BIOTHERAPIES: IS PK THE FORGOTTEN BIOMARKER?

Dr Joseph Ciccolini
PharmD. Ph.D

Aix*Marseille université
Assistance Publique Hôpitaux de Marseille
UNICANCER GPCO

WHO CARES ABOUT PK ?

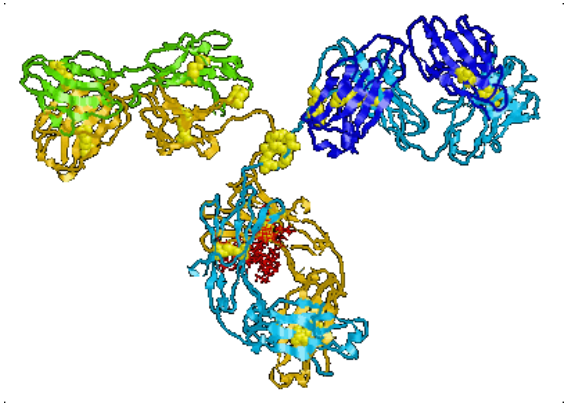
PK of biologics only starts to be considered!

Cytotoxics & TKIs

- Infusional or Oral absorption
- Goes through the membranes
- Strong liver metabolism
- Glomerular filtration
- Half-life in minutes / hours
- Extensive Distribution
- Biliary secretion

Biologics

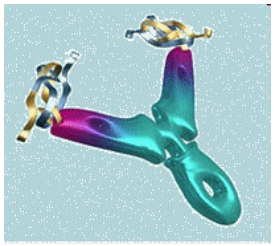
- Little resorption through membranes
- Limited distribution
- No liver metabolism
- No renal clearance
- Half-life in weeks
- Proteolytic degradation
- Receptor-mediated clearance (TMDD)
- Anti-MAB antibodies



WHO CARES ABOUT PK ?

How to anticipate MoABs PK for adjusting dosing?

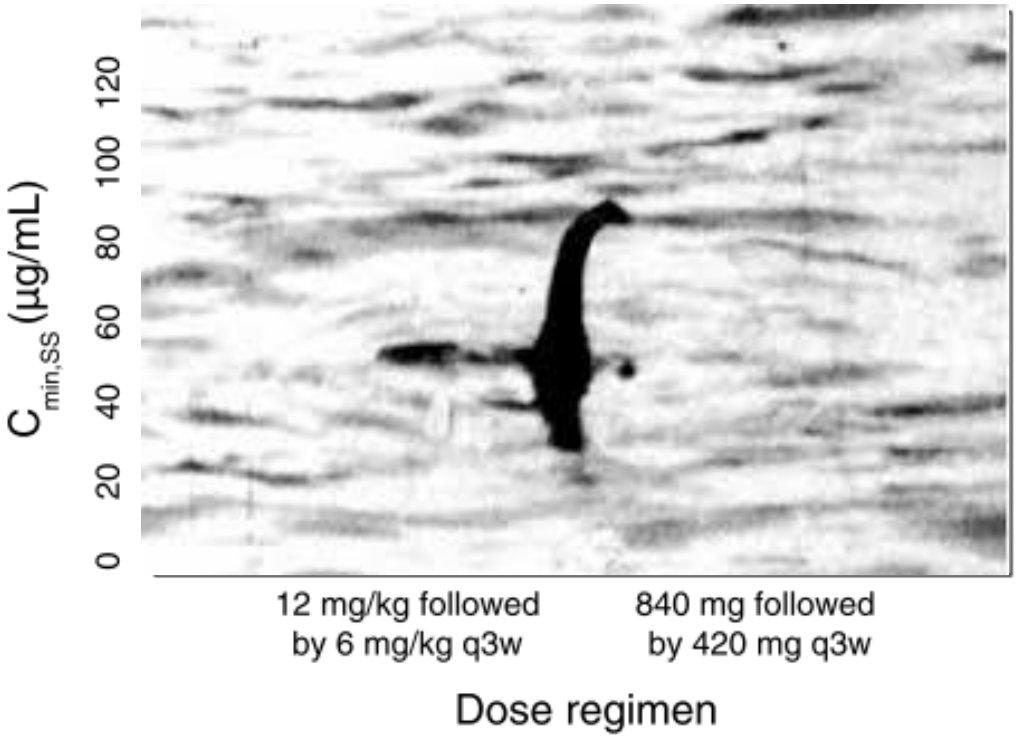
- Impaired kidney function
- Impaired Liver function
- age
- obesity
- ADME genetic polymorphisms
- sex
- co-medications



- age?
- sex?
- tumor burden ?
- Fc-γ-R genetic polymorphism ?
- ?
- ?

PK VARIABILITY WITH BIOTHERAPY IS NOT A HOAX!

Pertuzumab (Perjeta®)



Garg A et al. Cancer Chemother Pharmacol 2014

PK VARIABILITY WITH BIOTHERAPY IS NOT A HOAX!

Bevacizumab (Avastin®)

- mCRC Patients (CHU Timone, Pr Seitz)

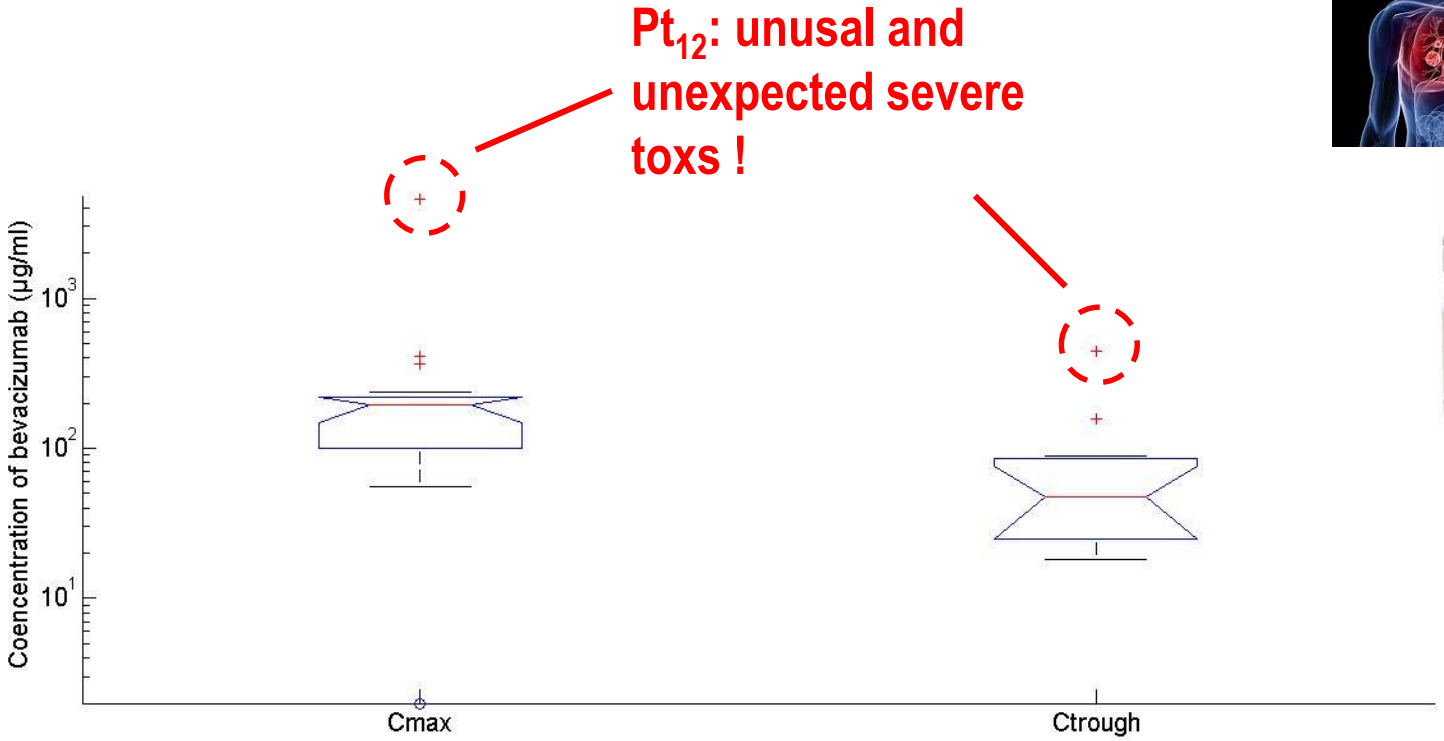
Assistance Publique
Hôpitaux de Marseille

- NSCLC Patients (CHU Nord, Pr Barlési)

Therapeutic Drug Monitoring (Cmax, Ctrough)

PK VARIABILITY WITH BIOTHERAPY IS NOT A HOAX!

Bevacizumab (Avastin®)



Inter-patient variability on drug levels: > 200%!

AACR American Association for Cancer Research ANNUAL MEETING 2014 SAN DIEGO
April 5-9, 2014
San Diego, Ca, USA

PK VARIABILITY WITH BIOTHERAPY IS NOT A HOAX!

Cetuximab (Erbitux®)

- Head & Neck Patients (CHU Timone, Pr Salas)

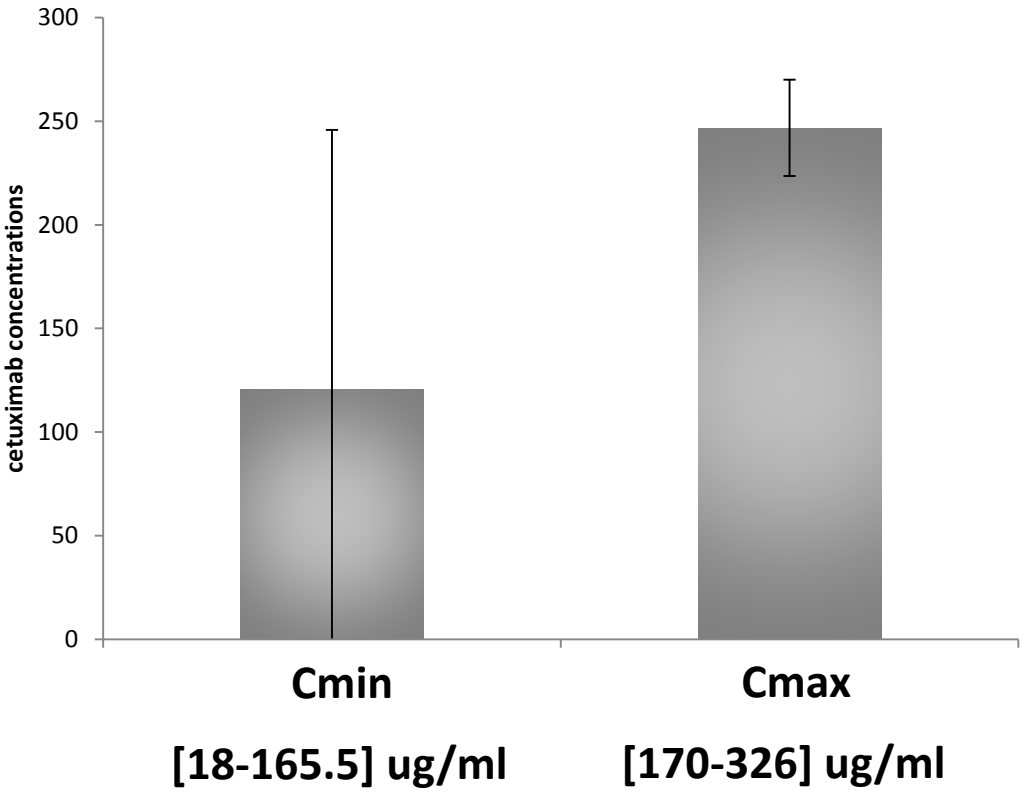
Assistance Publique Hôpitaux de Marseille

Therapeutic Drug Monitoring (Cmax, Ctrough)

Unpublished data

PK VARIABILITY WITH BIOTHERAPY IS NOT A HOAX!

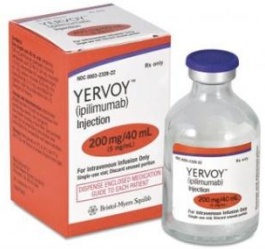
Cetuximab (Erbitux®)



Inter-patient variability on trough levels: > 125%!

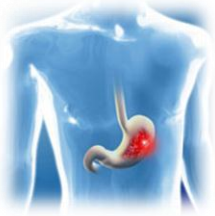
Unpublished data

BIOTHERAPIES:
EXPOSURE MATTERS!

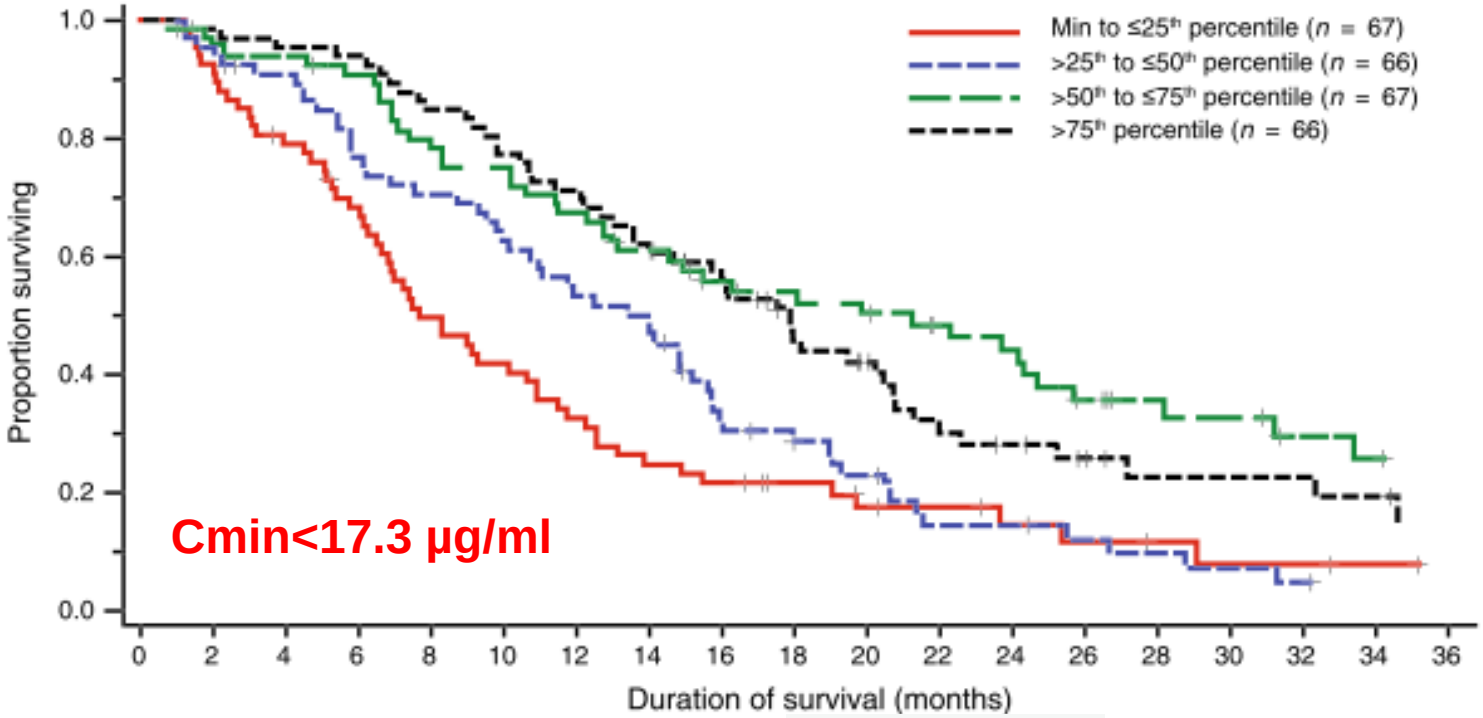


PK/PD OF BIOTHERAPIES

❖ **Trastuzumab in Gastric Cancer**



Cmin>36.9 µg/ml



Cmin<17.3 µg/ml

Cosson et al. 2014

Trastuzumab (Herceptin®)

PK/PD OF BIOTHERAPIES

❖ **Cetuximab in mCRC**

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]

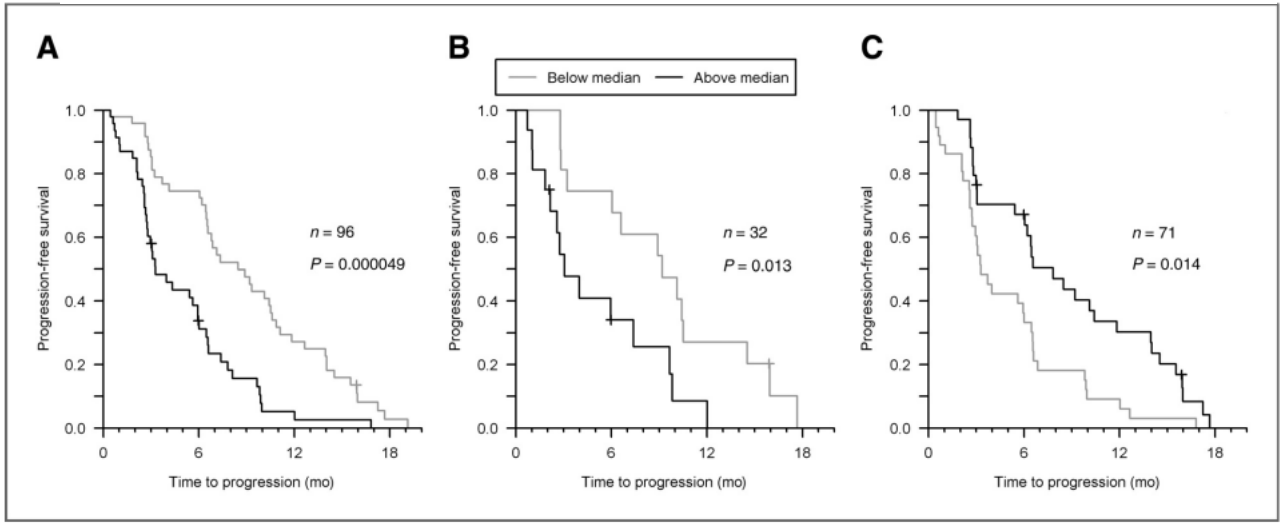


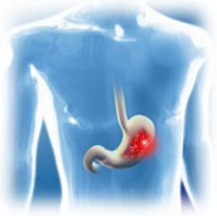
Figure 2. Kaplan–Meier curves of PFS according to (A) cetuximab global clearance in all patients, (B) cetuximab global clearance in patients with wild-type *KRAS* tumor, and (C) cetuximab residual concentration on day 14. Patients with values above and below the median value are displayed as black and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

Cetuximab (Erbitux®)

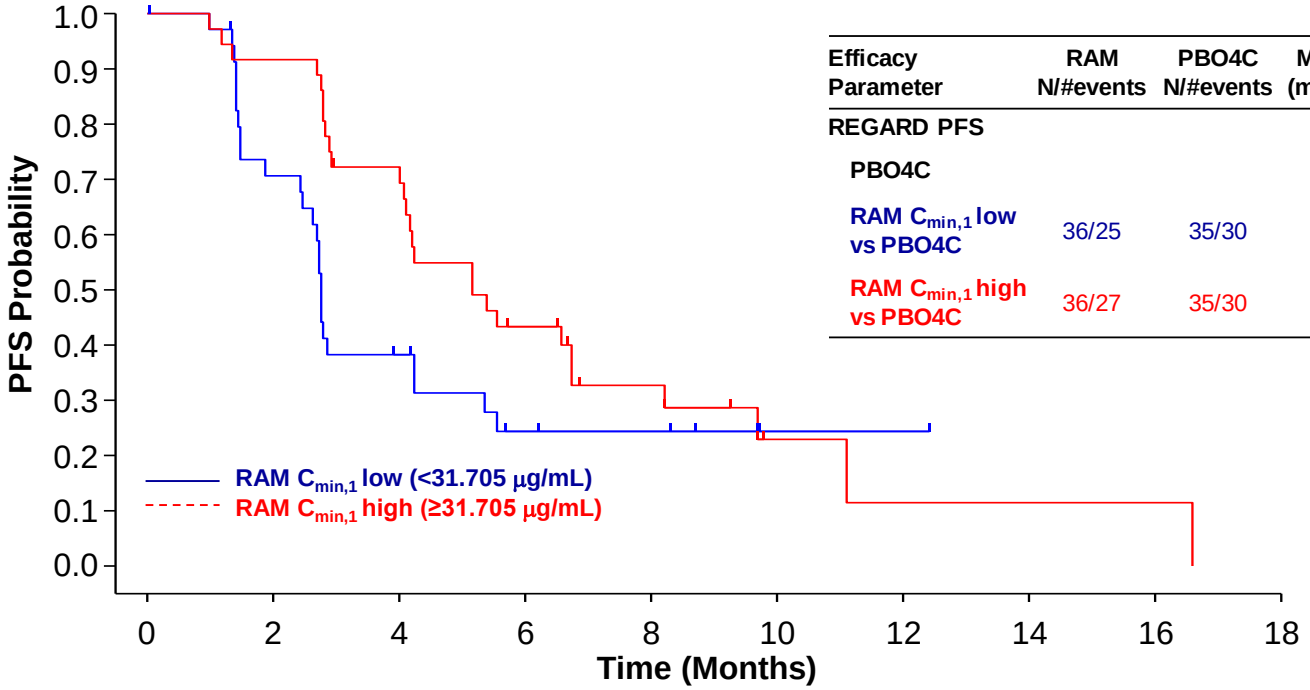
Azzopardi et al. 2009

PK/PD OF BIOTHERAPIES

❖ **Ramucirumab in Gastric Cancer**



Regard Phase-3 trial



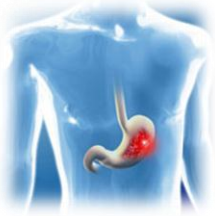
Efficacy Parameter	RAM N/#events	PBO4C N/#events	Median (months)	Hazard Ratio* (95% CI)	p-value
REGARD PFS					
PBO4C			2.8		
RAM $C_{min,1}$ low vs PBO4C	36/25	35/30	2.8	0.70 (0.40, 1.23)	0.2168
RAM $C_{min,1}$ high vs PBO4C	36/27	35/30	5.2	0.37 (0.20, 0.70)	0.0019

Ramucirumab (Cyramza)

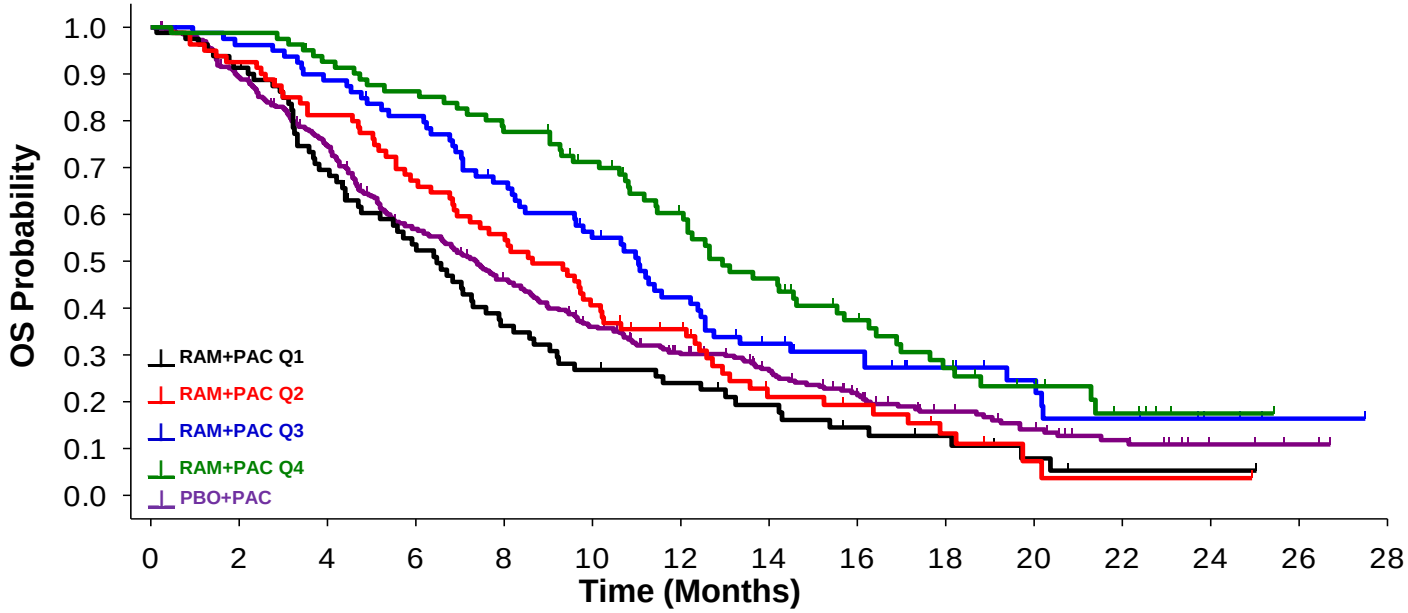
Tabernero et al. Asco-GI 2015

PK/PD OF BIOTHERAPIES

❖ **Ramucirumab in Gastric Cancer**



Rainbow Phase-3 trial



Ramucirumab (Cyramza®)

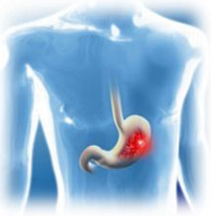
Efficacy Parameter	RAM+PAC N/#events	PBO+PAC N/#events	Median (months)	Hazard Ratio* (95% CI)	p-value
RAINBOW OS					
PBO+PAC			7.4		
RAM+PAC Q1	80/68	335/260	6.5	1.04 (0.79, 1.37)	0.7891
RAM+PAC Q2	80/67	335/260	8.6	0.84 (0.64, 1.11)	0.2168
RAM+PAC Q3	80/58	335/260	11.0	0.69 (0.51, 0.92)	0.0107
RAM+PAC Q4	81/57	335/260	12.9	0.53 (0.40, 0.71)	<0.0001

Tabernero et al. Asco-GI 2015

PK/PD OF BIOTHERAPIES

❖ **Ramucirumab in Gastric Cancer**

Rainbow Phase-3 trial



		RAM+PAC				
	PBO+PAC N=335	Overall N=321	Q1 N=81	Q2 N=80	Q3 N=80	Q4 N=80
$C_{min,1}$ concentration range, µg/mL	---	11.6 to 76.7	11.6 to ≤22.8	>22.8 to ≤28.0	>28.0 to ≤35.5	>35.5 to 76.7
Hypertension,* %	3.0	14.6	9.9	17.5	15.0	16.2
Neutropenia, %	20.9	42.1	25.9	35.0	47.5	60.0
Febrile neutropenia, %	2.7	3.1	3.7	1.3	3.8	3.8
Leukopenia, %	7.2	17.8	13.6	11.2	22.5	23.8
Fatigue/asthenia, %	5.4	12.1	11.1	11.3	13.8	12.5

Ramucirumab (Cyramza®)

Tabernero et al. Asco-GI 2015

PK VARIABILITY WITH IMMUNOTHERAPY PROBABLY MATTERS!

Ipilimumab (Yervoy®) in melanoma

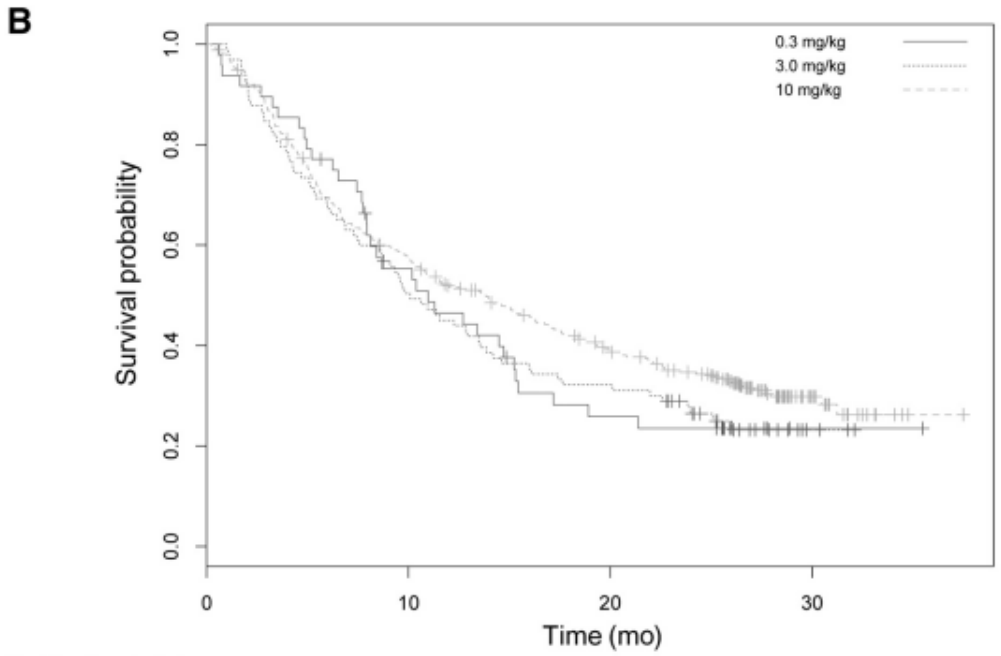
Cancer Therapy: Clinical

Clinical Cancer Research

Exposure–Response Relationships of the Efficacy and Safety of Ipilimumab in Patients with Advanced Melanoma

Yan Feng[1], Amit Roy[1], Eric Masson[1], Tai-Tsang Chen[2], Rachel Humphrey[1], and Jeffrey S. Weber[3]

No difference In dosing



Subjects at risk

0.3 mg/kg	48	37	22	13	11	2	0
3.0 mg/kg	98	66	43	31	22	4	0
10 mg/kg	352	240	172	134	101	23	2

PK VARIABILITY WITH IMMUNOTHERAPY PROBABLY MATTERS!

Ipilimumab (Yervoy®) in melanoma

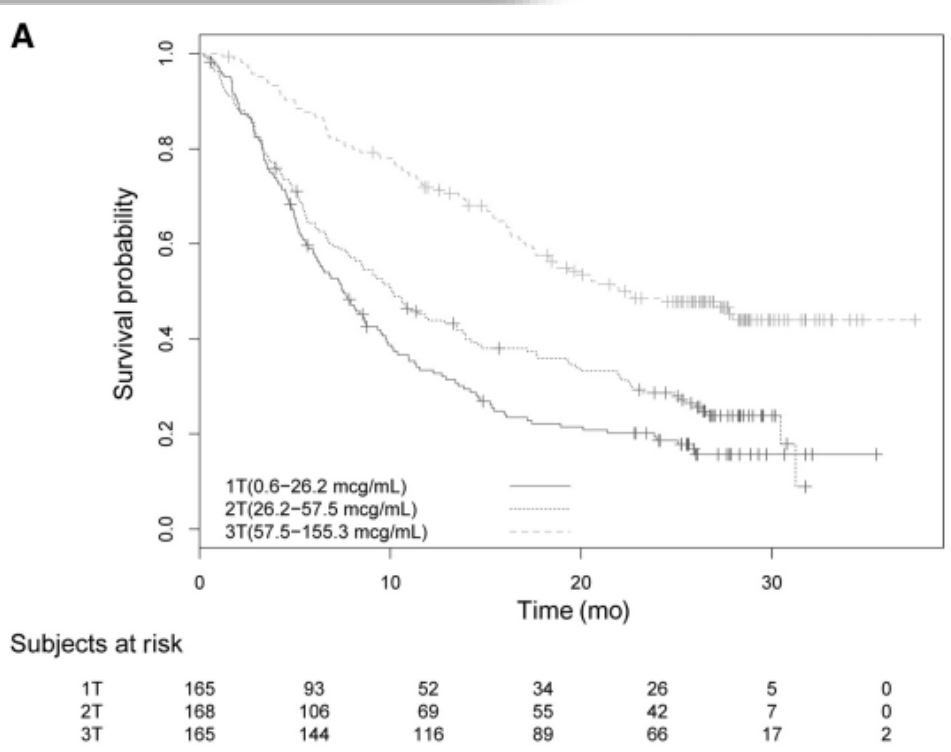
Cancer Therapy: Clinical

Clinical Cancer Research

Exposure–Response Relationships of the Efficacy and Safety of Ipilimumab in Patients with Advanced Melanoma

Yan Feng[1], Amit Roy[1], Eric Masson[1], Tai-Tsang Chen[2], Rachel Humphrey[1], and Jeffrey S. Weber[3]

… but exposure matters!



PK VARIABILITY WITH IMMUNOTHERAPY PROBABLY MATTERS!

Ipilimumab (Yervoy®) in melanoma

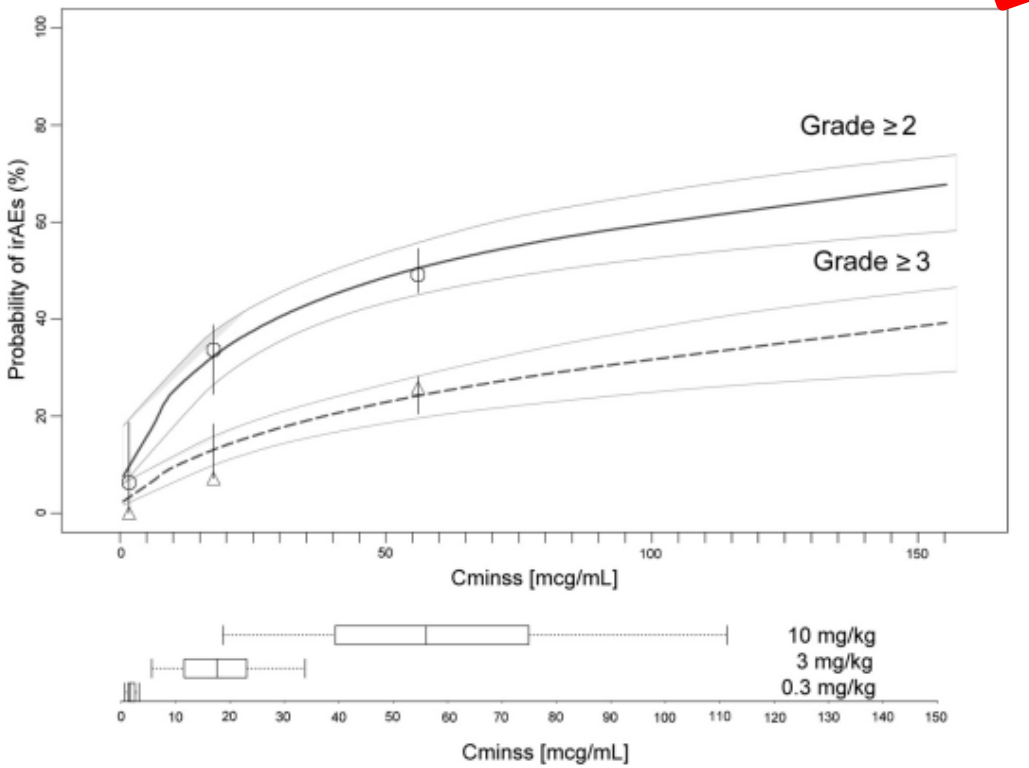
Cancer Therapy: Clinical

Clinical Cancer Research

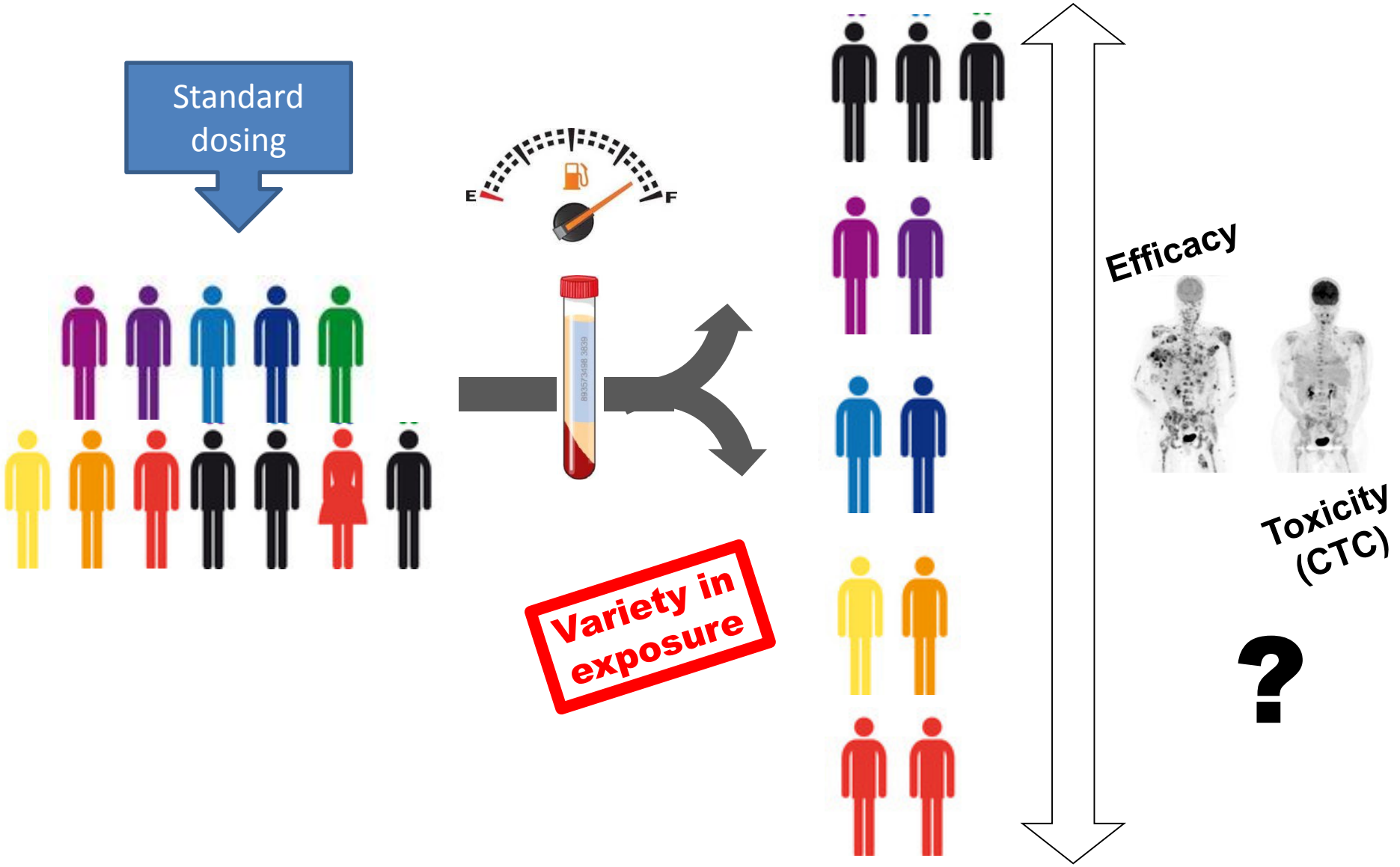
Exposure–Response Relationships of the Efficacy and Safety of Ipilimumab in Patients with Advanced Melanoma

Yan Feng[1], Amit Roy[1], Eric Masson[1], Tai-Tsang Chen[2], Rachel Humphrey[1], and Jeffrey S. Weber[3]

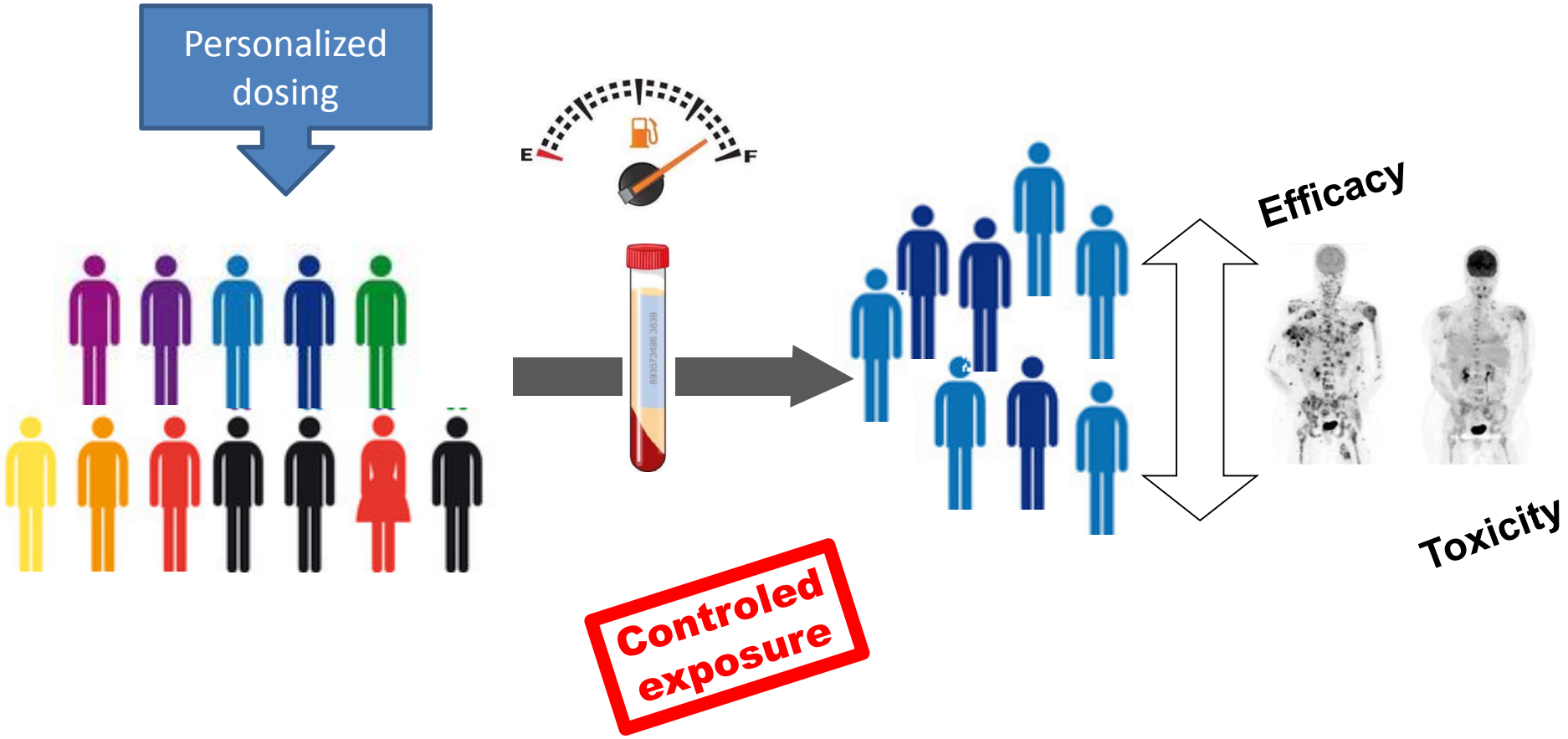
… but exposure matters!



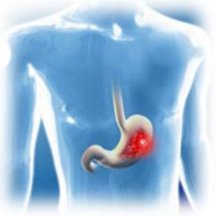
IMPLEMENTING MODEL-DRIVEN REGIMEN AT BEDSIDE

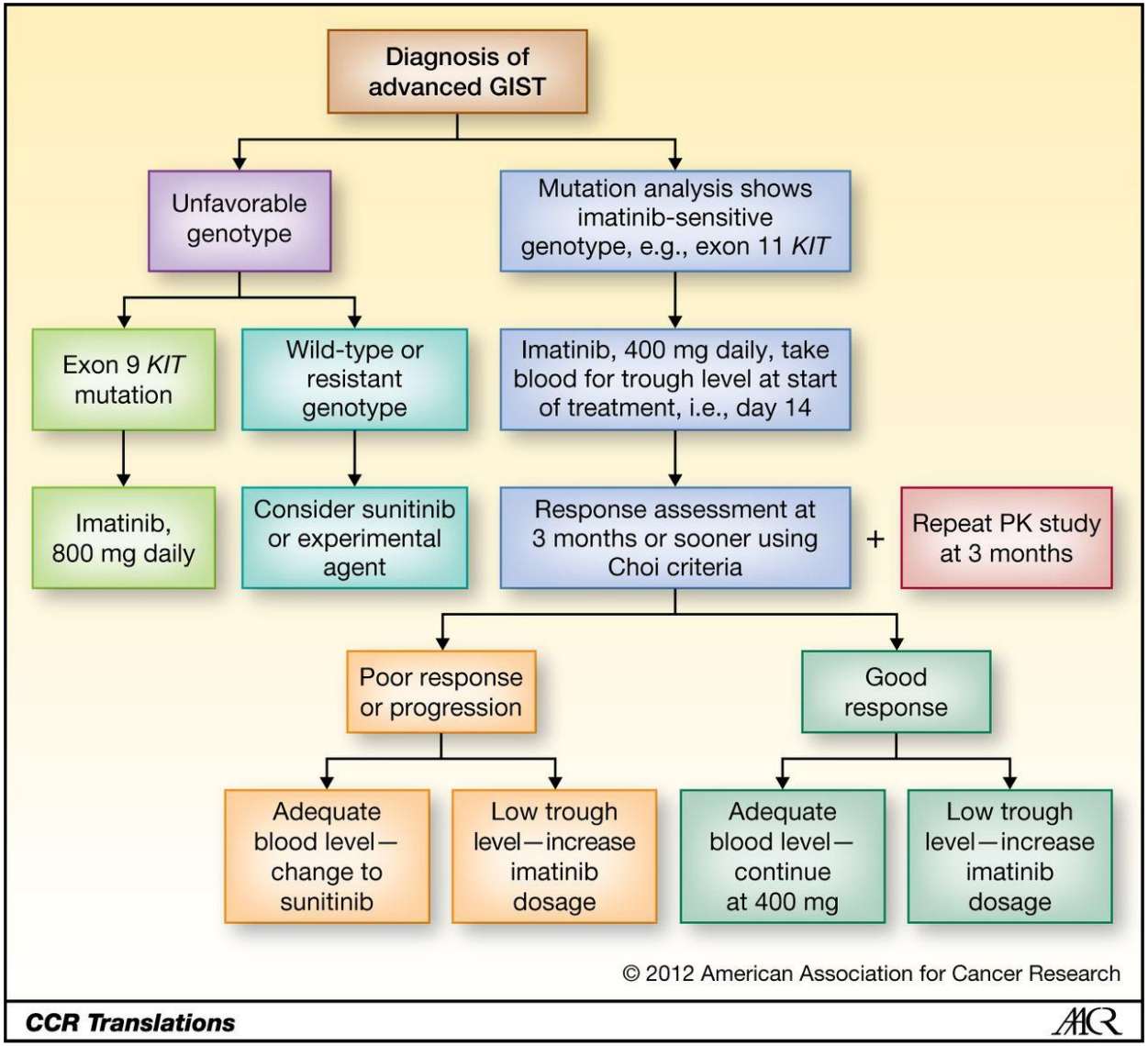


IMPLEMENTING MODEL-DRIVEN REGIMEN AT BEDSIDE



IMPLEMENTING MODEL-DRIVEN REGIMEN AT BEDSIDE





IMPLEMENTING MODEL-DRIVEN REGIMEN AT BEDSIDE

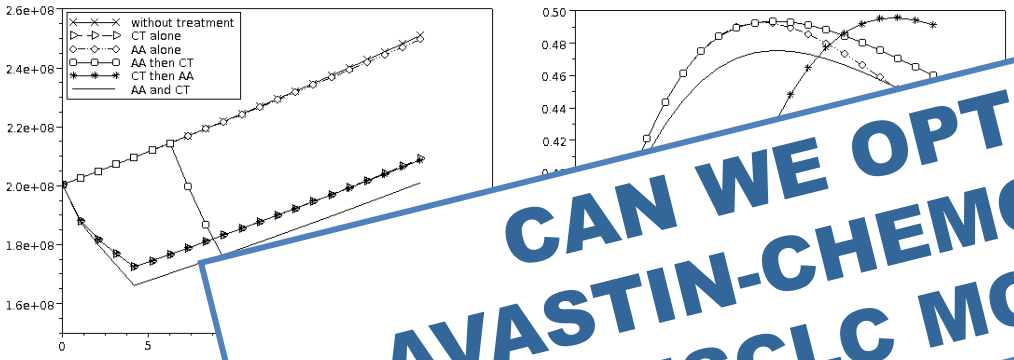
In addition to adaptive dosing strategies, extensive PK/PD support + TDM procedures could help to refine the exact place of biotherapies combined with chemotherapy!

- ✓ **How much?**
- ✓ **For how long?**
- ✓ **In which particular order?**

IMPLEMENTING MODEL-DRIVEN REGIMEN AT THE BENCH

- ❖Bevacizumab 20 mg/kg
- ❖Pemetrexed 100 mg/kg
- ❖Cisplatin 3 mg/kg

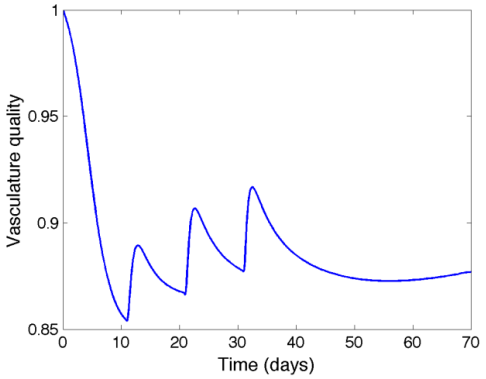
} 3 cycles



CAN WE OPTIMIZE AVASTIN-CHEMO COMBO IN NSCLC MODELS?

Tumor size ( ) vasculature

$$\begin{cases} \frac{dV}{dt}(t) &= \cdots(t)\log\left(\frac{S(t)}{V(t)}\right) - kq(t)S(t)C(t)n(t) \\ \frac{dS}{dt}(t) &= \chi U(t) - \tau S(t) \\ \frac{dU}{dt}(t) &= -\chi U(t) + \gamma V(t) - \delta V(t)^{\frac{2}{3}}U(t) - \eta q(t)S(t)A(t)U(t) \end{cases}$$

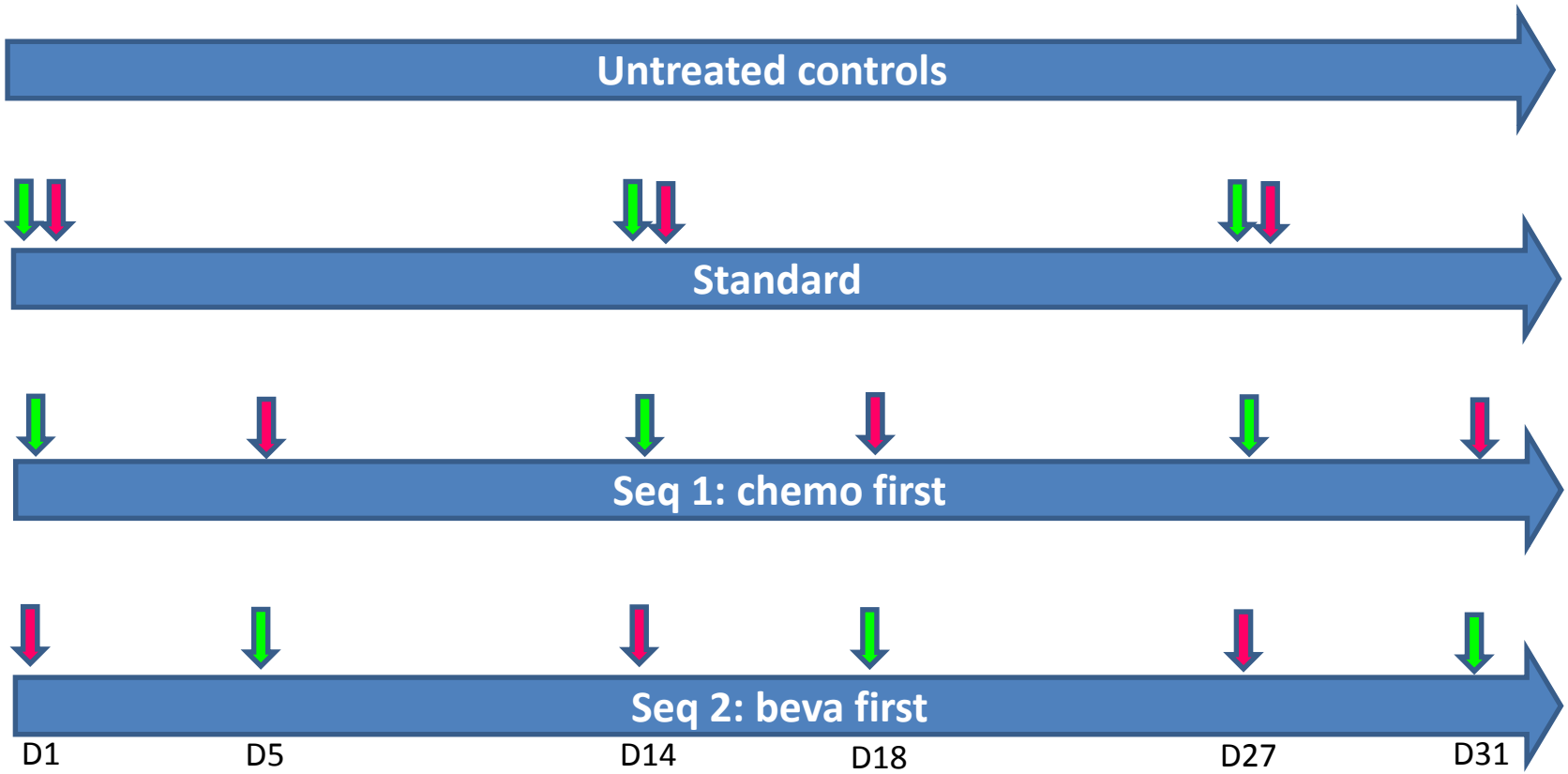


Benzekry et al. 2012

IMPLEMENTING MODEL-DRIVEN REGIMEN AT THE BENCH

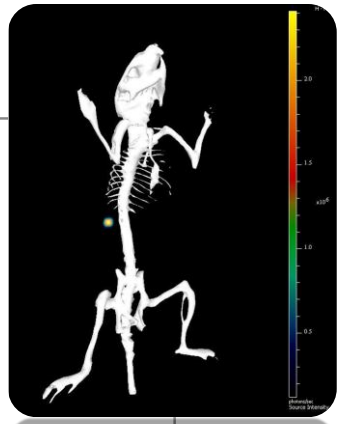
- ❖Bevacizumab 20 mg/kg
- ❖Pemetrexed 100 mg/kg
- ❖Cisplatin 3 mg/kg

} 3 cycles



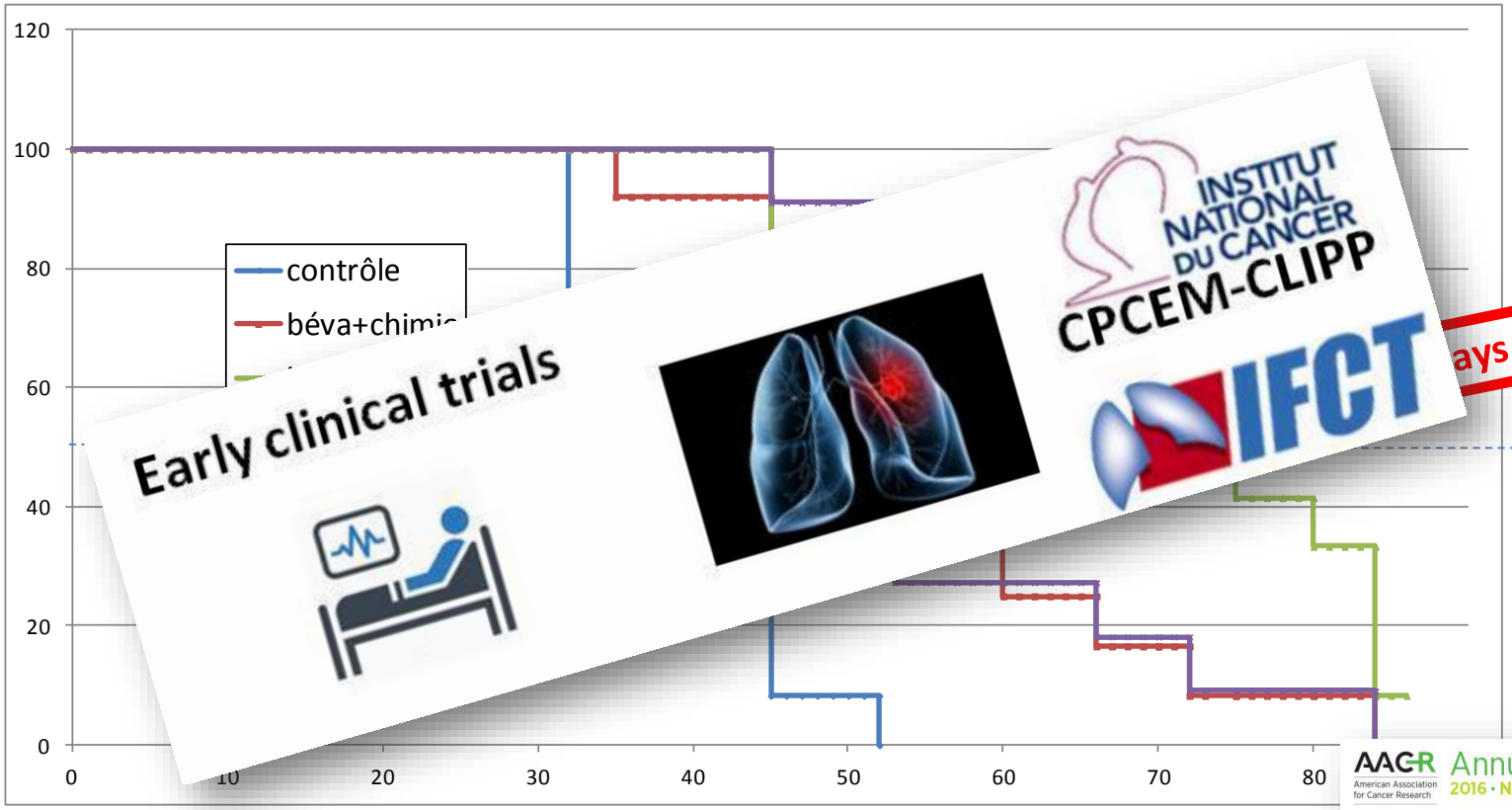
IMPLEMENTING MODEL-DRIVEN REGIMEN AT THE BENCH

✓ **Efficacy**



IMPLEMENTING MODEL-DRIVEN REGIMEN AT THE BENCH

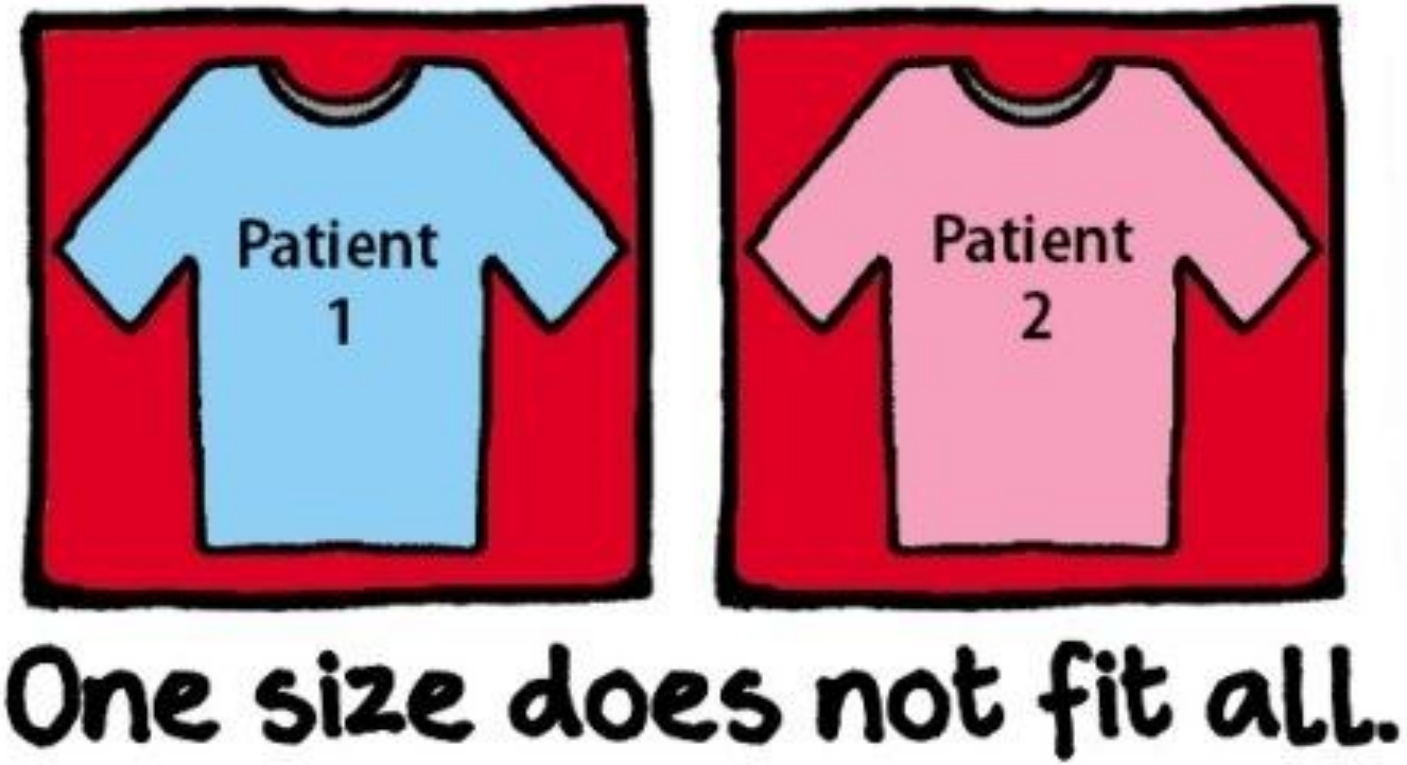
✓ **Survival**



⌦ **Sequential use (i.e., beva first) increases median survival by 44%!**

TAKE-HOME MESSAGE

How can standard dosing be part of personalized medicine?



TAKE-HOME MESSAGE

STOP THROWING DICE !

TAKE-HOME MESSAGE

"what if finding the right dose of medicine was a simple as taking our temperature?"

President Obama, January 2015

ACKNOWLEDGMENTS

Modelling & Simulation

Pr. D. Barbolosi

Dr . C. Meille

Dr. S. Benzekry

Dr. D..C Imbs

Translational/Bedside

Dr. N. André

Dr. E. Pasquier

Pr. F. Barlesi

Translational/Bench

A. Lombard

Dr. C. Serdjebi

S. Giacometti

SMARTc
SIMULATION MODELING ADAPTIVE RESPONSE FOR THERAPEUTICS IN CANCER

THANKS FOR LISTENING

« If it were not the great variablity among individuals, Medecine might as well be a science and not an art »

Sir William Osler, 1892, The Thoughts of William Osler