Targeted Therapies: is PK the forgotten biomarker?

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Aix*Marseille université

2001


MAY 28, 2001
www.time.com AOL Keyword: TIME
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

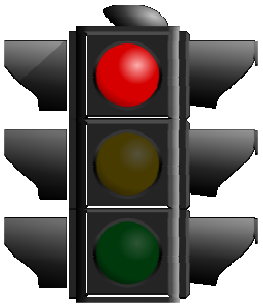
WHY ANTICANCER DRUGS FAIL?

2013

« I cure people »

« I manage survival »

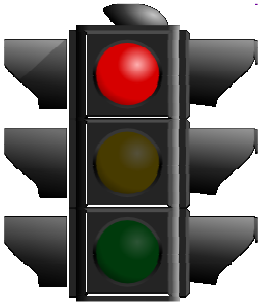
WHY ANTICANCER DRUGS FAIL?



Pharmacological issues?

- Resistances at the tumor level
- Target Amplification
- Mutations on Target
- Mutations on signaling pathways
- Increased Detoxification
- Repairing process
- Impaired apoptosis

WHY ANTICANCER DRUGS FAIL?



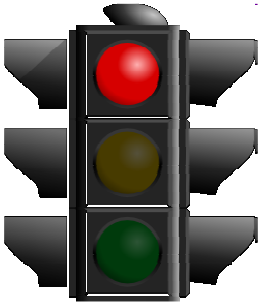
PD issues are addressed!

Within a given cancer type, genetic profiling (e.g., OncoType DX, MammaPrint in breast cancer) helps to discriminate tumor subtypes so as to help choosing the best treatment.

Different tumors require different treatments!

« One tumor = one treatment » paradigm

WHY ANTICANCER DRUGS FAIL?



PD issues are addressed!

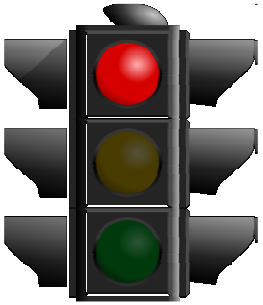
« Thou shalt not give cetuximab or panitumumab if mutated K-Ras »

« Thou shalt not give herceptin if Her2 is not expressed »

« Thou shalt not give tamoxifen if ER negative »

… ..

WHY ANTICANCER DRUGS FAIL?



PD issues are addressed!

Despite the ever-increasing number of valid biomarkers identified to select patients likely to respond…..

…. this does not necessarily lead to increased survival in patients!

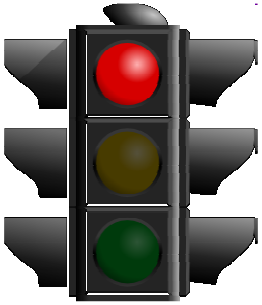
WHY ANTICANCER DRUGS FAIL?

- **Metastatic colorectal Cancer**

The latest targeted therapies have little impact on survival despite pre-therapeutic search for biomarkers (eg, EGFR-1 expression and K-Ras status)

	CRYSTAL Folfiri + cetu n=316	OPUS Folfox+ cetu n=82	PRIME Folfox4 + pani n=325	IFL + beva n=393	Folfox/ Xelox + beva n=699	TREE Folfox + beva n=71	FOLFIRI	FOLFOX
DFS (month)	9.9	8.3	9.6	10.6	9.4	9.9	8.7	8
OS (month)	23.5	22.8	23.9	20.3	21.3	26.1	21	18.5

WHY ANTICANCER DRUGS FAIL?



Beside Pharmacological issues…

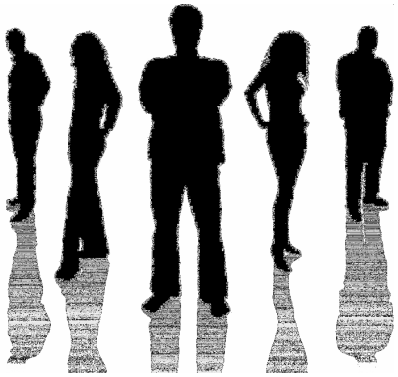
….. non-Pharmacological issues?

Prof. Merrill J. *Egorin* (1948–2010)

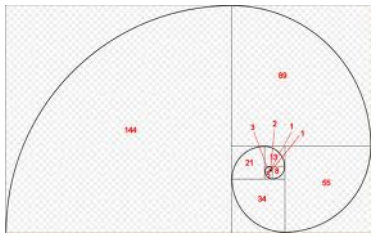
« It's the PK, stupid! »

WHY ANTICANCER DRUGS FAIL?

- Fibonacci, or Fibonacci-like designs?



- The Fibonacci numbers have been first theorized to count rabbits in the 13th century!



WHY ANTICANCER DRUGS FAIL?

- Modified-Fibonacci design (aka 3+3 design)

Treat 3 patients at dose K:

1.If 0 patients experience dose-limiting toxicity (DLT), escalate to dose K+1
2.If 2 or more patients experience DLT, de-escalate to level K-1.
3.If 1 patient experiences DLT, treat 3 more patients at dose level K
   A.If 1 of 6 experiences DLT, escalate to dose level K+1
   B.If 2 or more of 6 experiences DLT, de-escalate to level K-1

MTD: highest dose at which 1 or 0 out of six patients shows DLT.

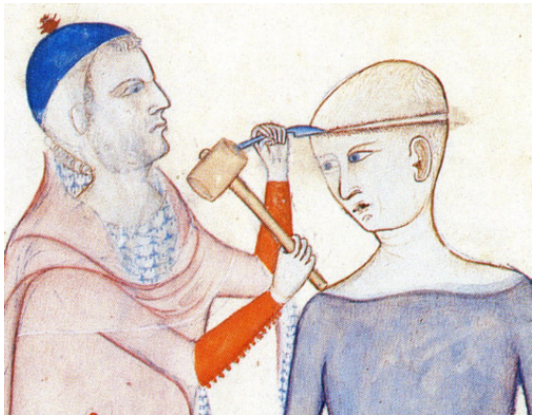
Imprecise MTD leads to weak phase-II studies

Weak phase-II studies lead to failing phase-III studies

Attrition-rate during clinical development: 90%

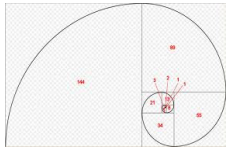
WHY ANTICANCER DRUGS FAIL?

- Since tumors are removed using 21th century surgery, and not 13th century…

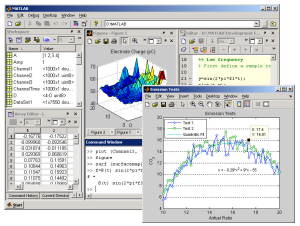


- Time to use 21th century mathematics!

WHY ANTICANCER DRUGS FAIL?



Standard Design



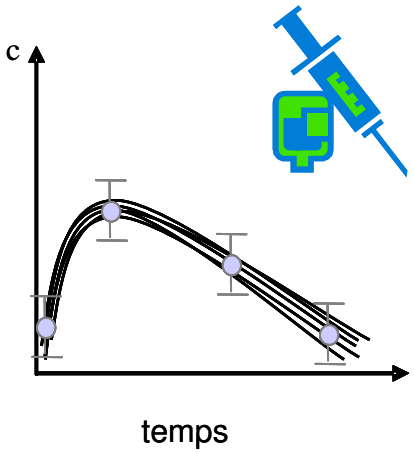
Adaptative Design

- Pre-specified doses before starting!
- Geometric dose-ranging
- MTD is not based on all the data
- Rates of toxicities is ignored
- Resulting MTD is imprecise!

- Upper doses constantly re-assessed
- Multi-level Model to calculate the doses
- All available data are used
- DLT definition can be customized

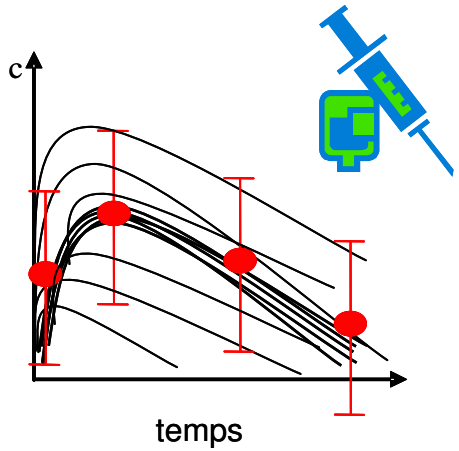
WHY ANTICANCER DRUGS FAIL?

Clinical Trial



- Limited population (n<1 000)
- Highly selected patients
- Smoothed clinical co-variates.
- Age: 18-65 years
- Little, or well-known comorbidities
- Controlled lifestyle

Real Life

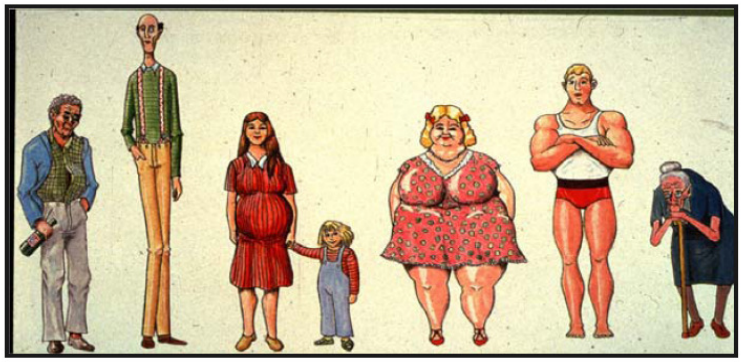


- Unlimited sample
- Unselected patients
- Dispersion of clinical covariates
- Elderly patients
- Many comorbidities, some unknown
- Variety in lifestyles

WHY ANTICANCER DRUGS FAIL?

Clinical Trial

Real Life



$$D = \frac{Cl \times C_{moy} \times \tau}{F}$$

?

PK OF ANTICANCER DRUGS

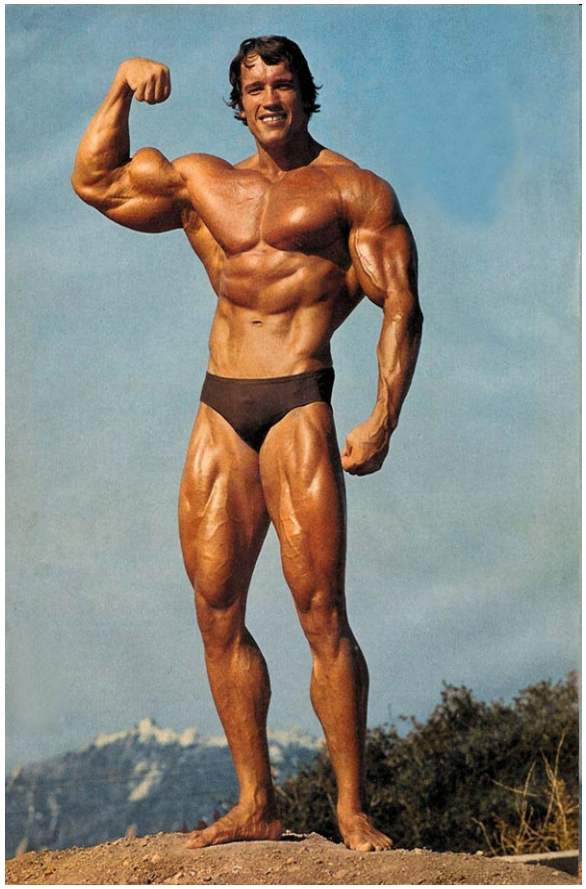
What makes PK changes?

- Age (most cancer patients are > 65 years)
- Drug-Drug Interactions (most cancer patients are heavily treated)
- Co-morbidities affecting kidneys and/or liver.
- Genetic polymorphism affecting drug transport – drug metabolism.
- Denutrition.
- Environmental factors.
- Food (most TKIs are oral drugs)
- Tumor burden (biotherapies)

WHAT MAKES PK CHANGES?

Age!

20 y.o.



60 y.o.

WHAT MAKES PK CHANGES?

Food!

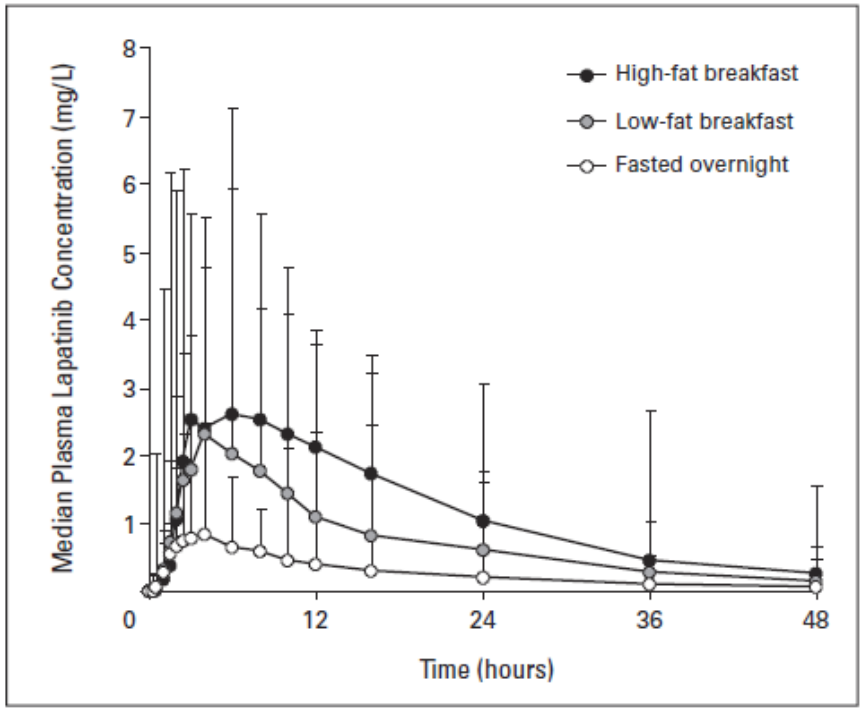
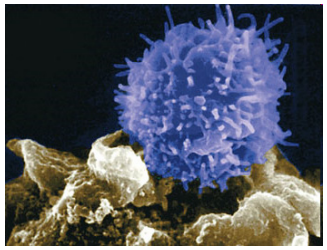


Fig 1. Median and upper ranges of plasma lapatinib concentrations versus time following a 1,500-mg dose administered after fasting overnight, after a low-fat breakfast, and after a high-fat breakfast.

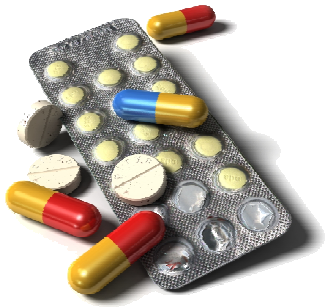
PK OF ANTICANCER DRUGS

PD issues are adressed
…. What about PK issues?

A unique patient



A unique tumor



A unique treatment

Personalized dosing
?

PK OF ANTICANCER DRUGS

Identifying individual PK parameters should allow to improve the efficacy/toxicity balance of anticancer drugs through identifying outliers requiring customized dosing:

- Identifying poor metabolizer (PM) patients.
- Identifying patients with impaired drug elimination/transport.
- Identifying patients displaying higher clearances requiring increase in dosing.
- Understanding the relationships between drug concentrations and antiproliferative effect.
- Understanding the relationships between drug concentrations and toxicities.

PK OF ANTICANCER DRUGS

ANTIMETABOLITES

CASE REPORT

CDA deficiency as a possible culprit for life-threatening toxicities after cytarabine plus 6-mercaptopurine therapy: pharmacogenetic investigations

Cancer Chemother Pharmacol (2006) 58: 272–275
DOI 10.1007/s00280-005-0139-8

SHORT COMMUNICATION

Joseph Ciccolini · Cedric Mercier · Laetitia Dahan
Alexandre Evrard · Jean-Christophe Boyer
Karine Richard · Jean-Philippe Dales · Alain Durand
Gerard Milano · Jean-François Seitz · Bruno Lacarelle

Toxic death-case after capecitabine + oxaliplatin (XELOX) administration: probable implication of dihydropyrimidine deshydrogenase deficiency

VOLUME 30 · NUMBER 4 · FEBRUARY 1 2012

JOURNAL OF CLINICAL ONCOLOGY | DIAGNOSIS IN ONCOLOGY

Sudden Death Related to Toxicity in a Patient on Capecitabine and Irinotecan Plus Bevacizumab Intake: Pharmacogenetic Implications

Introduction

Capecitabine is an oral alternative to fluorouracil (FU) frequently administered as part of combination therapies in digestive oncology. This prodrug is designed to be activated through a triple enzymatic

Case Report

Cancer Chemother Pharmacol
DOI 10.1007/s00280-008-0889-1

SHORT COMMUNICATION

Early severe toxicities after capecitabine intake: possible implication of a cytidine deaminase extensive metabolizer profile

CE: satish ED: raji Op: ns FPC: LWW_FPC_200795
Rapid communication 1

Toxic death case in a patient undergoing gemcitabine-based chemotherapy in relation with cytidine deaminase downregulation

Targeted therapies should have their PK checked too!

TARGETED THERAPIES

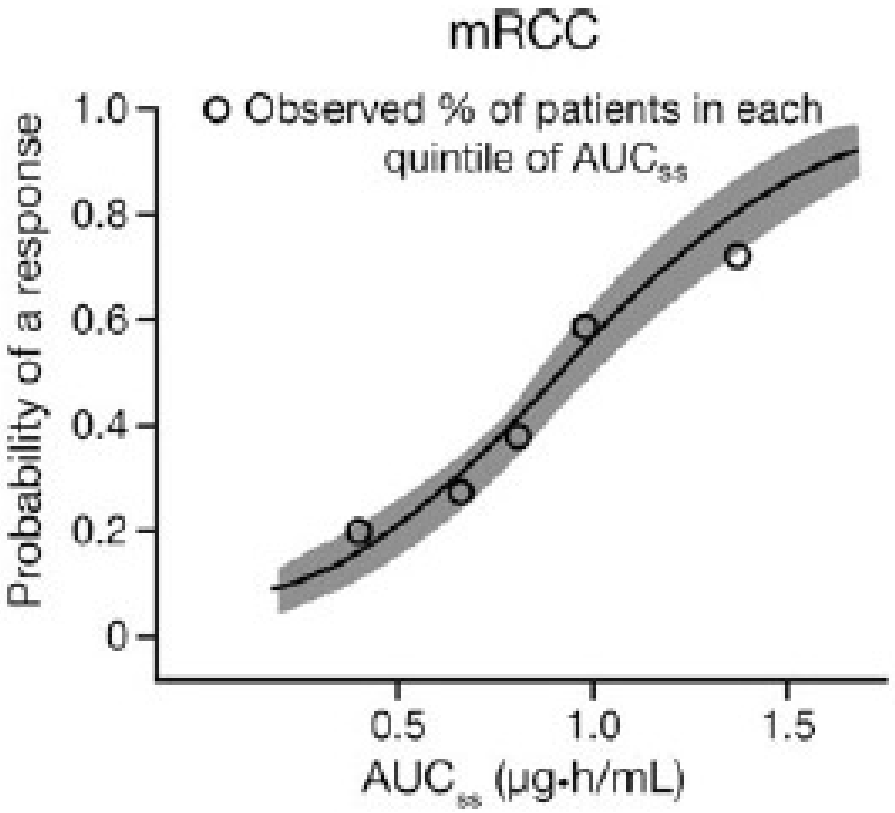
Hot Topic Cancer Treatment Reviews

Moving towards dose individualization of tyrosine kinase inhibitors

Heinz-Josef Klümpen [a,*,1], Caroline F. Samer [b,c,1], Ron H.J. Mathijssen [d], Jan H.M. Schellens [e]
Howard Gurney [g]

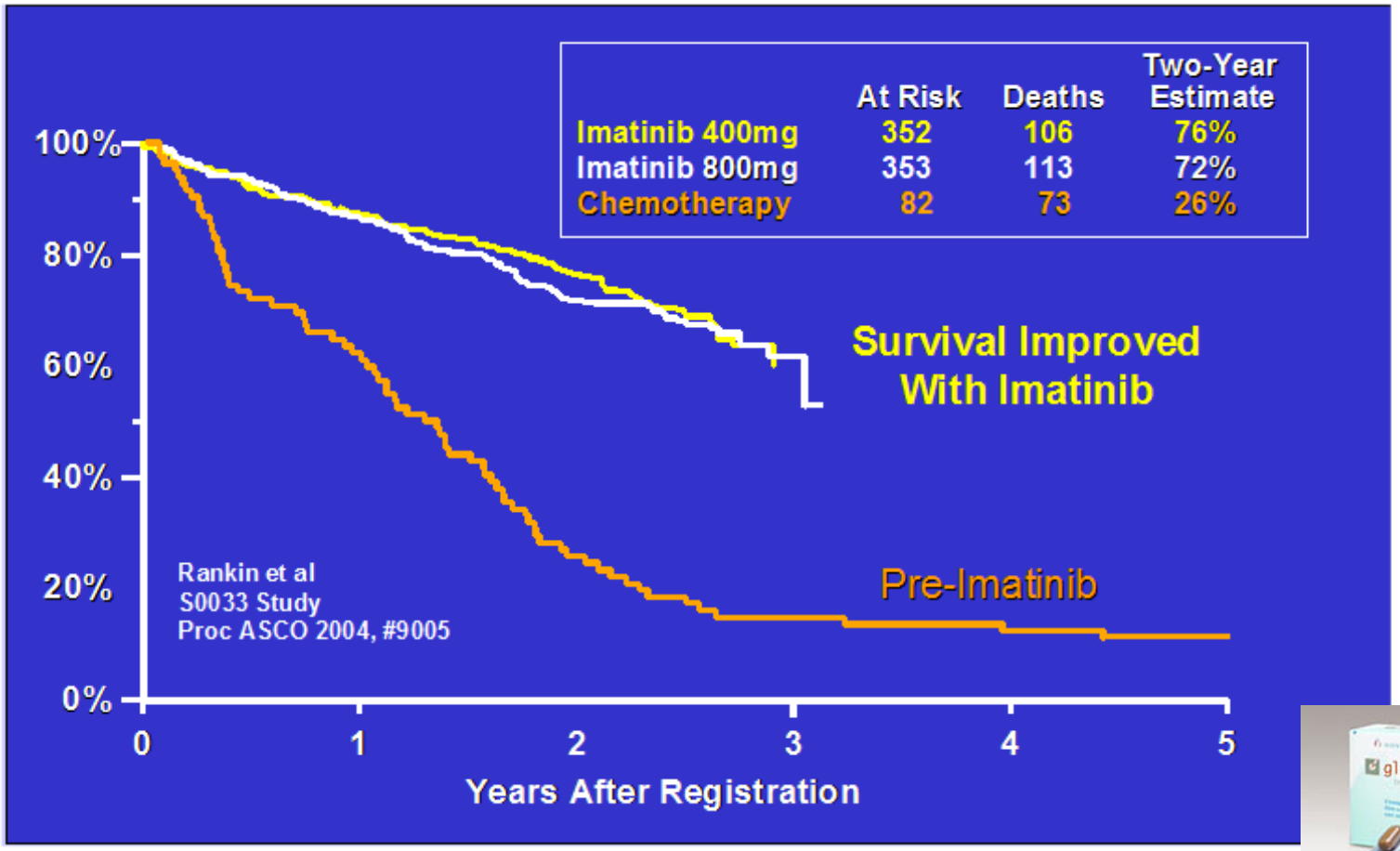
Targeted therapies should have their PK checked too.

Fig. 3 Probability of a partial or complete response (by RECIST criteria) versus average daily exposure (mean daily AUC at steady state, AUC_{ss}) to sunitinib. *Lines* represent model prediction and *shaded area* represents 95% confidence interval. Modeling results only displayed for relationships displaying statistical significance



Targeted therapies should have their PK checked too!

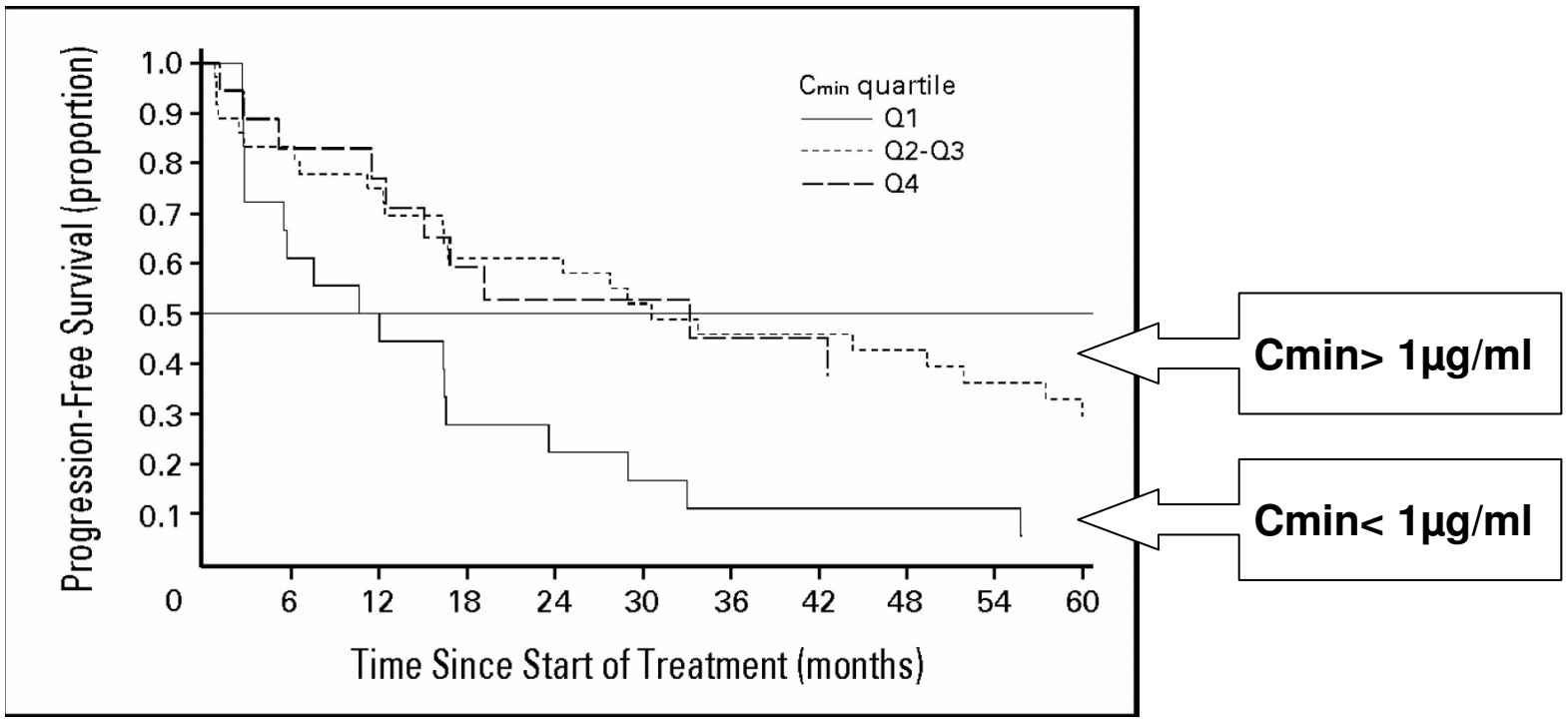
Plasma exposure drives the PD…. not the dosing!



2004: No difference between
400 mg et 800 mg imatinib?

Targeted therapies should have their PK checked too!

Plasma exposure drives the PD…. not the dosing!

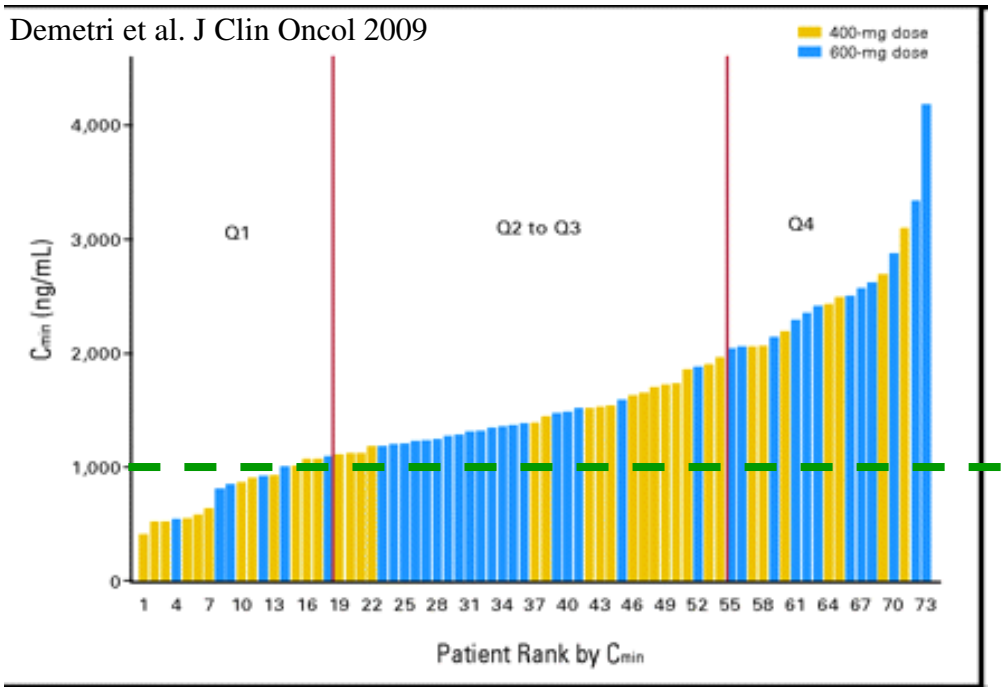


2009: difference between Q1 (low exposures) and Q2-4 (high exposures)!

Demetri et al. J Clin Oncol 2009

Targeted therapies should have their PK checked too!

Plasma exposure drives the PD…. not the dosing!



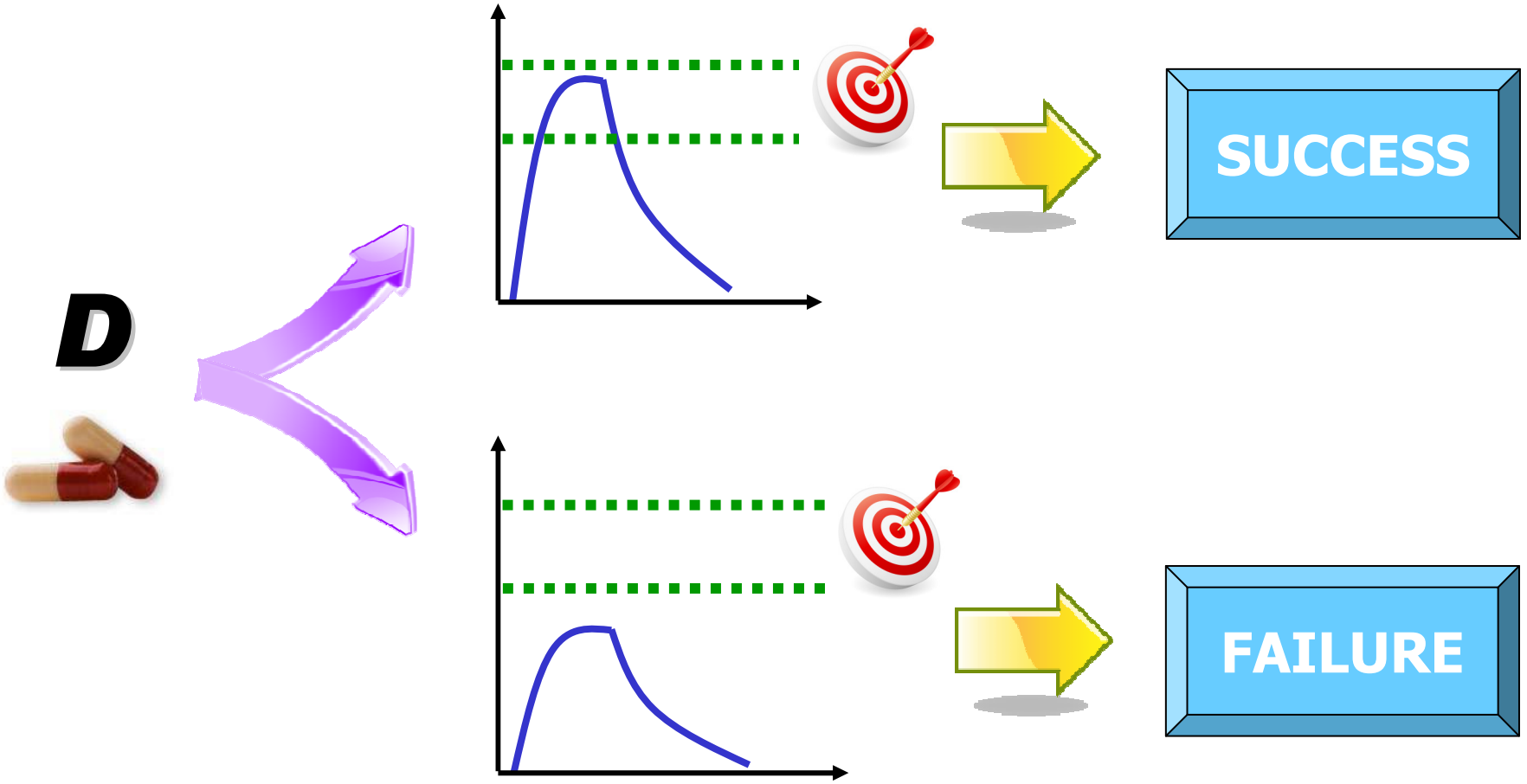
Cmin efficace

Les patients 400 et 800 mg se répartissent indistinctement de part et d'autres de la Cmin efficace!

Inter-patient PK variability makes 400 or 600 mg imatinib give highly variable exposure levels!

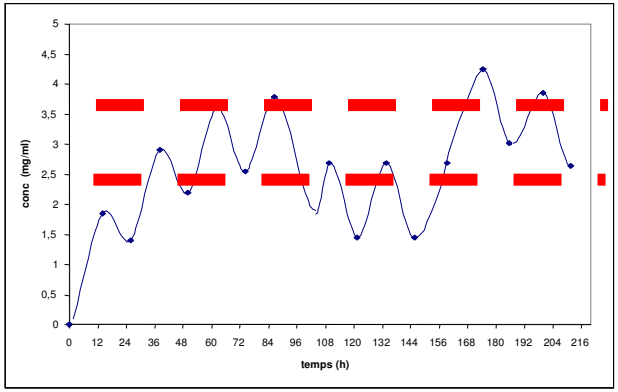
Targeted therapies should have their PK checked too!

Plasma exposure drives the PD…. not the dosing!



PK OF ANTICANCER DRUGS
Performing drug monitoring?

Biotherapies should have their PK checked too.



- Understanding PK and PK/PD of therapeutic antibodies is challenging.
- Lack for bioanalytical support.
- Linear, non-linear or Mixed PK. PD (e.g., receptor expression, tumor burden) can impact on PK parameters!
- Little data made available (Avastin? Rituximab?).
- Cetuximab: Clearance is associated with DFS!
- … Doses should be probably customized too!

PK OF ANTICANCER DRUGS
Performing drug monitoring?

Variable	Strata	Median Time to Progression (days)	p-value
AUC_{inf}	**> 4050 µg/mL.day**	**293**	**0.0059**
	≤ 4050 µg/mL.day	**84**	
CL	> 2.56 mL/kg/day	92	0.0018
	≤ 2.56 mL/kg/day	219	
C_{max}	> 270 µg/mL	233	0.1721
	≤ 270 µg/mL	171	
k_{10}	> 0.0629 / day	152	0.2804
	≤ 0.0629 / day	207	
Vol	> 39.3 mL/kg	171	0.0459
	≤ 39.3 mL/kg	213	

Approval package, *FDA* 2004

Genentech
IN BUSINESS FOR LIFE

FDA
Center for Drug Evaluation and Research

Biotherapies should have their PK checked too!

Cancer Therapy: Clinical

Clinical Cancer Research

Cetuximab Pharmacokinetics Influences Progression-Free Survival of Metastatic Colorectal Cancer Patients

Nicolas Azzopardi[1,2], Thierry Lecomte[1,2,3], David Ternant[1,2,4], Michelle Boisdron-Celle[6], Friedrich Piller[7], Alain Morel[6], Valérie Gouilleux-Gruart[1,2,5], Céline Vignault-Desvignes[1,2,4], Hervé Watier[1,2,5], Erick Gamelin[6], and Gilles Paintaud[1,2,4]

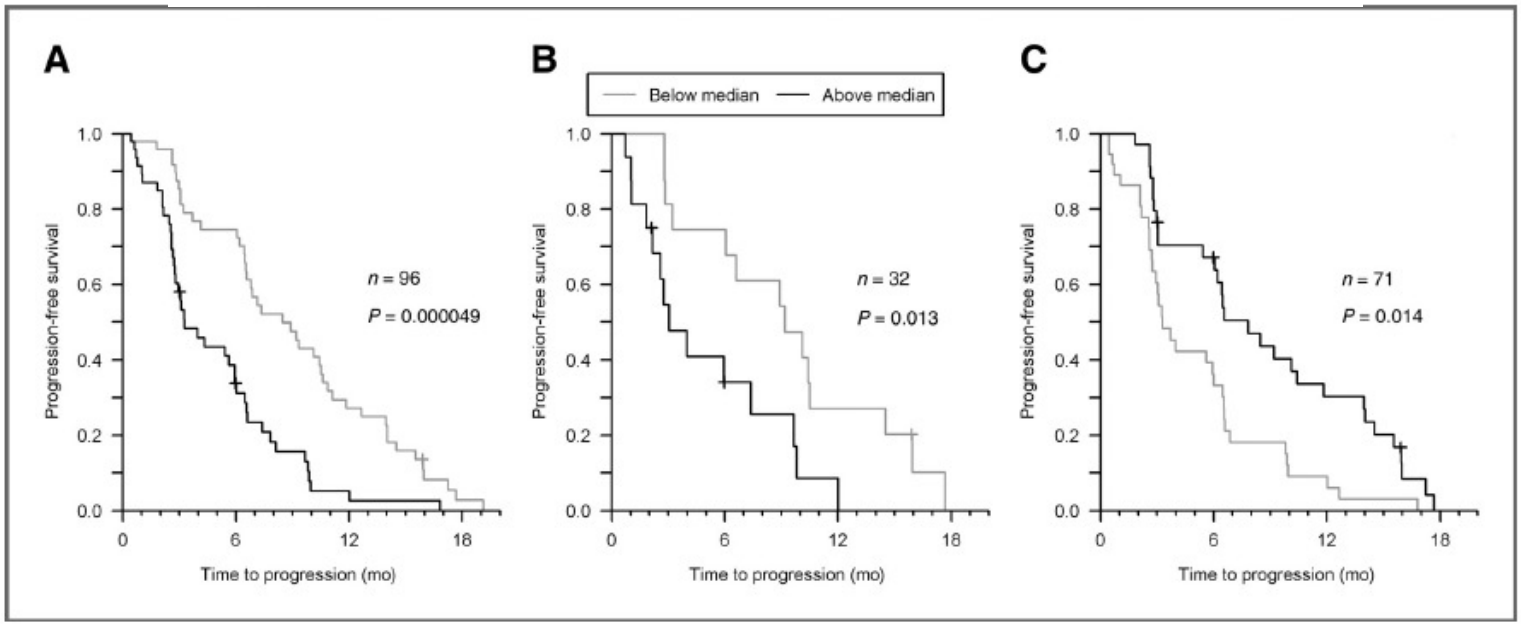


Figure 2. Kaplan–Meier curves of PFS according to (A) cetuximab global clearance in all patients, (B) cetuximab global clearance in patients with wild-type *KRAS* tumor, and (C) cetuximab residual concentration on day 14. Patients with values above and below the median value are displayed as black and gray lines, respectively.

Cétuximab (Erbitux)

Biotherapies should have their PK checked too!

J Clin Oncol. 2012 Nov 10;30(32):4017-25. doi: 10.1200/JCO.2012.43.5362. Epub 2012 Aug 27.

Evidence for therapeutic drug monitoring of targeted anticancer therapies.

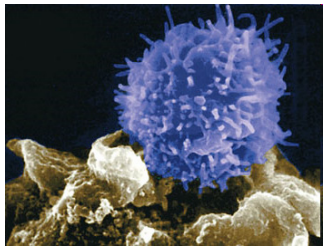
Gao B, Yeap S, Clements A, Balakrishnar B, Wong M, Gurney H.

Department of Medical Oncology, Westmead Hospital, Westmead 2145 NSW, Australia. howard.gurney@sydney.edu.au

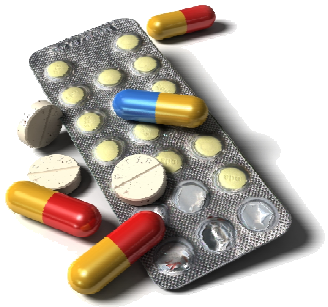
« Quit guessing, start measuring »

PK OF ANTICANCER DRUGS
….. in an ideal world?

A unique patient

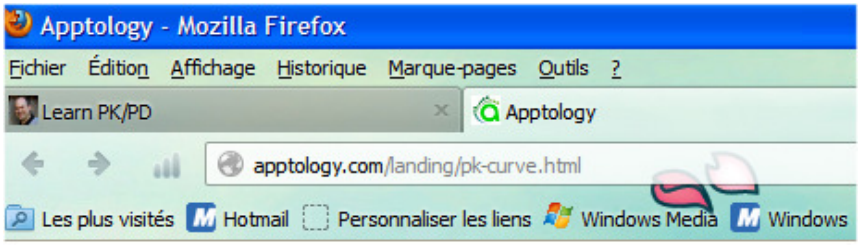


A unique tumor



A unique treatment

Personalized dosing



PK/PD Associates

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PK OF ANTICANCER DRUGS
Take-home Message

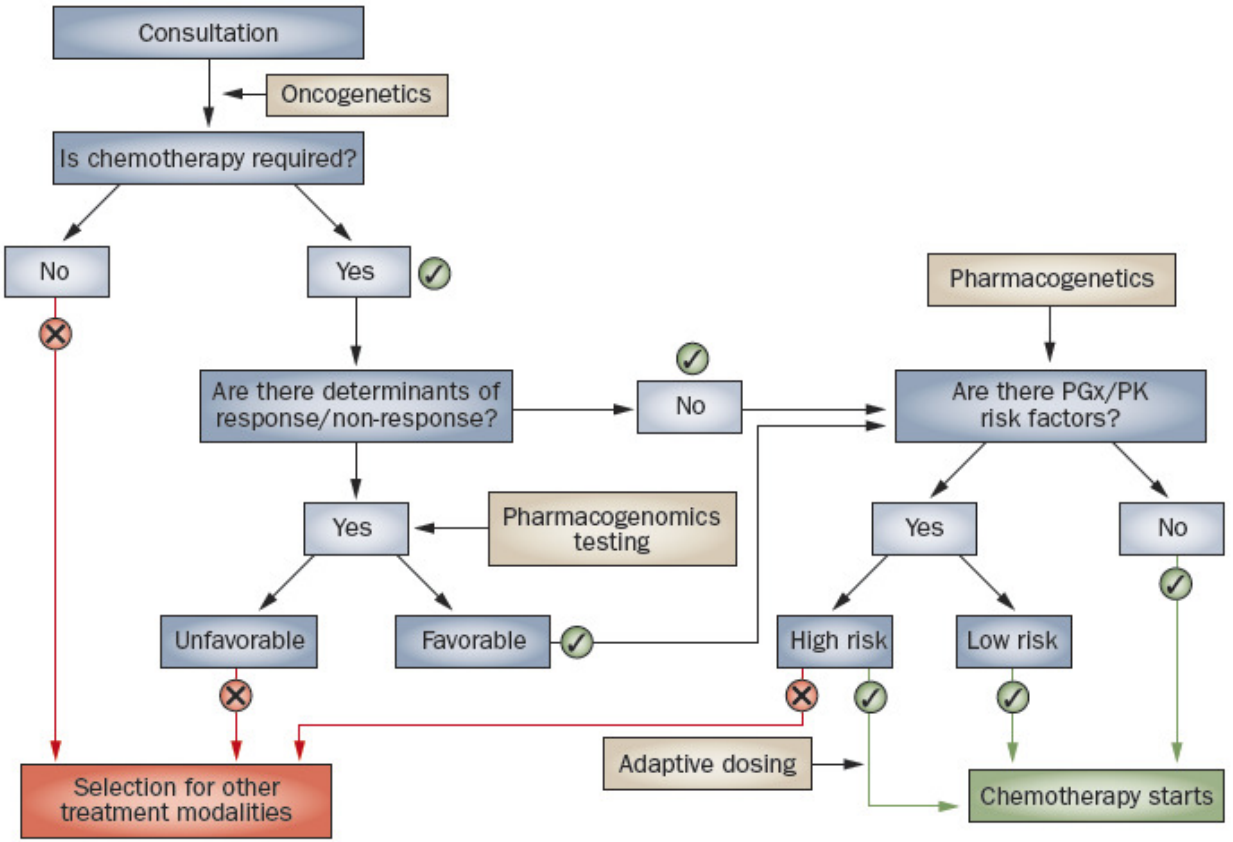

Figure 1 | Decision tree integrating oncogenetic, pharmacogenomic, and pharmacogenetic testing in oncology. Patients with biomarkers predicting an unfavorable response or presenting with altered pharmacokinetic profiles should be selected for other treatment modalities or treated with a personalized dose based on a pharmacogenetic strategy. Abbreviations: PGx, pharmacogenetic; PK, pharmacokinetic.

Ciccolini Nat Rev. 2011

PK OF ANTICANCER DRUGS
Take-home Message

« I cure people »

« Me too »

Thanks for listening!

Assistance Publique
Hôpitaux de Marseille