATG should be based on body weight and lymphocyte count
- Individualized ATG may lead to improved outcome of pediatric HCT
- TDM adds safety when using high doses of ATG
- Encouraging results of individualized ATG dosing (±TDM)

- Use of TDM of ATG in all patients depends on:
  - *Development of a validated active ATG assay*
  - Time (and costs) of assay
  - Necessity of TDM: residual variability in PK?

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DCOG.GOSH.GPOH

Section Applied LTI
Theme: Tumor Immunology

UDANCE
Utrecht - Dendritic Cells Against Cancer

AOMDOM

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