Exposure-Response relationships with immunotherapies: Could TDM make PK an actionable issue?

Pr. Joseph Ciccolini
COMPO CRCM
INRIA Inserm U1068
Biogénopôle
CHU Timone APHM

Declaration of Interest 2024

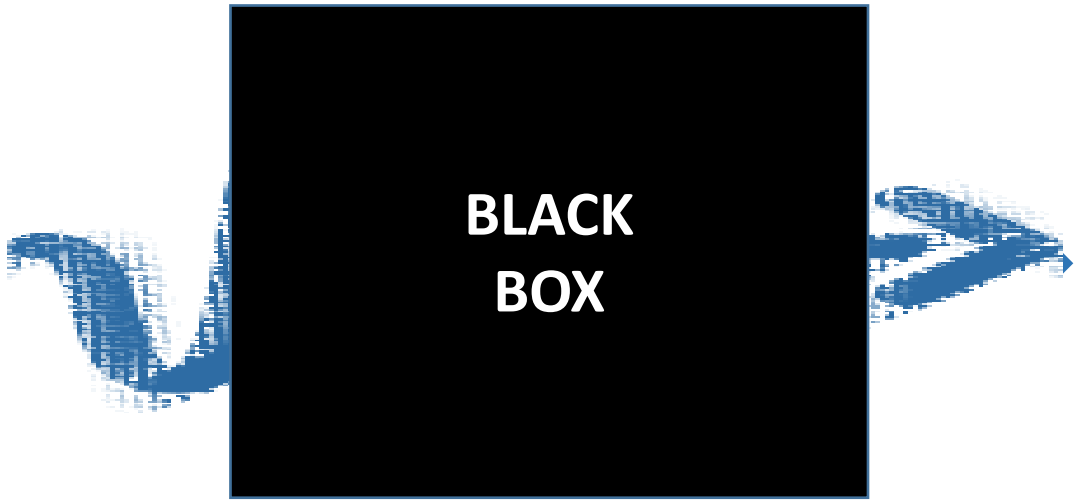
Fees:
- Pierre Fabre
- Pfizer
- Promise Proteomics
- Daiichi Sankyo
- Astra Zeneca
- Esai
- Roche

Research:
- Roche Institute - Genentech
- Pierre Fabre
- BMS
- Astra Zeneca
- Merck Serono

Back to the Roots!

- Dose-response relationships can be loose for most cancer drugs.
- There is a twofold relationship: between dose and exposure, and between exposure and PD endpoints.

Dosing



PK/PD
E-R relationships

Effects

Back to the Roots!

- Contrary to what Big Pharma claims….. E-R are not so flat with immune checkpoint inhibitors!

Back to the Roots!

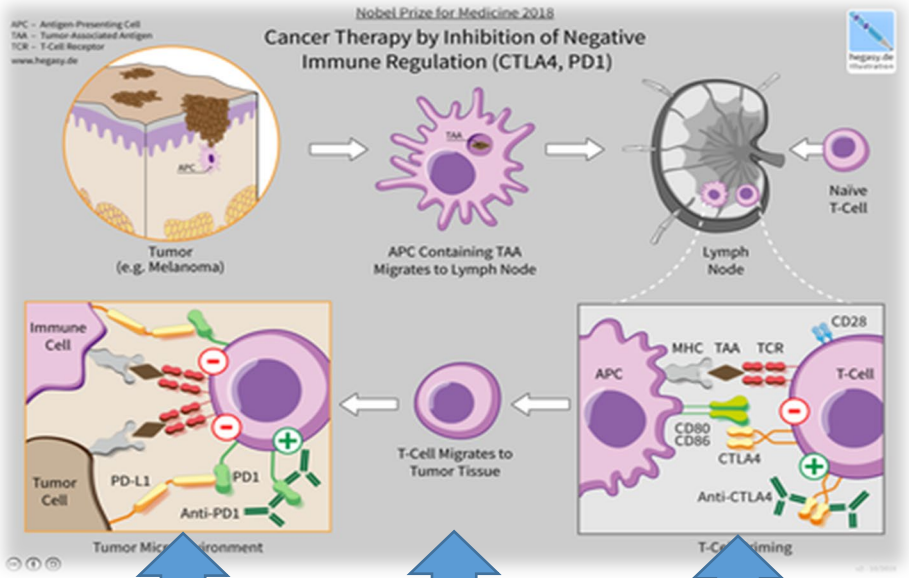
- **TDM & PK is:**

- Nothing but a waste of time

- **TDM & PK could be potentially:**

- Helpful to predict efficacy or tox?
- Helpful to de-escalate treatments?

Back to the Roots!



Infiltrated T cells ?

Circulating T cells ?

Prior (i.e., during Priming ?

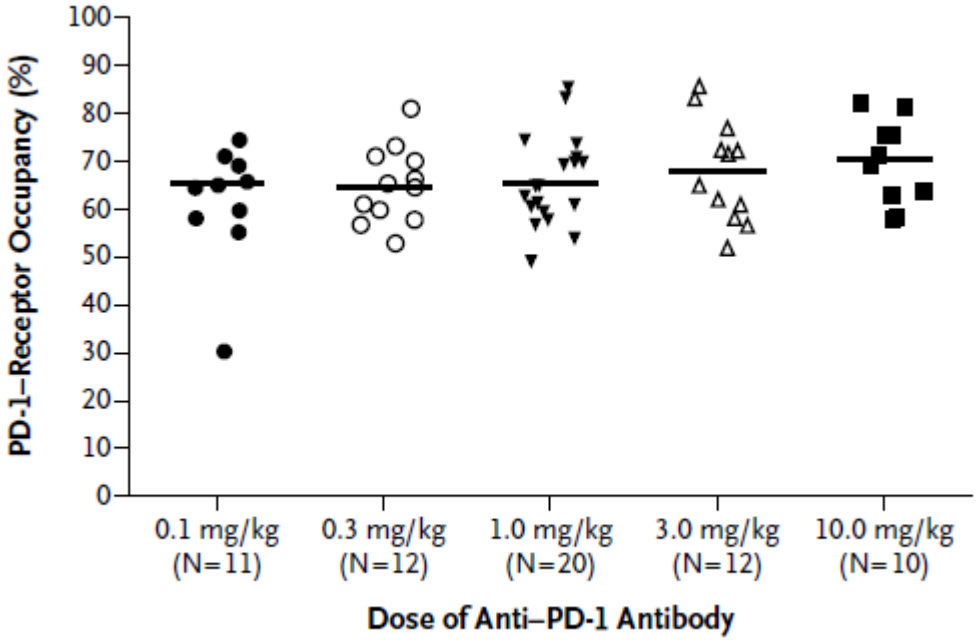
Both?

Where is the real action?

Back to the Roots!

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer



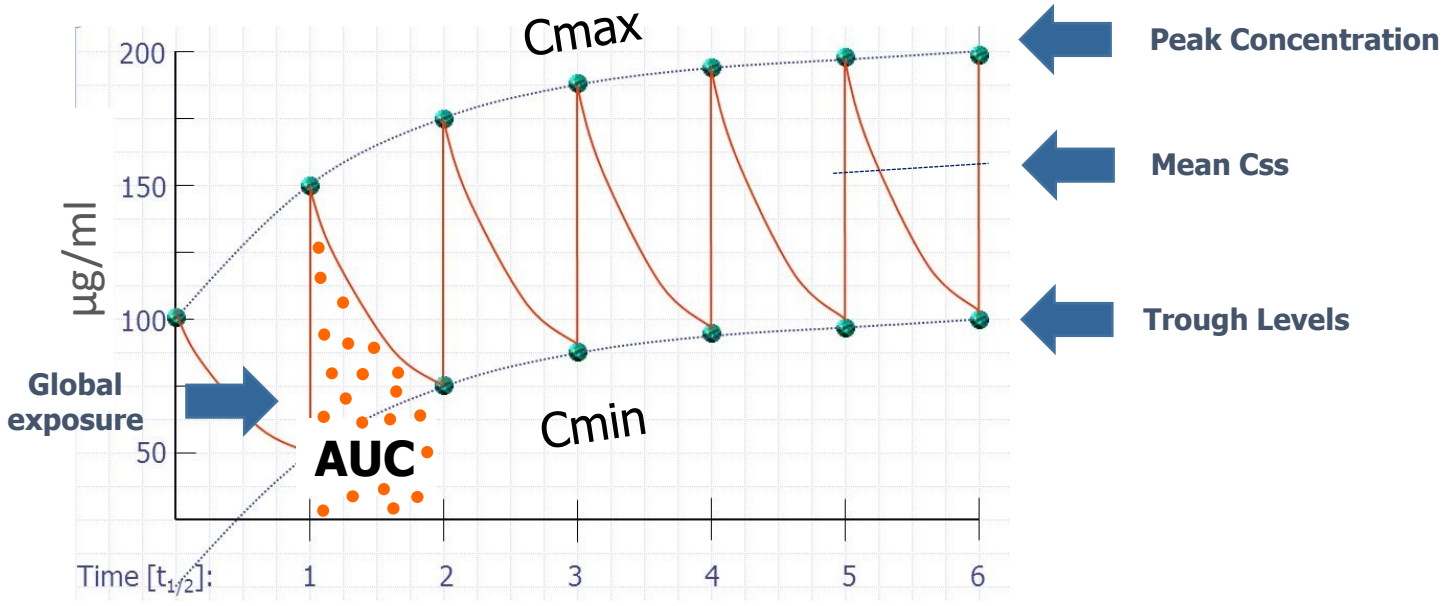
Even very low doses of nivolumab do the job.. So why should we bother?

Figure 2 (facing page). Pharmacodynamic and Molecular-Marker Assessments.

Panel A shows PD-1–receptor occupancy by anti–PD-1 antibody. The graph at the left shows PD-1–receptor occupancy on circulating T cells in 65 patients with melanoma after one cycle (8 weeks) of treatment at a dose of 0.1 to 10.0 mg per kilogram every 2 weeks. Bars indicate median values. The graphs at the right show PD-1–receptor occupancy on CD3-gated peripheral-blood mononuclear cells from a patient with melanoma who received 0.1 mg per kilogram, before treatment (top) and after one treatment cycle (bottom). Cells

…. But how is target engagment at the tumor level?

Back to the Roots!



Which metrics for exposure is actually relevant?

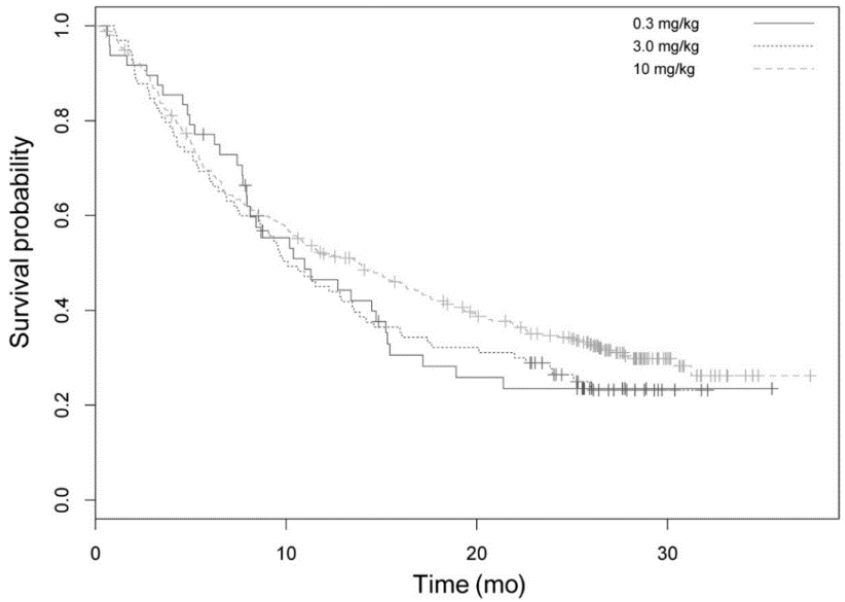
Dose-Exposure relationships with anti-CTLA4

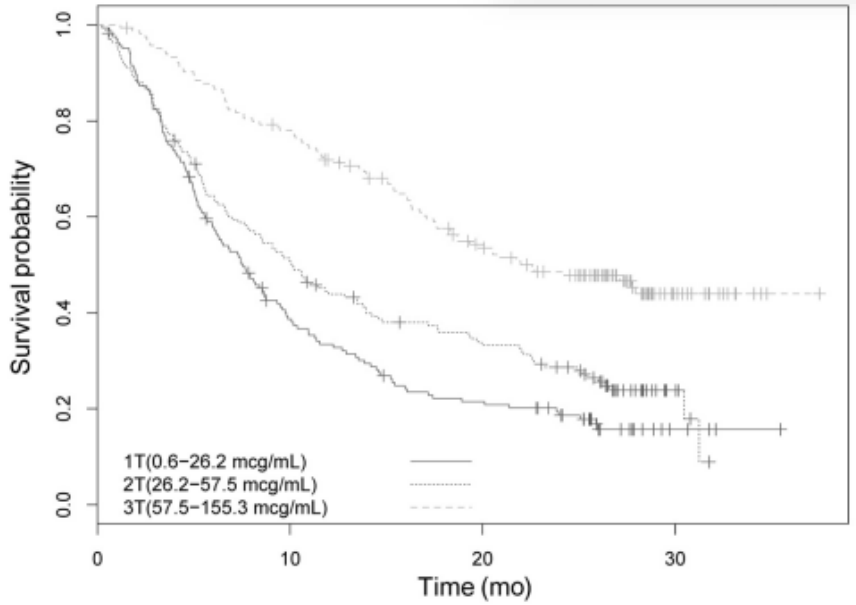
Clinical Cancer Research

Cancer Therapy: Clinical

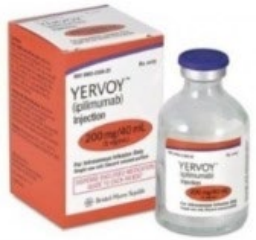
Exposure–Response Relationships of the Efficacy and Safety of Ipilimumab in Patients with Advanced Melanoma

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





Dosage does not predict survival…… but trough levels do!



Dose-Exposure relationships with anti-CTLA4

Clinical Cancer Research

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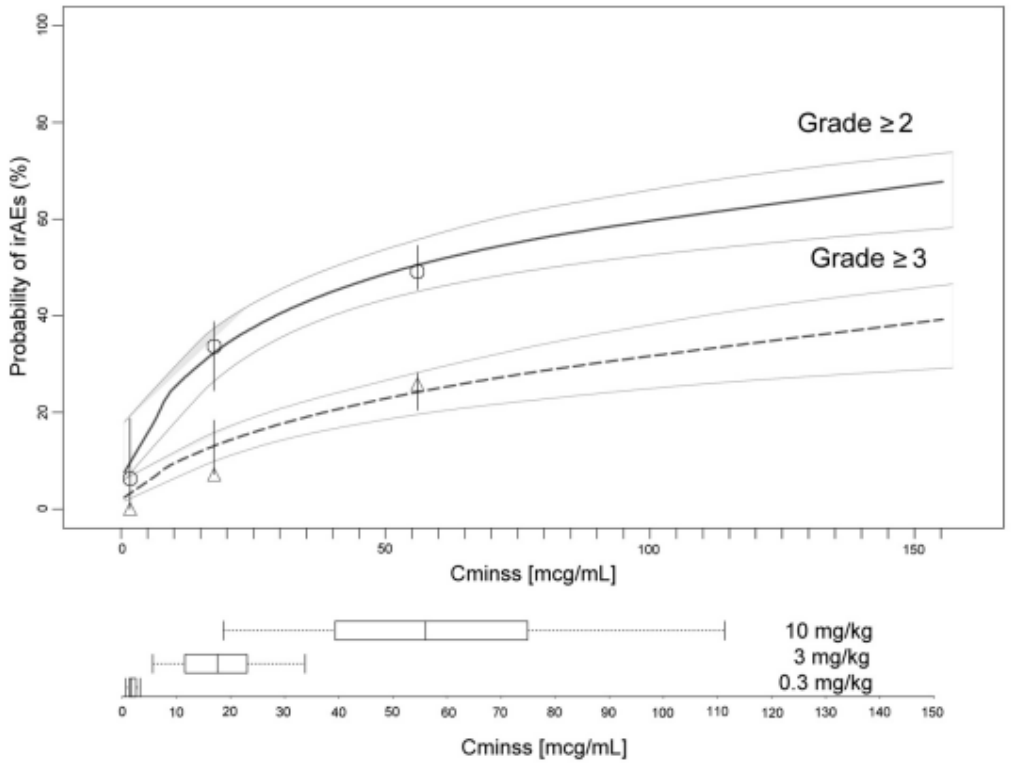
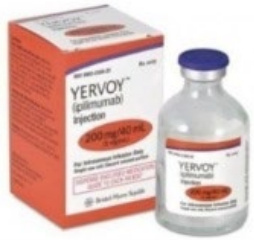
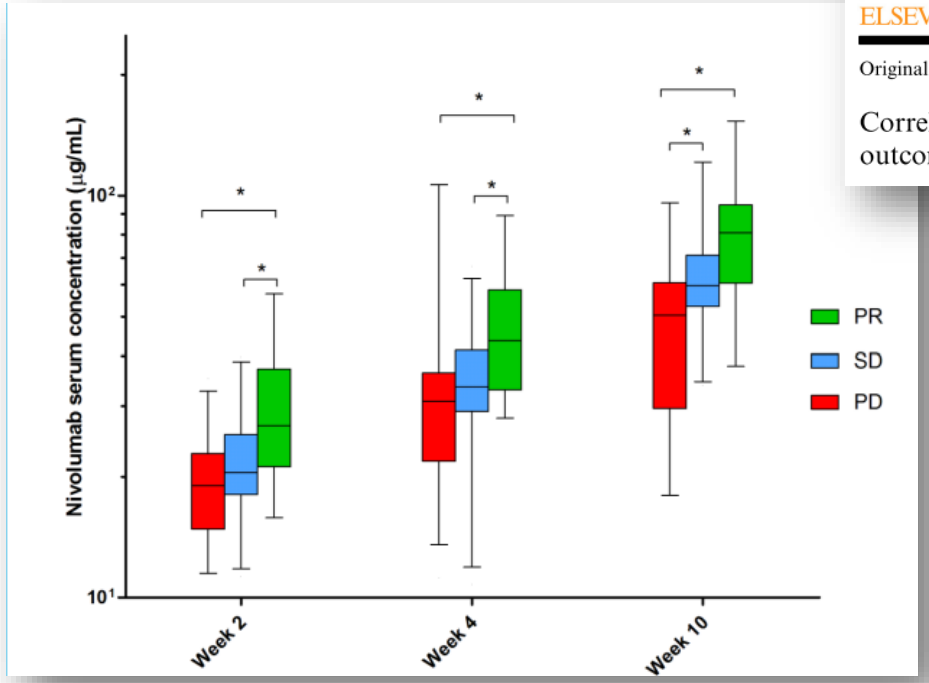


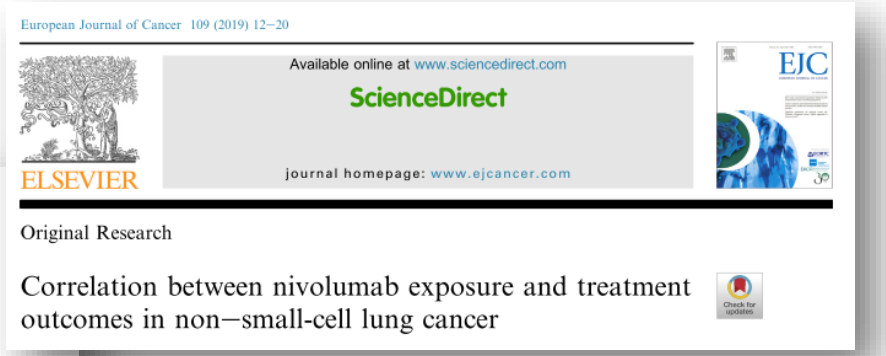
Trough levels predict IRAEs too!



Does it work with anti-PD1?

- E-R relationships with Nivolumab (NSCLC)




European Journal of Cancer 109 (2019) 12–20

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

Original Research

Correlation between nivolumab exposure and treatment outcomes in non–small-cell lung cancer

Responding patients have higher trough levels

Does it work with anti-PD1?

- E-R relationships with Nivolumab (NSCLC)

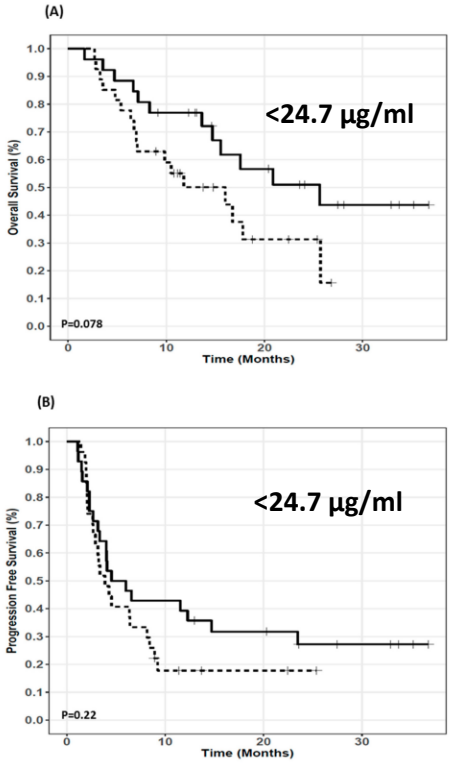


Figure 3. Kaplan-Meier curves of (**A**) overall survival and (**B**) progression-free survival according to plasma trough concentration of nivolumab at day 28 (≤24.7 µg/mL vs >24.7 µg/mL). The plain and dotted lines represent trough plasma concentration of nivolumab at day 28 ≤24.7 µg/mL (median value) and >24.7 µg/mL, respectively.

cancers MDPI

Article

Is there an Exposure–Response Relationship for Nivolumab in Real-World NSCLC Patients?

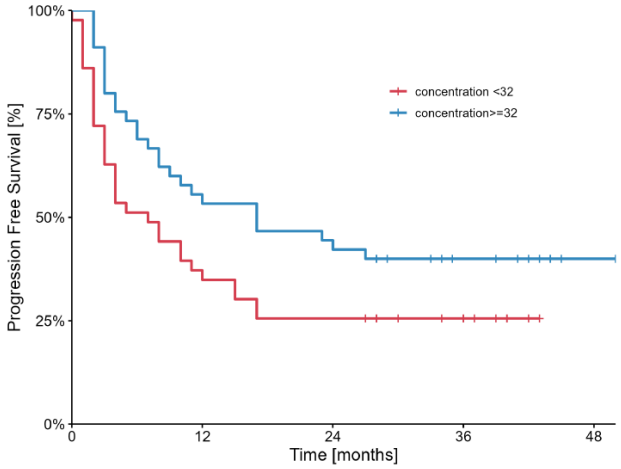
Audrey Bellesoeur [1], Edouard Ollier [2,3], Marie Allard [4], Laure Hirsch [1], Pascaline Boudou-Rouquette [1], Jennifer Arrondeau [1], Audrey Thomas-Schoemann [5,6], Manuela Tiako [4], Nihel Khoudour [4], Jeanne Chapron [7], Frédérique Giraud [7], Marie Wislez [7], Diane Damotte [8,9], Audrey Lupo [8,9], Michel Vidal [4,6], Jérôme Alexandre [1,10], François Goldwasser [1,10], Michel Tod [11,12,13] and Benoit Blanchet [4,5,*]

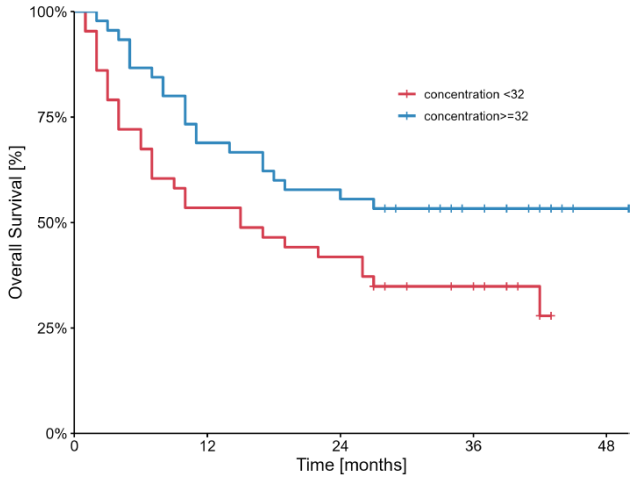
	Univariate Model HR (95%CI)	*p*-Value	Multivariate Model HR (95%CI) (*n* = 46)	*p*-value
Risk of death				
C_{min} D14 ≤median (*n* = 62)	1.03 (0.55–1.96)	0.9145		
C_{min} D28 ≤median (*n* = 53)	0.51 (0.24–1.09)	0.0786	1.37 (0.44-4.32)	0.586
ECOG Performance Status (*n* = 64)	2.06 (1.28–3.30)	0.0034	1.75 (1.86–3.57)	0.122
Number of metastasis (*n* = 64)	1.04 (0.80–1.35)	0.7987		
NLR > median (*n* = 58)	2.38 (1.05–5.55)	0.0036	1.82 (0.74–4.54)	0.189
PD-L1 > 5% (*n* = 37) [a]	0.43 (0.18–1.02)	0.055		
Baseline use of corticosteroids	2.62 (1.29–5.31)	0.008	6.29 (1.46–27.08)	**0.013**
Risk of progression				
Cmin D14 ≤ median (*n* = 65)	1.14 (0.66–1.96)	0.646		
Cmin D28 ≤ median (*n* = 55)	0.68 (0.37–1.27)	0.223	1.30 (0.49–3.39)	0.59
ECOG Performance Status (*n* = 67)	1.97 (1.28–3.02)	0.023	1.85 (1.02–3.38)	**0.043**
Number of metastasis (*n* = 67)	1.09 (0.87–1.37)	0.452	1.14 (0.70–1.88)	0.58
NLR > median (*n* = 60)	1.82 (1.02–3.22)	0.042		
PD-L1 > 5% (*n* = 38) [a]	0.44 (0.20–0.96)	0.041		
Baseline use of corticosteroids	2.51 (1.30–4.89)	0.008	8.08 [1.78–36.62)	**0.007**

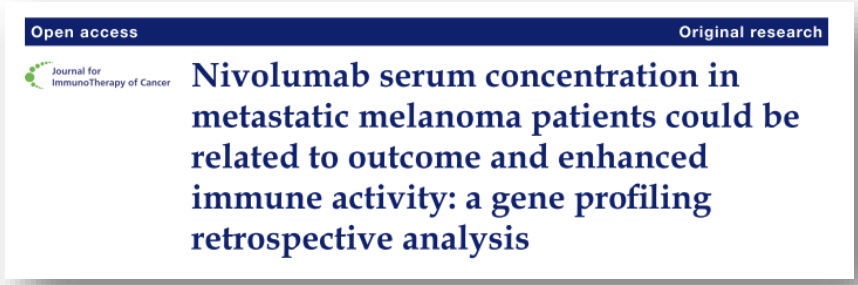
But multivariate analysis kills the E-R relationships!

Does it work with anti-PD1?

- E-R relationships with Nivolumab (melanoma)

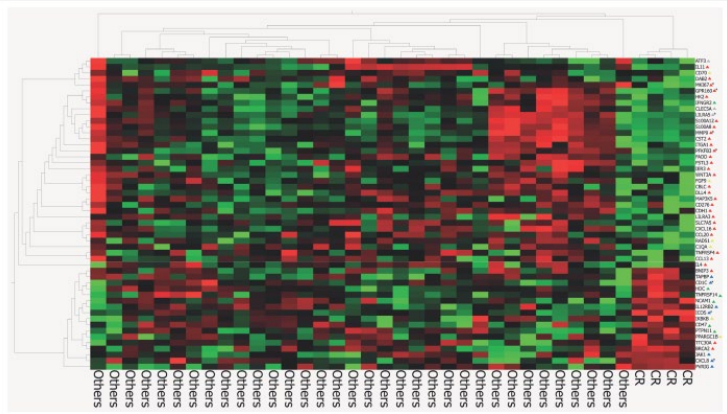





Open access Original research

Journal for ImmunoTherapy of Cancer

Nivolumab serum concentration in metastatic melanoma patients could be related to outcome and enhanced immune activity: a gene profiling retrospective analysis



Extended PFS + OS in patients with higher nivolumab levels

Better response if higher nivolumab levels + favorable genetic profile

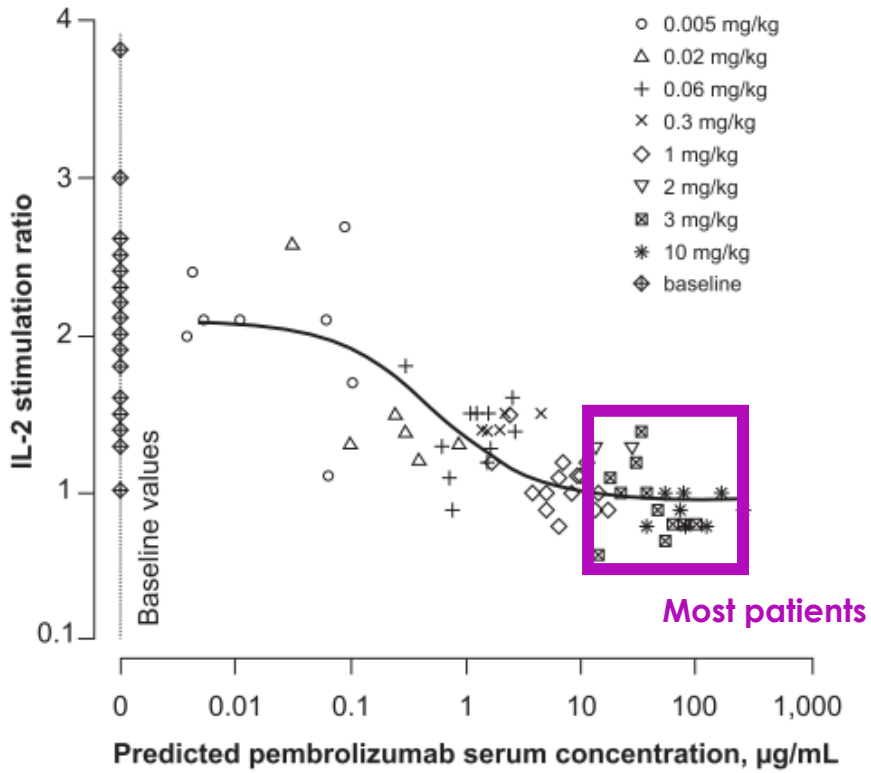
Does it work with anti-PD1?

- E-R relationships with Pembrolizumab

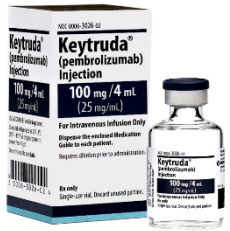
ORIGINAL ARTICLE

Using Model-Based "Learn and Confirm" to Reveal the Pharmacokinetics-Pharmacodynamics Relationship of Pembrolizumab in the KEYNOTE-001 Trial

J Elassaiss-Schaap[1,2*], S Rossenu[1,3], A Lindauer[1,4], SP Kang[1], R de Greef[4,5], JR Sachs[1] and DP de Alwis[1]

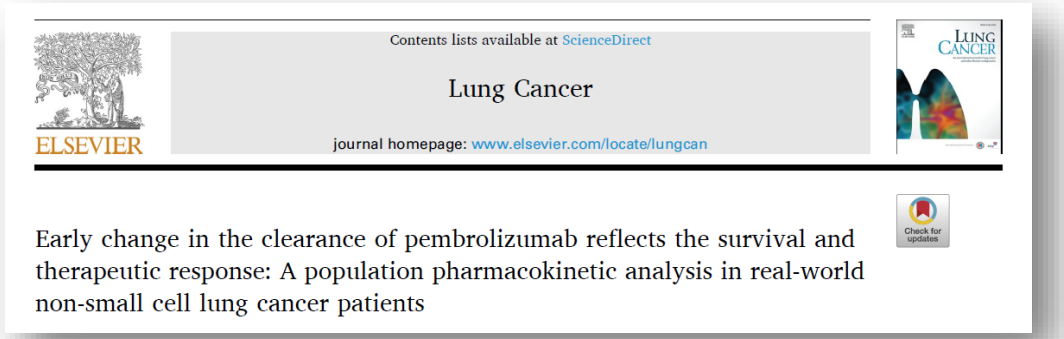


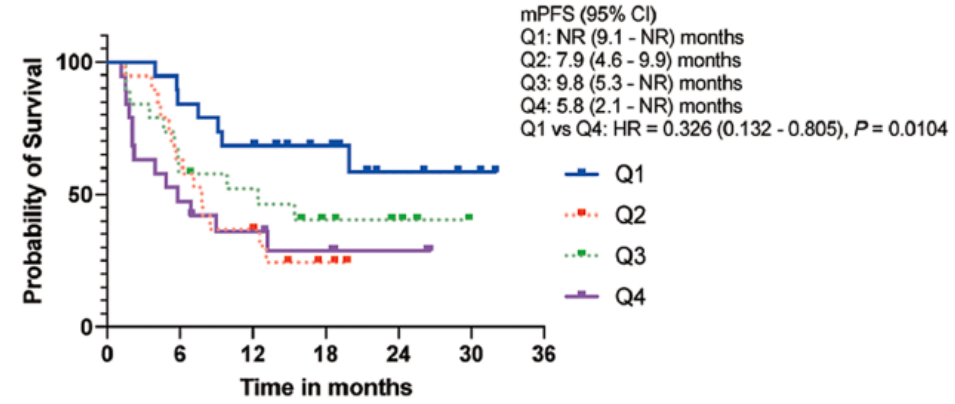
Most patients are > 10 µg/mL

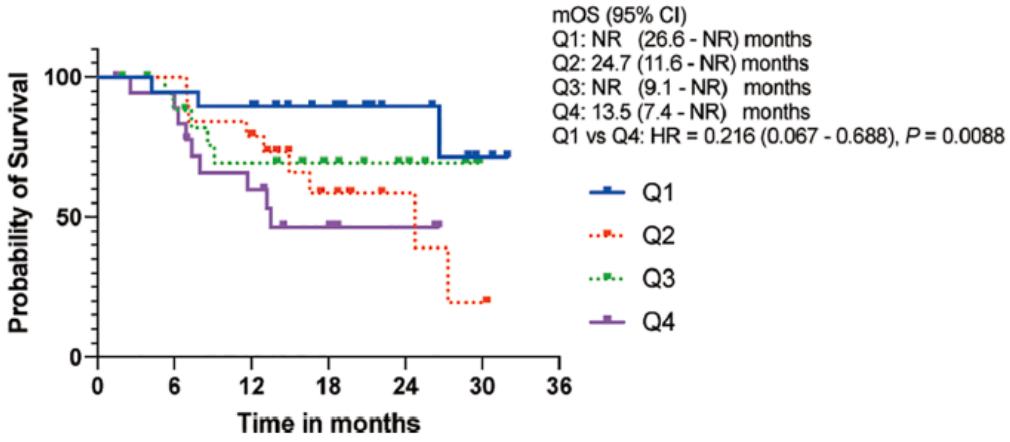


Does it work with anti-PD1?

- E-R relationships with Pembrolizumab







Baseline clerance predicts survival

Does it work with anti-PD1?

- E-R relationships with Pembrolizumab

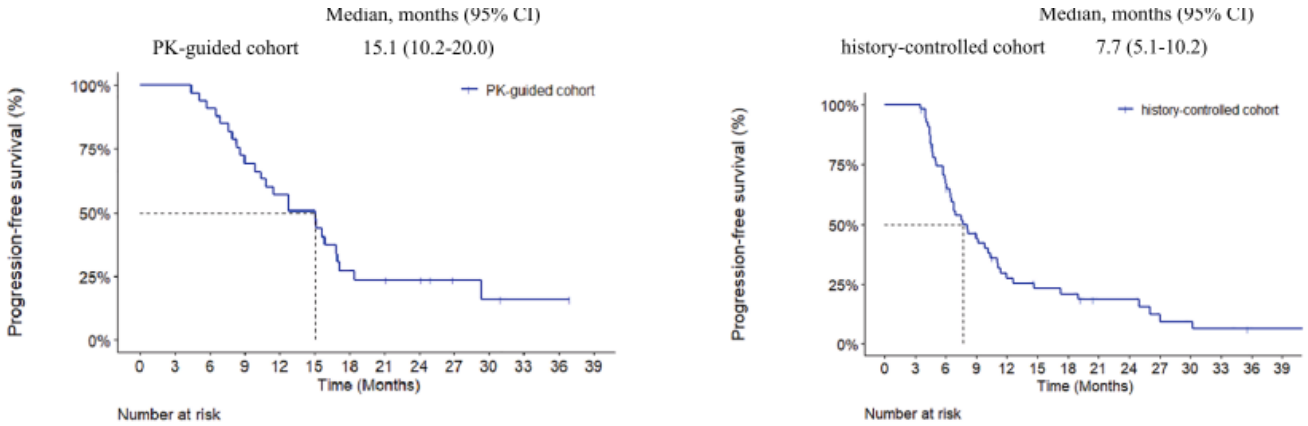
Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Clinical efficacy and safety of individualized pembrolizumab administration based on pharmacokinetic in advanced non-small cell lung cancer: A prospective exploratory clinical trial

Na Wang[a,1], Lie Zheng[b,1], Meichen Li[a,1], Xue Hou[a,1], Baishen Zhang[a], Jing Chen[a], Su Li[c,*], Likun Chen[a,*]



clinical responses	Experimental group (n = 33) (%)	history-controlled group (n = 56) (%)
CR	0 (0)	0 (0)
PR	19(57.6)	27(48.2)
SD	14(42.4)	29(51.8)
PD	0(0)	0(0)
ORR	19(57.6)	27(48.2)
DCR	100(100)	100(100)

Increasing dosing in patients with Pembro levels < 16 µg/mL stretches the PFS

Does it work with anti-PD1?

- E-R relationships with Pembrolizumab

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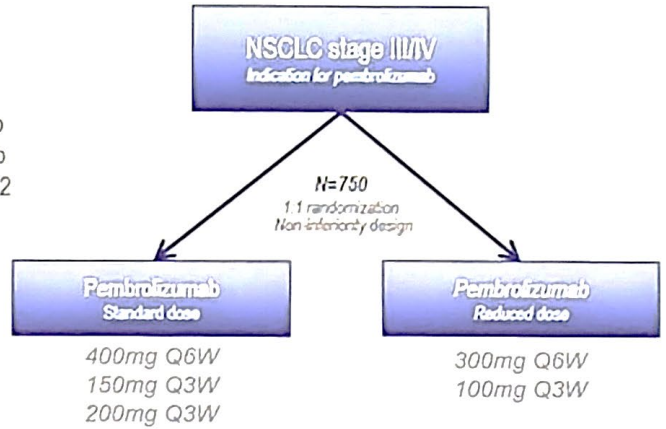
BARCELONA SPAIN
13-17 SEPTEMBER 2024

Design

DEDICATION-1 trial (NVALT-30)

Stratification factors:
- Type of treatment:
  - Pembrolizumab
  - Pemetrexed / platinum / pembrolizumab
  - Carboplatin / paclitaxel / pembrolizumab
- Smoking, PDL1 status, Gender, PS 0/1 vs 2



Primary objective:

To investigate the non-inferiority of reduced dose pembrolizumab vs. standard dose for treatment of advanced stage NSCLC in terms of overall survival

Secondary objectives:
- DCR, PFS, OS, 1yr-DCR, ORR
- To develop, assess, and validate immune checkpoint inhibitor response biomarkers

Unilateral de-escalation with Pembro does not compromise OS or PFS

Does it work with anti-PD1?

- E-R relationships with Pembrolizumab

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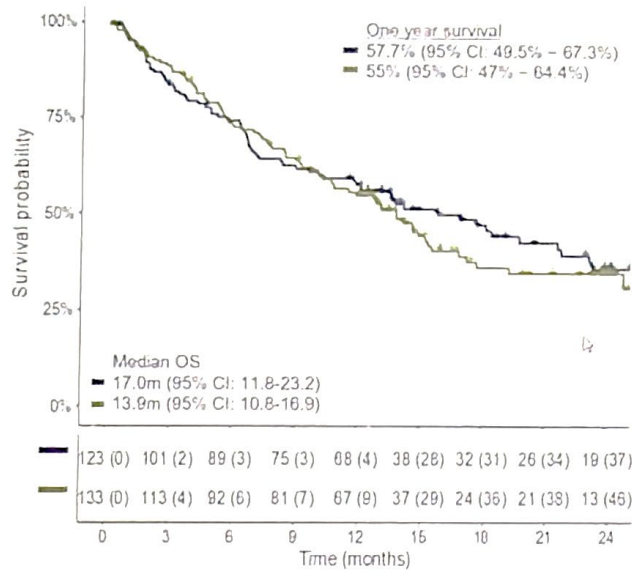
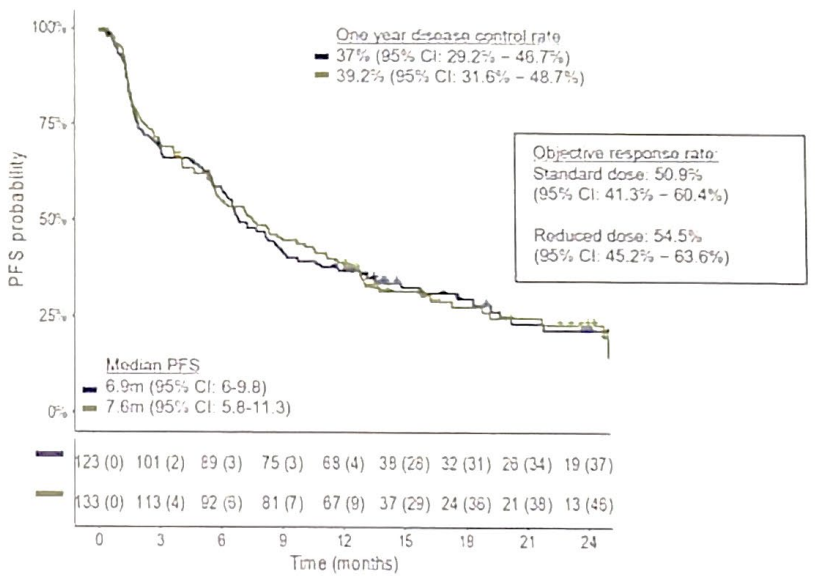
The DEDICATION-1 trial (NVALT-30)

Overall survival



Progression free survival



van den Heuvel, 1258 MO

Standard dose Reduced dose

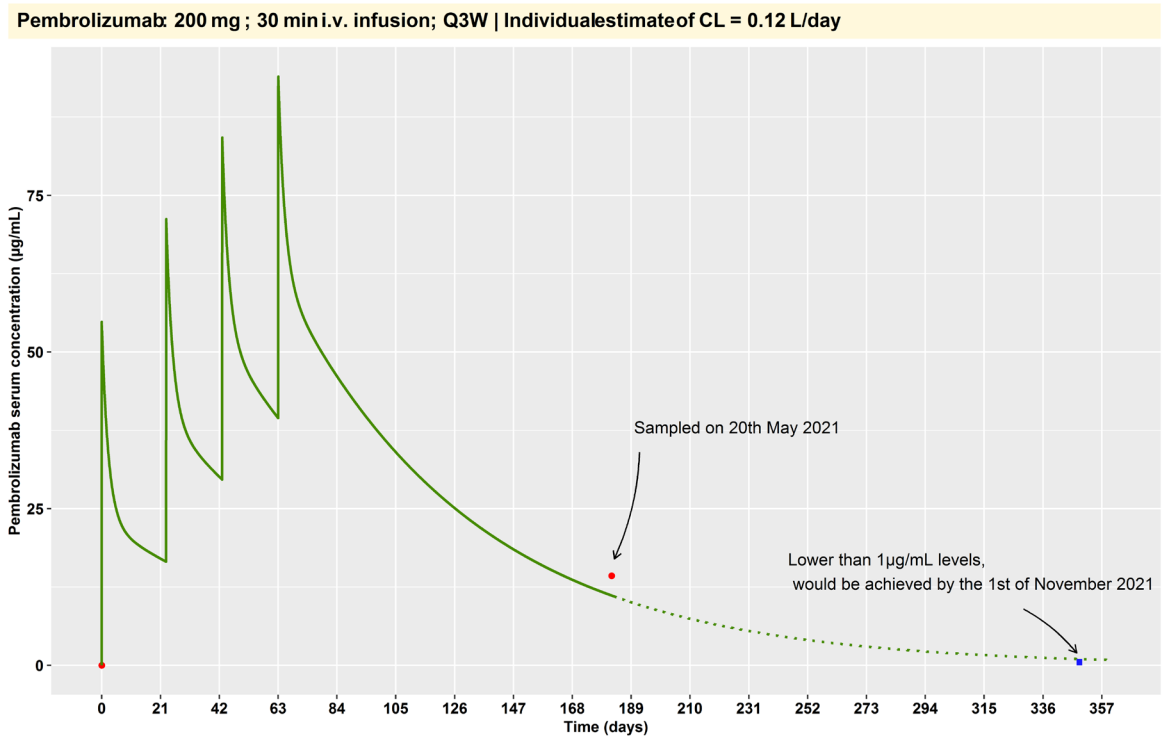
Unilateral de-escalation with Pembro does not compromise global efficacy

Does it work with anti-PD1?

- E-R relationships with Pembrolizumab

INSTITUT PAOLI-CALMETTES
unicancer Marseille

Dr S. Harbi

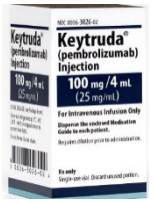


Case Reports > Cancer Chemother Pharmacol. 2024 Jun;93(6):627-632.
doi: 10.1007/s00280-023-04611-x. Epub 2023 Nov 13.

Life-threatening toxicities upon Pembrolizumab intake: could pharmacokinetics be the bad guy?

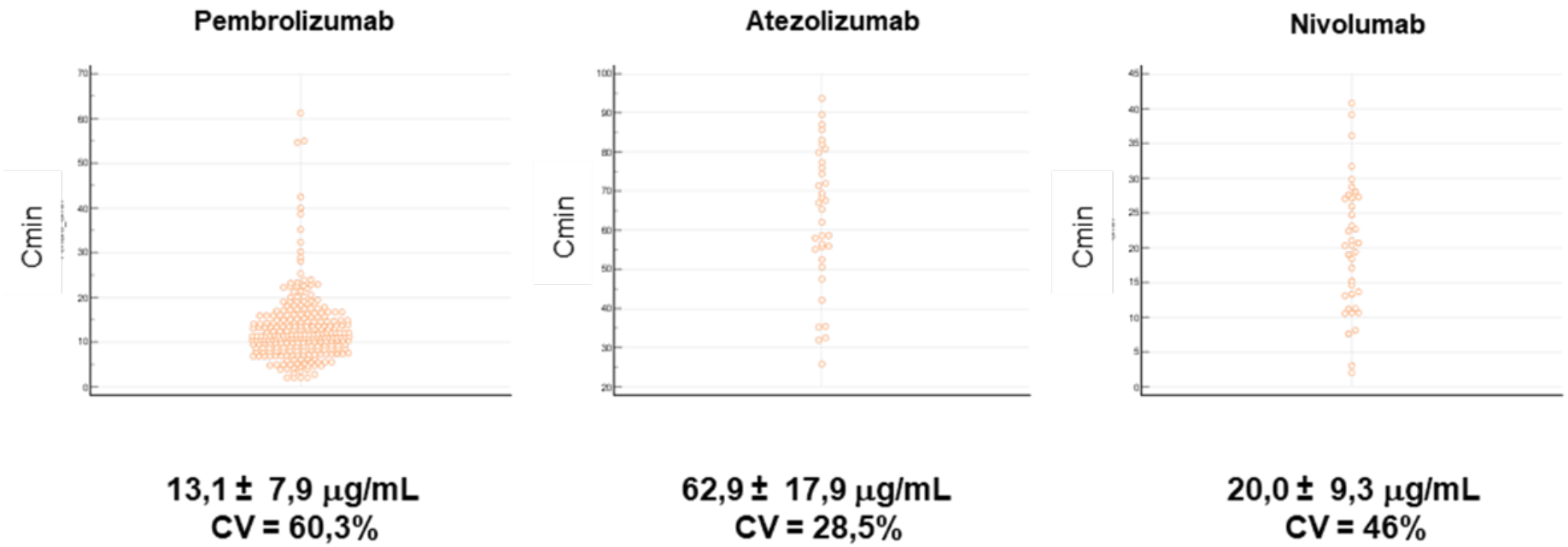
Mourad Hamimed [1 2], Raynier Devillier [3], Pierre-Jean Weiller [3], Clémence Marin [1 4], Jean-Marc Schiano [3], Nawel Belmecheri [3], Marie-Christine Etienne-Grimaldi [5], Joseph Ciccolini [6 7 8], Samia Harbi [3]

Patient with reduced clearance of pembrolizumab at risk of IRAEs?



Does it work with anti-PD1?

- Inter-patient variability



Marked inter-patient variability on PK!

Does it work with anti-PD1?

THE PIONEER PROJECT

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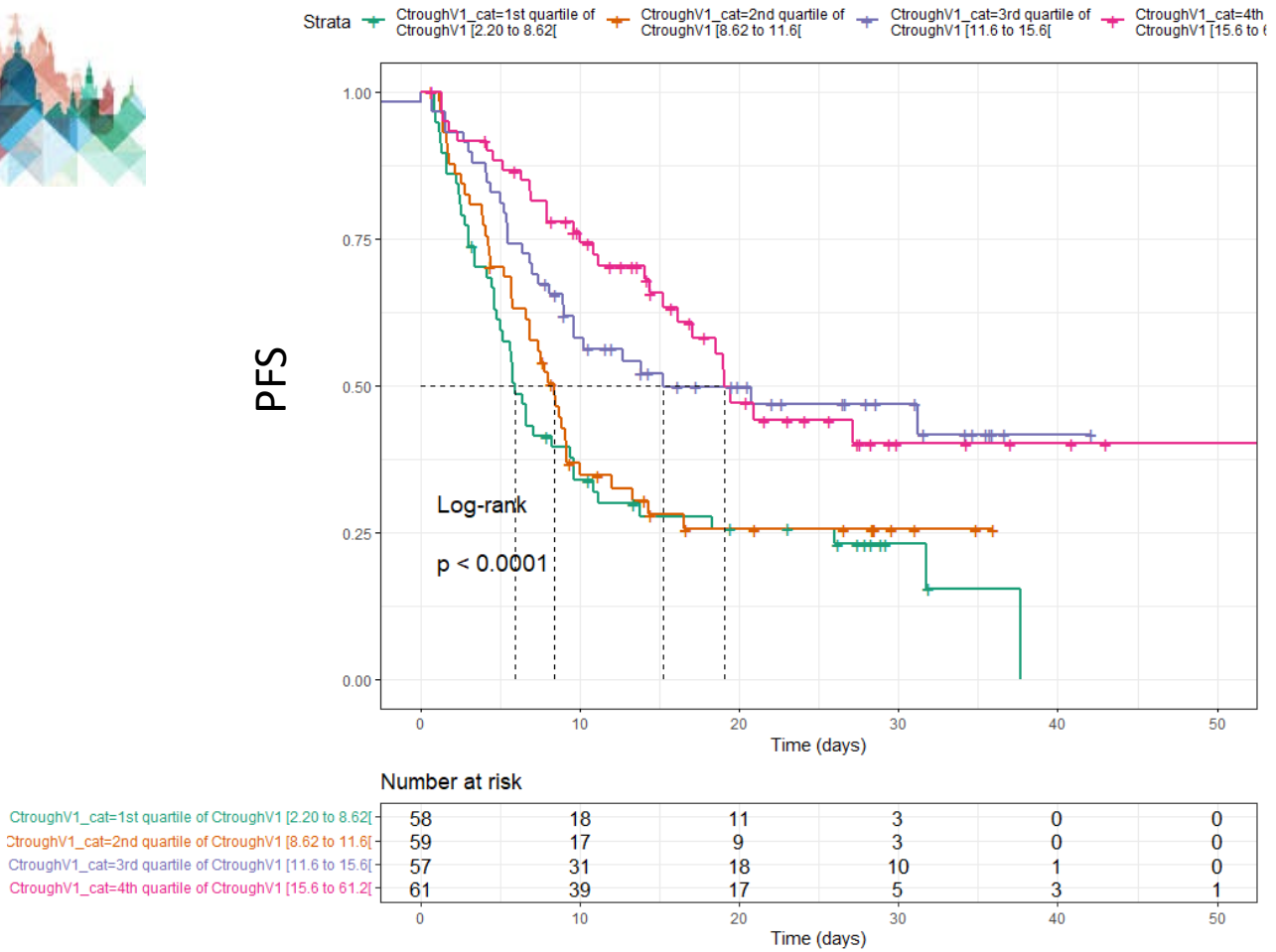
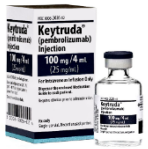
- Clearance values and Trough level at C1 are both strong predictors of the PFS in patients treated with pembrolizumab (log-rank test p< 0,0001).

- Independent predictor after multivariate analysis [Age, Sex, Associated chemo, PDL1 status, Albuminemia, Creat, tumor size, LDH, NLR, Ecog status]: Cmin Cycle1 p = 0,0034.





Pembrolizumab: Clearance values and trough levels at C1 predicts PFS and early-progression!

Does it work with anti-PD1?

THE PIONEER PROJECT

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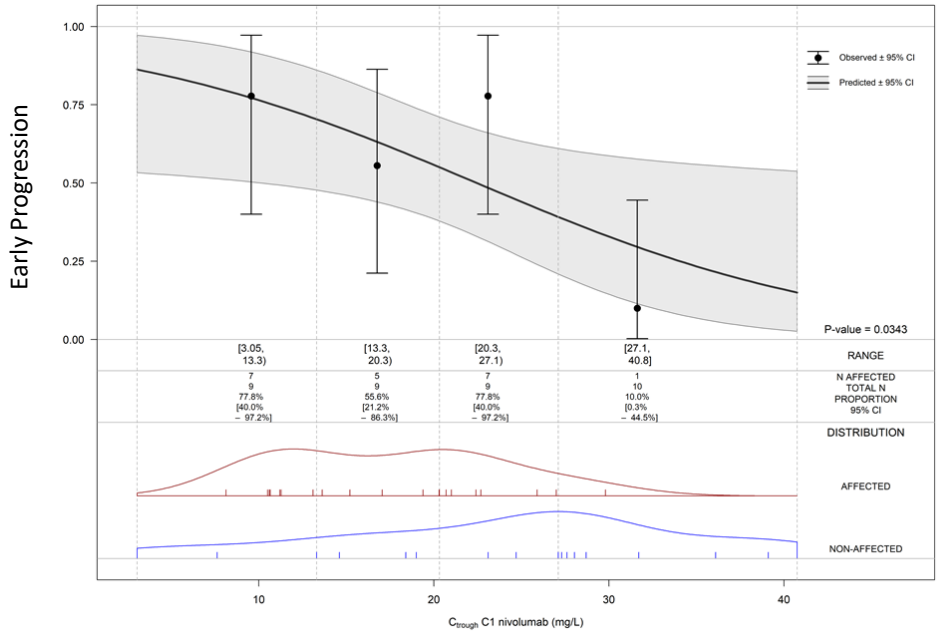

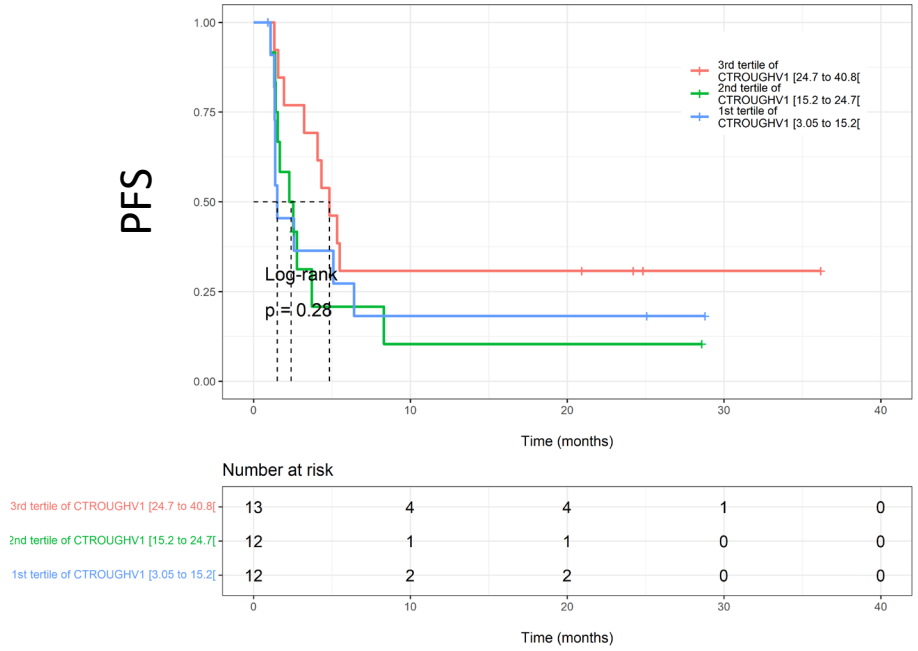

Nivolumab: Trough levels at C1 predicts early-progression + trend on PFS!

Does it work with anti-PD-L1?

THE PIONEER PROJECT

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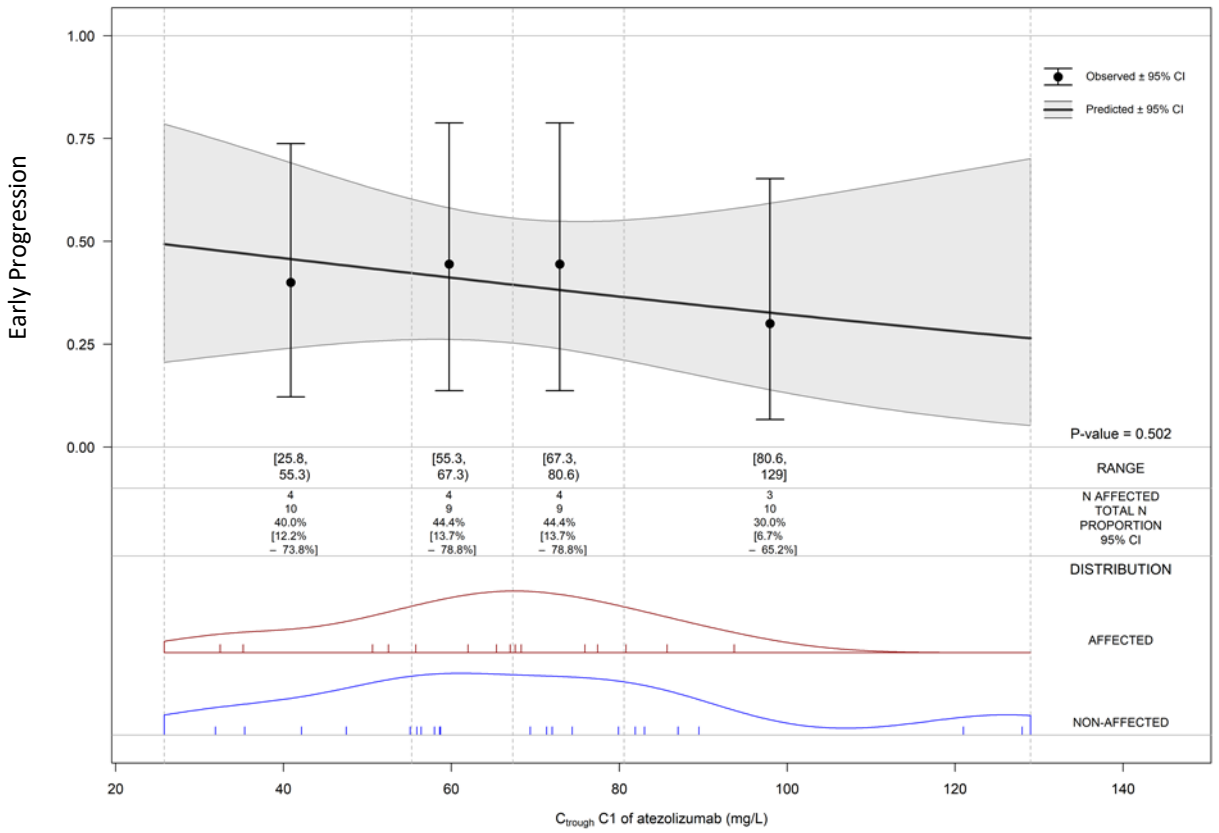
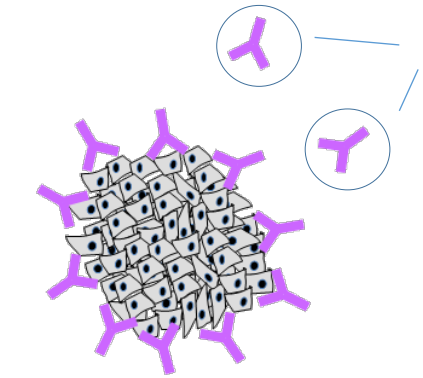


Atezolizumab: no E-R relationships !

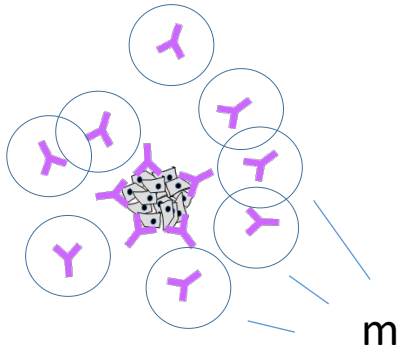
Is the truth out there?

Target Mediated Drug Disposition (TMDD) with mAbs

Low drug levels make big tumors!



measured



measured

Exposure Clearance

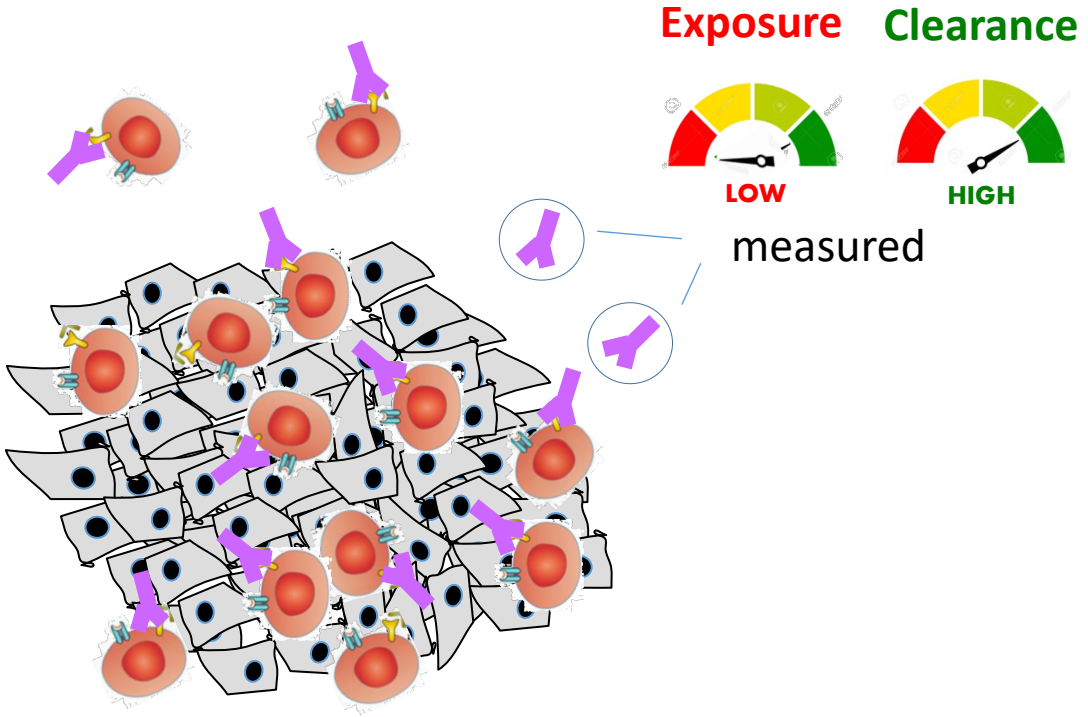
No! Big tumors make low drug levels!

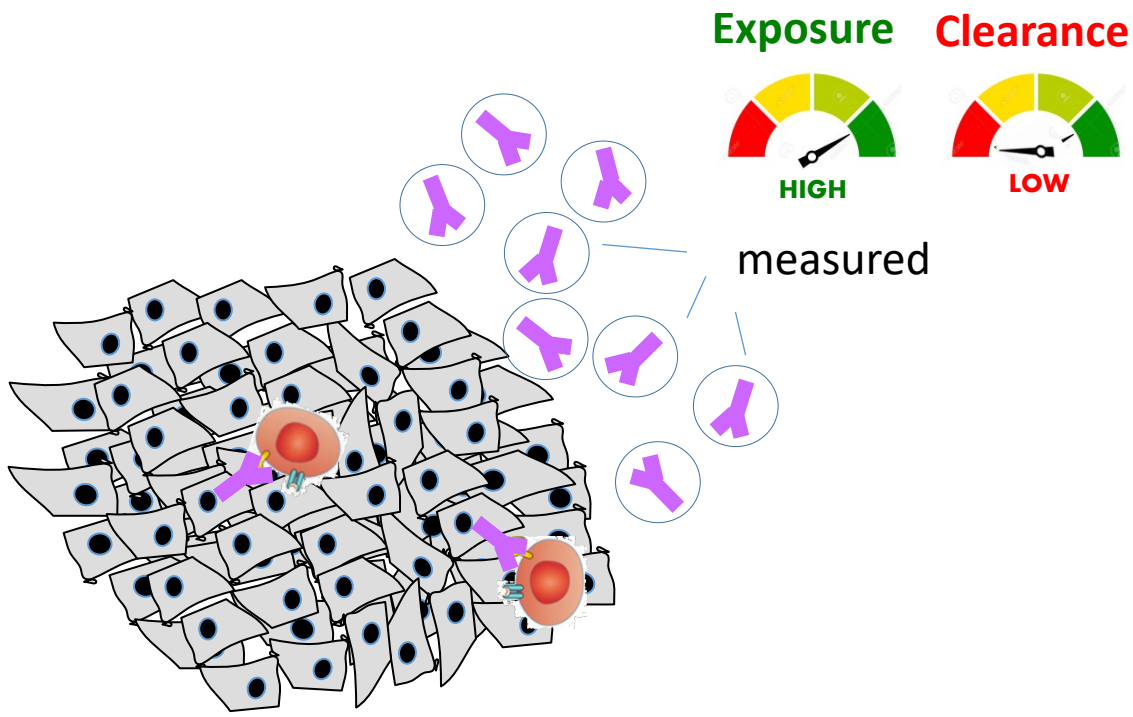
Exposure Clearance

DOES EXPOSURE REALLY MATTER?

Is the truth out there?

Target Mediated Drug Disposition (TMDD)… with immune checkpoint inhibitors?





TMDD with anti-PD1/PDL1 would then suggest that:

- The more infiltrated T lymphocytes in tumor…. the lower the efficacy?
- The higher PDL1 expression….. the lower the efficacy ?

Is the truth out there?

Target Mediated Drug Disposition (TMDD)… with immune checkpoint inhibitors?

- The targets of most immunotherapies are immune cells, not tumor cells!
- The antigenic mass is not correlated to tumor burden (i.e., anti-PD1, anti-CTLA4)!
- But big tumors and poor performance status could lead to cachexia

Disease Progression could thus indirectly increase mAb clearance!

Can PK help de-escalate dosing?

- **Nivolumab**

3 mg/kg Q2W → 240 mg Q2W → 480 mg Q4W

- **Pembrolizumab**

2 mg/kg Q3W → 200 mg Q3W

Flat-Dosing could lead to strong overexposure in some patients!

It is assumed that ALL cancer patients weight 80-100 kg

Can PK help de-escalate dosing?

Can PK help de-escalate dosing?

REVIEW-THEMED SECTION

BJCP BRITISH PHARMACOLOGICAL SOCIETY

Opportunities for using in silico-based extended dosing regimens for monoclonal antibody immune checkpoint inhibitors

Cody J. Peer[1] | Daniel A. Goldstein[2] | Jennifer C. Goodell[1] | Ryan Nguyen[1] | William D. Figg[1] | Mark J. Ratain[3]

STATE OF THE ART

Dose Rationalization of Pembrolizumab and Nivolumab Using Pharmacokinetic Modeling and Simulation and Cost Analysis

Kayode Ogungbenro[1], Alkesh Patel[2], Robert Duncombe[2], Richard Nuttall[3], James Clark[2] and Paul Lorigan[2,4]

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JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Time Is Money: Optimizing the Scheduling of Nivolumab

Mark J. Ratain, *The University of Chicago, Chicago, IL*
Daniel A. Goldstein, *Rabin Medical Center, Petach Tikvah, Israel, and University of North Carolina at Chapel Hill, Chapel Hil*

The Journal of Clinical Pharmacology

Official Publication of the American College of Clinical Pharmacology

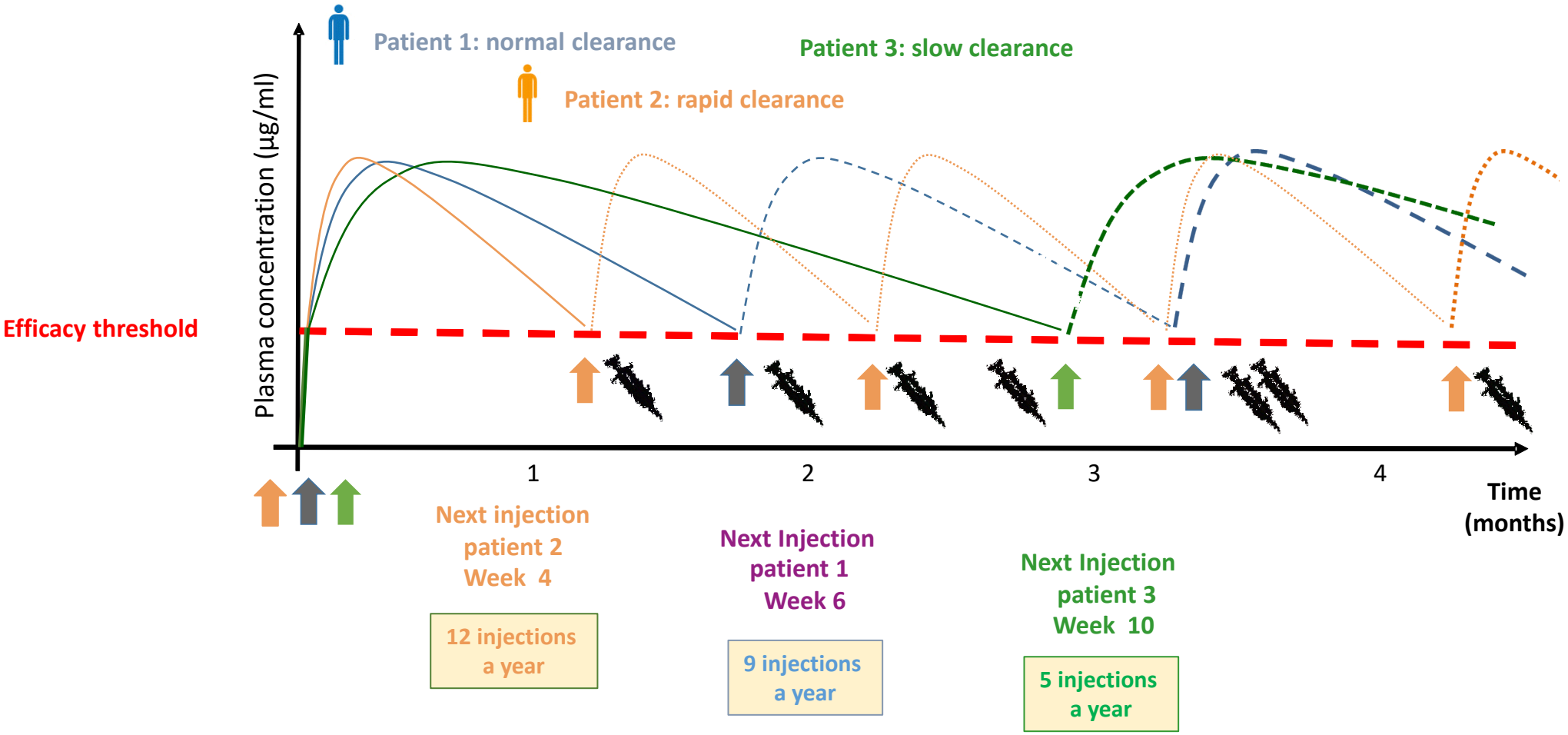
Pharmacokinetics

Pharmacokinetic Simulation Analysis of Less Frequent Nivolumab and Pembrolizumab Dosing: Pharmacoeconomic Rationale for Dose Deescalation

Cody J. Peer PhD, Brian L. Heiss MD, Daniel A. Goldstein MD, Jennifer C. Goodell BS, William D. Figg PharmD, FCP, Mark J. Ratain MD, FCP

In silico modeling helps select alternative dosing/scheduling

Can PK help de-escalate dosing?



In silico modeling helps select alternative and personalized dosing/scheduling

Can PK help de-escalate dosing?

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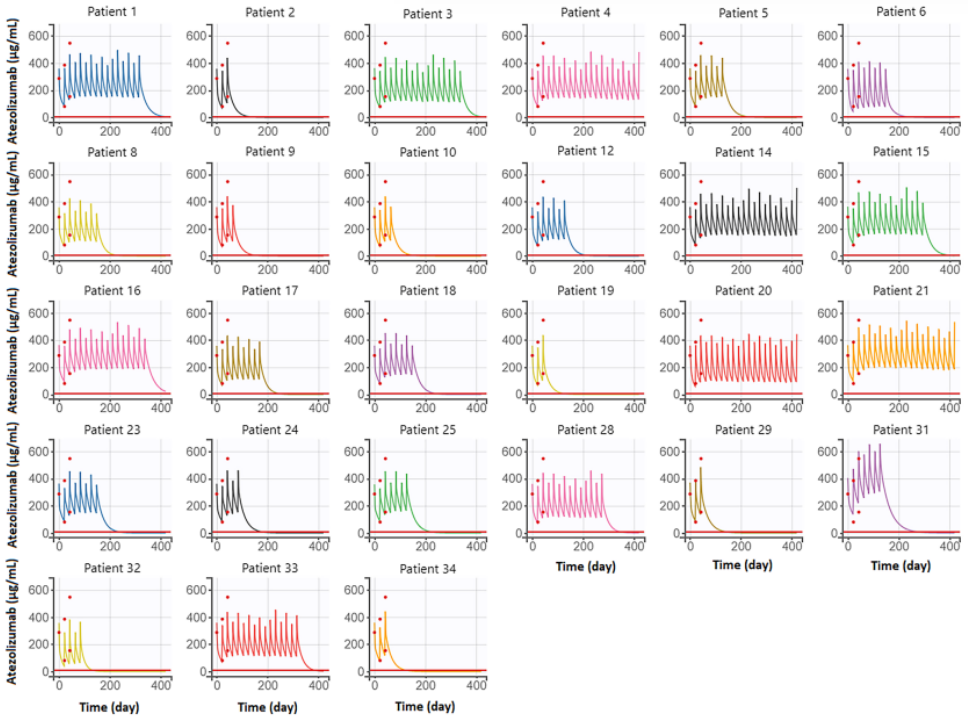
ARTICLE

Killing a fly with a sledgehammer: Atezolizumab exposure in real-world lung cancer patients

Sophie Marolleau[1] | Alice Mogenet[2] | Clara Boeri[1] | Mourad Hamimed[1] | Joseph Ciccolini[1] | Laurent Greillier[1,2]

Pr L. Greillier
CHU Nord



$$CL = CL_{ini}\, e^{-\frac{T_{max} t^{\gamma}}{T_{50}^{\gamma} + t^{\gamma}}}$$

PK characteristics and exposure metrics	$n = 27$
Baseline clearance (L/day)	0.26 (0.05)
$t½$ (day)	15.96 (3.39)
Distribution volume (L)	5.87 (0.07)
AUC C1 (µg.day/mL)	4615 (932)
C_{min1} (µg/mL)	78.81 (15.31)
C_{max1} (µg/mL)	359.54 (3.90)
T6 (day)	82.65 (15.19)

100% patients are strongly over-exposed !

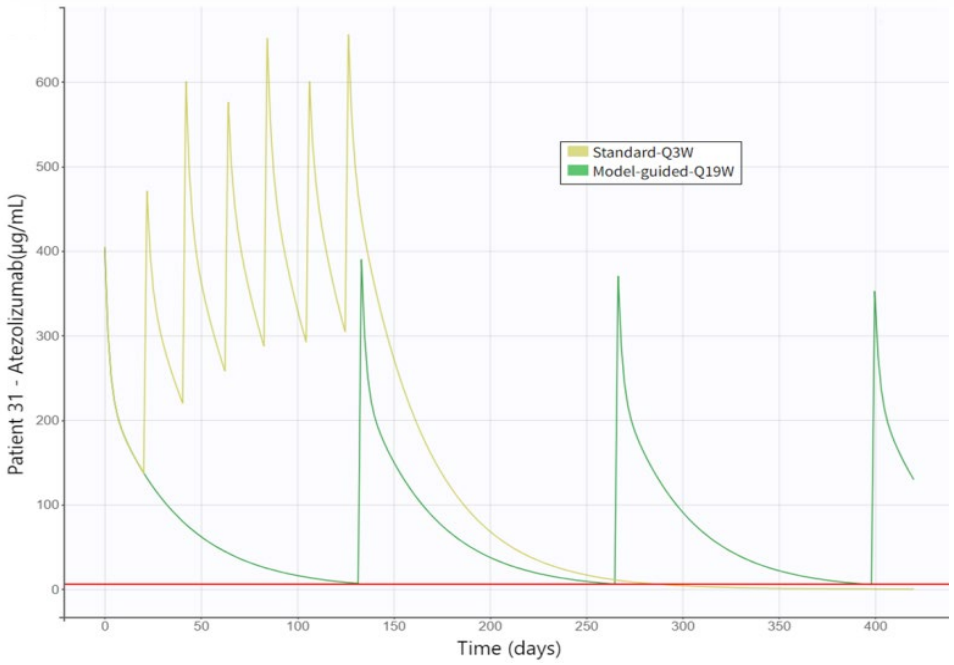
Can PK help de-escalate dosing?

Hôpitaux Universitaires de Marseille | ap hm

ARTICLE

Killing a fly with a sledgehammer: Atezolizumab exposure in real-world lung cancer patients

Sophie Marolleau[1] | Alice Mogenet[2] | Clara Boeri[1] | Mourad Hamimed[1] | Joseph Ciccolini[1] | Laurent Greillier[1,2]



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Possible to shift from 1200 mg Q3W to 1200 mg Q12W !
Alternative: 1200 mg Q3W to 96 mg Q3W !

Can PK help de-escalate dosing?

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CRCM 50 years Cancer Research Center of Marseille

Standard atezolizumab leads to severe overexposure in real-world patients with lung cancer: How far could we go in extending dosing intervals and saving money?

Sophie Marolleau[1]; Alice Mogenet[3]; Clara Boeri[3]; Mourad Hamimed[1]; Laurent Greillier[2,3]; Joseph Ciccolini[1,2,3]
[1] SMARTc Unit, CRCM, France. [2] Inria – Inserm COMPO team, Centre Inria Sophia Antipolis, CRCM Inserm 1068-CNRS UMR 7258 AMU, Marseille, France. [4] APHM, University Hospitals of Marseille, France.

COMPO COMPUTATIONAL ONCOLOGY

TRANSLATE-IT CRCM

Simulation for Cost-reduction

- Yearly-cost could be reduced by -77% (Q12W 1200 mg) to -79% (Q3W 96 mg) per patient.

Cost for one-year treatment per patient

	Standard dosing	Model-Guided Q12W 1200 mg	Model-Guided Q3W 96 mg
Drug cost	58854	13848	4708
Daily Care	9 299	2352	9299
Total (€)	**68153**	**16200**	**14007**
Total (U.S. $)	**63105**	**15000**	**12969**

TDM could be cost-effective!

Can PK help de-escalate dosing?

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2023

2 435 000 €

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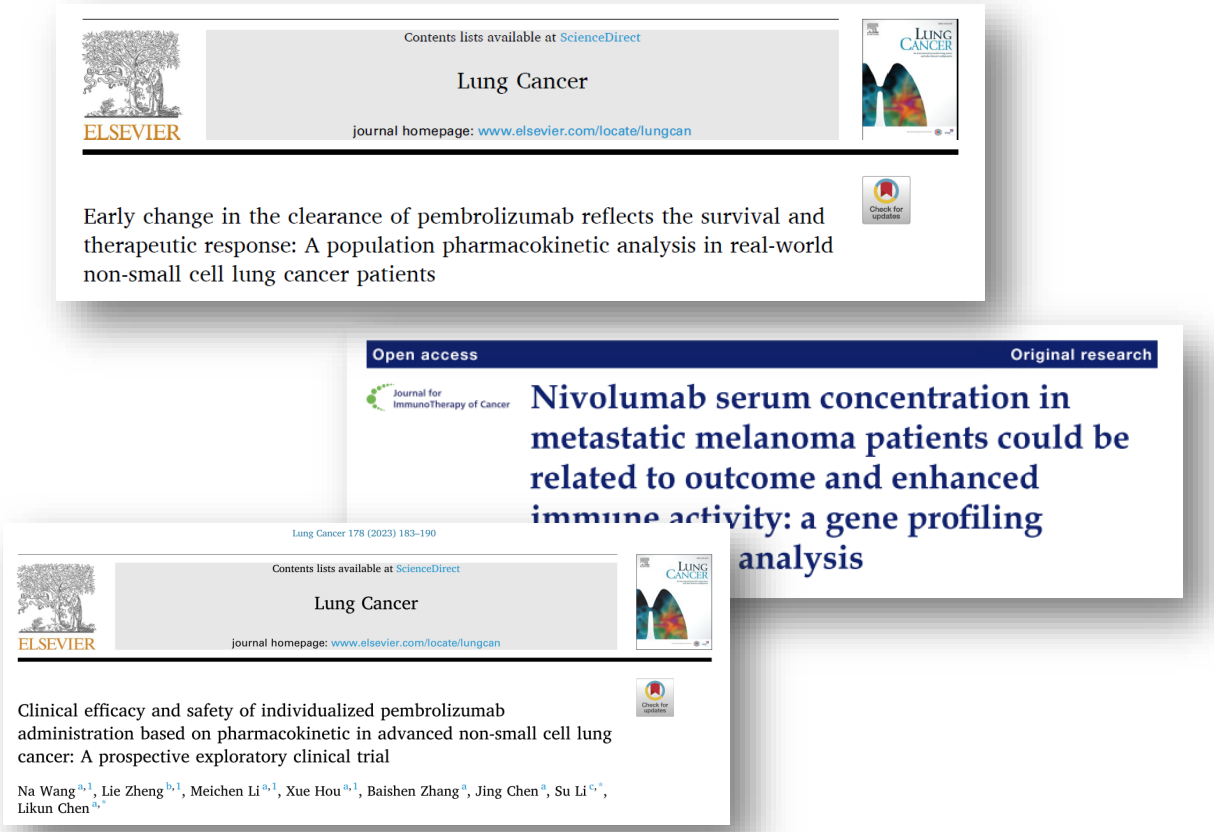
572 000 €

TDM could be cost-effective!

To sum up

« We shall de-escalate dosing»



« we shall customize dosing»

TDM makes sense

To sum up

- Customizing Pembrolizumab

THE PIONEER PROJECT

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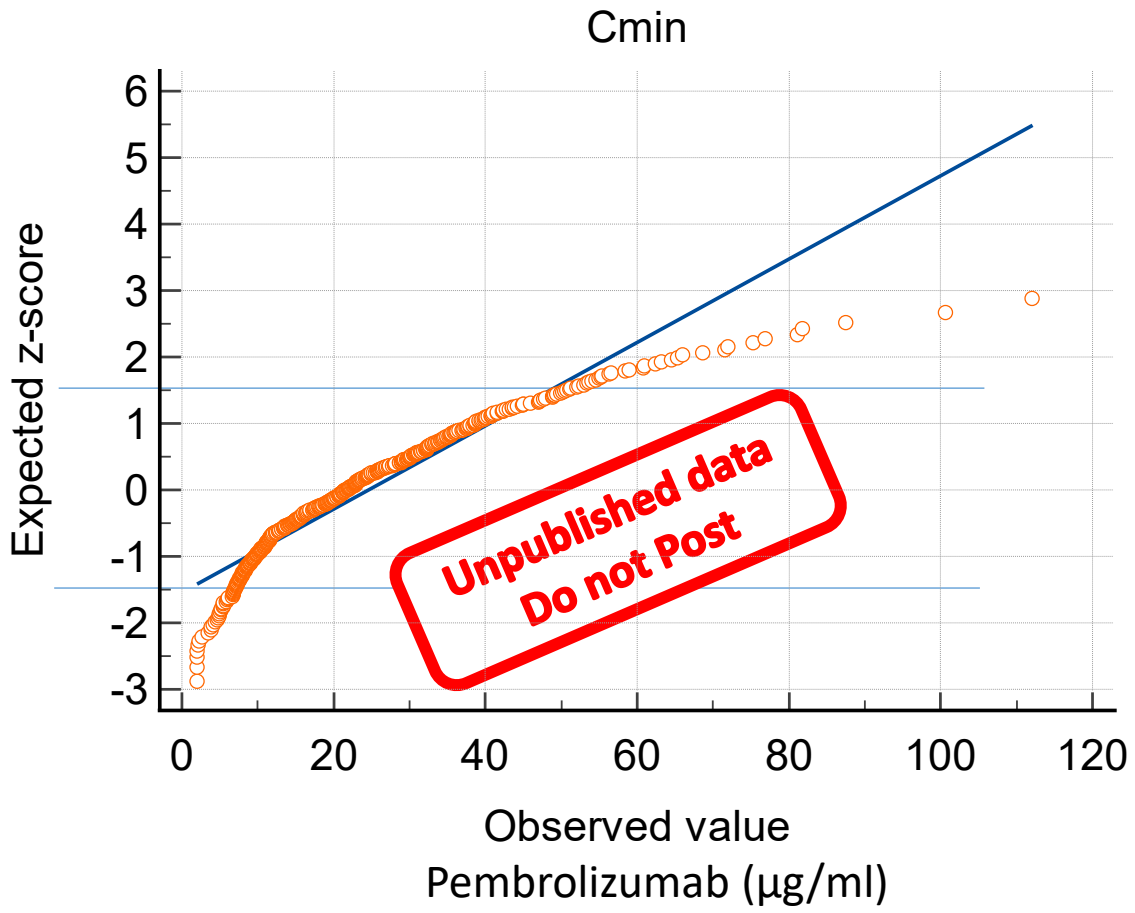


Outlier patients with lower concentrations

⇩

Target Engagement?

⇩

Increase dosing

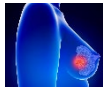
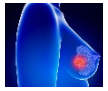
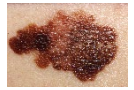
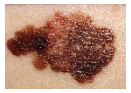
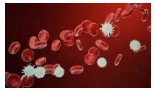
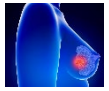
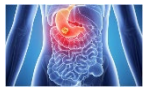
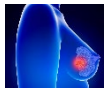
Outlier patients with higher concentrations

⇩

Decrease dosing

>60% inter-patient variability on PK!

To sum up

- ✓ Atezolizumab (Tecentriq®)  
- ✓ Bevacizumab (Avastin®)    
- ✓ Cetuximab (Erbitux®)  
- ✓ Ipilimumab (Yervoy®) 
- ✓ Nivolumab (Opdivo®)    
- ✓ Pembrolizumab (Keytruda®) Agnostic (MSI-H) 
- ✓ Rituximab (Endoxan®) 
- ✓ Trastuzumab (Herceptin®)  
- ✓ Trastu-emtansine, Trastu-deruxtecan 

Routine TDM in Marseille


YOU CAN'T
IMPROVE
WHAT YOU
DON'T
MEASURE.