

PK and PKPD considerations for dose selection in the development of pembrolizumab

Dinesh de Alwis, PhD
Quantitative Pharmacology and Pharmacometrics. MSD

Disclosure Information

Dinesh de Alwis, Ph.D.

I have the following financial relationships to disclose:

- I am an Employee and Stockholder of MSD

Outline

- Dose finding in oncology – A “historical” perspective
 - Why we hope focus on MTD is historical?
- Keytruda

MTD: Maximum Tolerated Dose

Traditional Dose Finding in Oncology

All focus on finding MTD!

3+3, CRM, mCRM, TITE-CRM, accelerated titration, ...

What about efficacious dose?

Deserves more attention

Ph1: Dose escalation

MTD/MAD

MTD/MAD

Perceived benefit: Fast to registration

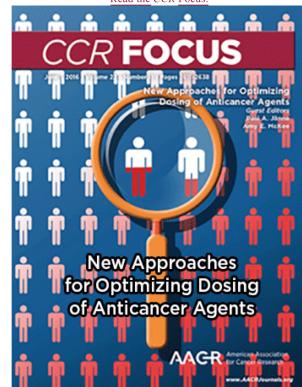
Historically oncology has performed relatively poorly in identifying “optimal” doses in the pre-market setting

FDA can issue **post-marketing commitments/requirements** to study optimal dose considering safety and efficacy

Table 1. Dose interruptions and reductions in initial registration trials for small-molecule KIs approved for oncology indications with PMC or PMR to study alternate doses (percentage of patients on registration studies)

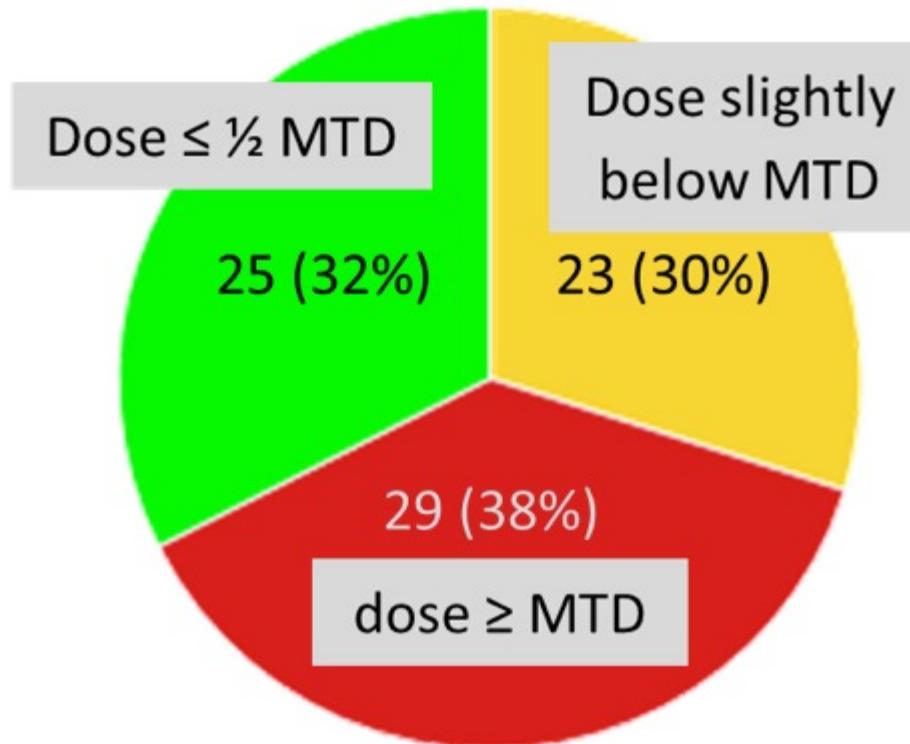
Drug	Dose interruption	Dose reduction	Dose interruption or delay
Erlotinib	62%	19%	NA
Vandetanib	47%	49%	80%
Cabozantinib	NA	79%	86%
Ponatinib	66%	52%	74%
Ceritinib	69%	59%	71%
Idelalisib	NA	34%	53%
Lenvatinib	56%	68%	90%

Read the *CCR Focus*:



MTD/MAD \neq Optimal dose/regimen

Oncology Early Phase Dose Selection needs Significant Improvement

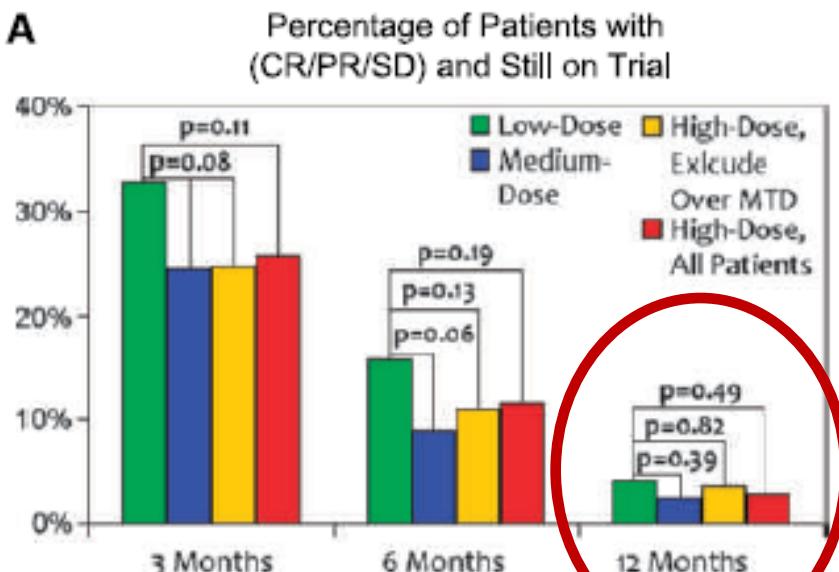


Roughly 2/3rd (48/77) of the compounds are approved at doses lower than MTD

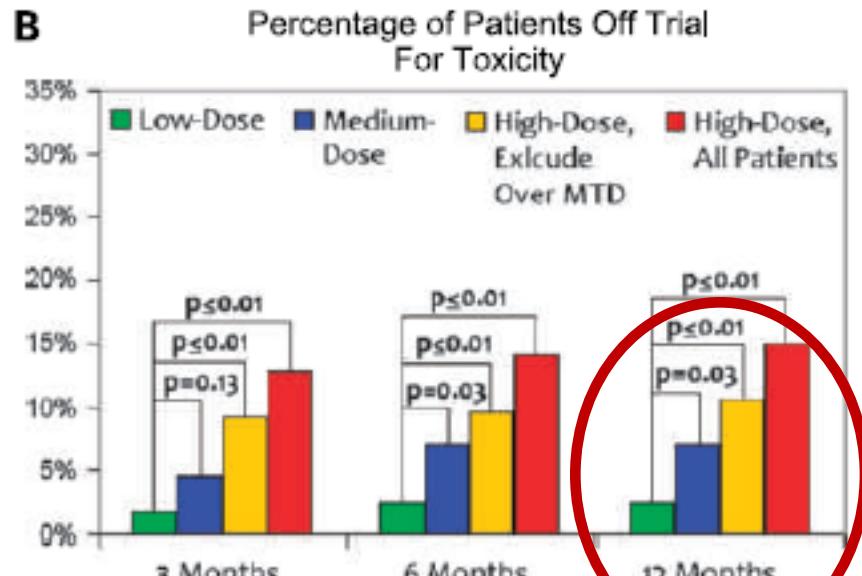
Roughly 1/3rd (25/77) are approved at less than MTD/2

For Targeted Therapies, Doses Reaching MTD Increase Toxicity Without Necessarily Improving Response in Phase I

A



B



MTD does not necessarily improve response

Doses approaching MTD led to more patients off trial due to toxicity

Normalization to combine data from different trials:

low-dose: ≤25% MTD of the trial

High-dose: ≥75% MTD of the trial

Medium-dose: 25-75%

24 trials treating 683 patients between Oct, 2004 - Jun, 2008, at MD Anderson Cancer Center

Clin Cancer Res 2010;16:1289-1297

Proper Dose Finding in Oncology – MTD/MAD and BED

All focus on finding MTD!

3+3, CRM, mCRM, TITE-CRM, accelerated titration, ...

Ph1: Dose escalation

MTD/MAD

What about efficacious dose?

Deserves more attention

MTD/MAD

Biologically Effective Dose
(BED)

KEYTRUDA®
(MK-3475, pembrolizumab)
Case Study

Initiation of KEYTRUDA® Clinical Program

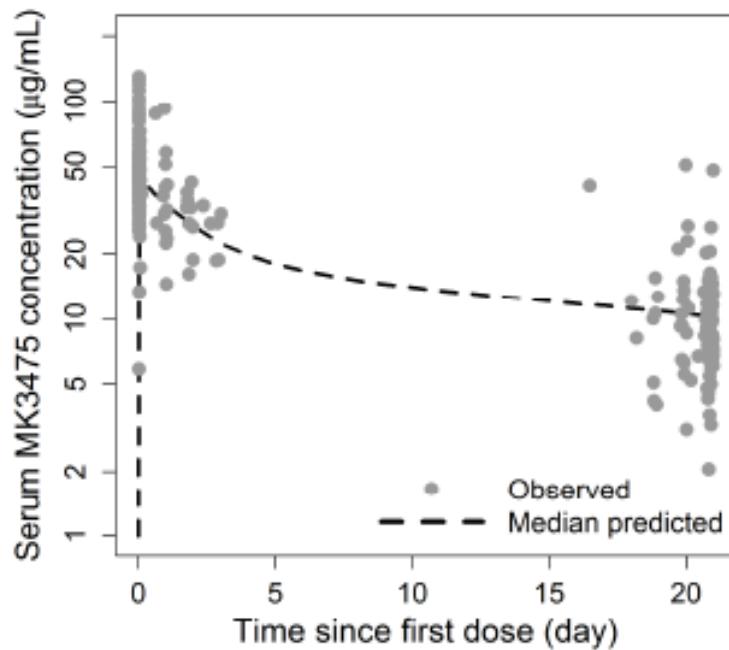
- Preclinical data suggested that KEYTRUDA® would have anti-tumor activity in multiple cancers
- US IND was opened on **Jan 7, 2011**
 - *A Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinomas and Melanoma (Protocol 001)*
 - *Initial intent was to define DLT, characterize PK, and establish POC*

Part A: FIH Dose Escalation and PK/PD Evaluation

- Part A-1 dose escalation study
 - Objectives:
 - To define DLT, MTD (Maximum Administered Dose), and characterize PK
 - Design:
 - Open label, non randomized traditional 3+3 dose escalation followed by a small expansion cohort n~32
 - 1mg/kg Q2W → 3 mg/kg Q2W → 10 mg/kg Q2W
 - Results
 - No DLT at tested doses
 - Objective response in 2 out of 3 first melanoma patients
 - First response at 3 mg/kg Q2W in melanoma
 - Based on a strong activity signal, amendment was issued to expand melanoma cohort
 - 10 mg/kg Q2W (MAD) selected as the first dose

PK profile support for Q3W dosing

- *Pharmacokinetic profile is typical for a therapeutic mAb with low clearance (0.22 L/h), limited volume of distribution (3.7 L) and low variability (28 % CV on CL)*
- *26 day half life (95% CI 24-28 days)*



A Strong Data, from Cohort B1, Accelerated the Development Program

Objective Response Rates and Duration of Response based on Independent Radiology Review using RECIST 1.1 Criteria

	Objective Response (N, 95% CI)	Complete Response (N, 95% CI)	Duration of Response (days) Median (Range)
All MEL N=85	40% (34‡; 29% - 51%)	3.5% (3; 0.7% - 10%)	Not reached (28-240+)
IPI Naïve N=58	43.1% (25; 30% - 57%)	3.4% (2; 0.4% - 11.9%)	Not reached (30-240+)
IPI Treated N=27	33.3% (9‡; 16% - 54%)	3.7% (1; 0.1% - 19%)	Not reached (28-169+)

All patients dose at 10 mg/kg.

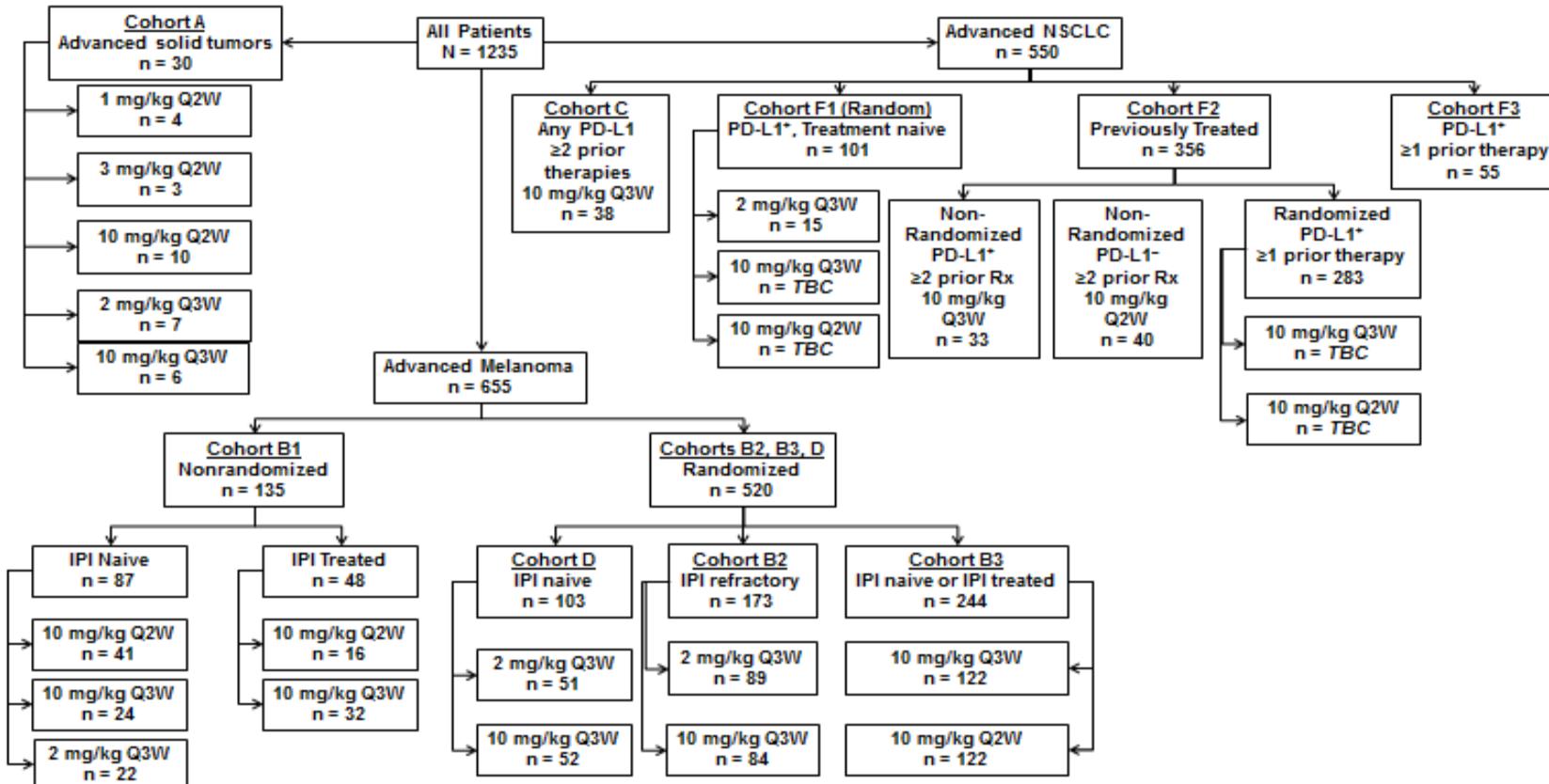
Includes all patients who received the first dose as of April 25, 2012. Centrally available response information as of Dec. 3, 2012.

‡ Confirmed objective response is defined as a complete response or partial response that is evident on two consecutive CT scans obtained at least 4 weeks apart.

Protocol 001 First in Human to Registration

From a small Phase 1-the study expanded to a 655-melanoma patient multi-part study

- 5 amendments, between Dec-2011 to Sep-2013, to answer emerging questions
- 4 “phase 2 study-like” parts including 3 randomized dose comparison sub-studies



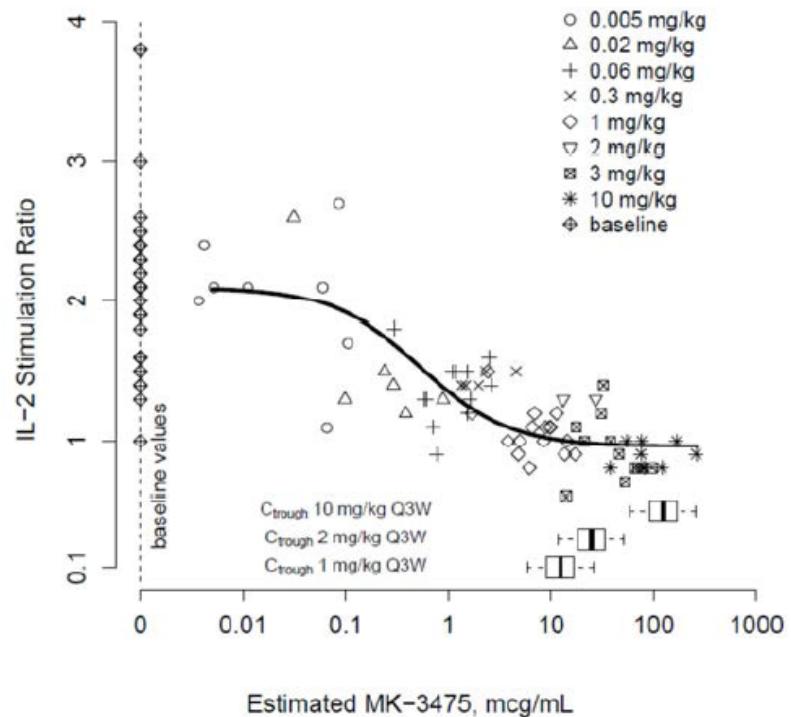
Kang, S.P., Gergich, K., Lubiniecki, G.M., de Alwis, D.P., Chen, C., Tice, M.A. and Rubin, E.H., 2017. Pembrolizumab KEYNOTE-001: an adaptive study leading to accelerated approval for two indications and a companion diagnostic. *Annals of Oncology*, 28(6), pp.1388-1398.

Defining a dose range for the pivotal B2 cohort

- Part A-2 dose expansion study
 - Objectives:
 - To evaluate PK/PD of Q3W dosing schedule
 - Intra-patient dose escalation to explore PK PD of KEYTRUDA® in 0.005 to 10 mg/kg Q3W
 - Basis for translational PK/PD to define the efficacious dose of 2 mg/kg Q3W
 - Patients were escalated in 3 steps (at days 1, 8 and 22) from low (0.005 to 0.06 mg/kg) to high doses (2 and 10mg/kg)
 - Ex vivo IL-2 assay developed
 - » No IL-2 release from lymphocytes with activated PD-1 pathway
 - » SEB causes release, further enhanced by pembrolizumab effect on PD-1

Ex-vivo IL2 assay: Peripheral PK-PD in the Clinic to inform efficacious dose

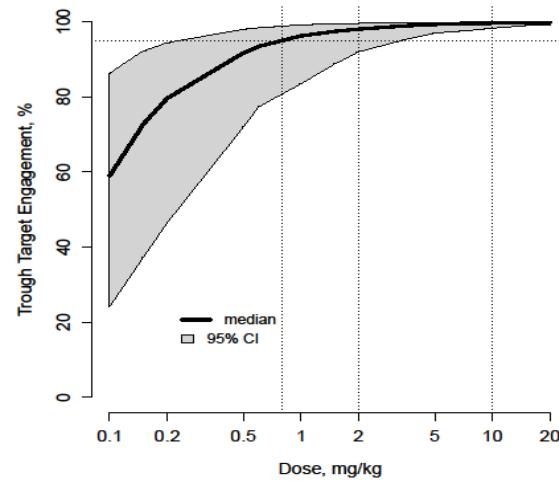
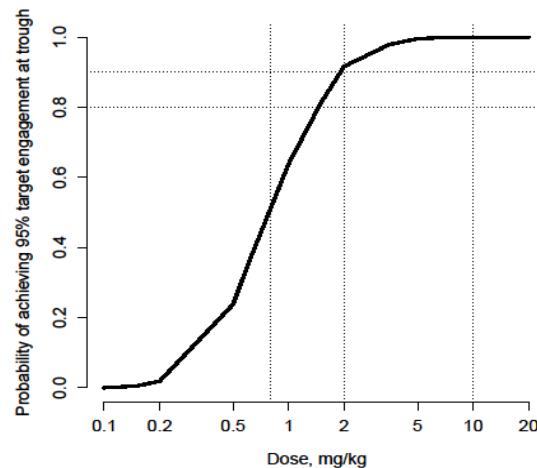
- 95-% saturation level reached at ~1 mg/kg Q3W
- Simulations show, > 95% of the effect of Keytruda on the ex vivo IL-2 release is achieved at C_{trough} reached with a dose regimen of ~1 mg/kg Q3W
- Therefore, 1 mg/kg Q3W is lower boundary for clinical efficacy



Keytruda Exposure is Associated with Complete Functional Blockade of PD-1 in the *ex vivo* IL-2 Release Assay at Doses of 1 mg/kg Q3W or Higher

PK-PD simulations to select BED

- PK-PD model was developed for simulations considering PK and PD variability
- At 1 mg/kg Q3W, the probability of achieving full target engagement is 64%. \geq 2 mg/kg the probability is \geq 90%.
 - Dose of 2 mg/kg falls likely near the plateau of the underlying exposure-response
- Proposed BED: 2 mg/kg Q3W



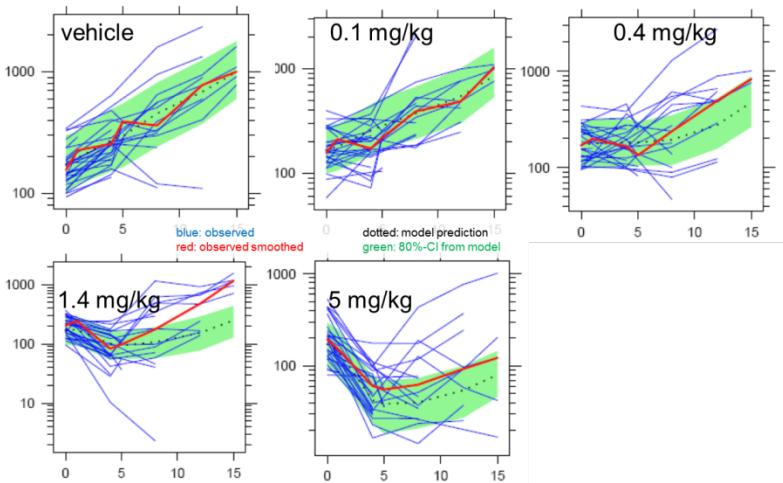
Can Translational PK-PD further inform our choice ?

Semi-mechanistic tPKPD model

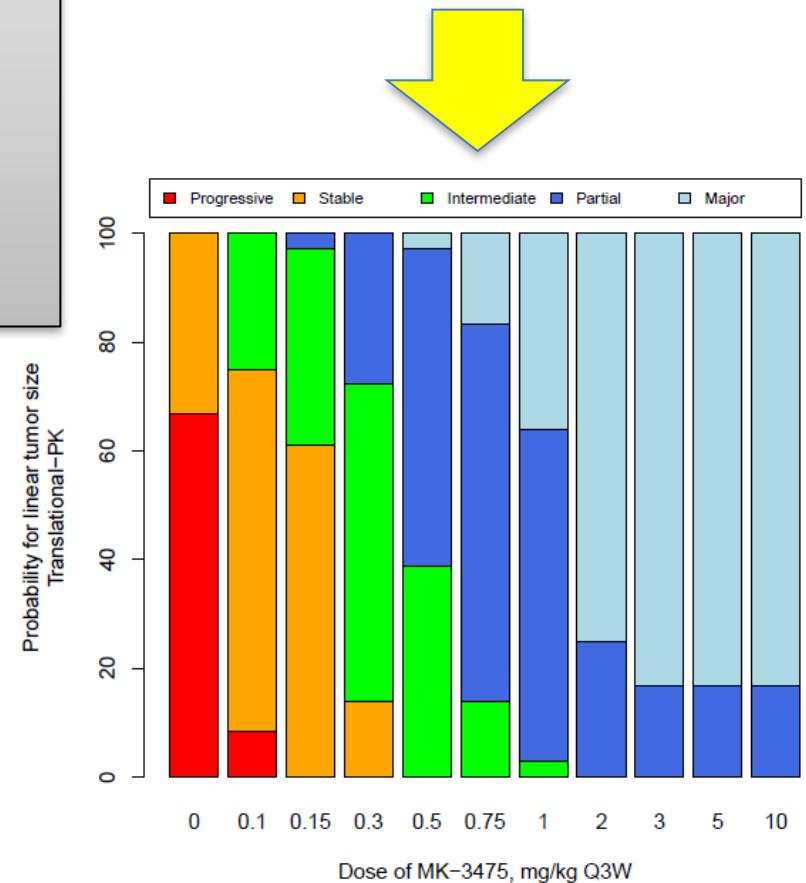
Step 1: Develop mouse model relating
PK → Target binding → tumor growth inhibition

Step 2: Translation to human by adjusting PK and tumor
growth parameters

Model fit tumor data from mouse



Dose of **2 mg/kg**
every 3 weeks or more shows **maximal**
response. Dose range of 2 - 10 Q3W
determined for clinical trials



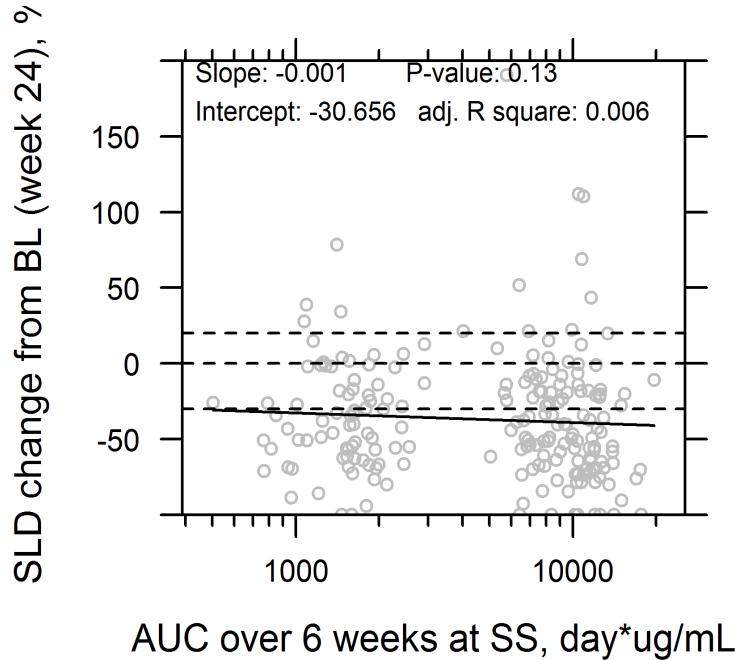
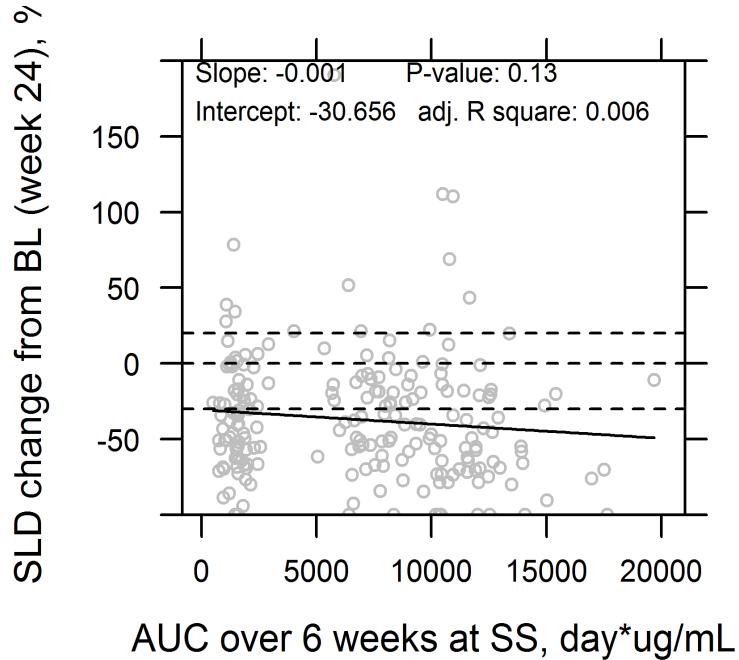
PK-PD modeling guides a critical decision on KEYTRUDA®

- Team discussion on what doses to take forward based on results **from non-randomized studies (B1)**
 - ORR ipi treated 10Q2: 56% > 10Q3: 27%
 - ORR ipi naïve 2Q3 : 45%, 10Q3: 37%, 10Q2 :46%

Based on the Translational modeling, ex-Vivo IL-2 data and observed clinical data, what dose or doses would you take forward into B2 pivotal cohort?

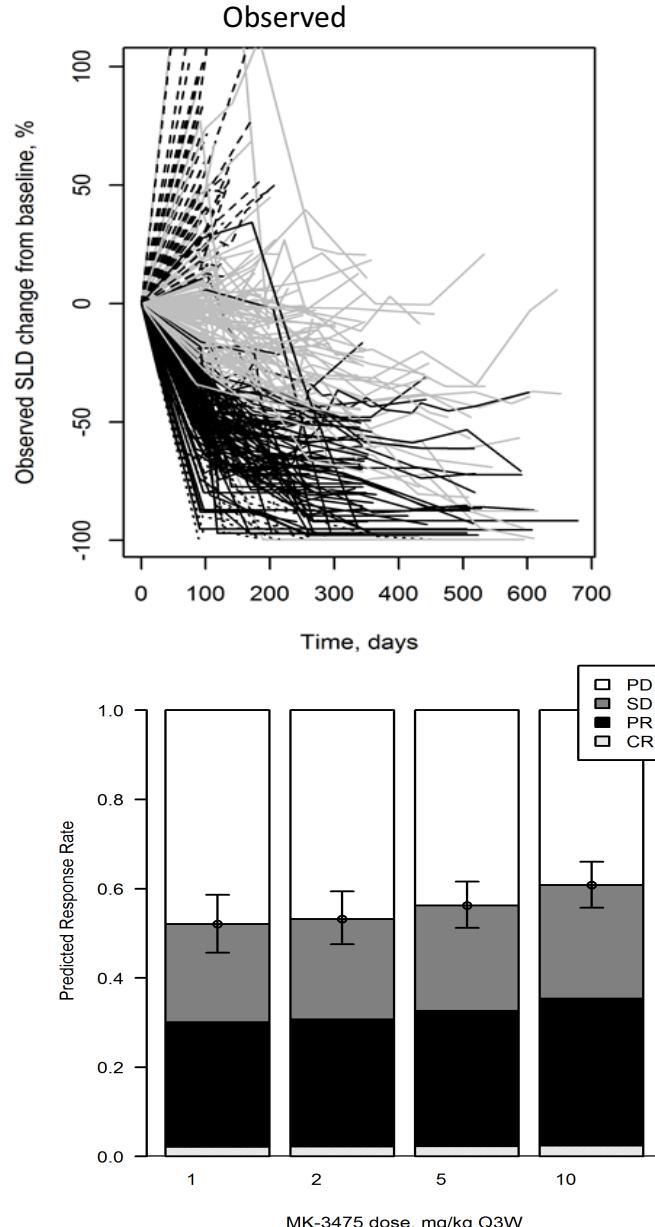
PK-PD modeling guides a critical decision on KEYTRUDA® dose

- Exposure-response analysis: flat exposure-response between 2Q3, 10Q3, 10Q.
 - Key point: Tumor size change was used for modeling as response instead of conventional RECIST criterion
 - Change in Tumor size vs Exposure: no difference between 2Q3, 10Q3, 10Q2



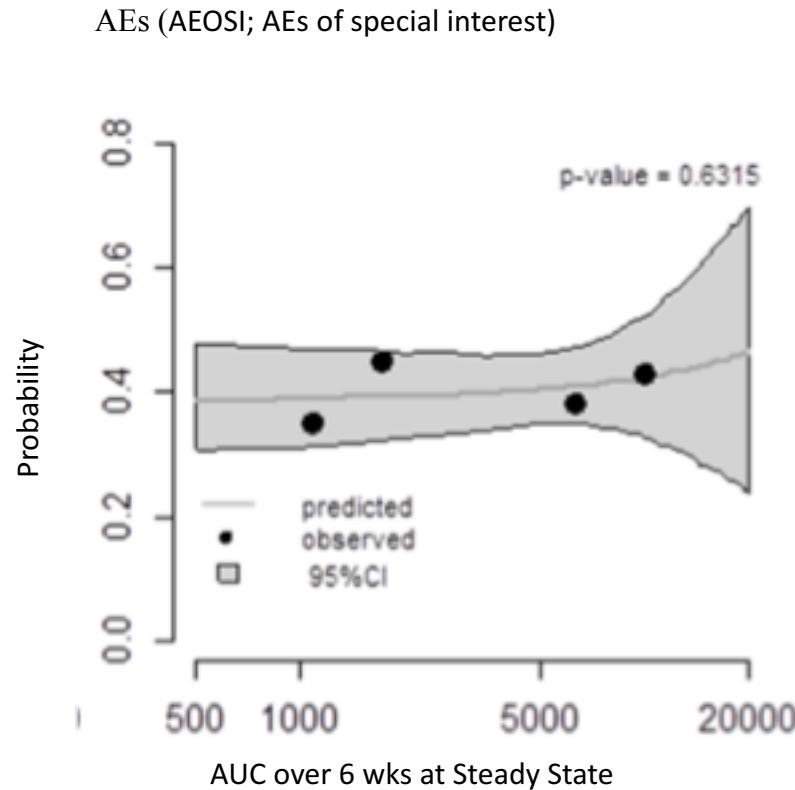
The black line shows the (log)linear regression of change from baseline vs. AUC.
Dashed reference lines indicate +20%, 0 and -30% change.

Tumor Response model Characterizes Growth Patterns and Overall Predictions with Dose



Relatively flat exposure-response relationships in efficacy [tumor size reduction] resulting in optimally efficacious dose of 2 mg/kg Q3W

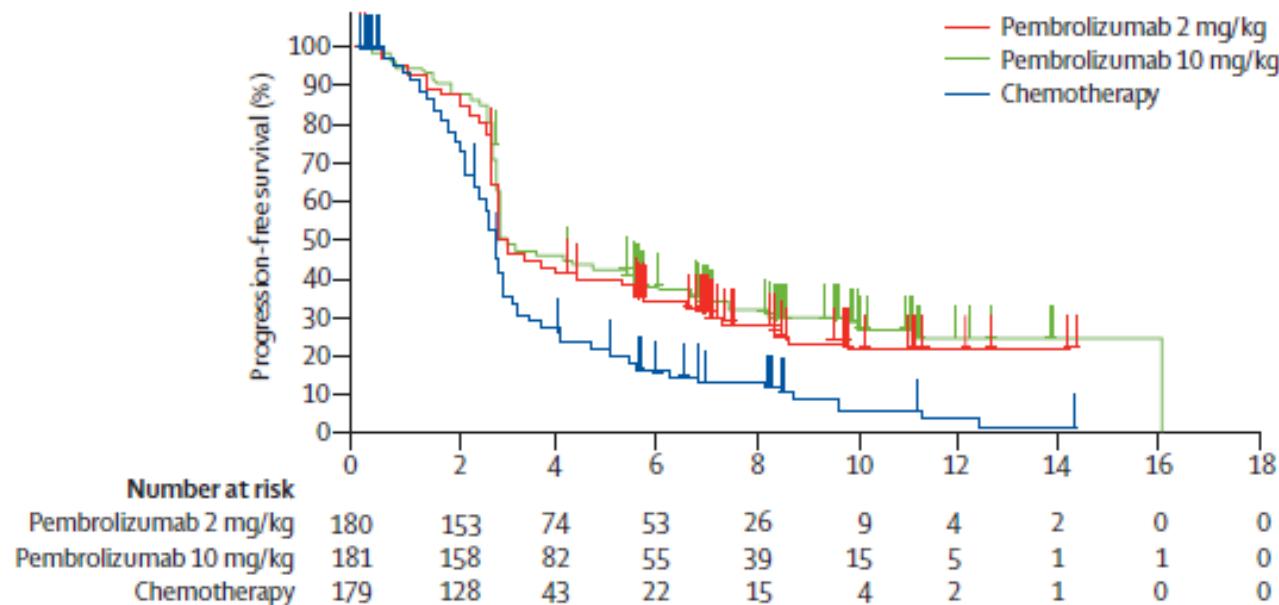
Flat exposure-AE relationship resulting in supporting optimally efficacious dose of 2 mg/kg Q3W



Solid lines represent model estimated probability and shaded areas represent the 95% confidence intervals. P-values represent significance level of the exposure-response term when forced into the model.

PFS from randomized studies confirmed 2 mg/kg as an optimal dose

Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial



PK/PD Findings supported Development and Approval

- Exposure-Response analysis was key to identifying optimal dose.
- A wide therapeutic range was established, based on Exposure-Response, Exposure-Safety analyses
- **Approval of KEYTRUDA® based upon positive risk/benefit**
 - Efficacy based on cohort B2 173 IPI-refractory patients, with 80 patients at the 2 mg/kg recommended dose
- **Received Accelerated Approval on Sept 4, 2014**
 - Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit.
 - Two confirmatory trials (P002 (IPI-treated) and P006 (IPI-naïve)) were conducted to confirm the safety and efficacy of KEYTRUDA

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