Reducing waste from single dose vials

Zoom web conference - Tuesday, June 30th

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I don’t want to do this type of research….

- …..but it’s the second best option.
- Is the cost to the manufacturer related to the liquid inside the vial?
- Definitely not
- But prices for payers have escalated – only response is to be more efficient with the “liquid”

- Many current cancer drugs in the USA cost > $100K/QALY
  - Eg regorafenib = $900k/QALY

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E D I T O R I A L

Can Money Really Be No Object When Cancer Care Is the Subject?

Leonard B. Saltz, *Memorial Sloan Kettering Cancer Center, New York, NY*

"…cost effectiveness research has become an academic exercise of no meaningful consequence…"

Introduction

- Approx $3 bn wastage due to oversized vials – (Bach et al. BMJ)

- Ideal situation
  - Make a Market Access Agreement between payer and manufacturer, to get a discount in order to not do vial sharing etc.

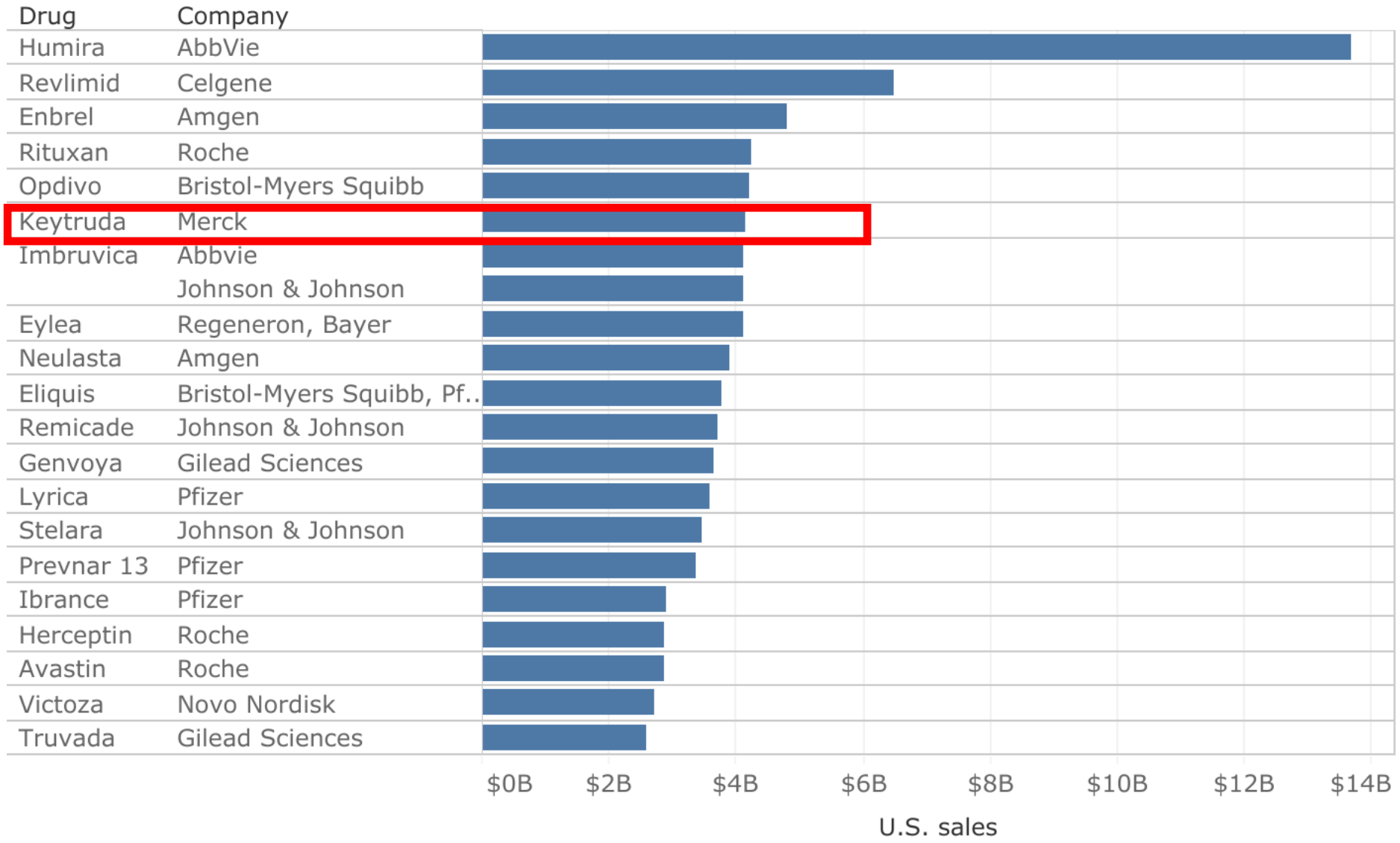
The example of Pembrolizumab

- Labelled dosing initially 2 mg/kg every 3 weeks
- Changed to 200 mg every 3 weeks
- Average patient of 75 kg requires only 150 mg
- If using 2 mg/kg, US could save $0.8 billion annually – but dependent on vial sharing

Goldstein et al. JNCI, 2017

Projected 2020

Top drug sales of 2018



FiercePharma, Jun 17, 2019

Update in 2020

- New approval for 400 mg every 6 weeks
- We propose 4 mg/kg every 6 weeks
  - Patients < 75 Kg (or 82.5 kg accounting for rounding rules), receive three 100 mg vials instead of 4.
- Global annual revenue for pembrolizumab = $11 billion.

Goldstein, Ratain, Saltz, JAMA Oncology 2020

Vial Sharing – Issues and challenges

- Patients in a clinic need to be from a single payer – or from payers that have the same policy regarding wastage/sharing
  - Veterans Affairs System / Kaiser have incentive to share vials
- Need financial incentive for vial sharing
  - JW Modifier provides a disincentive (Goldstein & Hirsch, JAMA Oncology 2018)
- Drug Stability important
  - Pembrolizumab – 24 hours refrigerated
  - Trastuzumab – 28 days
  - More research needed
- Group infusions on specific days of the week?

Is vial sharing possible with single use vials?

- The cautious and risk-averse approach = No
  - CDC
- The more cost-conscious approach = Yes
  - CMS – acceptable if done carefully
- Stability vs sterility?

Japan: Stability of Nivolumab after vial is opened

	Day							
Storage condition	**0 (baseline)**	**1**	**2**	**3**	**7**	**14**	**21**	**28**
4°C								
20-mg vial								
IgG concentration (mg/mL)	10.1 ± 0.1	10.1 ± 0.1	10.1 ± 0.1	10.2 ± 0.1	10.1 ± 0.1	10.1 ± 0.1	10.1 ± 0.1	10.1 ± 0.1
Binding activity to PD-1 (% of control)	104 ± 3	102 ± 2	105 ± 2	104 ± 4	103 ± 4	102 ± 2	104 ± 3	105 ± 2

Masahide Fukudo et al. JCO Oncology Practice 2020.

Cost of convenience?

Cost of minor safety risk?

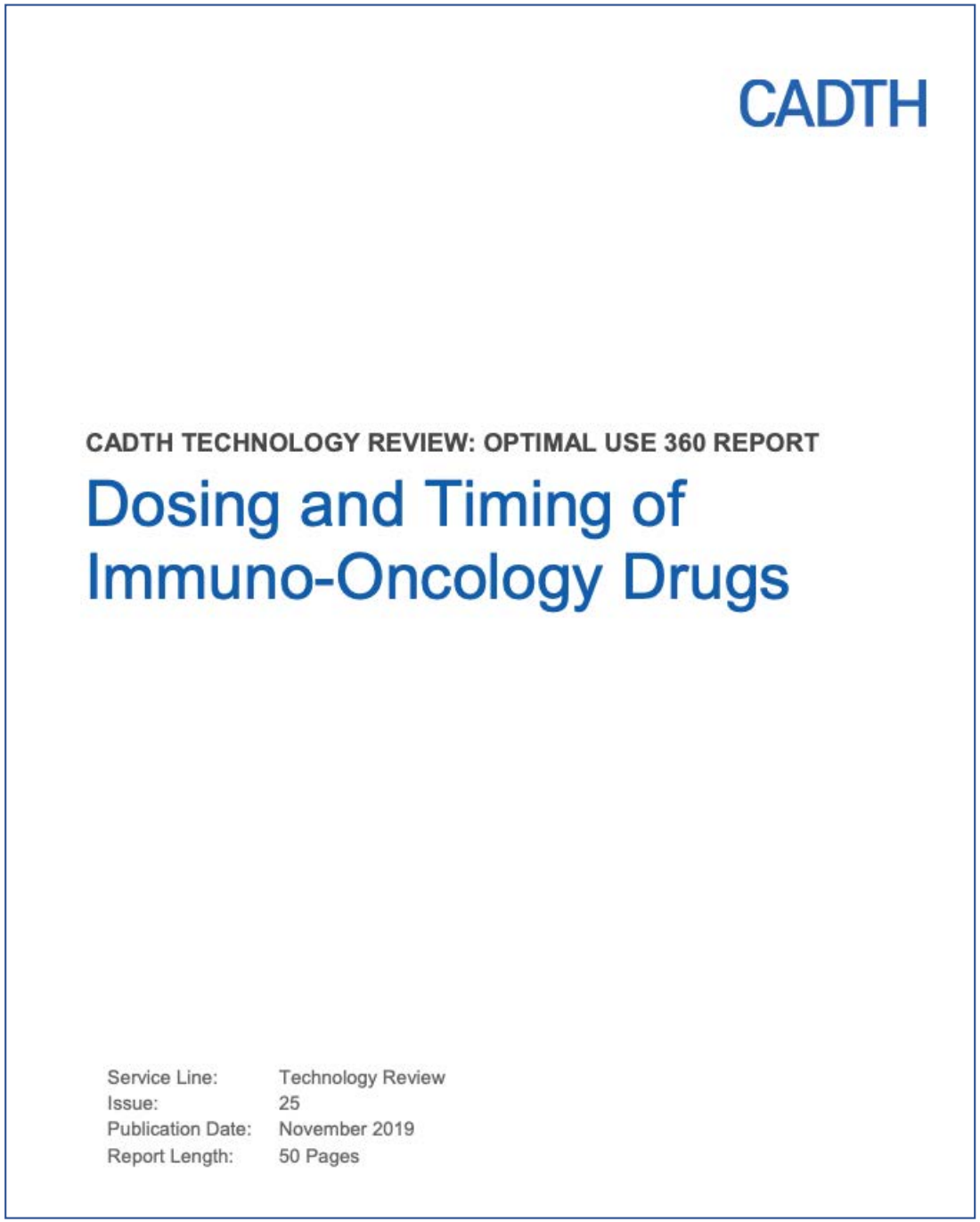
Need to consider tradeoff/opportunity cost

Net health impact

Different countries approaches

- Very dependent on the mechanisms of how the drug is paid for
- Who pays?
- Do the payers pay per vial or per mg?

Canada


CADTH
CADTH TECHNOLOGY REVIEW: OPTIMAL USE 360 REPORT
Dosing and Timing of Immuno-Oncology Drugs
Service Line: Technology Review
Issue: 25
Publication Date: November 2019
Report Length: 50 Pages

Canada

- 10 provinces and 3 territories - usually aligned in policy
  - CADTH provide non-binding advice and recommendations.
- Cancer Care Ontario – 40% of population:
  - Develop policies for hospital reimbursement
- Weight-based pembrolizumab
  - Most provinces use weight-based pembrolizumab
  - No reimbursement for wasted drug.
  - Most centers share single-dose vials.
  - Some provinces, (eg Alberta and BC), only share within same day (within 6 hours).
    - Follow NAPRA guidelines (the US equivalent of USP797)
- Sunnybrook
  - Drugs with stability of at least 7 days use “closed system” and sterile techniques for vial sharing
  - Drugs with short stability – patient grouping and treatment on one day of the week.

Information courtesy of Dr Kelvin Chan, Sunnybrook Research Institute, Canada.

British Columbia

- Large Savings possible
- Real world data

Jang et al., Journal of Oncology Pharmacy Practice, 2020

What happens in the UK?

Israel

- Israeli policy makers are very risk averse – very difficult to do anything outside of FDA label
- gradually making progress

Low Income Countries

- These drugs are not affordable for the broad population

Alternative Approaches

- Instead of dealing with vial sizes and wastage, just spread out the infusions – longer intervals – using the fixed dosage.
- Use Pharmacokinetic Modelling
- Pembrolizumab 200mg every 4 weeks instead of every 3 weeks.

A Modeling and Simulation Study of Less Frequent Dosing of Nivolumab 480 mg

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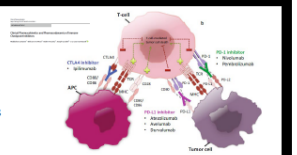
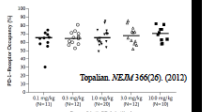
Abstract

Background: Nivolumab was originally approved at 3 mg/kg q2w. However, there is abundant evidence that doses as low as 0.1 mg/kg q2w are effective, and a randomized trial in RCC demonstrated equivalence across a dose range of 0.3-10 mg/kg q3w. Modeling and simulation have been used to amend the labeled dosage to 240 mg q2w or 480 mg q4w, with the latter yielding an estimated steady-state trough concentration (C_{trough}) of ~50 µg/mL. Given the high cost of nivolumab and the lack of a dose-response relationship, we hypothesized that less frequent dosing of 480 mg would maintain therapeutic serum concentrations. The objective of this study was to use modeling and simulation to develop alternative dosing strategies.
Methods: A simulation model was built from a published population pharmacokinetic model, incorporating time-dependent clearance. Various alternative dosing schedules were simulated, beginning with the third dose (doses 1 and 2 were 480 mg at wk 1 and 5). We conservatively chose 6.9 µg/mL as the target concentration (TC), slightly above the mean simulated C_{trough} at 0.3 mg/kg q3w (6.9 µg/mL), although even lower levels are likely efficacious. The simulated dose schedules were q8w, q10w, q12w and q14w, beginning with the third dose. Simulations were performed on 200 simulated patients.
Results: The simulated C_{trough} following doses 2-5 demonstrated that dosing q8w should maintain TC in >75% of patients, and q10w dosing should achieve TC in >88% of patients.
Conclusions: Modeling and simulation provide evidence that nivolumab can be effectively dosed q8-10w (after the first 2 doses), resulting in a potential 50% cost savings. As responding patients generally have a 35-45% decrease in clearance over the first 6 months of treatment, even less frequent dosing may be required for subsequent doses. Randomized trials of this interventional pharmacoeconomic strategy are indicated. Similar opportunities may exist for other checkpoint inhibitors.

Introduction



- T-cells use receptor binding to antigen-presenting cells (APCs) through T-cell receptors (TCR) binding to the major histocompatibility complex (MHC) on APCs
- Expression of PD-L1/2 helps keep this immune response in check to avoid autoimmunity
- Certain tumors take advantage of this, expressing PD-L1/2
- Immune checkpoint inhibitors, like nivolumab, overcome the tumors ability to override the immune response by blocking the PD-1/PD-L1 pathway via PD-1 inhibition
- Nivolumab is a fully-humanized IgG4-based monoclonal antibody designed to selectively bind PD-1 with great affinity (Kd = 2.6 nM)
- Because of the sensitive and selective binding, it achieves a max target occupancy (~70%) at a very low clinical dose spanning a 100-fold range
- Demonstrates clinical responses in melanoma over a 100-fold dose range



Topalian, *NEJM* 366(26), (2012)

Table 4. Overview of ORR of nivolumab in advanced melanoma in study MDX1106-03

Dose (mg/kg)	0.1	0.3	1	3	10	Overall
Melanoma	35.3 (14.2, 61.7) N=17	27.8 (9.7, 53.5) N=18	31.4 (16.9, 49.3) N=35	41.2 (18.4, 67.1) N=17	20.0 (5.7, 43.7) N=20	30.8 (22.3, 40.5) N=107

Source: Tables 7.2.1-1, 7.3.1-1 and 7.4.1-1 of MDX1106-03 CSR

There is apparently flat exposure-efficacy relationship between individual exposures derived from population PK modeling and the primary endpoint of ORR in Study CA209037 with nivolumab administered at 3 mg/kg Q2W (Figure 1). Population PK model predicted trough concentrations (7- 28 µg/mL) after first nivolumab dose (C_{min1}) were used as the measure of nivolumab exposure.

From FDA CDER Clinical Pharmacology and Biopharmaceutics Review

Introduction (cont)

- FDA recommended dose for most indications is 240 mg q2w or 480mg q4w
- The cost of 3 cycles (6 weeks' worth) of Opdivo® (nivolumab) at the 240mg q2w dose is $19,551.60, which per year amounts to $156,413
- The aim of this study was to simulate alternative dosing regimens to:
  1. Maintain therapeutic trough serum concentrations
  2. Reduce financial burden on patients and payers
- The focus of this presentation is the optimization of these alternative dosing regimens via trough-guided dosing

eTable 3: Drug dose and costs

Drug	Dose	Unit price ($)	Cost for 1 model cycle ($, 6 wks)
Nivolumab (induction phase)	3 mg/kg * 70 kg every 3 weeks for 4 doses	27.155/mg	11405.10
Nivolumab (maintenance phase)	240 mg every 2 weeks	27.155/mg	19551.60

First-line Nivolumab Plus Ipilimumab vs Sunitinib for Metastatic Renal Cell Carcinoma: A Cost-effectiveness Analysis

Methods

- Chose a conservative trough of 6.9 ug/mL to maintain in simulations
  - Based on 0.3 mg/kg q3w dosing shown to be effective

Table 1. Trough Nivolumab Concentrations by Dose from nivolumab Clinical Pharmacology and Biopharmaceutics Review, July 2014[6]

Dose (mg/kg)	Mean Trough (µg/mL)
0.1	2.5
0.3	6.9
1	19
3	57
10	188.8

- Used the population PK model from Bajaj et al (2017)
  - Used by FDA to change label from 240 mg q2w to 480 mg q4w purely based on *in silico* modeling & simulation

$$VC = VC_{REF} \cdot \left(\frac{BW_i}{BW_{REF}}\right)^{VC_{BW}} \cdot \left(e^{VC_{SEX}}\right)^{SEX}$$

$$CL_{t,\ i} = CL_i \cdot \exp\left(\frac{E_{max,i} \cdot t^{\gamma_i}}{TS0_i{}^{\gamma_i} + t^{\gamma_i}}\right)$$

$$CL_i = CL_{Base,REF} \cdot \left(\frac{BW_i}{BW_{REF}}\right)^{CL_{BW}} \cdot \left(\frac{eGFR_i}{eGFR_{REF}}\right)^{CL_{eGFR}} \cdot \left(e^{CL_{ETA}}\right)^{PS} \cdot \left(e^{CL_{SEX}}\right)^{SEX} \cdot \left(e^{CL_{RACE}}\right)^{RACE}$$

Table 1 PPK final model parameter estimates

Parameter* [units]	Estimate*	95% confidence interval†
Structural model parameters		
CL_{REF} [mL/h]	9.4	8.7 – 10
VC_{REF} [L]	3.63	3.5 – 3.75
Q_{REF} [mL/h]	32.1	25.9 – 37.4
VP_{REF} [L]	2.78	2.59 – 3.04
CL_{BW}	0.566	0.479 – 0.658
CL_{eGFR}	0.186	0.126 – 0.25
CL_{RACE}	0.163	0.119 – 0.216
CL_{SEX}	0.172	0.132 – 0.212
$CL_{RACE:AS}$	−0.125	−0.180 – −0.057
$CL_{RACE:B}$	−0.295	−0.395 – −0.216
CL_{TS0}	1.41 × 10^3	1.21 × 10^3 – 1.65 × 10^3
CL_{ALL}	3.15	1.65 – 7.52
VC_{BW}	0.997	0.914 – 0.981
VC_{SEX}	0.152	0.11 – 0.2
Interindividual variability model parameters		
ω^2_{CL}	0.123 (0.35)	0.106 – 0.143
ω^2_{VC}	0.103 (0.321)	0.0829 – 0.156
ω^2_{VP} [‡]	0.268 (0.518)	0.197 – 0.316
ω^2_{EMAX}	0.0719 (0.268)	0.0488 – 0.119
$\omega_{CL,VC}$	0.0432 (0.352)	0.0344 – 0.0547
Residual error model parameters		
Proportional error (√)	0.213	0.202 – 0.229

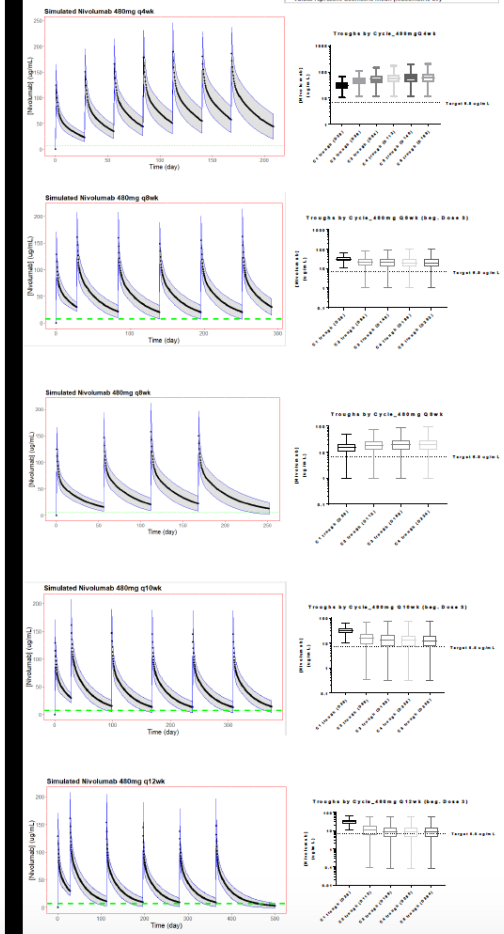
BW, body weight; BPS, baseline performance status; CL, clearance; eGFR, estimated glomerular filtration rate; Q, inter-compartmental clearance; RAAS, Race (Asian); VC, volume of central compartment; VP, volume of peripheral compartment.
*ETA shrinkage: ETA_CL, 14.2; ETA_VC, 13.4; ETA_VP, 41.4; ETA_EMAX, 48.8; and EPS shrinkage (%), 10.8. CL_{REF} and VC_{REF} are typical values of CL and VC at the reference values. Covariate effect was estimated relative to a white female reference weighing 80 kg with an eGFR of 90 mL/min/1.73 m^2, and EPS of 0.
†Estimate values in parentheses are standard deviation for estimated variance and correlation for estimated covariances.
‡Confidence interval values are taken from bootstrap calculations (1,918 successful out of a total of 2,000).

Results

Table 2: Simulated Nivolumab Exposure by Regimen

Summary Exposure (ug/mL)	480mg Q4WK NCI	480mg Q4WK Long et al (2018)
C_{min_ss}	54.4 (43.2)	55.2 (62.8)
C_{avg_ss}	93.2 (25.2)	90.0 (46.4)
C_{max_ss}	190.7 (24.9)	184.8 (57.7)

*steady-state is at time 2688 hr (day 112)
** values represent Geometric Mean (%Geometric CV)



Conclusions

- Dosing nivolumab **480mg q10 week**, starting with third dose, can still maintain a *conservative* target level of 6.9 ug/mL in ~75% of patients
- Dosing nivolumab **480mg q8 week**, starting with third dose, can still maintain a *conservative* target level of 6.9 ug/mL in ~88% of patients
- Since 0.1 mg/kg shown to be effective, we could likely use a lower target level to justify q10wk dosing (trough ~ 2.5 ug/mL)
- ~93% of patients given 480mg q10w would maintain target level >2.5 ug/mL
- Would be patient-dependent, as some patients respond, some don't even if increased dose

Future Directions

- Apply this methodology to therapeutic drug monitoring (TDM)
- Should be able to identify responders from non-responders using TDM
  - Non-responders will have a faster clearance and a lower trough level as drug binds to target
  - Non-responders won't have much change in drug clearance, can be identified after several cycles
    - Can cease therapy, saving them time, money, and potentially unnecessary side effects.
  - Responders will have a more drastic slowing of clearance over time as their disease burden decreases over time
- Applicable to other PD-1/PD-L1 inhibitors
- Needs a clinical trial to support these *in silico* predictions

Acknowledgements

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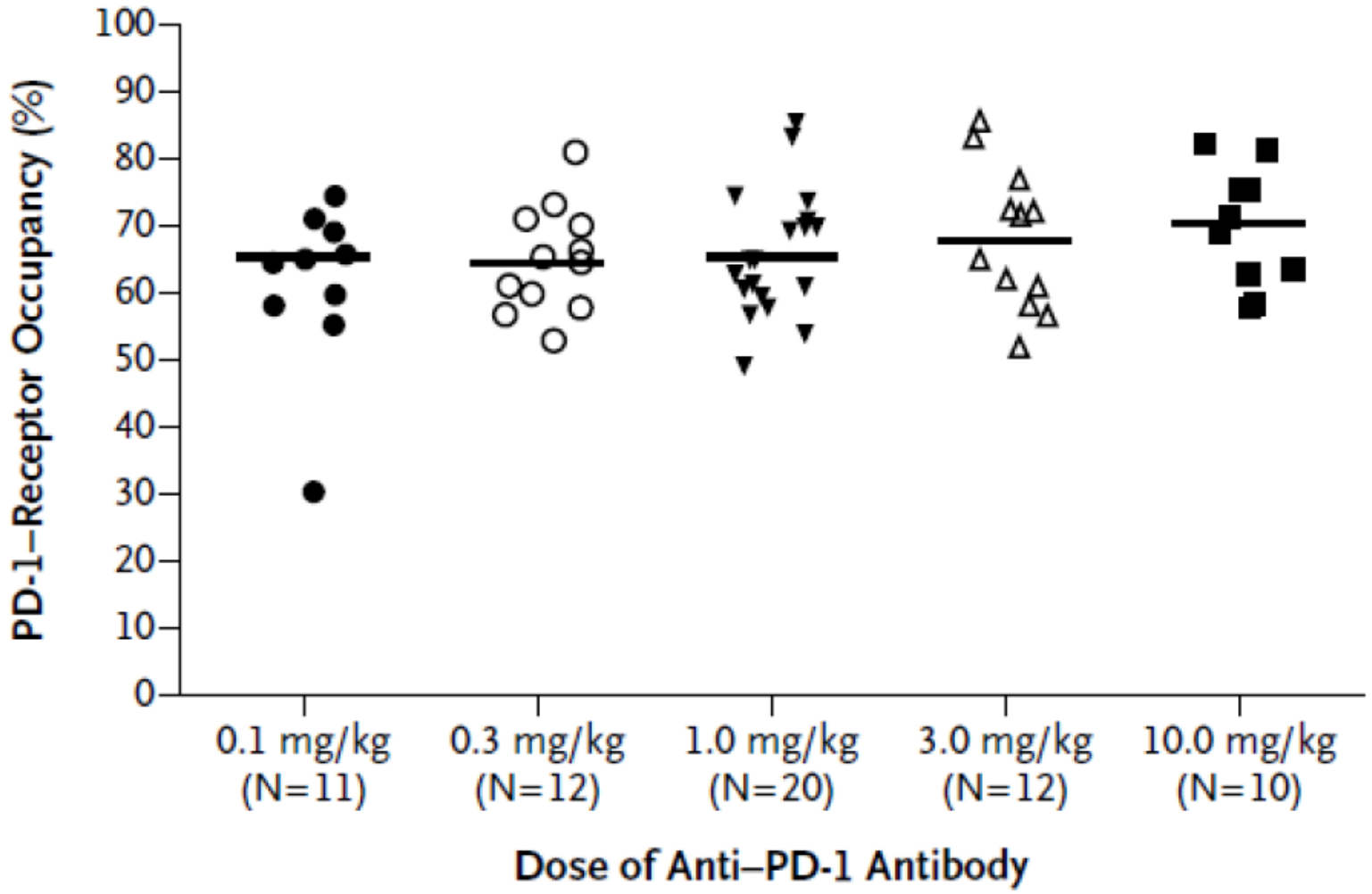
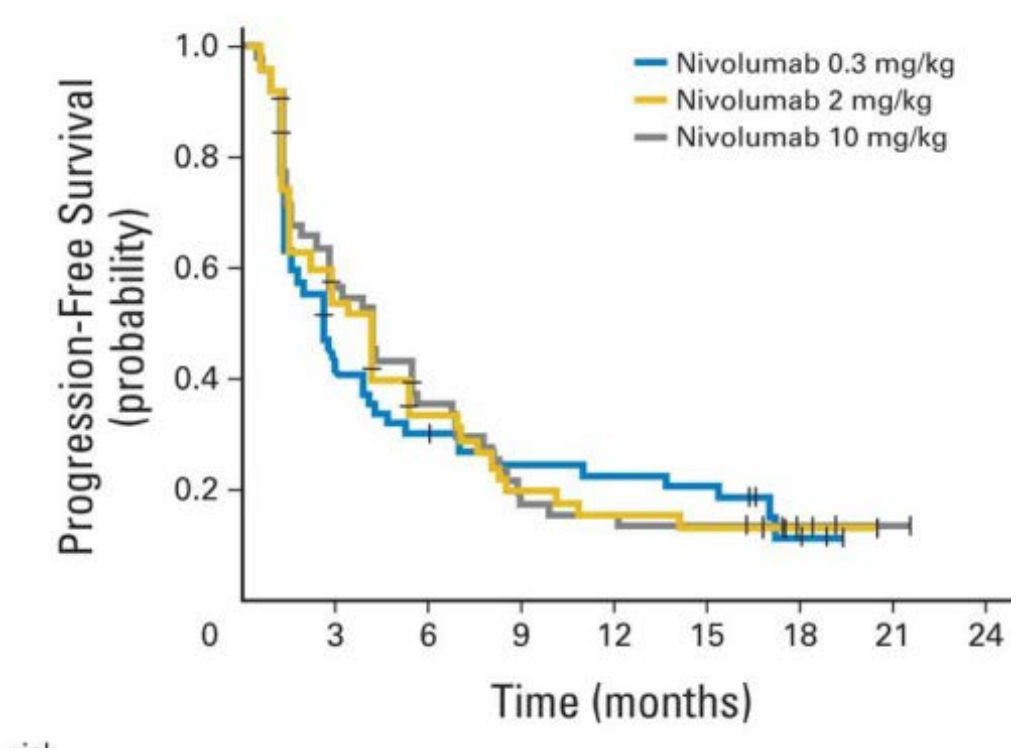
- The authors thank Certara Corp and Joga Gobburu for their helpful discussions
- For further inquiries, please contact cody.peer@nih.gov

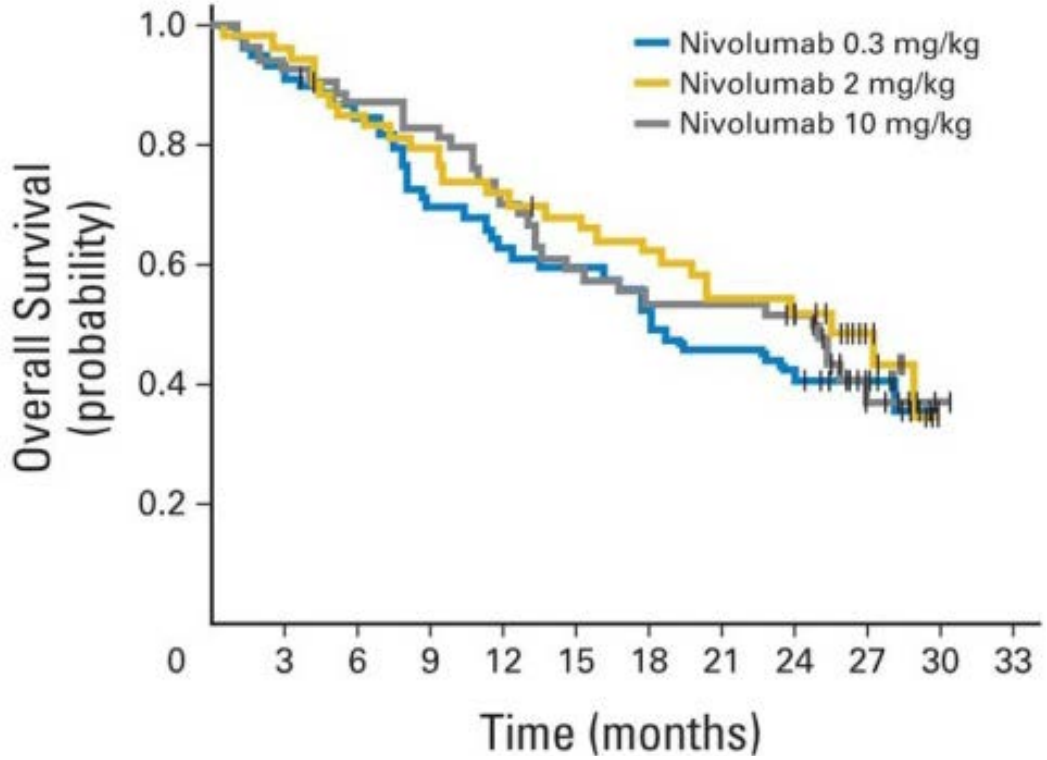
PD-1 Receptor Occupancy



Topalian, NEJM, 2012

Nivolumab for metastatic renal cell carcinoma: randomized phase II trial

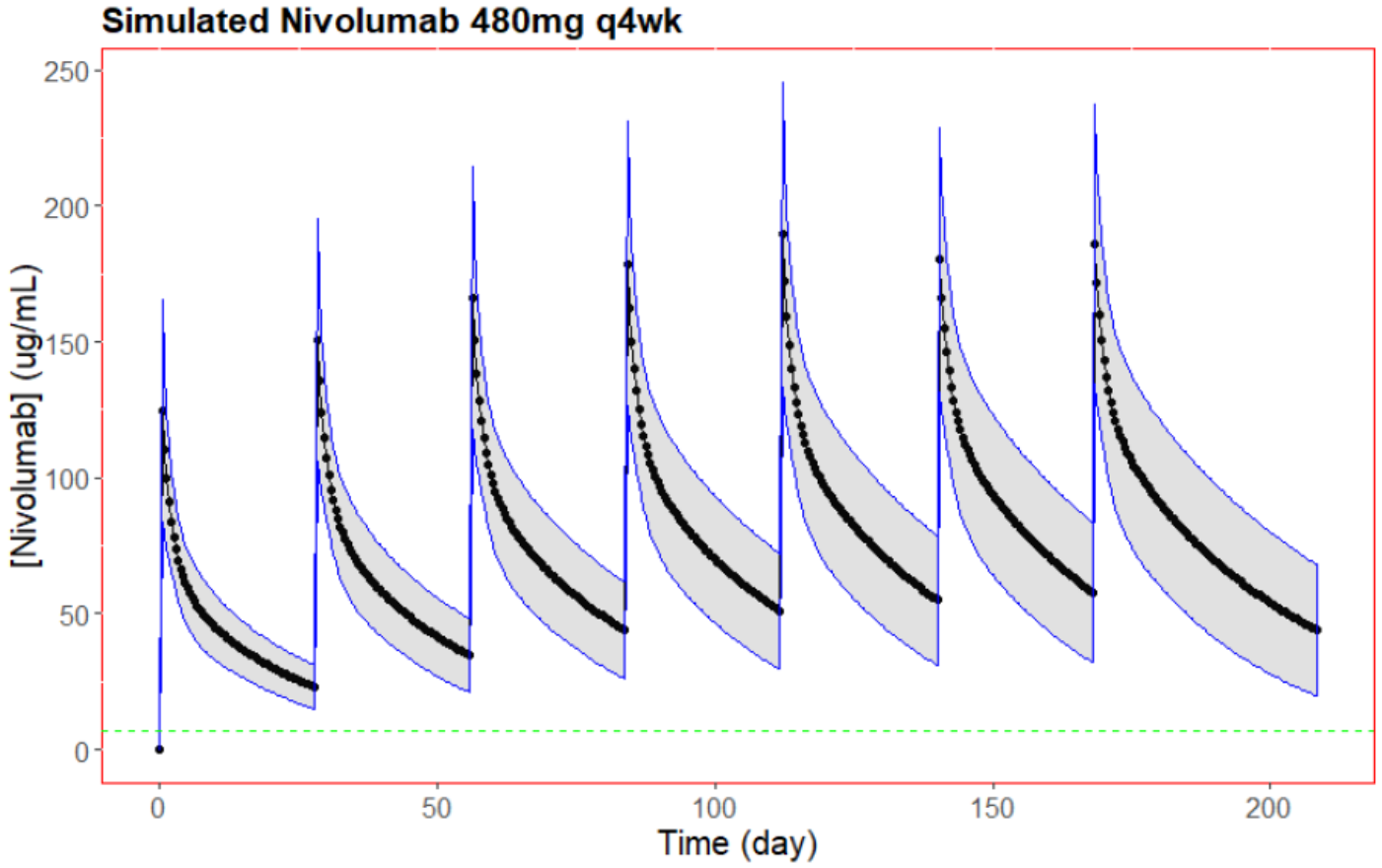


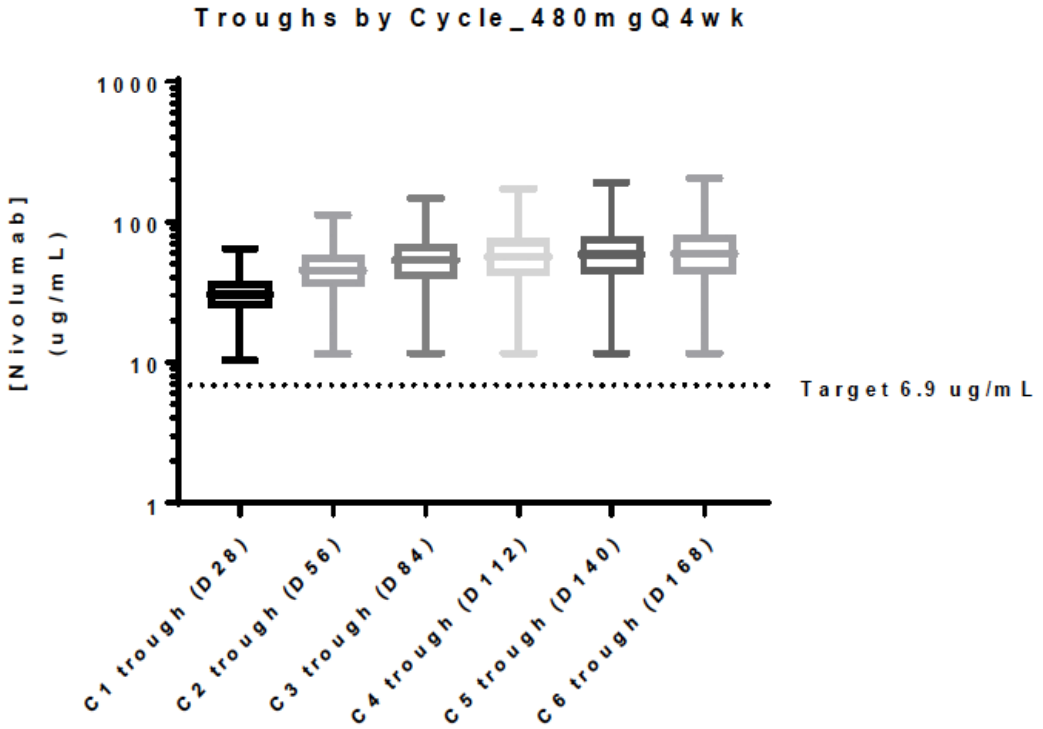


Flat dose-response over range of 0.3-10 mg/kg q3w

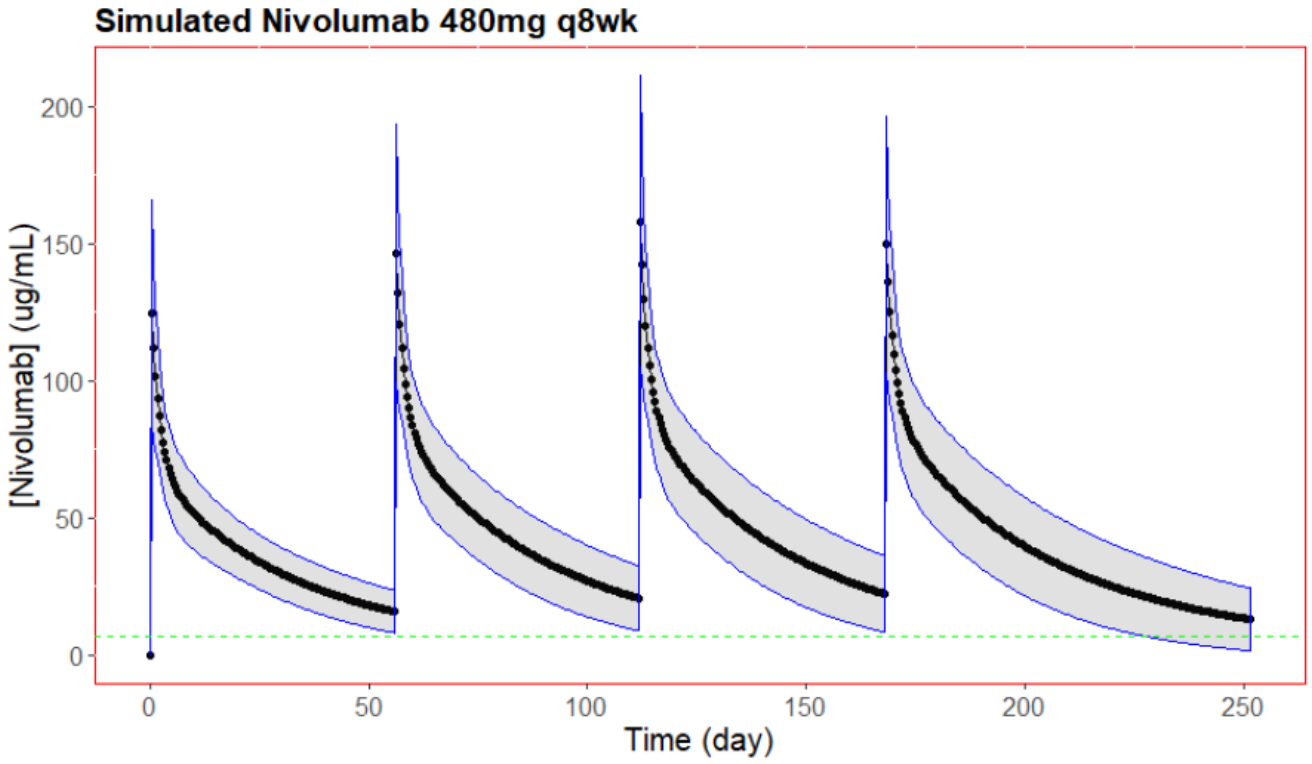
Motzer, JCO, 2015

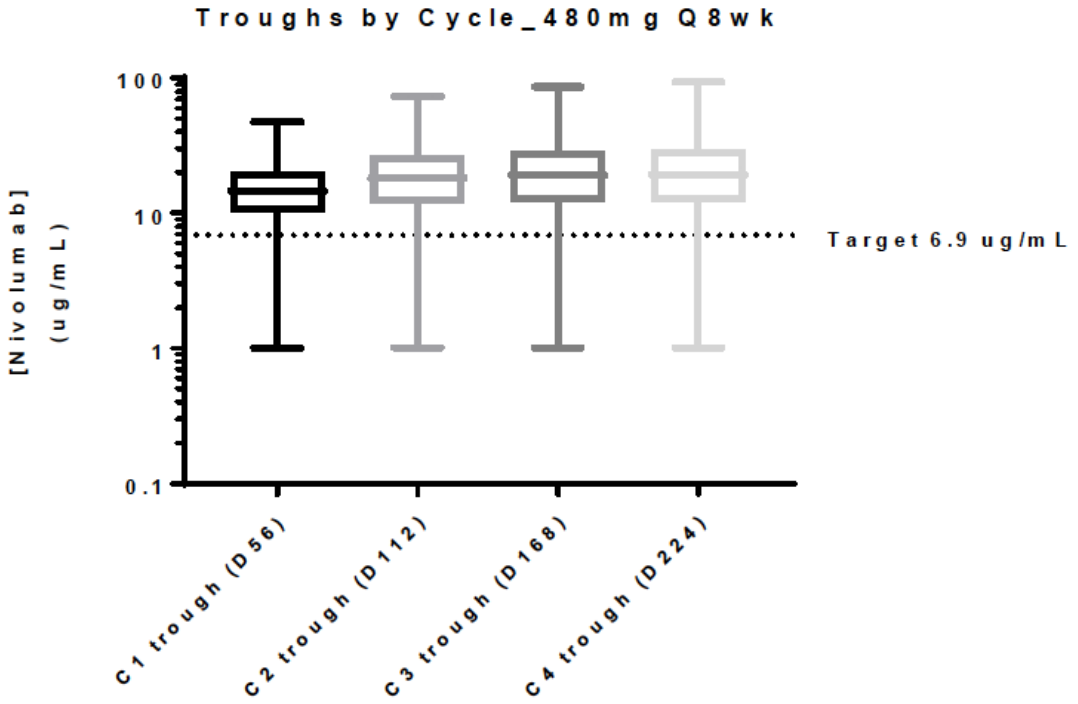
Standard dosing – 480mg every 4 weeks





480mg every 8 weeks – from 1st dose





Atezolizumab

- Target trough as stated by manufacturer = 6 µg/ml [1]
- First dose trough at 1200mg = 95 µg/ml
- Steady State trough = 225 µg/ml
- Potential for **logarithmic dose reductions!**
- Personalized dosing?

[1] Deng R, et al. (2016) Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. Mabs 8(3):593-603.

The future

- The problem of drug prices will not disappear
- Payers need to get smarter
- Use knowledge as a negotiating strategy for Market Access Agreement