Therapeutic Drug Monitoring in Oncology Improves Patient Outcomes

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Therapeutic drug monitoring (TDM) or target-concentration intervention (TCI)

- Definition: involves adjustment of drug doses on the basis of concentrations measured in individual patients, is a dosing alternative for many narrow-therapeutic-index drugs[1]
- Prerequisites: narrow therapeutic index, wide inter-patient variability, well-defined concentration – effect relationship, reliable and clinically feasible assays[2]

[1]Lledó-García, Clin Pharm Ther 2009; 86(1): 62-69; [2]Gao J Clin Oncol. 2012 Nov 10;30(32):4017-25

TDM in Oncology

- Although the limitations of body surface area (BSA) dosing are well recognized in the clinical pharmacology community, many medical oncologists are still believers[1]
- Any dose personalization method – TDM, germline pharmacogenomics, new -omics tool – must improve efficacy or avoid lethal toxicity. Reducing manageable toxicity not enough[2]
- Even new genetic tools predicting cancer risk (BRCA1/2 in young women with breast cancer) or relapse risk in breast cancer patients (Oncotype Dx® to guide adjuvant chemotherapy) aren't quickly adopted[3]

[1]Bins Clin Pharmacol Ther. 2014 Apr;95(4):361-4 [2]Relling and Evans. Nature. 2015 Oct 15;526(7573):343-50; 3; Newcomer. J Clin Oncol. 2015 May 10;33(14):1620-1; Kehl Breast Cancer Res Treat 2016 155:165–173

TDM in Oncology Improves Patient Outcomes?

- Build and validate more population pharmacokinetic models. Use limited sampling schedules to better understand concentration-effect relationship.[1]
- Therapeutic target ranges should be prospectively validated through 'phase II' case series (randomized clinical trials are highly unlikely to be funded in the US)
- Technological advances towards point-of-care TDM (but slow uptake of these technologies[2])

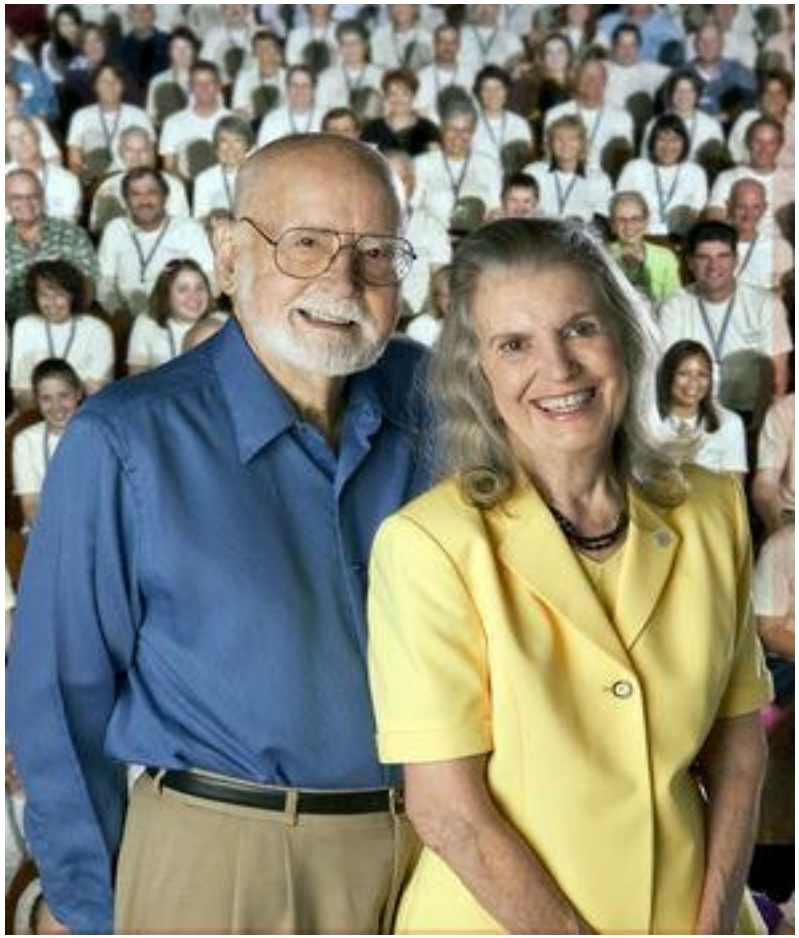
Bardin. Eur J Cancer 2014 50(12): 2005-2009. [2]Front Bioeng Biotechnol. 2015 Feb 26;3:20

Allogeneic hematopoietic cell transplant (alloHCT)

- Procedure used predominantly in patients with inherited disorders or refractory cancers
- Goal: Cure patient with no regimen-related toxicity or graft versus host disease (GVHD)

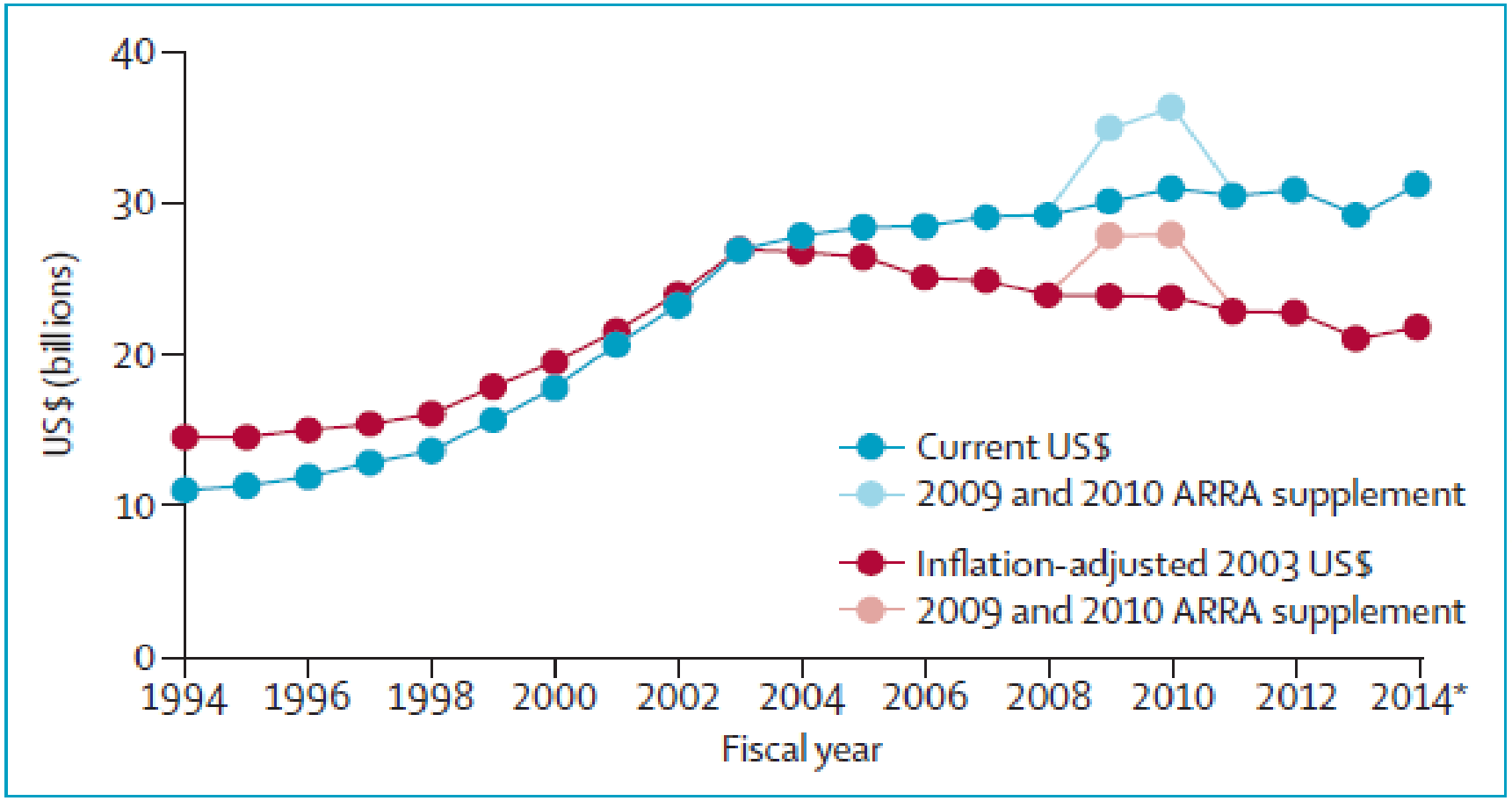
	Conditioning regimen	Day of rest	Allogeneic Graft infusion	Post grafting immunosuppression
Day:	-8 to -2	-1	0	0 to ~+30

“You have to deal with the time you live in” – Dottie Thomas



http://www.seattletimes.com/seattle-news/dottie-thomas-lsquomotherrsquo-of-bone-marrow-transplant-dies/
accessed 29 Feb 16

Reduced NIH Funding from 2002 to 2014
(& elimination of Pharmacology study section)



Lancet; 2014: 384

AlloHCT

- Initially based on premise of high dose radiation and chemotherapy to myeloablate the recipient's own hematopoietic system
- High doses of older (off-label) chemotherapy with substantive (historically fatal) toxicity

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Seattle Approach: Does TDM Improve Outcomes in AlloHCT?

- Almost all (very old) drug use is off label
- Develop (usually novel) analytical method
- Characterize the pharmacokinetic variability
- Conduct pharmacodynamic study to determine the association of clinical outcomes with plasma area under the curve (AUC) or trough concentration in a (relatively) homogeneous population
- If association found, then conduct 'phase II' (Phase III not feasible) study evaluating the benefit of TDM
- Personalize doses with TDM

RCT of Conventional vs. TDM Dosing: Too Few AlloHCT Patients

First author Patient population	TDM (regimen)	TDM dosing cohort
Evans[1] 182 pediatric acute lymphoblastic leukemia	Methotrexate, teniposide, cytarabine (120 week regimen)	B-cell ALL patients had ↑ 5 year continuous complete remission
Fety[2] 122 adults locally advanced head and neck cancer	5-fluorouracil only (5-fluorouracil and cisplatin)	↔Relapse free survival ↓ toxicity
Gamelin[3] 208 adults stage IV colorectal cancer	5-fluorouracil (5-fluorouracil and leucovorin)	↑ objective response rate Trend towards ↑ survival ↓ toxicity

[a]Evans N Engl J Med 1998 338(8): 499-505; [2]Fety Clin Cancer Res 1998; 4(9): 2039-2045; [3]Gamelin J Clin Oncol 2008; 26(13): 2099-2105.

Does TDM of AlloHCT Conditioning Regimen Improve Outcomes?

	Busulfan (BU)	Cyclophosphamide (CY)			Fludarabine (FLU)	
Active metabolites?	CA182963	Yes			Yes	
PK Variability (max/min)	2.8 fold	16-fold			3.7 fold	
Conditioning regimen	various	CY/TBI	^{T}Bu/CY	CY/^{T}Bu	FLU/^{T}BU/ ATG	FLU/ TBI
AUC associated w/ clinical outcomes?	Most	Yes (metab)	No	Yes (metab)	Yes	No
Phase II study of TDM benefit?	Yes	Yes	N/A	Not likely	Regimen too toxic	N/A
Clinical use of TDM?	Yes	No	N/A	Not likely	N/A	N/A

Alkylating Agent Busulfan (BU) AlloHCT Conditioning

1953: Activity in chronic myeloid leukemia

1968: First preclinical study of busulfan and cyclophosphamide (BU/CY) as HCT conditioning

Blood. 1968 Oct;32(4):629-37 (Santos & Tutschka at Hopkins)

1978: First publication of BU/CY in humans

Blood. 1978 Sep;52(3):627-36

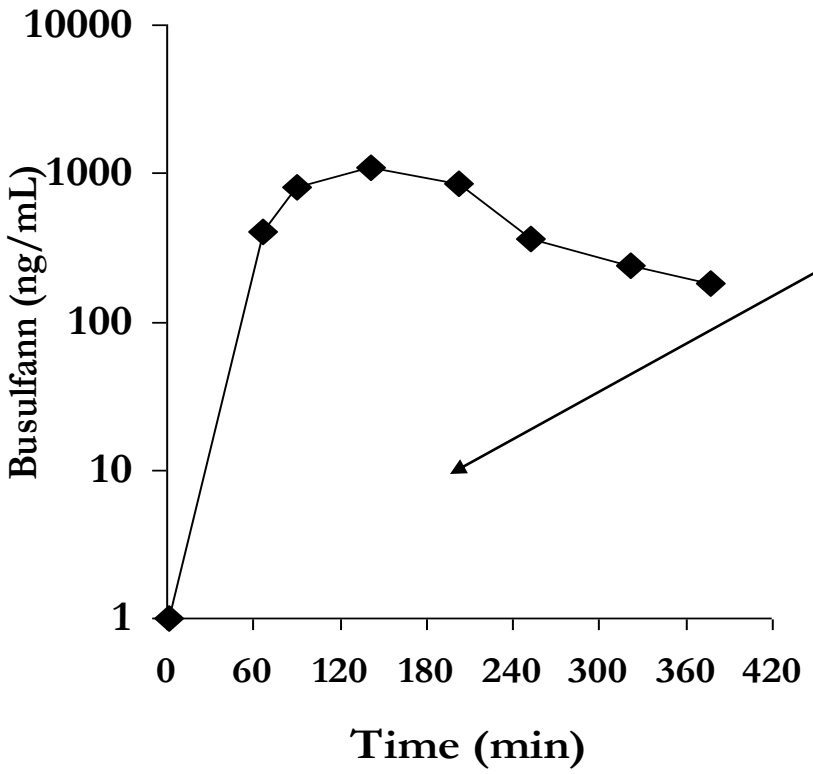
1980: First report of hepatotoxicity

Am J Pathol. 1980 May;99(2):369-86

1989: First pharmacokinetic/dynamic report of AUC with hepatotoxicity (then lethal) in adults

Cancer Chemother Pharmacol. 1989;25(1):55-61

(Targeted) Busulfan TDM



- First dose based on body surface area (BSA) or body weight
- Get multiple blood samples to estimate AUC
- Clearance = dose divided by AUC
- Know target AUC
- Adjust dose based on patient's clearance to achieve target AUC
- Must be quick – busulfan only administered over four days

$$\text{Css}\left(\frac{\text{ng}}{\text{mL}}\right)=\text{AUC}\left(\frac{\mu\text{mol*min}}{\text{L}}\right)\left(\frac{1\text{ hr}}{60\text{ min}}\right)\frac{}{24\text{hr}}\left(\frac{246.3\mu\text{g}}{1\mu\text{mol}}\right)\left(\frac{1000\text{ng}}{1\mu\text{g}}\right)\left(\frac{1\text{L}}{1000\text{ mL}}\right)$$

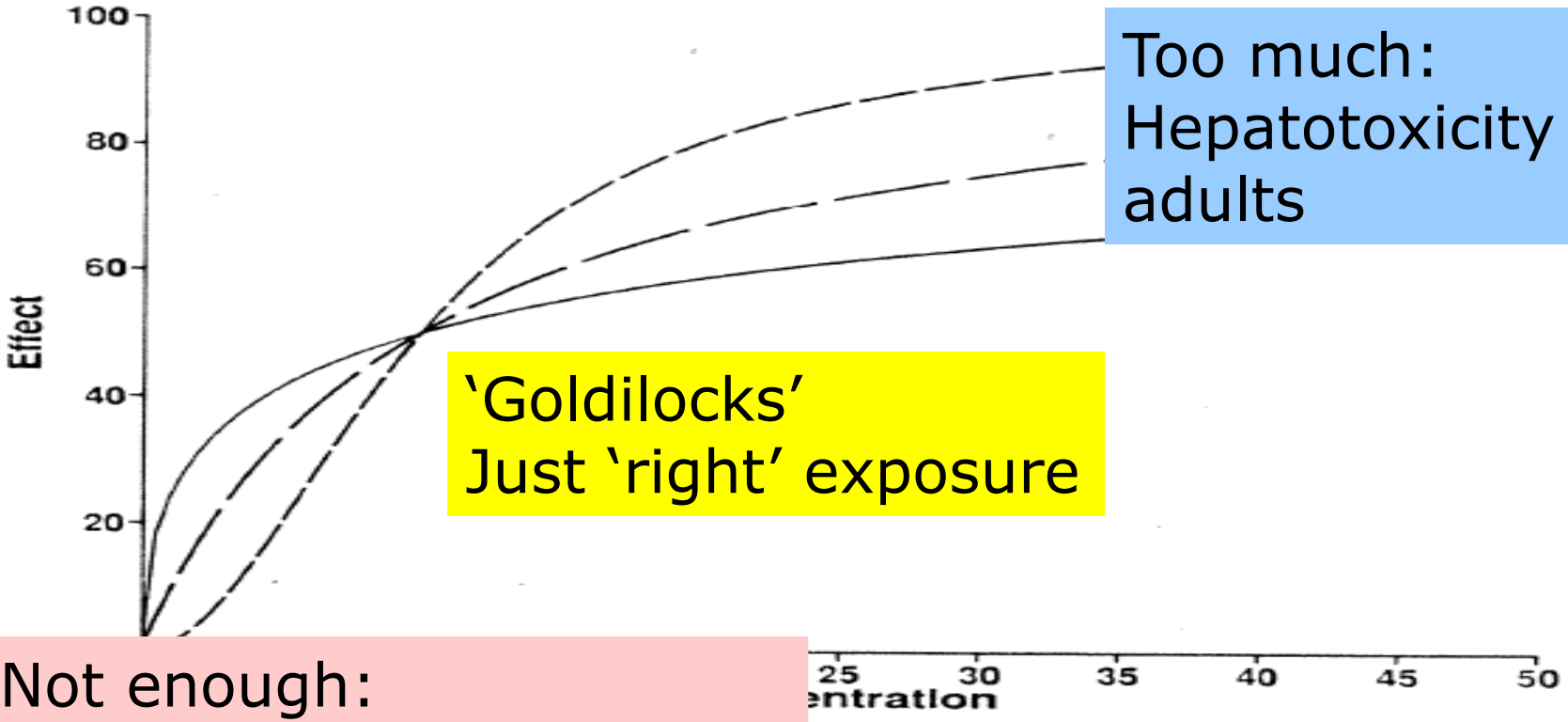
Busulfan TDM Improves Outcomes

Outcome	PD Association	TDM Benefit
Rejection	Yes (N=24 – 41)[1]	↑ engraftment rates from 74% to 96% (N=32)[2]
Hepato-toxicity	Yes (N=35-51)[1]	↓ hepatotoxicity rates from 75% to 18% (N=27)[3]
Relapse in CML	Yes (N=45)[1]	↓ relapse rate from 15% to 8% (N=131)[4]

[1]McCune. *Clinical Pharmacokinetics*, 2000; 39 (2): 155-165. [2]Bolinger. Bone Marrow Transplant. 2001 Dec;28(11):1013-
[3]Grochow. Semin Oncol. 1993 Aug;20(4 Suppl 4):18-25; [4]Radich. *Blood* 2003; 102: 31-35

Google Images, accessed 26 Nov 13

Busulfan's Hill Equation In Bu/CY



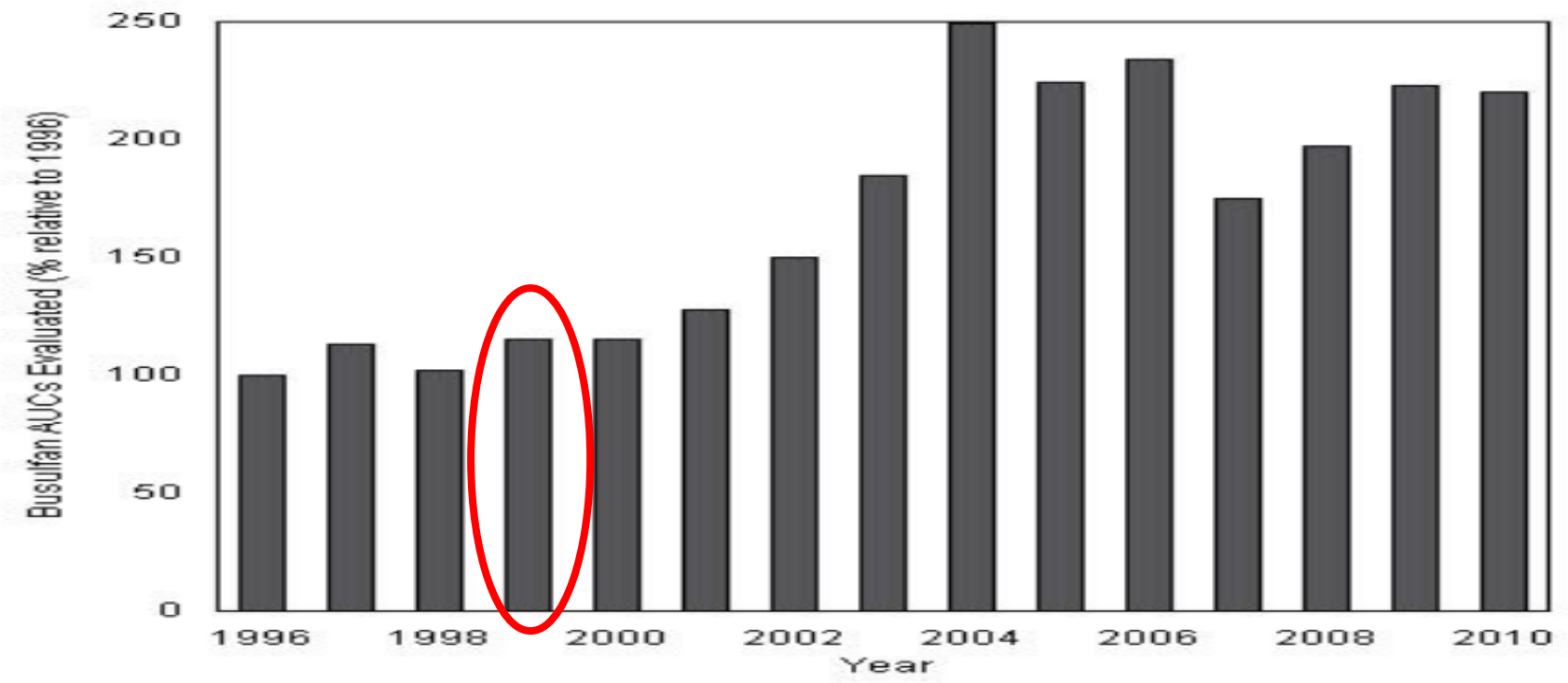
Too much:
Hepatotoxicity in adults

'Goldilocks'
Just 'right' exposure

Not enough:
Rejection
Relapse in select diseases

Pharmacokinetics and Pharmacodynamics Volume 2, 1988

Busulfan TDM Is Clinically Accepted



In 2008, more than 60% of patients reported to the CIBMTR who received oral busulfan and 50% of those receiving IV busulfan had pharmacokinetic data

McCune J Clin Pharmacol. 2013 Mar;53(3):264-75; Copelan Blood. 2013 Dec 5;122(24):3863-70

Improving Busulfan TDM

- Only 23% of adults and 24% of children achieve their target exposure with weight based dosing of IV busulfan

J Clin Pharmacol. 2013 Mar;53(3):264-75

- Personalizing either IV or oral busulfan dosing cannot be simplified on the basis of *GSTA1* or *GSTM1* genotype

J Clin Pharmacol. 2011 Oct; 51(10): 1429 – 1438

- Population pharmacokinetic models:
  - Use shorter sampling schedules to allow for outpatient TDM of daily IV busulfan using post-Bayesian estimates of individual patient data after model validation and clinical decision support construction

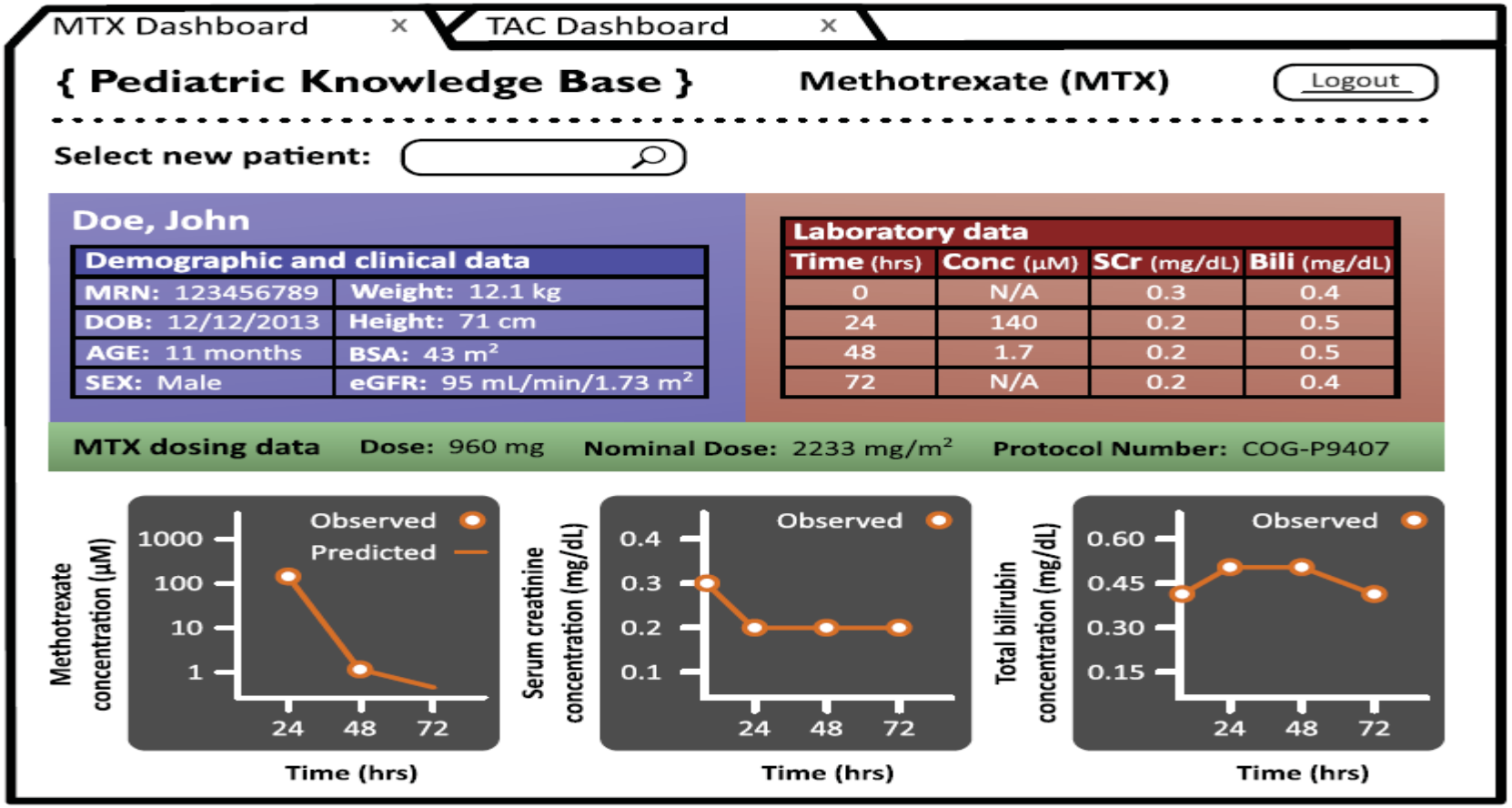
J Clin Pharmacol. 2010 Nov;50(11):1292-30

  - Initial dosing and TDM in children (N=1,492) and adults (N=128)

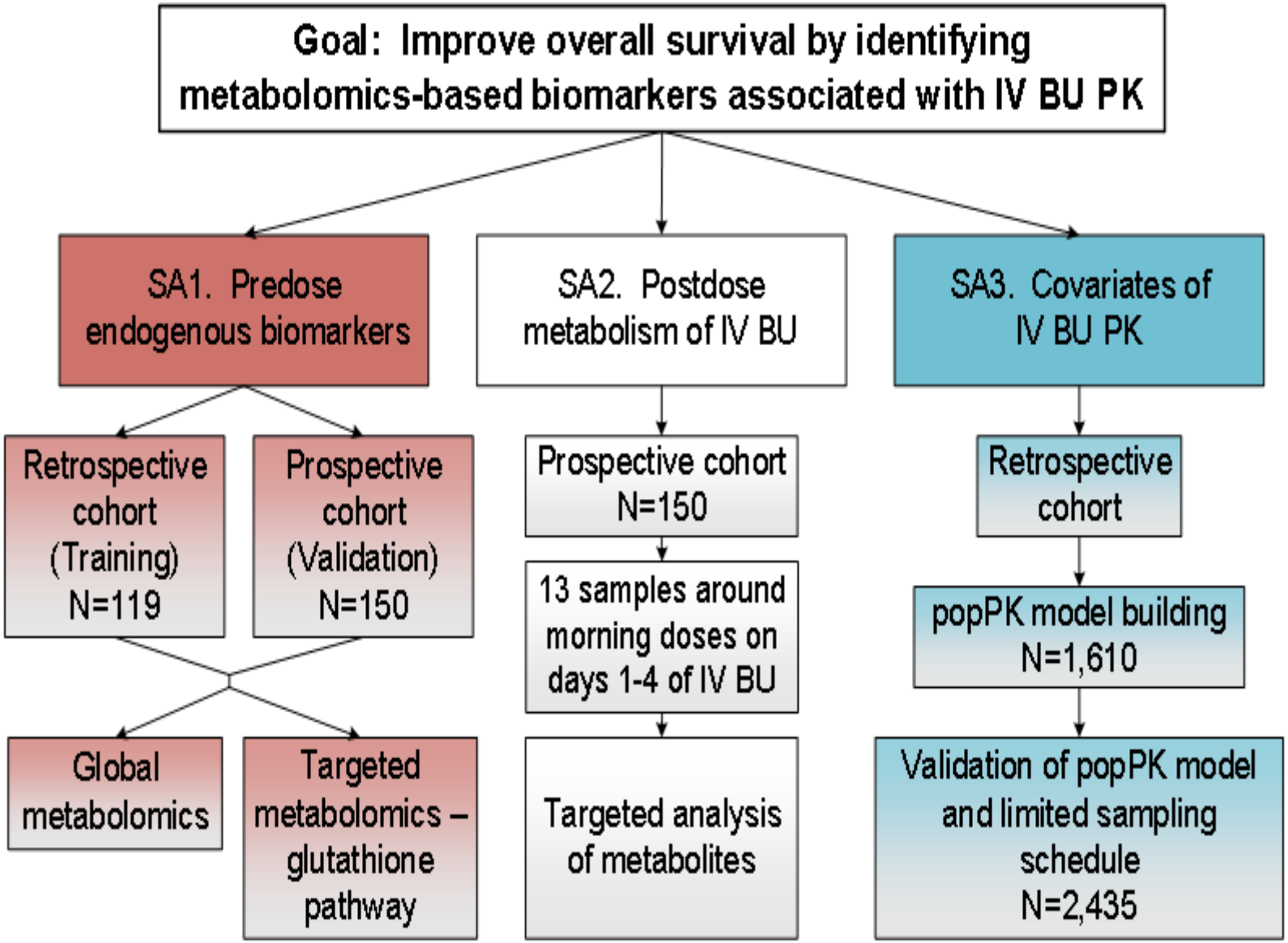
Clin Cancer Res. 2014 Feb 1;20(3):754-6

Dashboards

http://www.paganz.org/abstracts/busulfan-target-concentration-intervention-audit-and-model-evaluation/ ds



CPT Pharmacometrics Syst Pharmacol. 2015 Nov;4(11):630-40


Goal: Improve overall survival by identifying metabolomics-based biomarkers associated with IV BU PK
SA1. Predose endogenous biomarkers
SA2. Postdose metabolism of IV BU
SA3. Covariates of IV BU PK
Retrospective cohort (Training) N=119
Prospective cohort (Validation) N=150
Prospective cohort N=150
Retrospective cohort
13 samples around morning doses on days 1-4 of IV BU
popPK model building N=1,610
Global metabolomics
Targeted metabolomics – glutathione pathway
Targeted analysis of metabolites
Validation of popPK model and limited sampling schedule N=2,435

Key Points

- Any dose personalization method **must improve efficacy** or avoid (the rare) lethal toxicity
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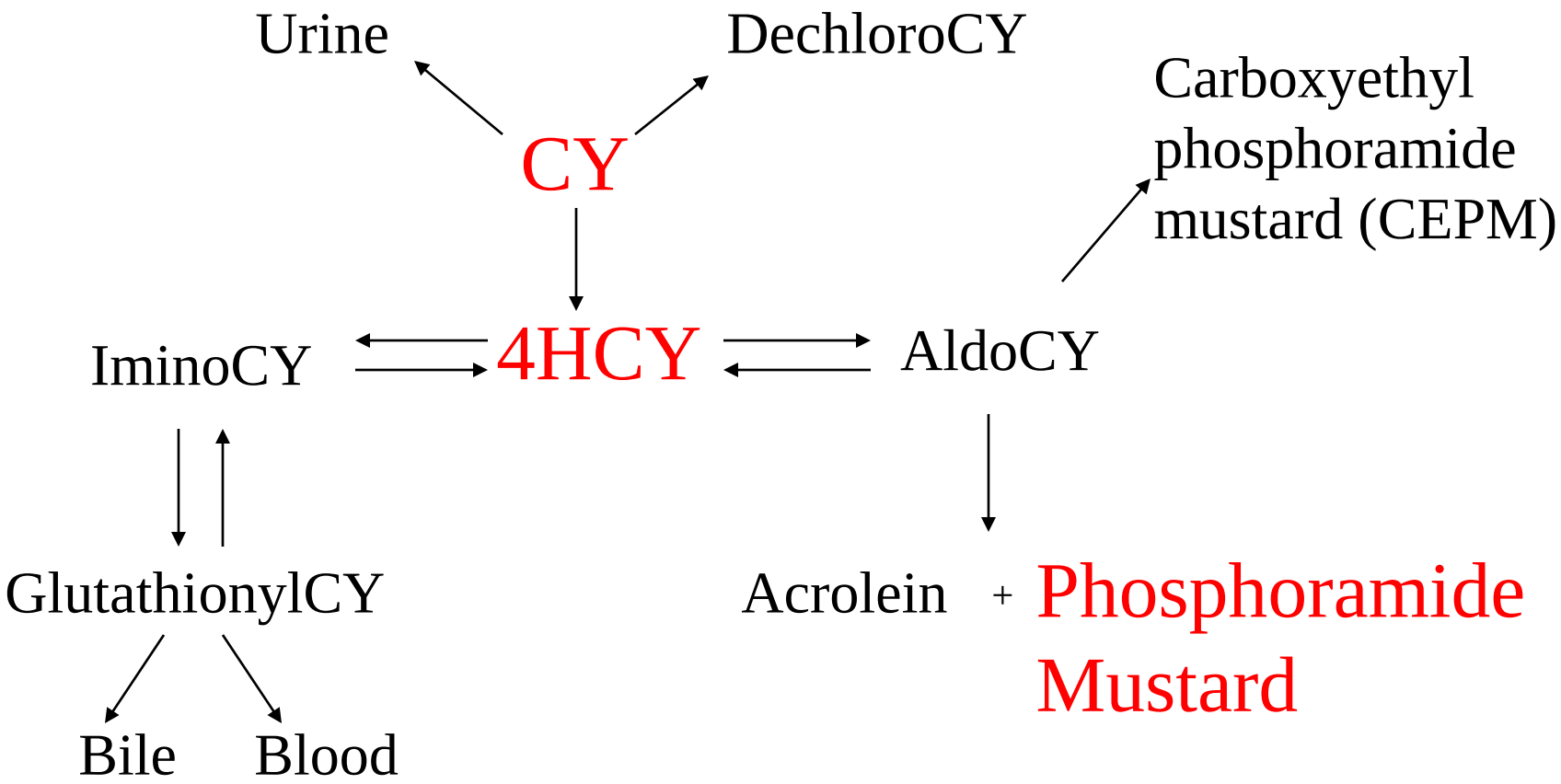
Phase II study of TDM benefit?	Yes	Yes	N/A	Not likely	Regimen too toxic	N/A
Clinical use of TDM?	Yes	No	N/A	Not likely	N/A	N/A

Prodrug Cyclophosphamide (CY) Pharmacokinetics (partial schema)



Efforts to improve CY in HCT

- Considerable interpatient variability in the exposure of CY and its metabolites

Blood. 2003 Mar 1;101(5):2043-8

- In CY/TBI, personalizing CY doses to metabolite exposure using a population pharmacokinetic model decreased liver and renal toxicity

Clin Pharmacol Ther. 2009 Jun;85(6):615-22

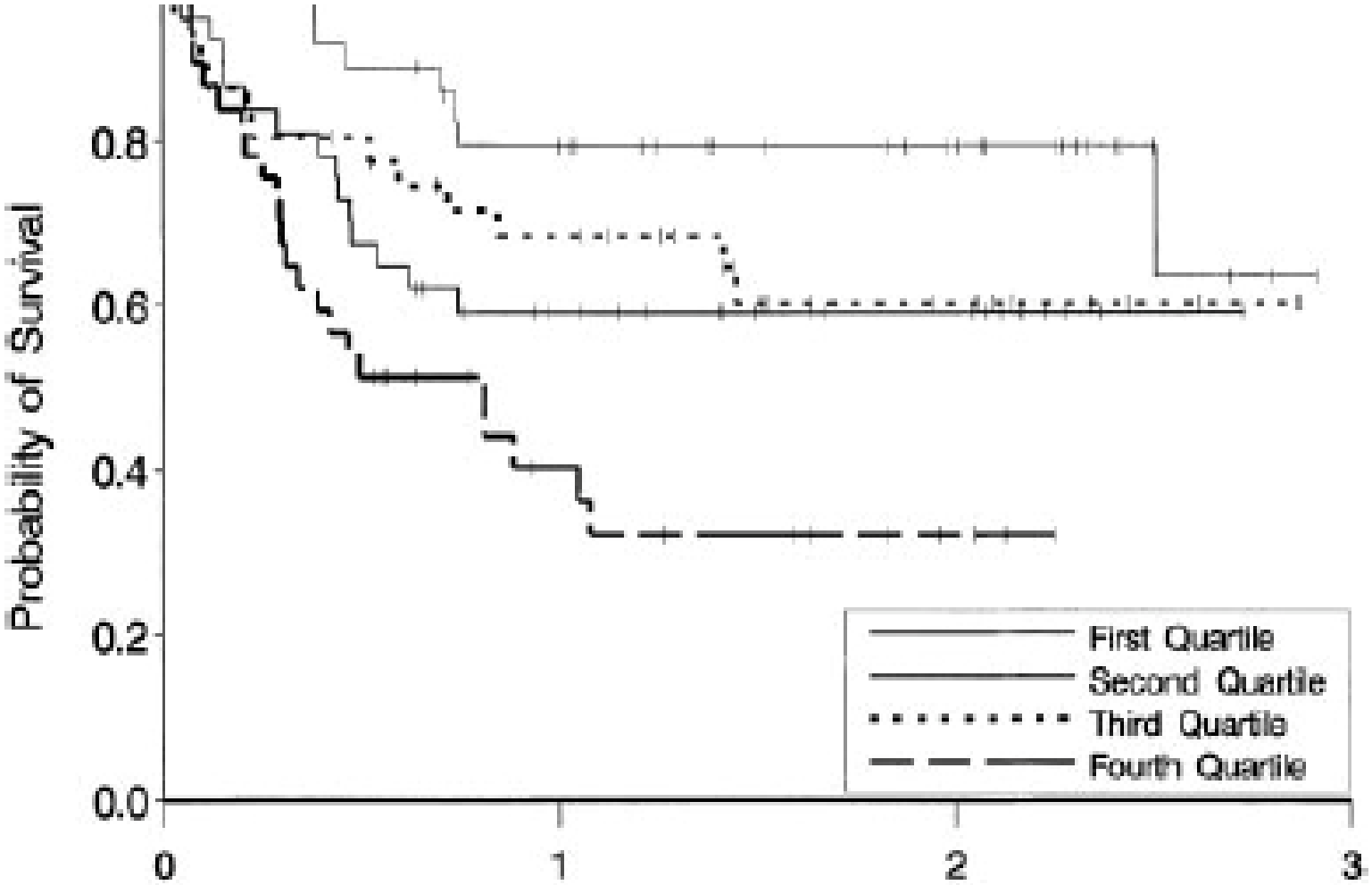
- In ^{T}BU/CY, clinical outcomes were not associated with CY or its metabolite exposure

BBMT. 2007 Jul;13(7):853-62

- Outcomes may be improved by switching order of administration (CY/^{T}BU). Pharmacodynamic associations with overall survival

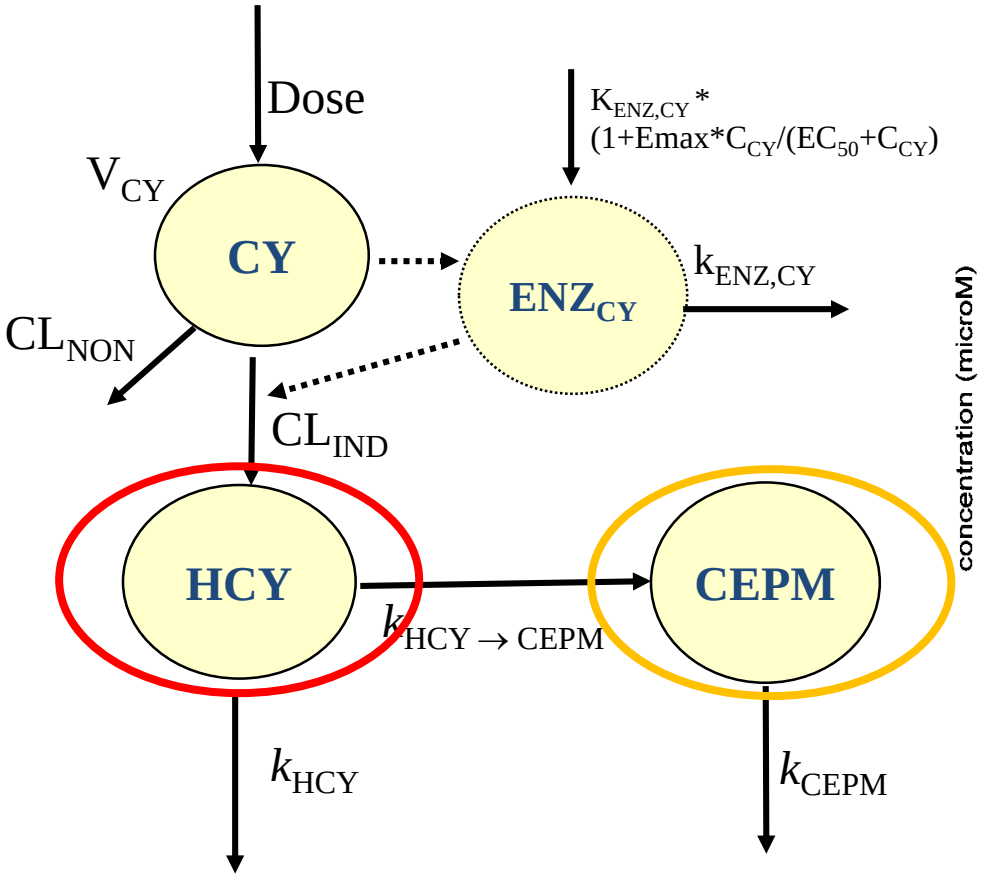
BBMT. 2013 Jul;19(7):1033-9

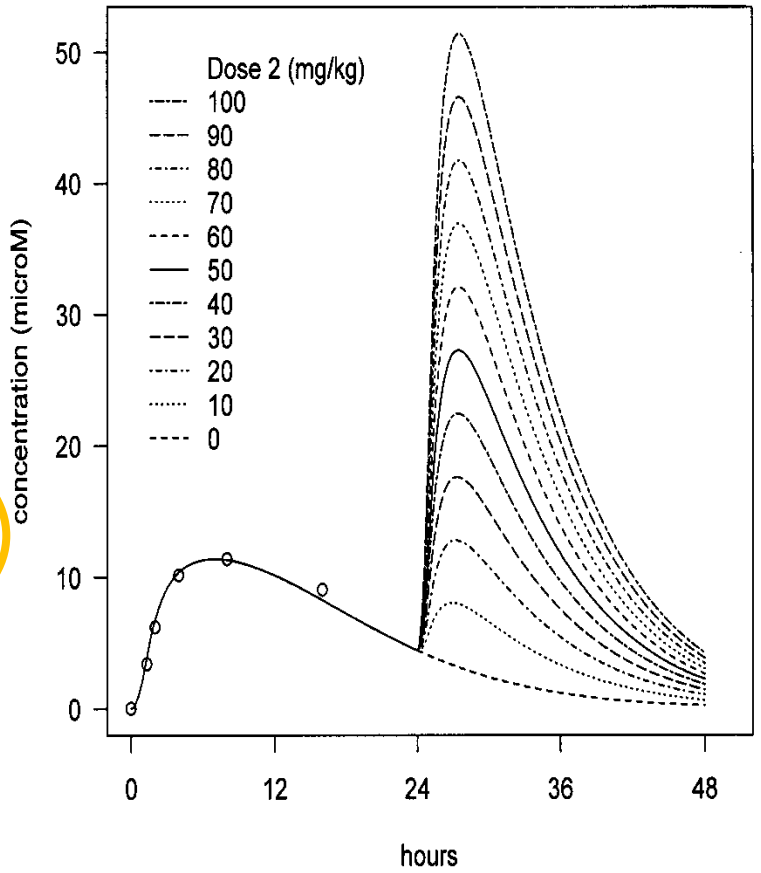
Higher CEPM AUC Associated With Hepatotoxicity and Worse Overall Survival



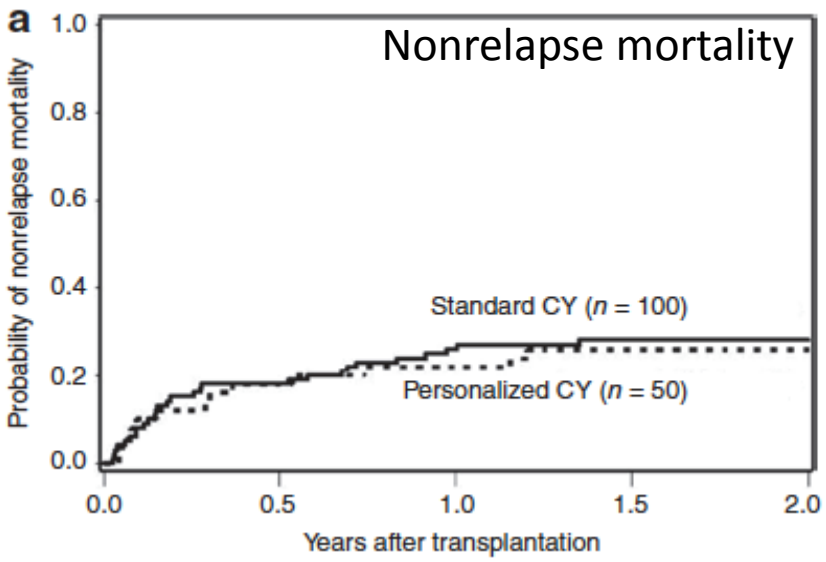
McDonald Blood. 2003;101:2043-8

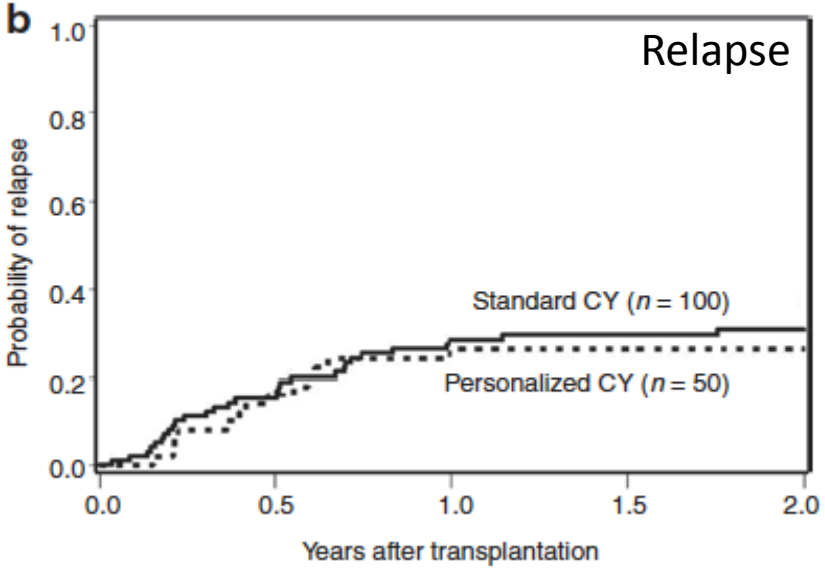
Population PK-based Dosing of CY to Target AUC of HCY and CEPM

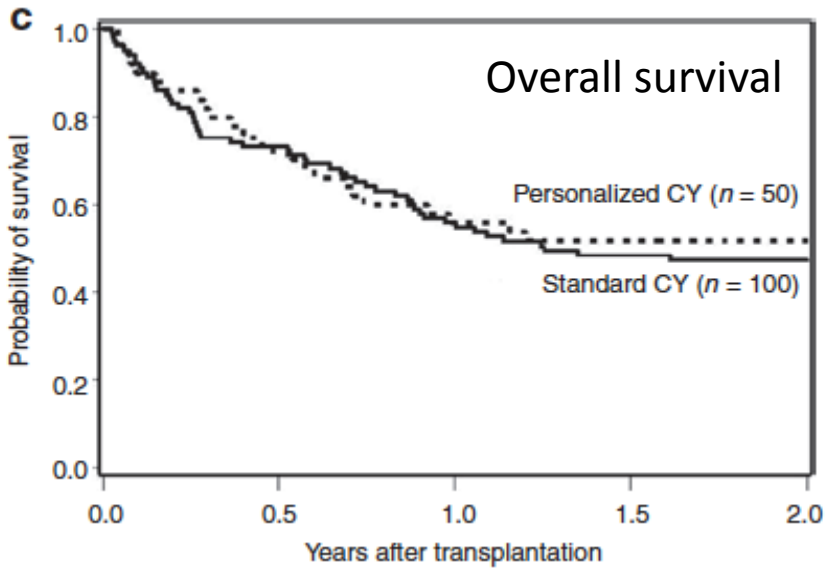




Salinger Clin Cancer Res. 2006;12:4888-98







McCune Clin Pharmacol Ther. 2009 Jun;85(6):615-22

Replace CY with FLU for Lymphotoxicity

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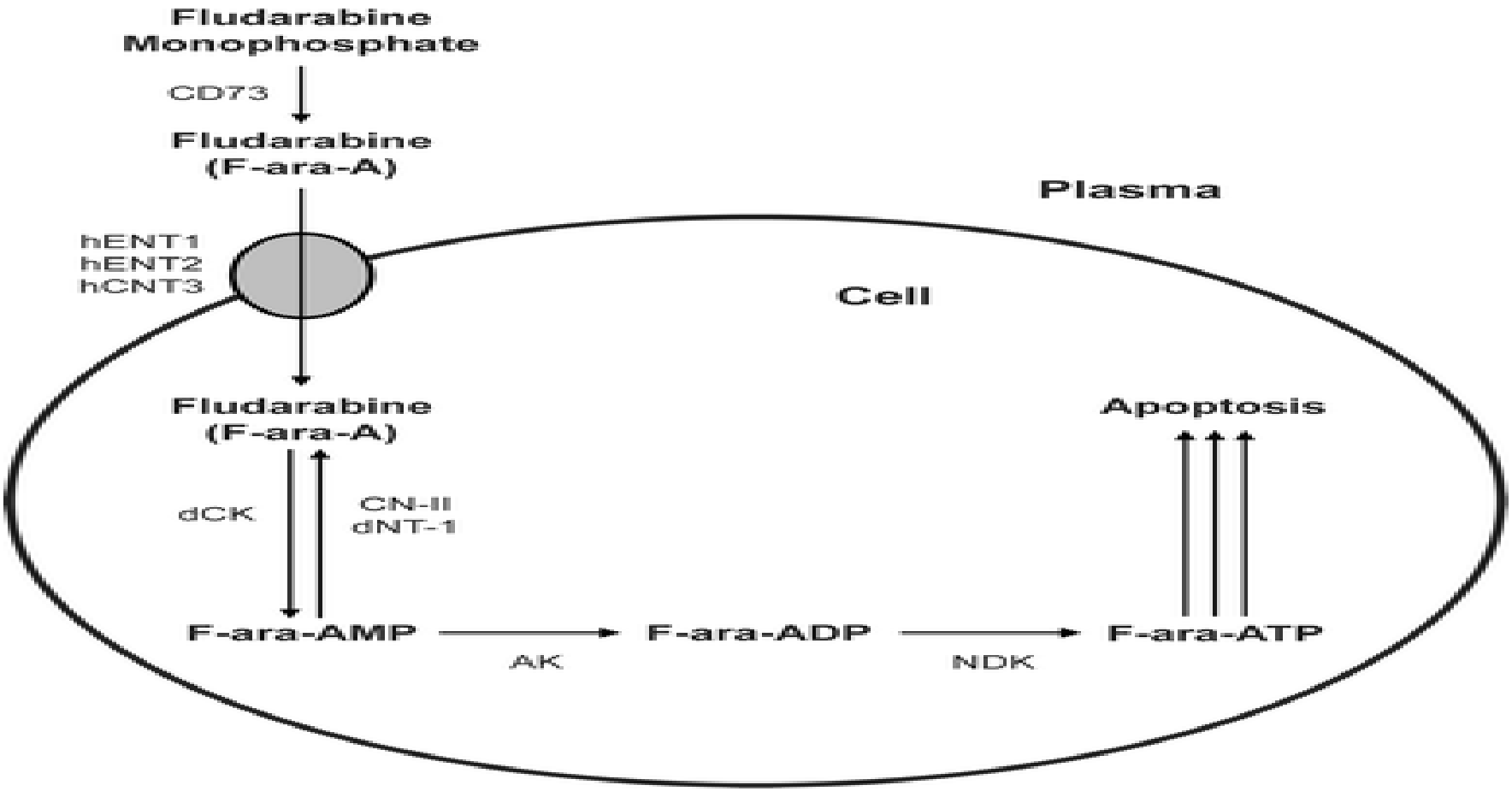
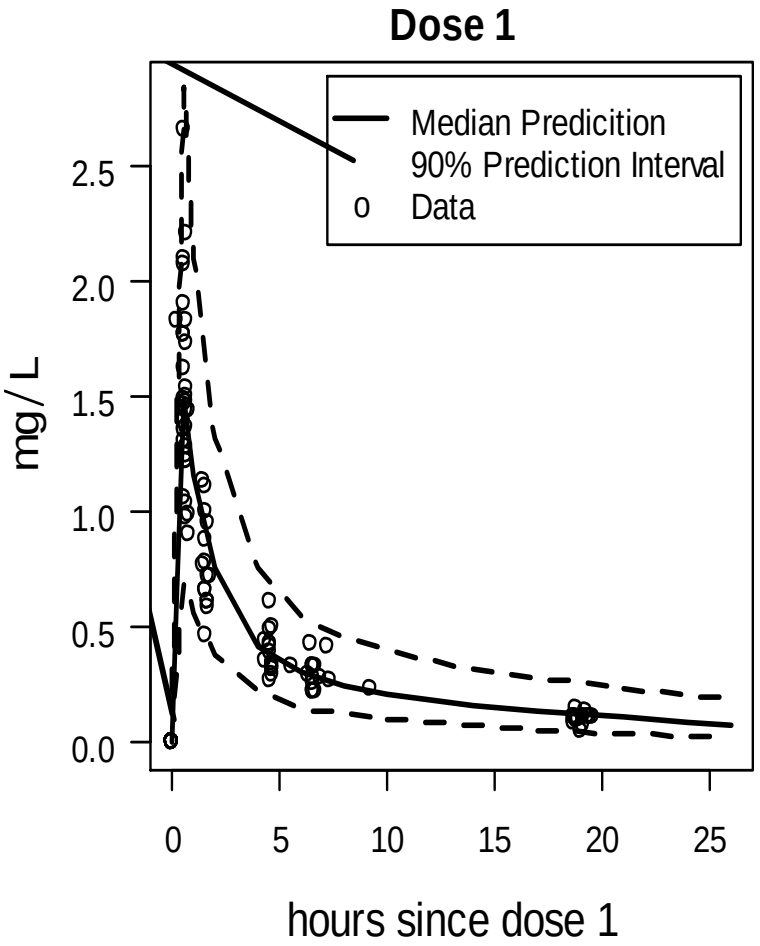
Fludarabine Intracellular Disposition



Woodahl. Cancer Chemother Pharmacol, SEP 2008 62 (4): 735-739.

Plasma F-ara-A Exposure

- Created population pharmacokinetic model and limited sampling schedule (LSS) for F-ara-A
- LSS increased outpatient compliance with PK sampling from 75% to 98%
- No associations observed between F-ara-A AUC and clinical outcomes (N=102)



Salinger. Clin Cancer Res. 2009 Aug 15;15(16):5280; McCune Cancer Chemother Pharmacol. 2015 Jul;76(1):85-96

PopPK Tools Essential for TDM

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- Fred Hutch study coordinators for various clinical trials which have busulfan TDM, PK studies of CY, MMF or fludarabine
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  - David Salinger
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  - HL91744S1 (McCune)
  - CA182963 (McCune)

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TDM in Oncology: Oral Targeted Therapy

- Use TDM if no therapeutic response, adherence concerns, severe or unexpected toxicities[1]
- Interaction with drugs or natural products (NP)
  - Concomitant chemotherapy – NP interactions can be a controversial issue with believers and non-believers regarding the risk of such interactions[2]
  - 27% at risk of an adverse interaction[2]
  - Only 30-55% of patients stated they'd discontinue their NP if an adverse interaction found[2]
  - Best practices will be established for evaluating NP – drug interactions (AT008909)

[1]Bardin. Eur J Cancer 2014 50(12): 2005-2009. [2]McCune Support Care Cancer 2004; 12: 454-462

Drug – Disease	Select examples of exposure – efficacy associations of TKIs
Axitinib – mRCC	↑ AUC ↑ overall survival and ↑ progression free survival
Erlotinib – NSCLC	No association between AUC and progression free survival, overall survival and response rate in 308 patients
Pazopanib – mRCC	↑ C_{trough} >20.6 mcg/ml ↑ progression free survival, ↑ response rate and ↑ tumor shrinkage
Sunitinib – mRCC	↑ AUC (>800 ng-h/ml) ↑ time to progression, ↑ overall survival, ↑ objective response rate
Sunitinib – GIST	↑ AUC (>600 ng-h/ml) ↑ time to progression, ↑ overall survival
Vemurafenib - melanoma	↑ AUC tertile ↓ tumor growth
Imatinib – GIST	↑ C_{trough} >1110 ng/ml ↑ time to progression

mRCC: metastatic renal cell carcinoma; NSCLC: non-small cell lung cancer; GIST: gastrointestinal stromal tumor;

de Wit Drug Discov Today 2015 20(1): 18-36; Petit-Jean Ther Drug Monit 2015;37:2–21

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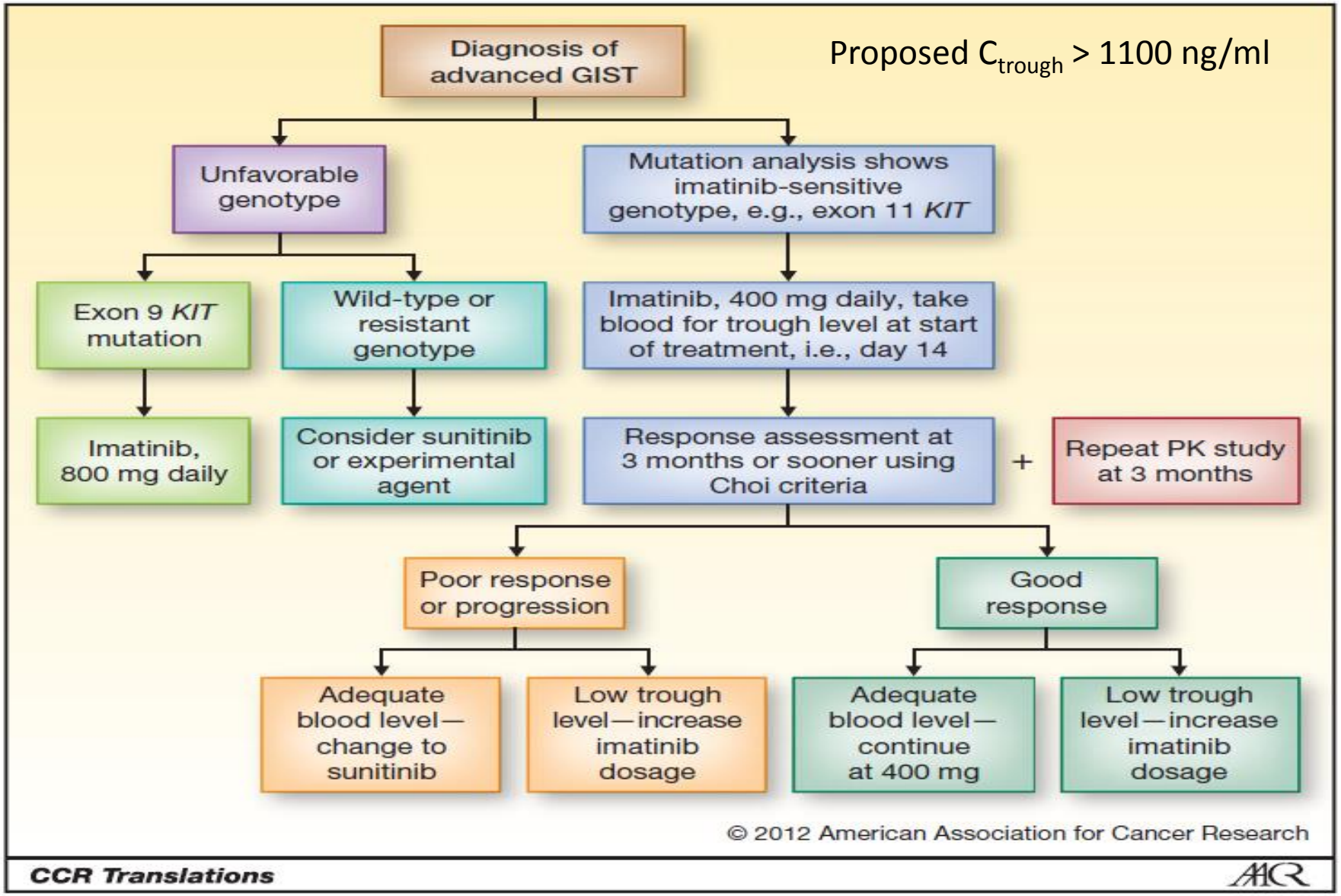


Judson Clin Cancer Res. 2012 Oct 15;18(20):5517-9; Beumer Ther Drug Monit. 2015 Aug;37(4):486-92

Imatinib

- BCR-ABL TKI imatinib revolutionalized initial treatment of gastrointestinal stromal tumors (GIST) and chronic myeloid leukemia (CML)
- Variable response rates
- Problematic adherence rates in CML: One-third of patients are non-adherent[1]; adherence lowers with higher copayments[2]
- 10+ trials have shown an association between imatinib trough – cytogenetic response in CML

[1]Blood. 2009 May 28;113(22):5401-11 & Anticancer Res. 2011 Apr;31(4):1407-9;
[2]J Clin Oncol. 2014 Feb 1;32(4):306-11;

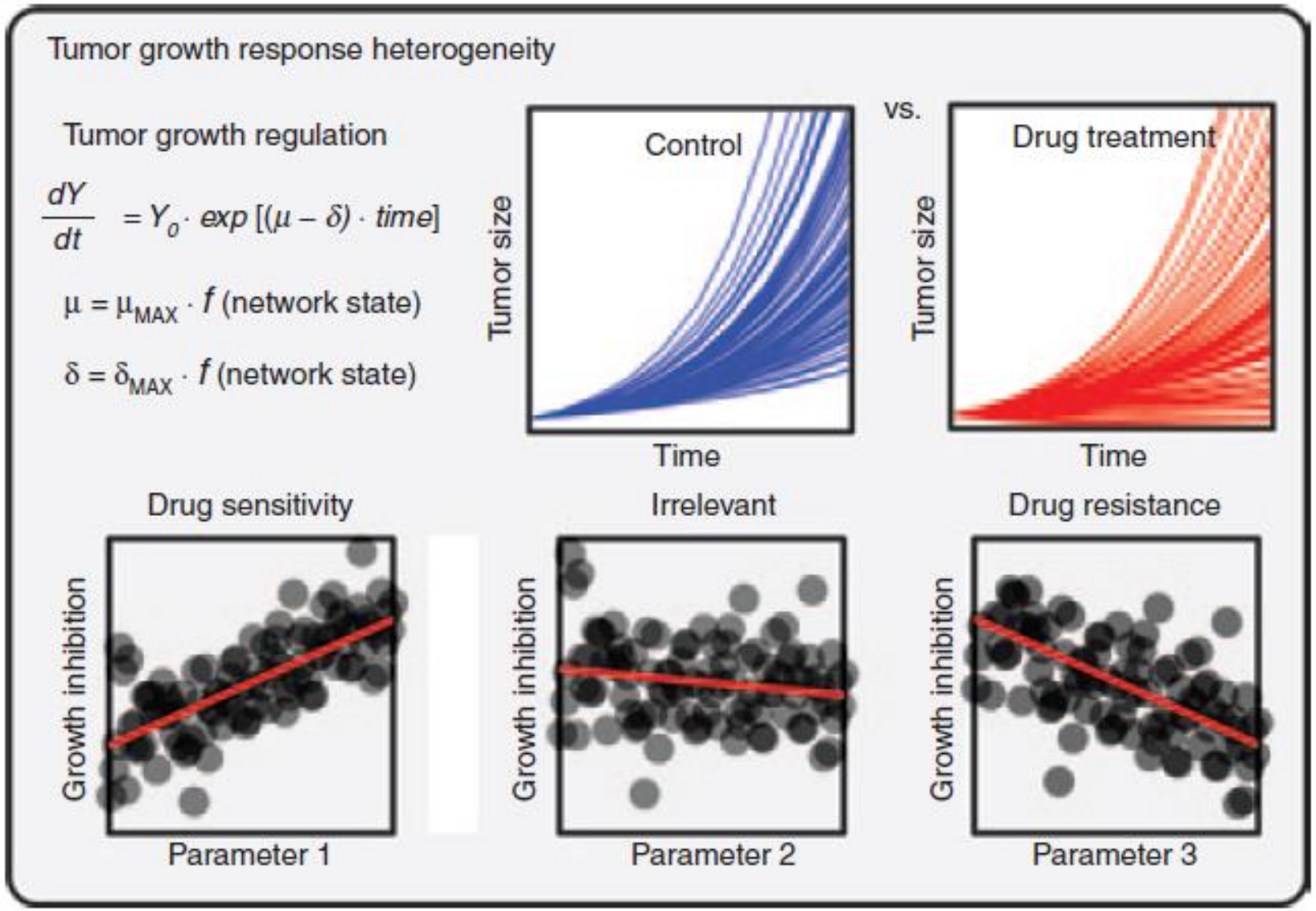
TDM with Imatinib C_{trough} in CML

- Established centralized imatinib TDM service at the Bordeaux University Hospital in France.[1] Eventually open to all of Europe, in collaboration with European Treatment and Outcome Study (EUTOS) for CML[1]
- Two prospective studies evaluating if TDM can improve long-term response in CML
  - I-COME (N=55), no benefit[2] of routine TDM vs. rescue TDM
  - OPTIM (N=139), higher major molecular response at 12 months with TDM of C_{trough} >1000 ng/ml vs. standard management (63% vs. 37%)[3]

[1]Bouchet Fundam Clin Pharmacol. 2013 Dec;27(6):690-7; [2]Gotta Cancer Chemother Pharmacol. 2014 Dec;74(6):1307-19; [3]Rousselot ASH 2015, abstract 133

MoABs TDM in *Clin Pharmacol Ther*

- April 2016: Oude Munnink Review: TDM of monoclonal antibodies in inflammatory and malignant disease: Translation TNF-α experience to oncology.
- April 2016 Mould DR Commentary: Why TDM in needed for monoclonal antibodies and how do we implement this?
- June 2016: Stroh & Lum Commentary: Should TDM for monoclonal antibodies remain the exception or become the norm?



Kirouac & Onsum. CPT Pharmacometrics Syst Pharmacol. 2013 Sep 4;2:e71

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Questions?

jmccune@uw.edu
http://sop.washington.edu/pklab

Q&A slides

Tests for Molecularly Targeted Therapies from the National Academies of Sciences, Engineering and Medicine's report "Key to Unlocking Precision Medicine"

- Establish common evidentiary standards of clinical utility – using evidence generated both within and outside the context of clinical trials – across all stakeholders.
- Establish a more coordinated and transparent federal process for regulatory and reimbursement decisions.
- Enhance communication to patients and providers about the performance characteristics and evidence for use of specific tests.
- Update and strengthen oversight and accreditation of laboratories providing these tests.
- Ensure ongoing assessment of the clinical utility of the tests.
- Ensure development and use of electronic health records (EHRs) and related biomedical informatics tools and assessment that support the effective clinical use of biomarker tests for molecularly targeted therapies.
- Develop and maintain a sustainable national database for these tests through biomedical informatics technology to promote rapid learning for the improvement of patient care.
- Promote equity in access to these tests and the expertise for effective use of test results in clinical decision making.
- Enhance specimen handling and documentation to ensure patient safety and the accuracy of biomarker test results.
- Improve the processes for developing and updating clinical practice guidelines for the effective use of these tests.

https://www.fredhutch.org/en/news/center-news/2016/03/precision-medicine-report-lays-plans-for-improved-patient-care.html

Where do pharmacokinetics /pharmacodynamics (PK/PD) fit in the translational spectrum?

T1: Discovery: translation to humans PK/PD found here most often

Testing basic science discoveries for translation to humans

T2: Development: translation to patients PK/PD sometimes here

Testing new interventions in human subjects

T3: Delivery: translation to practice PK/PD sometimes here

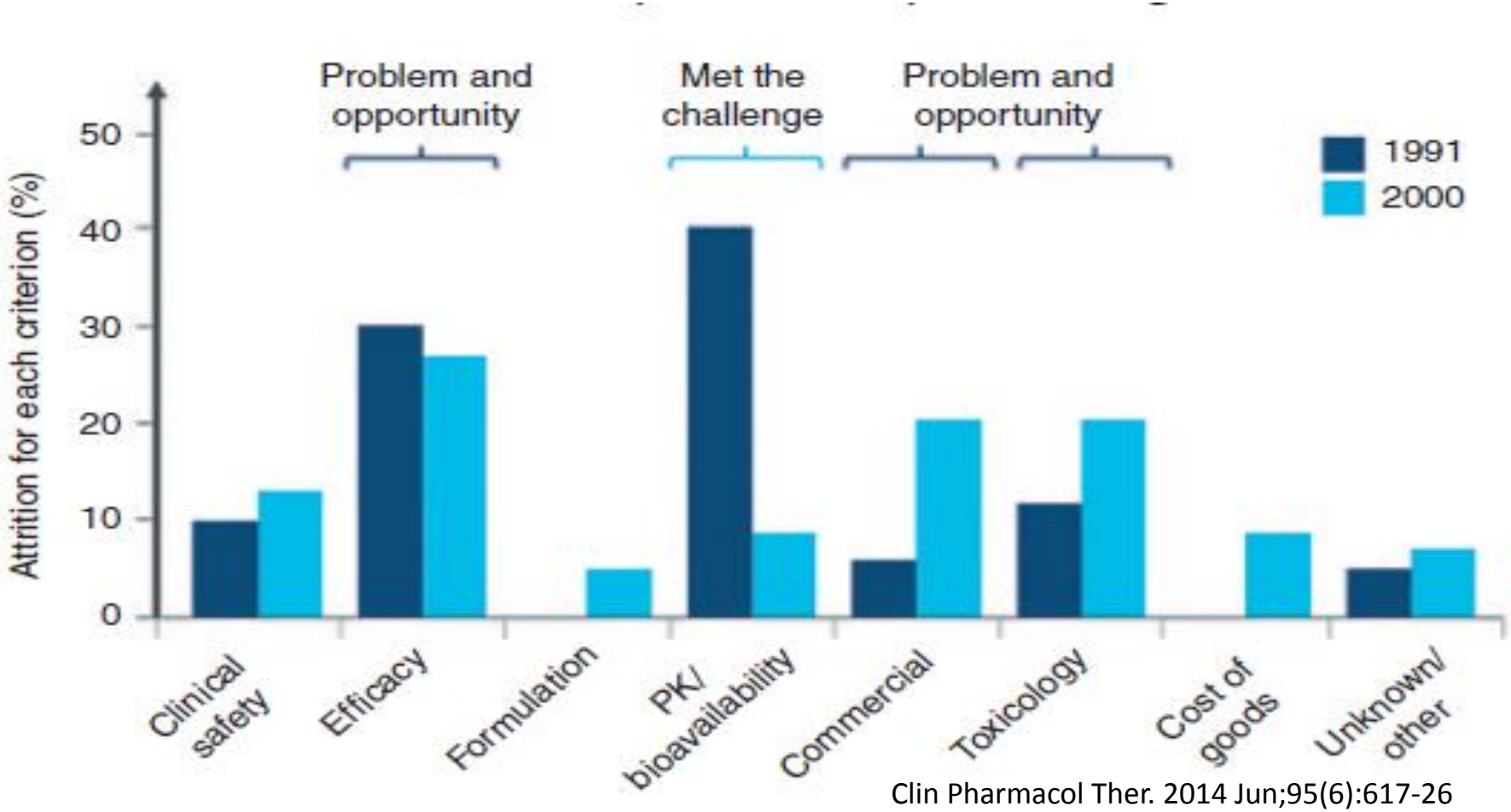
Research on the application of new interventions in general practice

T4: Outcomes: translation to populations

Investigating factors/interventions that influence the health of populations

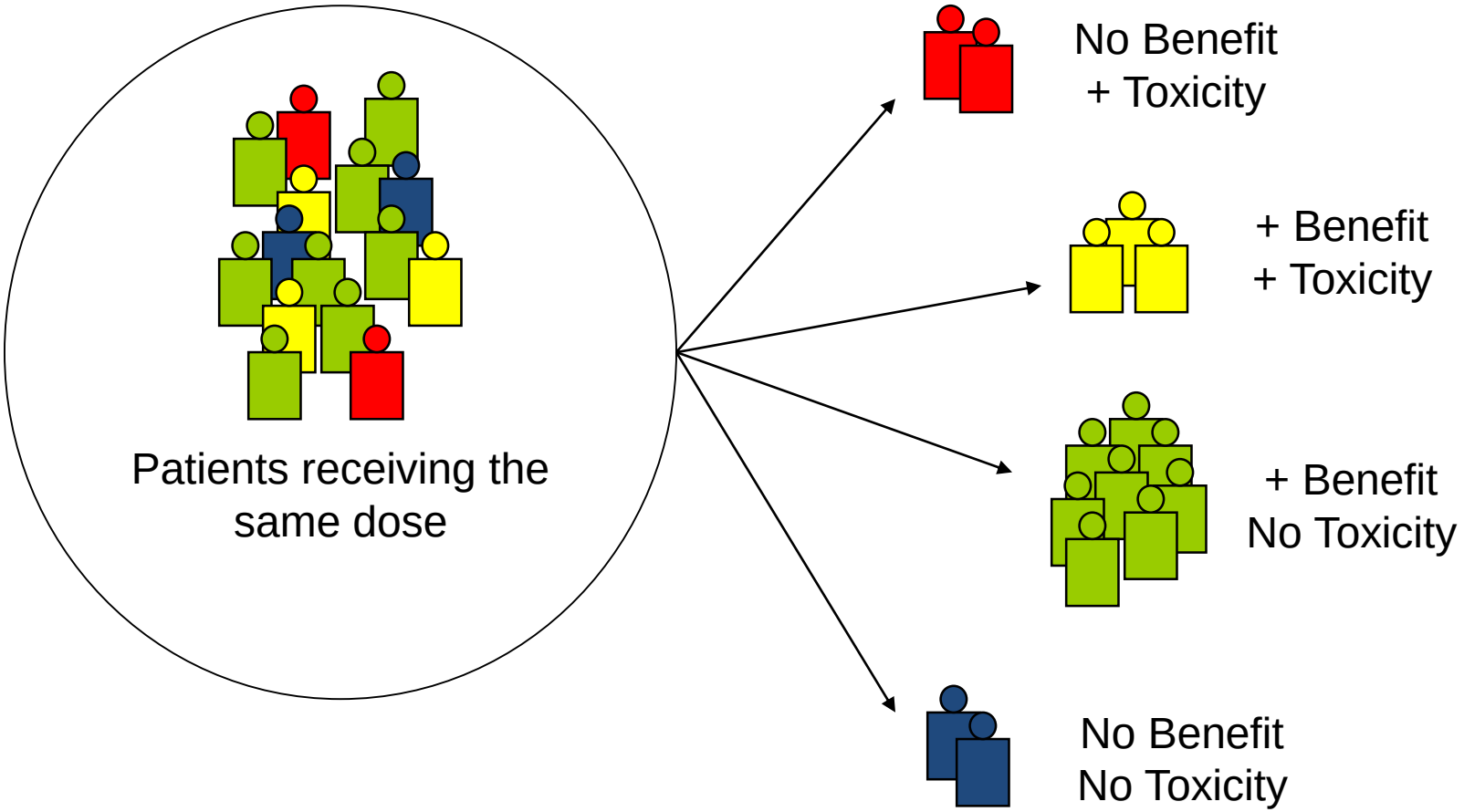
http://ncats.nih.gov/translation/spectrum

PK substantively improved on T1: Attrition of new drugs 1991-2000



Clin Pharmacol Ther. 2014 Jun;95(6):617-26

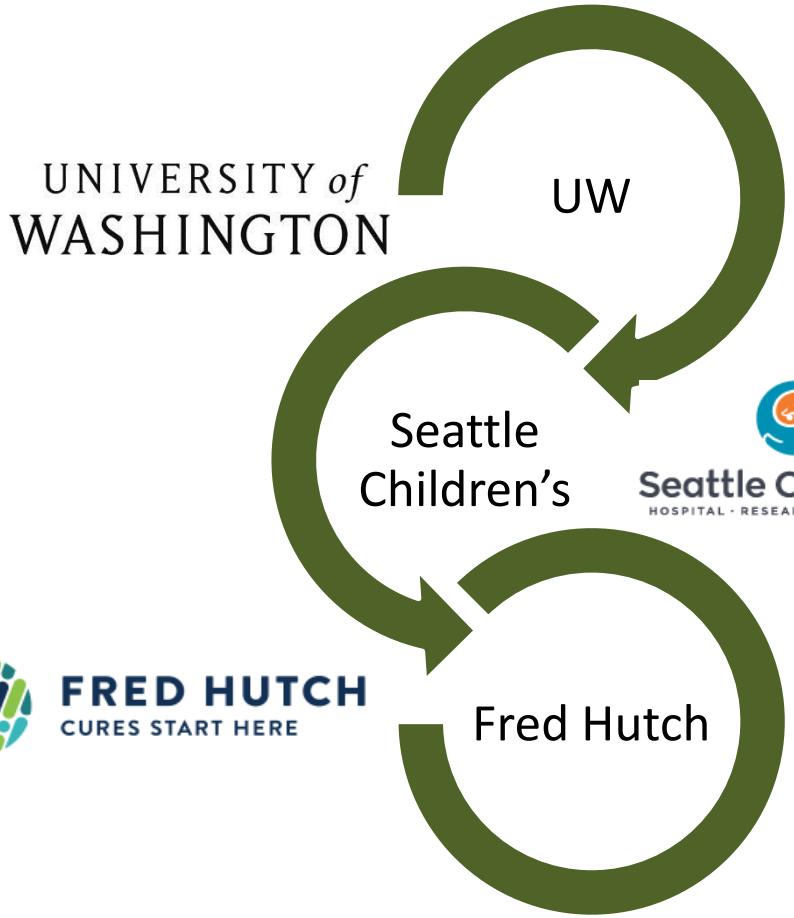
PK/PD in T2 and T3: Focus on Precision Medicine



Science. 1999 Oct 15;286(5439):487-91

PK/PD in T2 and T3

- Almost exclusively conducted in academic medical centers in underserved populations
- Goal is to make FDA approved drugs work better.



Comprehensive review of medical literature for the cost-effectiveness of TDM

	Evidence Rating
A1	Systematic review containing several studies of A2 level and with consistent outcomes
A2	Prospective randomized clinical trials of good quality
B	Randomized clinical trials of moderate quality (eg, too few patients) or other comparative trials (eg, not randomized, cohort studies, case-control studies
C	Noncomparative trials
D	Experts' opinions (eg, according to the authors)

Touw DJ et al. Ther Drug Monit. 2005 Feb;27(1):10-7

Drug Class (Evidence rating)	Conclusion & Recommendation for TDM
Aminoglycosides (A2-B)	• Lowers mortality, toxicity, and cost-effective. Recommend, but studies conducted before extended interval dosing
Vancomycin (A2-B)	• Lowers renal toxicity and is cost-effective in select patient populations (intensive care units, oncology, concomitant nephrotoxic drugs). Recommended for those patients.
Antiepileptics (B-D)	• Improved efficacy, less toxicity, and cost-effective with classic antiepileptics (i.e., phenobarbital, phenytoin, carbamazepine, primidone, valproic acid). Recommend. • Not useful with newer antiepileptics
Immuno-suppressants (D)	• Must be performed because of a shortage in donor organs, the wide pharmacokinetic variability, and the risk of drug-drug interactions. Recommend.

Touw DJ et al. Ther Drug Monit. 2005 Feb;27(1):10-7

Drug Class (Evidence rating)	Conclusion & Recommendation for TDM
Theophylline (B-D)	• Optimizes treatment and can be cost-effective. Recommend that it can be helpful
Digoxin (B-D)	• Optimizes treatment in patients with cardiac failure or with atrial fibrillation (no cost-effectiveness data). Recommend that it may be useful in those patients.
Psychiatric Drugs (A1-D)	• Useful for lithium, nortriptyline, desipramine, imipramine, haloperidol, and clozapine (no cost-effectiveness data). Recommend that is should be used • For other psychiatric drugs, can help in questions of adherence and drug-drug interactions
Protease inhibitors (A2-C)	• Must be used for nelfinavir • Could be useful for other protease inhibitors and nonnucleoside reverse transcriptase inhibitors.

Touw DJ et al. Ther Drug Monit. 2005 Feb;27(1):10-7

Efforts to improve CY in HCT

- Considerable interpatient variability in the exposure of CY and its metabolites

Blood. 2003 Mar 1;101(5):2043-8

- In CY/TBI, personalizing CY doses to metabolite exposure using a population pharmacokinetic model decreased liver and renal toxicity

Clin Pharmacol Ther. 2009 Jun;85(6):615-22

- In TBU/CY, clinical outcomes were not associated with CY or its metabolite exposure

BBMT. 2007 Jul;13(7):853-62

- Outcomes may be improved by switching order of administration (CY/^{T}BU). Pharmacodynamic associations with overall survival

BBMT. 2013 Jul;19(7):1033-9

Can Personalized Dosing Improve CY/TBI?

- Pharmacodynamic relationships
  - High plasma AUC of carboxyethylphosphoramide mustard (CEPM) associated with higher risk of liver toxicity, nonrelapse mortality, and lower overall survival
  - Presumably plasma CEPM concentrations reflective of hepatic CEPM concentrations, which result from metabolism of hydroxycyclophosphamide (HCY)
  - HCY toxic to murine sinus endothelial cells
- Feasible to personalize CY doses based on the AUC of CEPM and AUC of HCY
  - Lower CEPM AUC to lower risk of liver toxicity
  - Maintain AUC of HCY to lowest AUC in prior study to maintain engraftment
  - Rapid population pharmacokinetic modeling needed in future studies to more accurately personalize CY dose to achieve metabolite AUCs

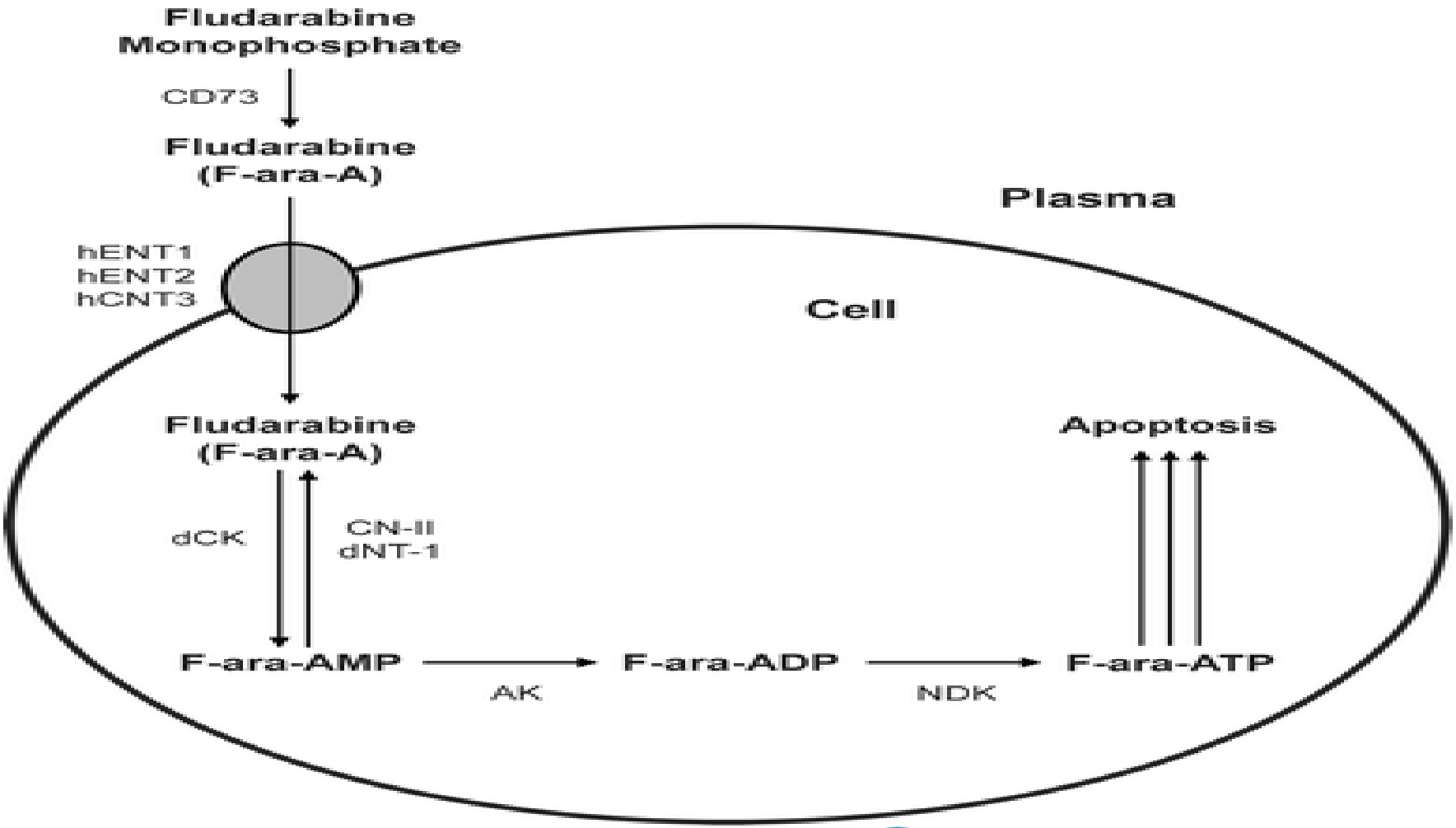
McDonald. Blood. 2003;101:2043-8; McDonald GB. Clin Pharmacol Ther. 2005;78:298-308; Salinger DH, Clin Cancer Res. 2006;12:4888-98.

Impact of Personalized CY Dosing upon Outcomes in CY/TBI Patients

- Fifty patients received personalized CY dosing
- The use of population TDM – a blend of population and individual information – led to more precise CY dose recommendations
  - Mean second CY dose was 66 (0-100) mg/kg, and the mean total CY dose was 111 (45-145) mg/kg
- Compared to 100 controls receiving CY 120 mg/kg in patients receiving 12 Gy total body irradiation (TBI)

Clin Pharmacol Ther. 2009 Jun;85(6):615-22. Epub 2009 Mar 18

Fludarabine Intracellular Disposition



Woodahl EL et al. Cancer Chemother Pharmacol. SEP 2008;62(4):735-739. Epub 2007 Nov 15.

	FLU/^{T}BU[1]	FLU/^{T}BU/ THY	FLU/^{T}BU/ THY[2]	^{T}BU/FLU
FHCRC protocol #	1519	1913	2041	2270
Total N	27	22	15	90
Busulfan (Css target 800-1000 ng/ml)				
Starting dose	1 mg/kg PO Q6hr	3.2 mg/kg IV Q24h	4 mg/kg IV Q24h	130 mg/m^2 IV Q24h
Days	-5 to -2	-5 to -2	-5 to -2	-5 to -2
Fludarabine				
Dose, in mg/m^2 (total)	30 (120)	30 (120)	50 (250)	40 (160)
Days	-9 to -6	-9 to -6	-9 to -6	-5 to -2
F-ara-A PK	Yes/no association	No	Yes/highest HR for NRM	No
Thymoglobulin	0	6	6	0
Post-grafting immunosuppression	CsA/MTX	TAC/MTX	TAC/MTX	CY/TAC/ MMF
Reason for closure	Accrual goal met	Low donor chimerism	high NRM	Accrual goal met

[1]Bornhauser M et al. Blood 2003; 102:820-826. [2]Cancer Chemother Pharmacol 2012 Jan;69(1):263-72

Efforts to improve fludarabine in FLU/^{T}BU HCT conditioning

- Pharmacodynamics of F-ara-A are influenced by the conditioning regimen, same as busulfan and CY

Cancer Chemother Pharmacol 2012 Jan;69(1):263-72

- F-araA AUC can be characterized using a population pharmacokinetic model and limited sampling schedule

Clin Cancer Res. 2009 Aug 15;15(16):5280

- Ex vivo F-ara-ATP accumulation rate in $CD4^{+}$ and $CD8^{+}$ cells can be characterized

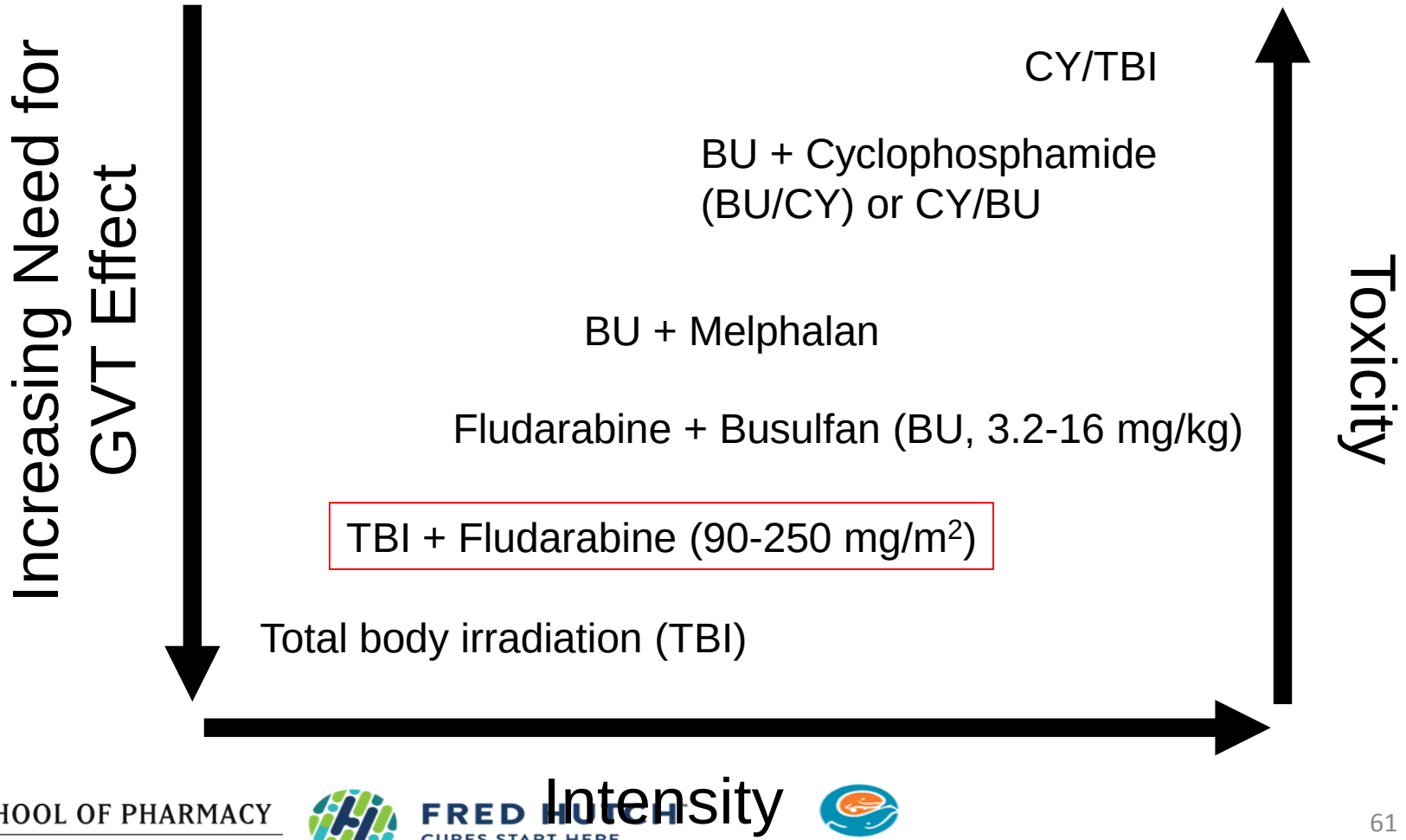
Cancer Chemother Pharmacol, SEP 2008 62 (4): 735-739

- Suppression of absolute lymphocyte count after fludarabine administration can be characterized using a population pharmacokinetic – pharmacodynamic model

Cancer Chemother Pharmacol. 2015 Jan;75(1):67-75

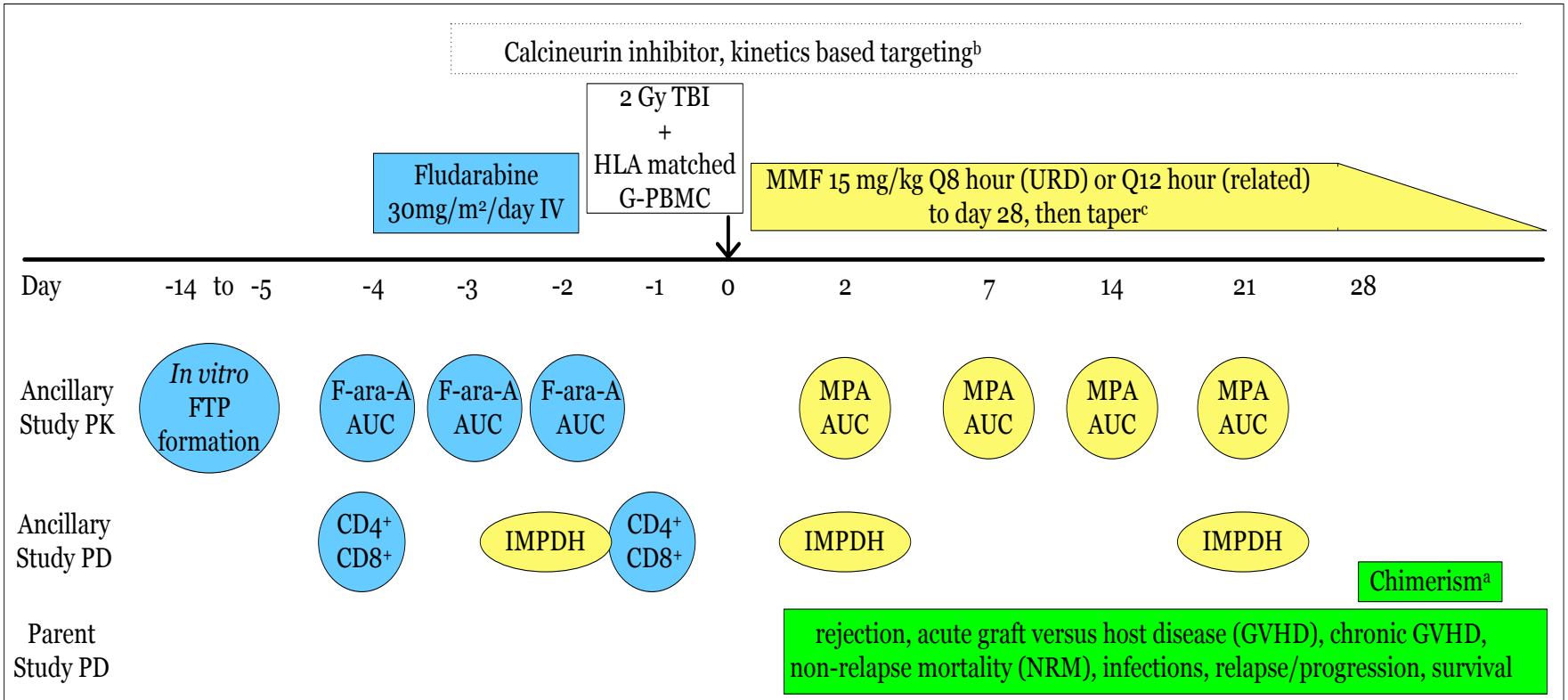
- Proposed evaluating F-ara-A AUC prior to gene therapy

Efforts to improve fludarabine in nonmyeloablative HCT



Deeg HJ, et al. *Leukemia* 2006;20:1701-5.

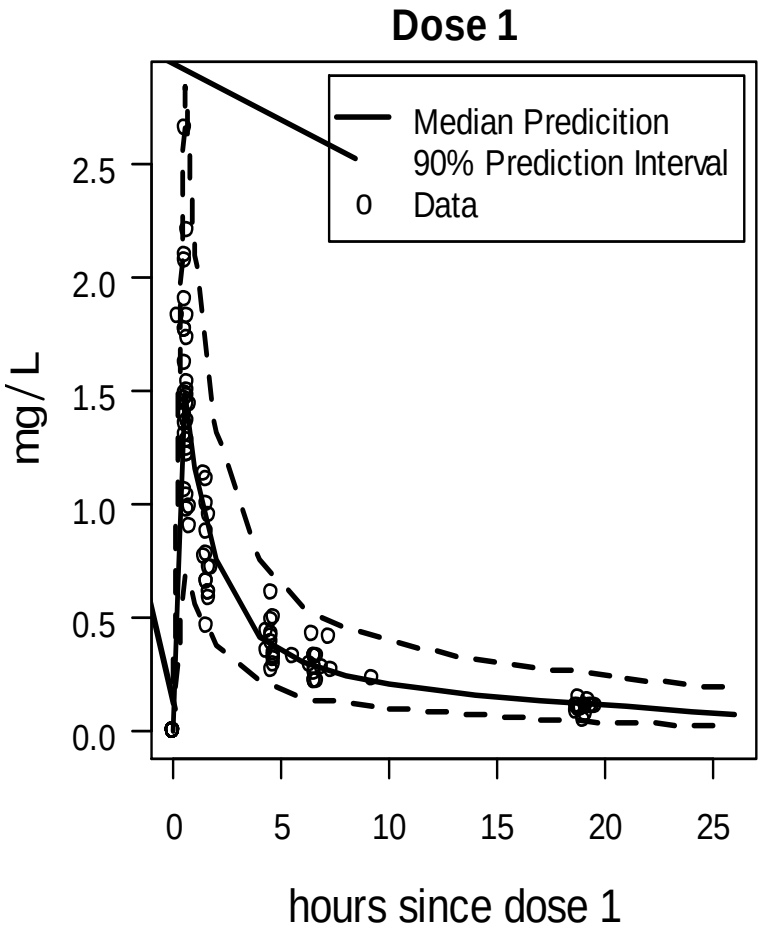
Protocol 1980: PK/PD in Nonmyeloablative PBSC Recipients



[a]Rectangles represent the HCT procedure and the endpoints obtained during clinical care or FHCRC treatment protocol (Section 8). Ovals designate ancillary study PK and PD which are highlighted by relevant Aim. Aim 1 highlighted blue, Aim 2 yellow and Aim 3 green using the candidate PK and PD biomarkers from Aims 1 and 2; [b]Calcineurin inhibitor used will be cyclosporine or tacrolimus, which will be dose adjusted to achieve target trough concentrations, based on FHCRC treatment protocol; [c]MMF dose not adjusted based on AUC or trough MPA concentration. MMF taper started at day 28 and specified per FHCRC treatment protocol; [d]Day 28 T cell chimerism is the primary endpoint of Aim 3. Endpoints will be assessed beyond day 28 based on clinical need or FHCRC treatment protocol.

Plasma F-ara-A Exposure

- Retrospective analysis of 41 patients receiving fludarabine 30 or 50 mg/m2/day
- First population pharmacokinetic model for F-ara-A
  - Best fit with a two compartment model
  - Interpatient variability 37%
- BSA was the only covariate that was associated with pharmacokinetic variability
- Limited sampling schedule (LSS) by simulation, seeking to minimize precision and bias
- Led to successfully estimating F-ara-A AUC in outpatient population



Salinger et al. Clin Cancer Res. 2009 Aug 15;15(16):5280; submitted to Cancer Chemotherapy and Pharmacology

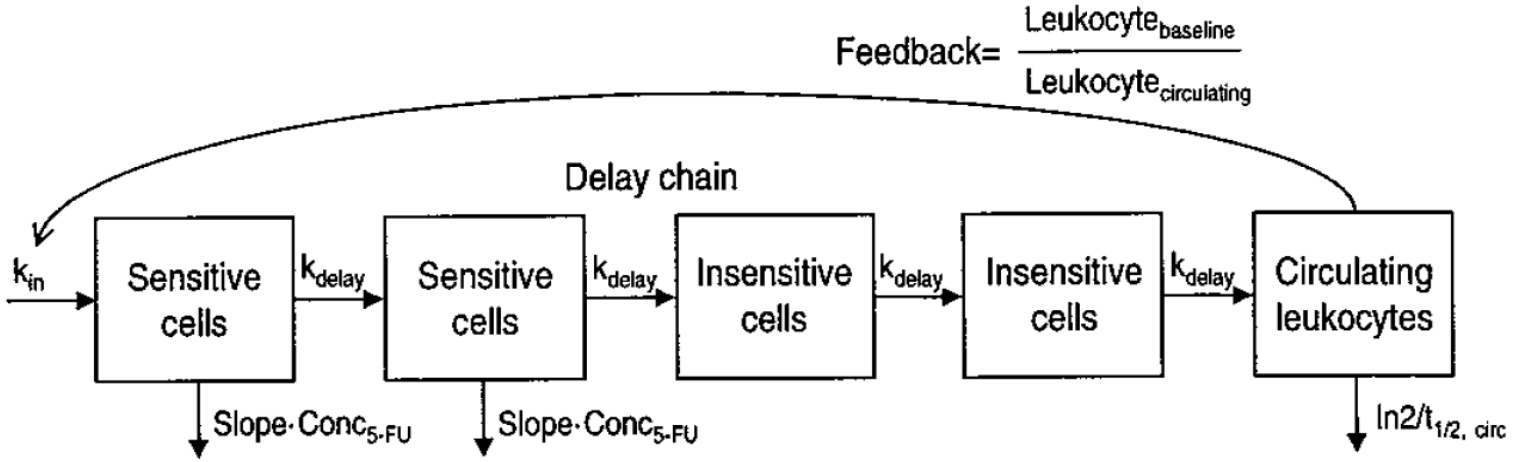
Fludarabine biomarkers in nonmyelaboablative HCT

- Biomarkers for fludarabine evaluated
  - Before conditioning started, F-ara-ATP accumulation rate quantified in enriched $CD4^+$ and $CD8^+$ cells isolated from 34 and 36 patients, respectively.
  - After the first fludarabine dose, F-ara-A AUC in 102 patients
  - After the last fludarabine dose, the ratio of circulating $CD4^+$ and $CD8^+$ cells ($CD4^+/CD8^+$ ratio) in 102 patients
- Interpatient variability in the pharmacologic biomarkers was high, ranging from 3.7-fold (F-ara-A AUC) to 39-fold (F-ara-ATP in $CD8^+$ cells).
- Poor correlation between the F-ara-AUC and the F-ara-ATP accumulation rate in $CD4^+$ (R^2=0.01) and $CD8^+$ cells (R^2=0.00).

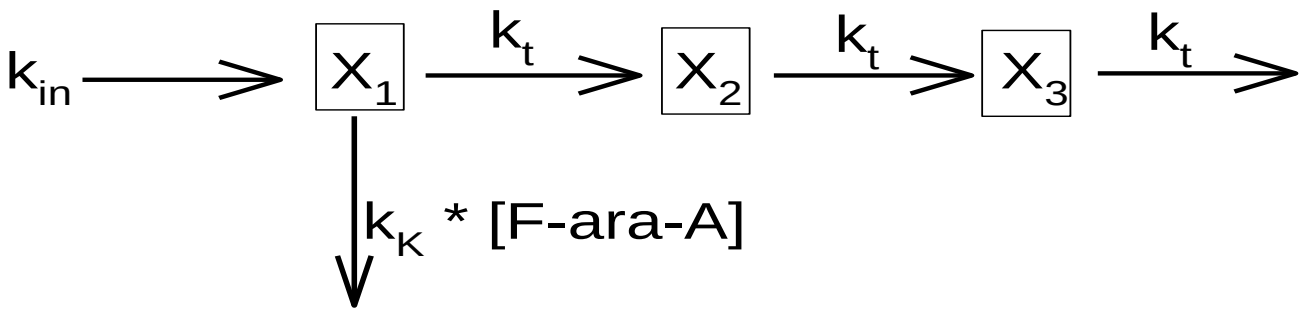
Fludarabine biomarkers in nonmyelaboablative HCT

- Circulating $CD8^+$ cells were more sensitive to fludarabine administration, with an average (range) decline of 82% (-20 – 100%) compared to 68% (range: -47 – 100%) for circulating $CD4^+$ cells.
- No associations were seen between the four biomarkers and clinical outcomes (day +28 donor T-cell chimerism, acute graft-versus-host disease (GVHD), neutrophil nadirs, cytomegalovirus reactivation, chronic GVHD, relapse, non-relapse mortality, or overall mortality).

F-ara-A - Lymphocyte Population Pharmacodynamic Model



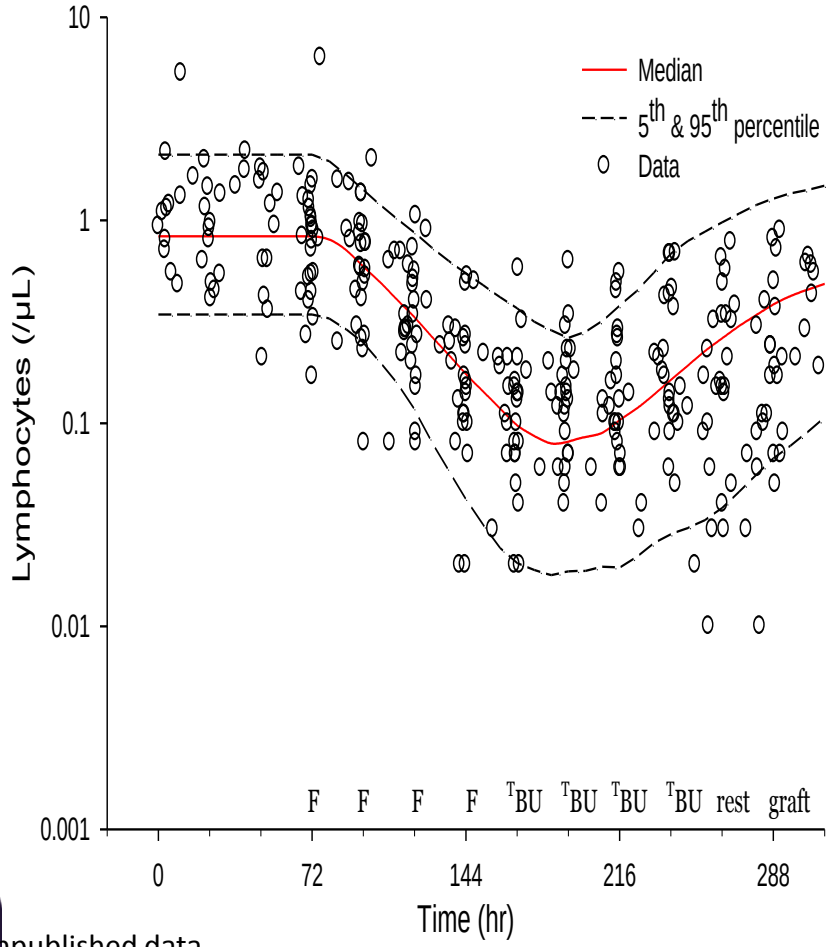
Friberg et al. J Pharmacol Exp Ther 2000; 295: 334



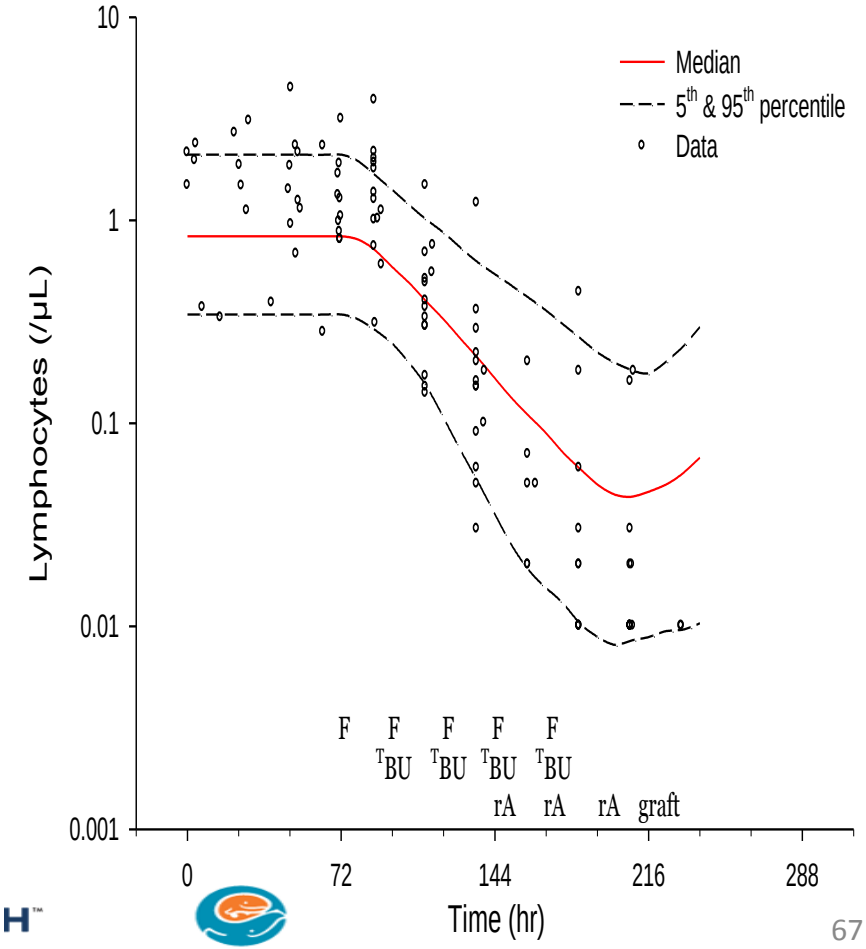
Lo = baseline absolute lymphocyte count $k_{in} = Lo * k_t$ $k_t = 1/\tau$

Lymphodepletion Can Be Characterized by F-ara-A Concentrations

Protocol 1519



Protocol 2041



Unpublished data

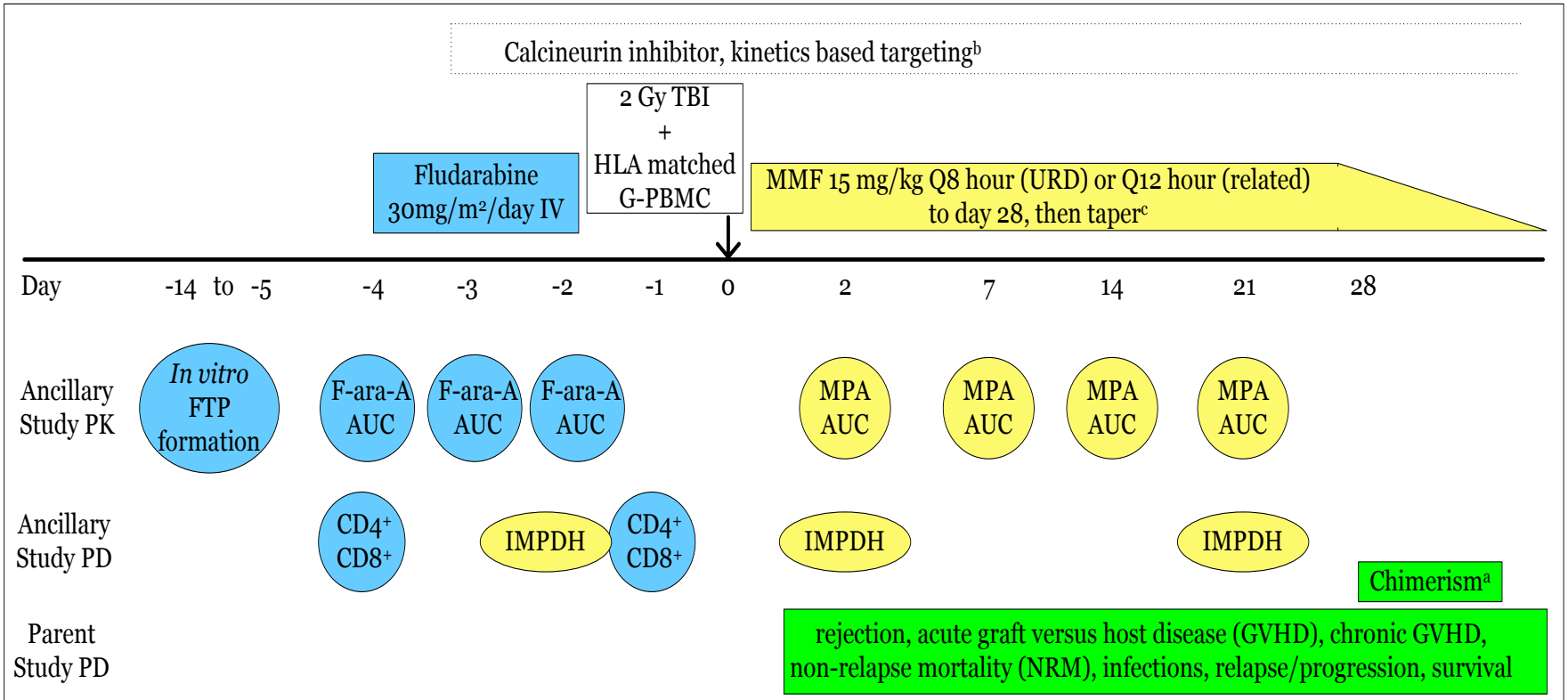
Plasma F-ara-A Population Pharmacodynamic Model

Structural Model Parameter Values				BSV (as % CV, on diagonal) and correlation (as Pearson r), off diagonal)		
Parameter	Design ation	Parameter Estimate (SE)		Lo	k_t	k_K
Baseline ALC	Lo	0.954/μL (10.8%)		59%		
Rate constant - transit between cell compartments	k_t	0.0441/hr (15 hr) (7.39%)		0.23	38.9%	
Rate constant - cell kill	k_K	30.2/hr (1.4 min) (41.7%)		0.42	0.26	211%

- BSV of pharmacokinetic parameters ranged from 35.1 to 46.2%

Unpublished data

Protocol 1980: PK/PD in Nonmyeloablative PBSC Recipients



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TDM of Imatinib Trough Concentrations

Picard et al:

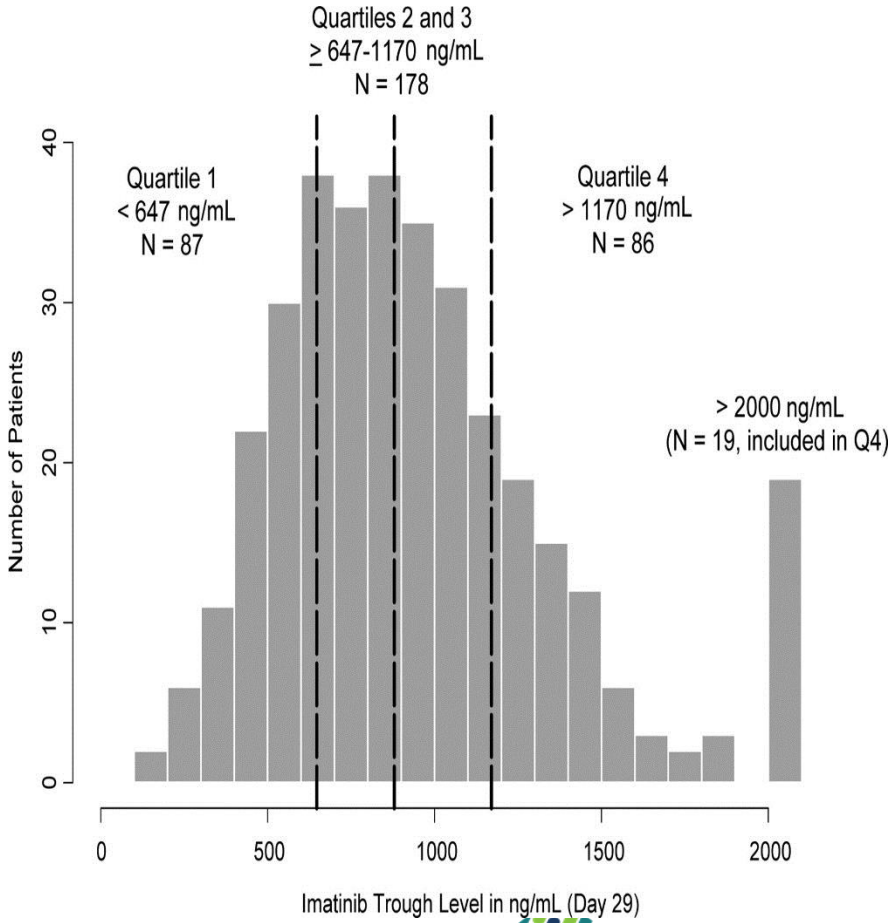
- 68 CML chronic or accelerated phase patients receiving daily imatinib doses of 400 mg or 600 mg, respectively, for at least 12 months
- Higher trough imatinib concentrations associated with higher rates of complete cytogenetic response and major molecular response
- Daily imatinib dose not associated with major molecular response

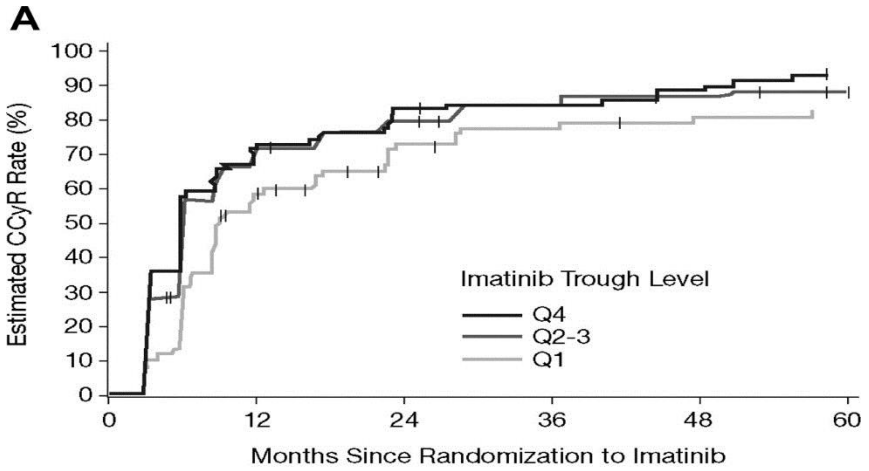
IRIS trial: 5 year followup

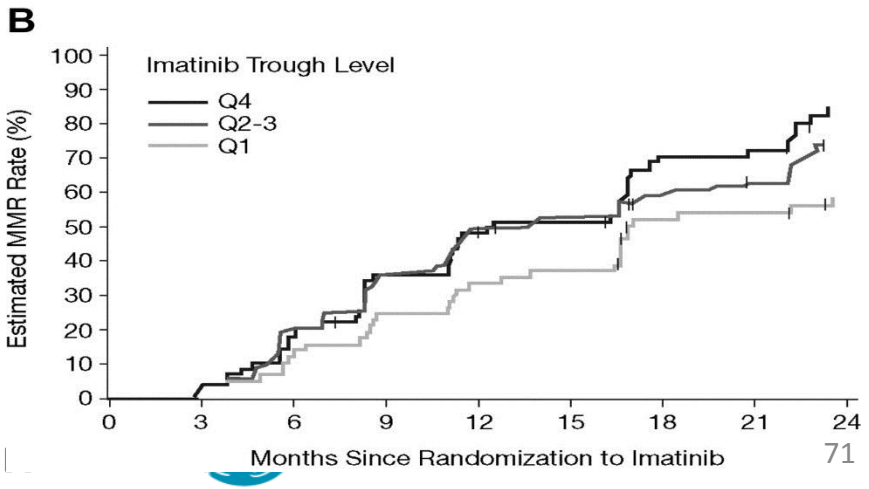
- Significant correlation between a complete crytogenic response (CCyR) and higher imatinib plasma concentration
- Average imatinib trough concentrations
  - CCyR: 1009 + 544 ng/ml
  - No CCyR: 812 + 409 ng/mL
  - P = 0.01
- Similar correlation with major molecular response (MMR) (P=0.02)
- Conclusion: maintaining imatinib plasma trough levels above 1000 ng/mL is an independent prognostic factor that may be important for achieving CCyR and MMR

Picard et al. Blood. 2007 Apr 15;109(8):3496-9. Epub 2006 Dec 27. Larson et al Blood. 2008 Apr 15;111(8):4022-8. Epub 2008 Feb 6

IRIS Results

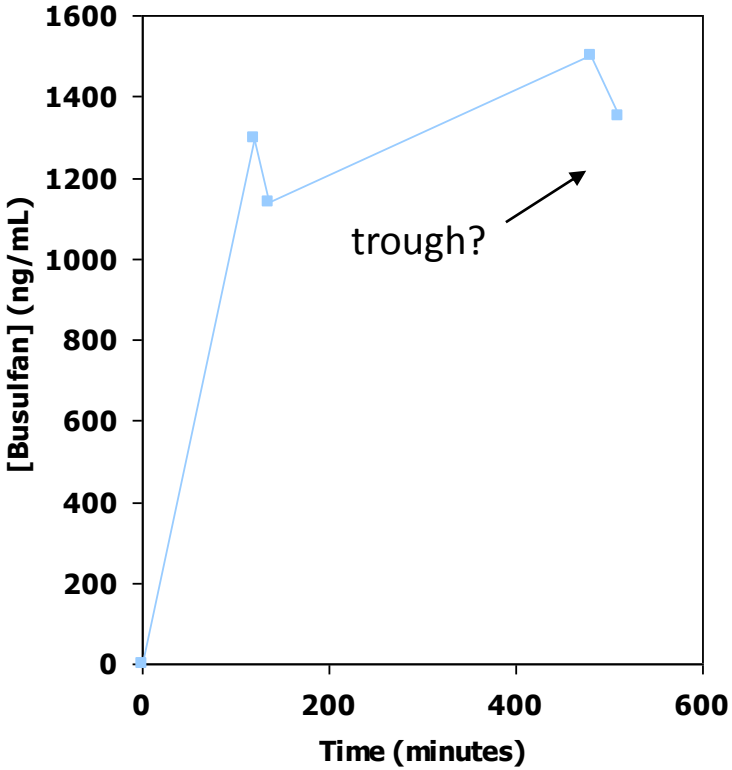






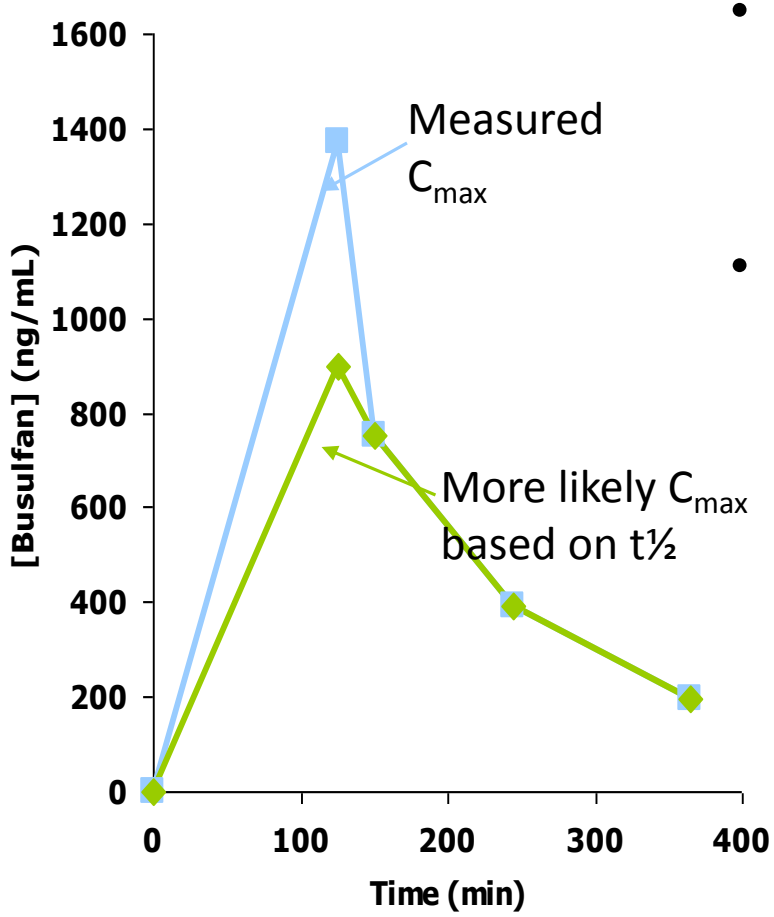
Careful Attention Needed for Busulfan Pharmacokinetic Sampling

- Ensure the exact time of blood draw, using the same clock, is written
- Ensure troughs are drawn prior to starting infusion of next dose



McCune JS, hypothetical data for teaching purposes.

Careful Attention Needed for Busulfan Pharmacokinetic Sampling



- At end of infusion, make sure administration and flush is completed. If not, concentrations may be high
- Example:

Time (min)	Conc (ng/mL)
125	1372
150	750
245	391
365	198

1 half-life = 25 min?

2 half-lives = 215 min

McCune JS, hypothetical data for teaching purposes.