Translational and Clinical Pharmacology Perspectives of Cancer Immunotherapy

Amit Roy

Bristol-Myers Squibb

ASCPT Annual Meeting
Washington, DC
15-March, 2019

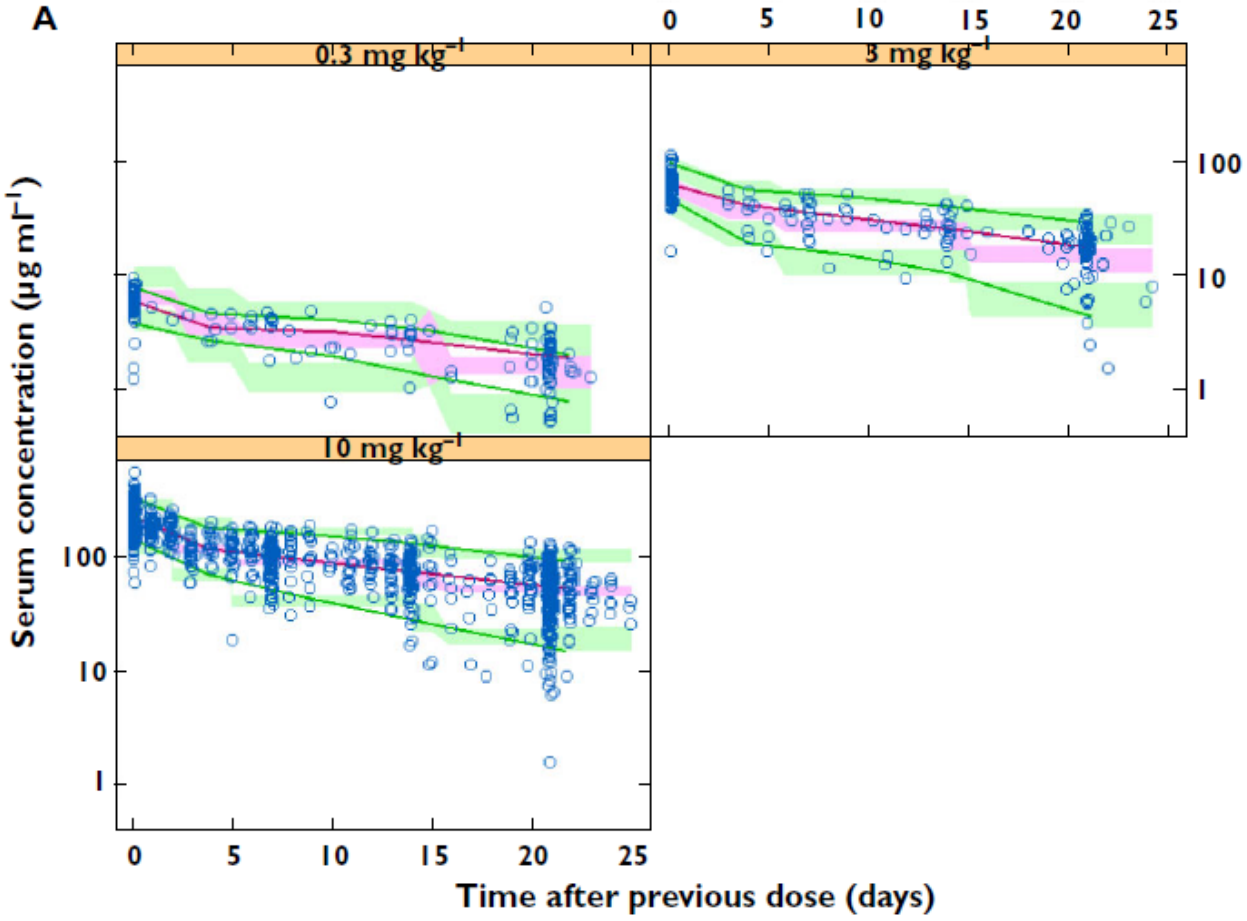
Learning Objectives

- What covariates should be assessed on PK parameters of anti-cancer mAbs?
- What is the association between disease severity and PK
- How should the effect of ADA be assessed?
- What measures of exposure should be utilized in exposure-response analyses
- How can E-R analyses be leveraged to address data gaps and inform drug development and regulatory decisions
- Considerations for FIH dose selection

Clinical Pharmacology Profiling of Ipilimumab

- Ipilimumab is a fully human a-CTLA4 mAb
- First immune-checkpoint inhibitor to demonstrate clinical benefit
- Dosing regimen: 3 mg/kg Q3W (4 doses)
- Ipilimumab PK is linear (T-half ~15 days)
- Approx 80% of steady-state is achieved by the 4th dose
- PK data available for clinical pharmacology profiling
  - Intensive PK (N=15): 10 mg/kg
  - Sparse PK (N=713): 0.3, 3, and 10 mg/kg

Visual Predictive Check:
Serum Conc vs Time After Previous Dose, by Dose Level

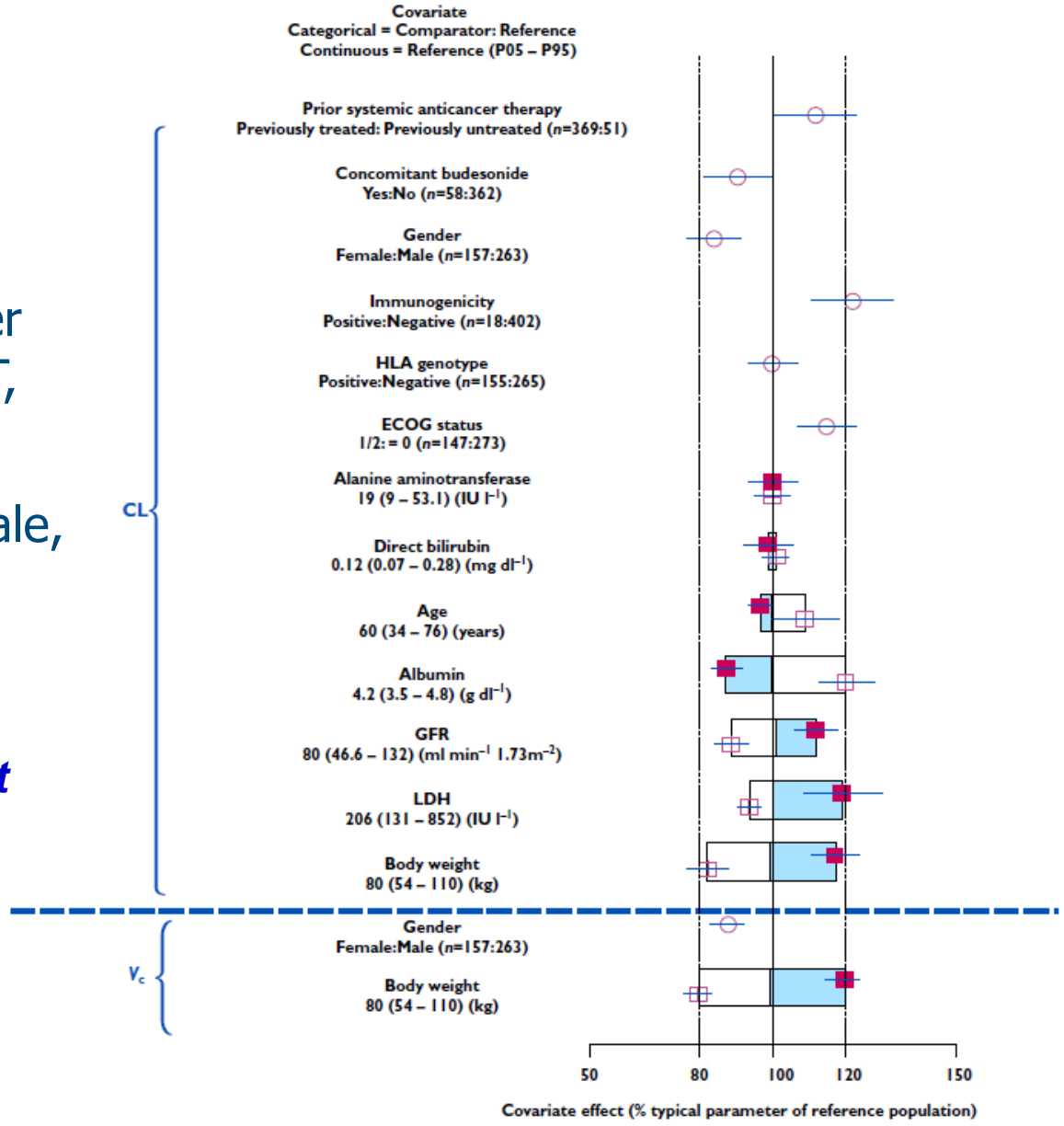


Hodi S, et al (2010) *NEJM*; Feng Y, et al. (2014) *Br J Clin Pharm*

Effect of Covariates on Ipilimumab PK

- CL was higher in patients who were: previously treated, male, ECOG>0, lower serum albumin, higher GFR, higher BWT, higher LDH
- VC was higher in patients who were: male, higher BWT

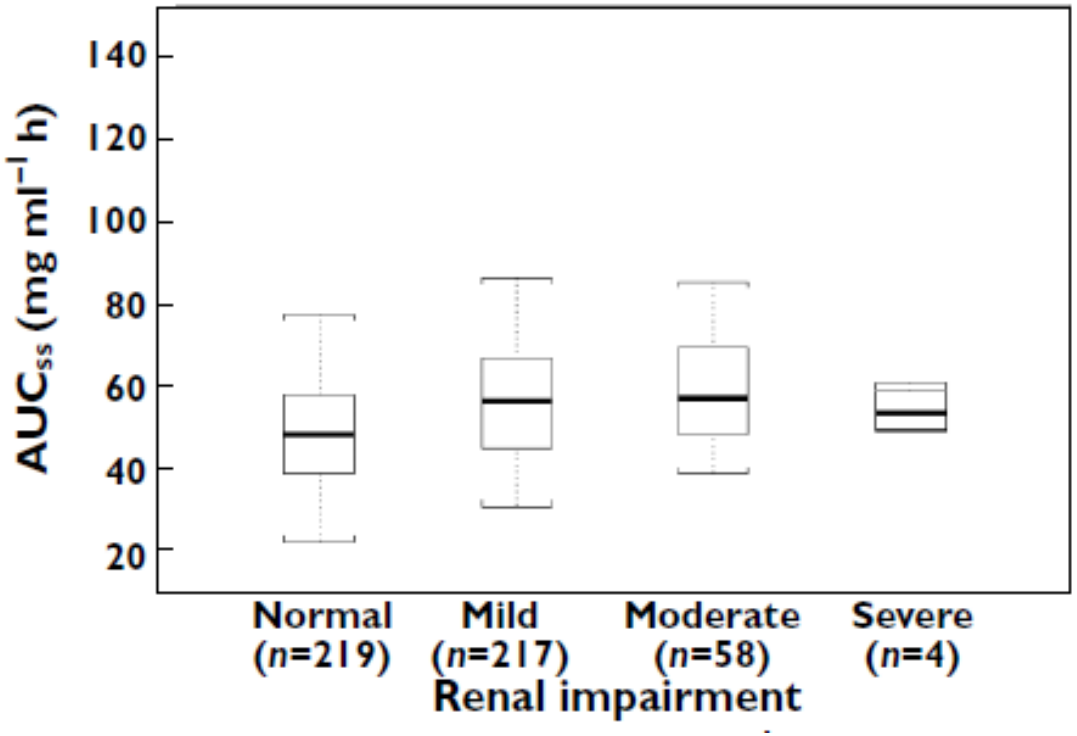
Magnitudes of the covariate-effects are not considered to be clinically relevant



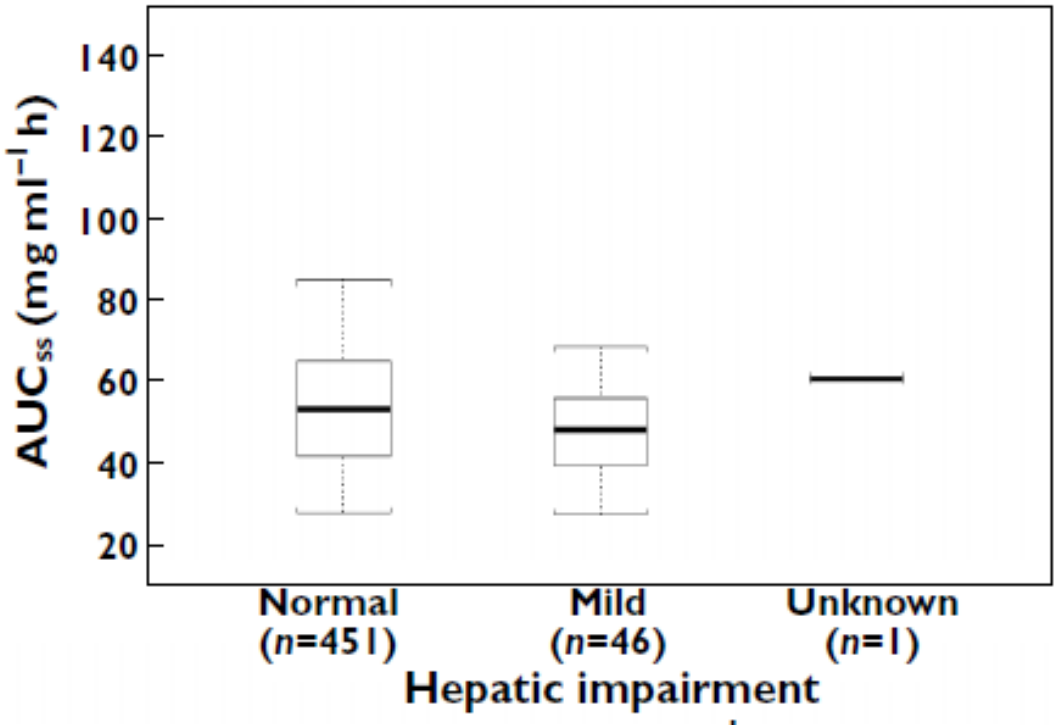
Feng Y, et al. (2014) *Br J Clin Pharm*

Assessment of Organ Dysfunction on Ipilimumab Exposure (3 mg/kg Q3W)

AUCss by Renal Impairment Status



AUCss by Hepatic Impairment Status*



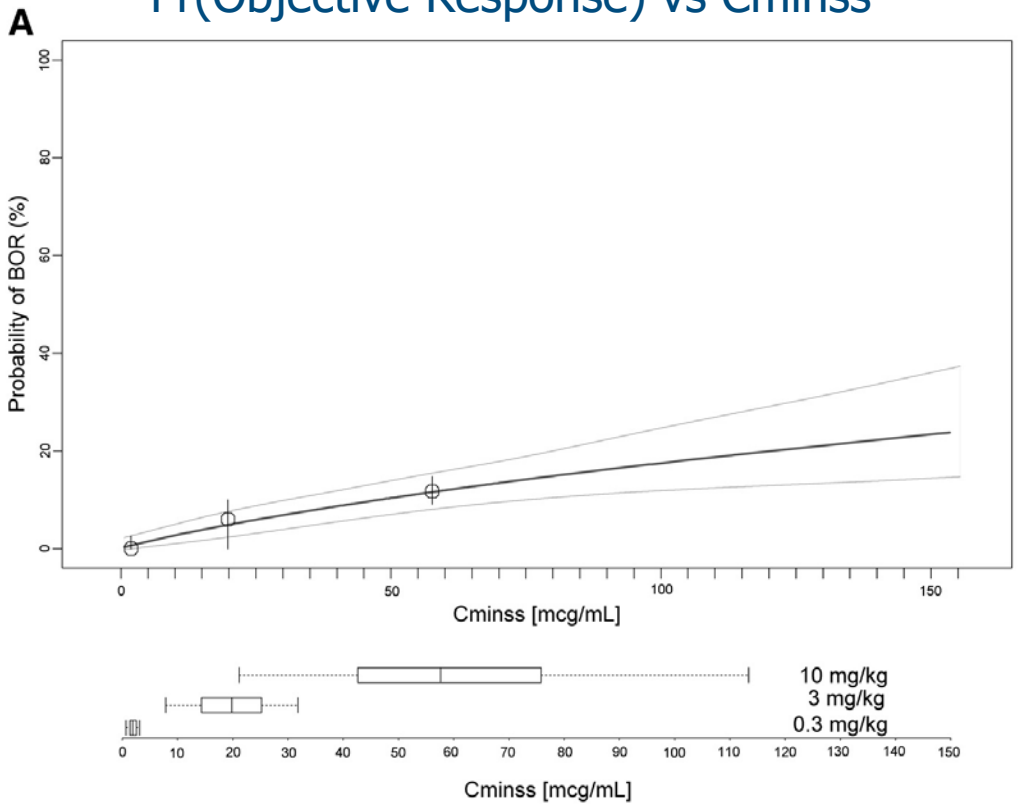
Neither renal nor hepatic impairment have a clinically relevant effect on exposure

Feng Y, et al. (2014) *Br J Clin Pharm*

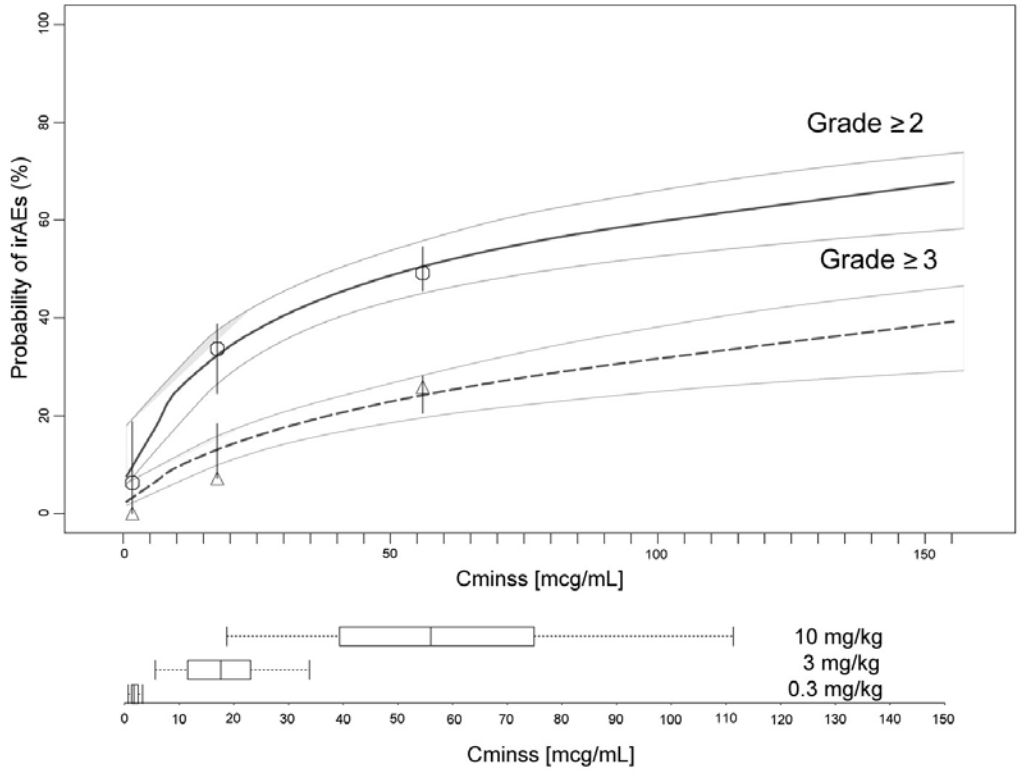
*As defined in: Ramalingam SS (2010), *J Clin Oncol*

Ipilimumab Exposure-Response of Efficacy and Safety

Pr(Objective Response) vs Cminss



Pr(irAEs) vs Cminss



Subjects with higher ipilimumab exposure have better efficacy and worse safety

Feng Y, et al. (2013) *Clin Can Res*

Model-Based Evidence of Ipilimumab Efficacy in Previously Untreated Advanced Melanoma

- In 2011, 3 mg/kg IPI monotherapy was approved in the US and EU
  - US: for advanced (metastatic unresectable stage III/IV) melanoma
  - EU: for previously treated advanced melanoma
- A Ph3 study of 10 mg/kg IPI in previously untreated advanced melanoma in combination with dacarbazine (DTIC) showed that
  - IPI 10 mg/kg + DTIC was more efficacious than DTIC alone
  - Toxicity of 10 mg/kg IPI + DTIC was markedly higher than IPI 3 mg/kg monotherapy (mTx)

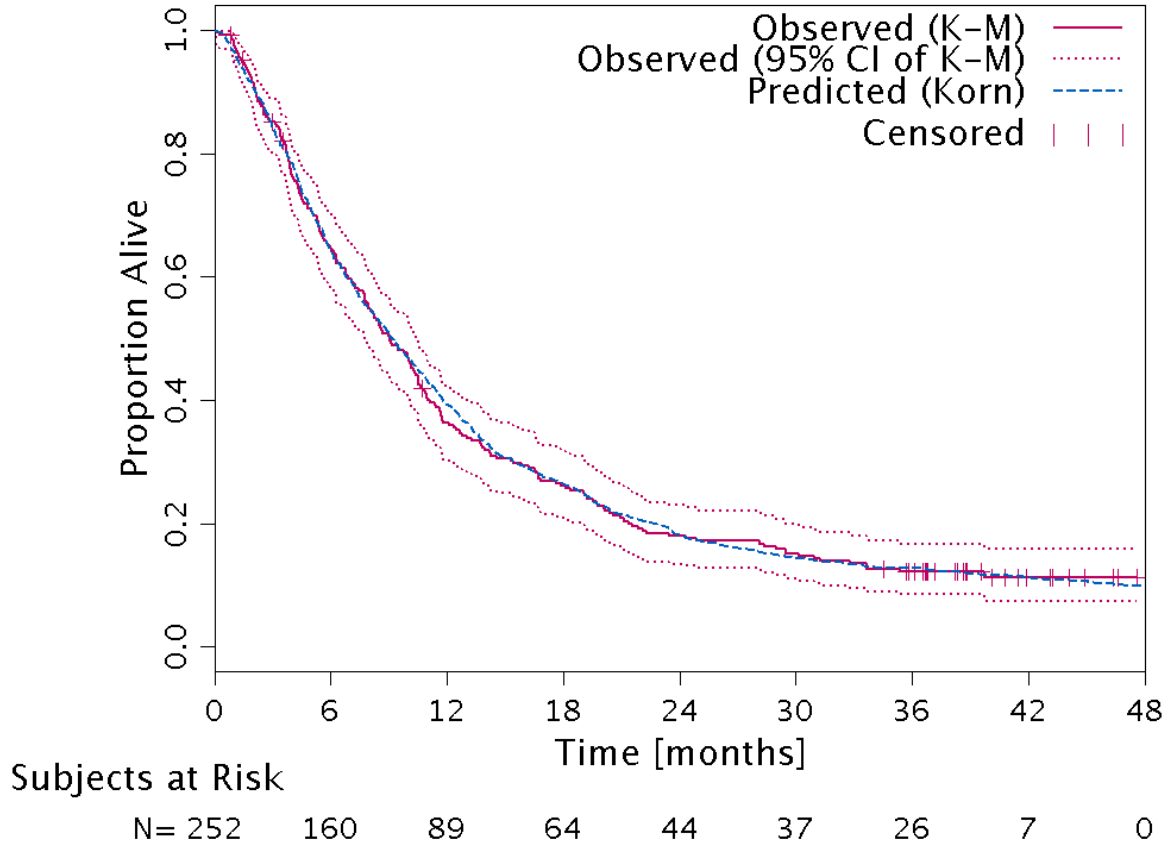
How can the understanding of E-R be leveraged to to obtain approval for 3 mg/kg mTx in previously untreated advanced melanoma patients without a RCT?

Challenge: Demonstrate efficacy of 3 mg/kg IPI mTx in Previously Untreated Advanced Melanoma Patients

- Available data
  - PK and OS data from 4 Ph2 studies of IPI mTx (mostly previously treated patients), and 1 Ph3 study (previously untreated patients)
  - OS data from 2 observational studies in previously untreated patients with IPI 3 mg/kg
- Approach:
  - Compare OS in observational studies with virtual historical controls generated by the Korn meta-analysis
  - Quantify effect of prior treatment on OS by exposure-response analysis

External Validation of Meta-Analysis Model

Observed and Predicted OS of Previously Untreated Advanced Melanoma Patients Receiving Only DTIC (CA184024)

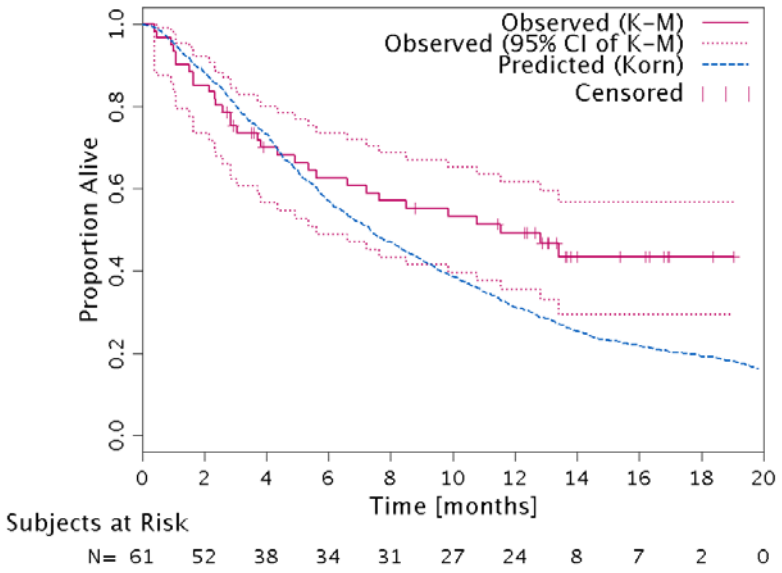


The OS of previously untreated patients receiving DTIC is similar to that of the Korn model predicted historical OS

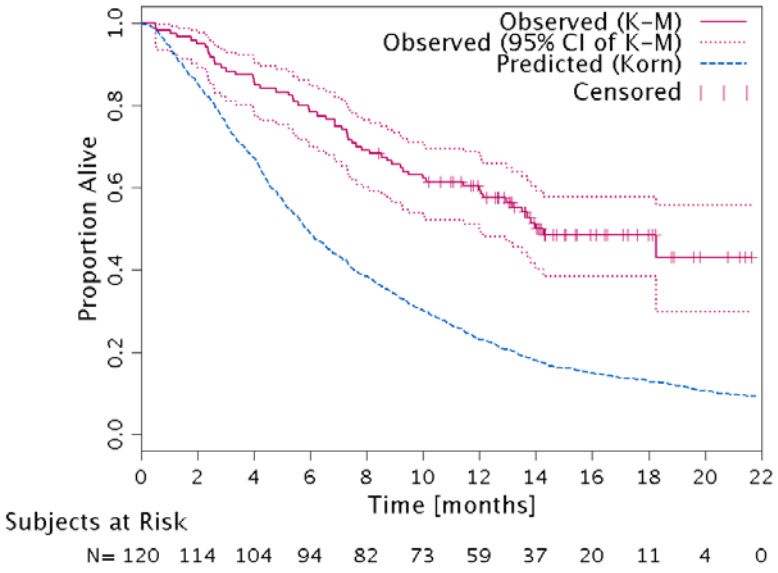
Feng Y, et al. (2014) *ESMO*

Evidence that 3 mg/kg Ipilimumab Confers a Survival Benefit to Previously Untreated Advanced Melanoma (2/2)

Overall Survival of Previously Untreated Advanced Melanoma Patients Receiving 3 mg/kg Ipilimumab Monotherapy (CA184332)



Overall Survival of Previously Untreated Advanced Melanoma Patients Receiving 3 mg/kg Ipilimumab Monotherapy (CA184338)

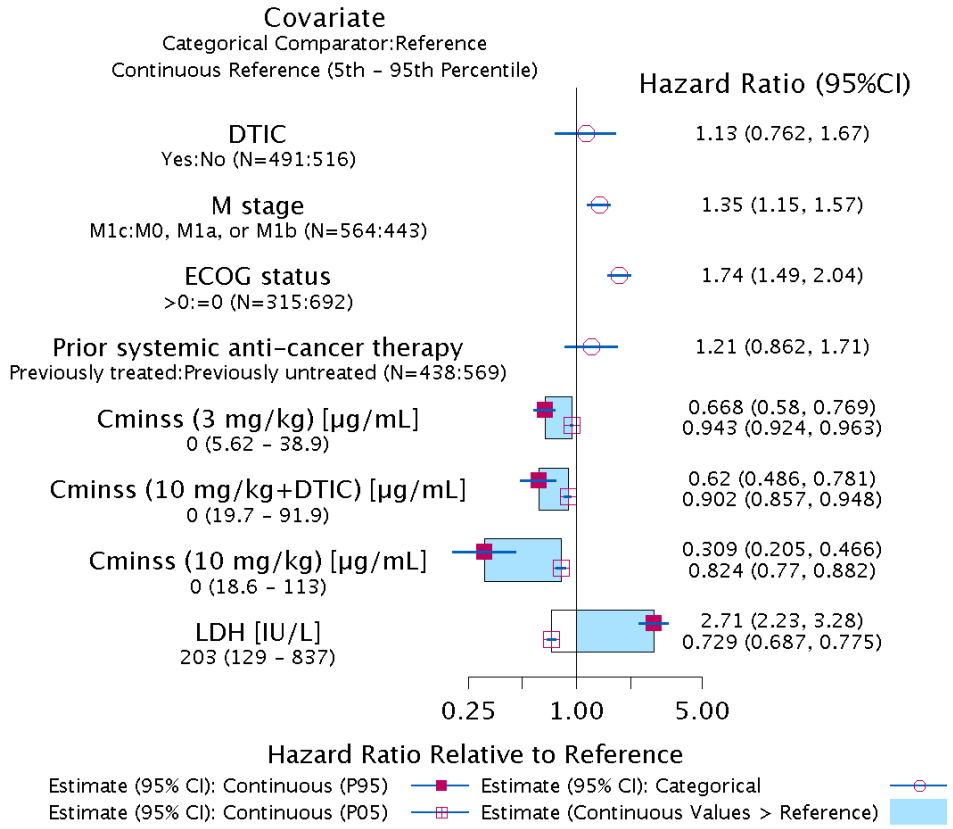


The OS of previously untreated patients receiving IPI is better than that of the Korn model generated historical controls

Feng Y, et al. (2014) *ESMO*

E-R Analysis of OS in Advanced Melanoma Patients

Hazard Ratio of OS (Pooled Ph2 and Ph3 Clinical Studies)



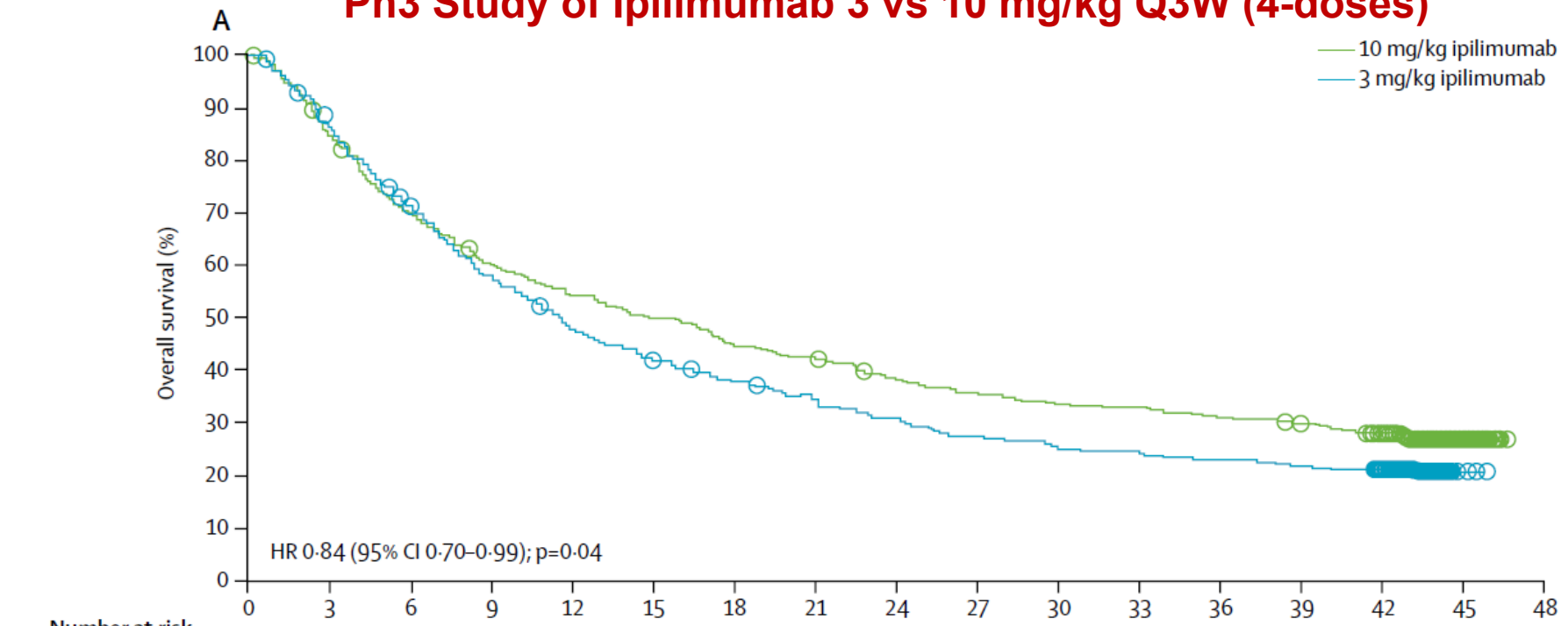
- ***The model-based analyses provided key supportive evidence for the EU approval of 3 mg/kg IPI mTx in previously untreated advanced melanoma***

- ***Yervoy SmPC: "OS was independent of prior systemic anti-cancer therapy, and increased with higher ipilimumab Cminss"***

Feng Y, et al. (2014) *ESMO*

Confirmation of Ipilimumab E-R of OS in Adv Melanoma

OS in Advanced Melanoma: Ph3 Study of Ipilimumab 3 vs 10 mg/kg Q3W (4-doses)



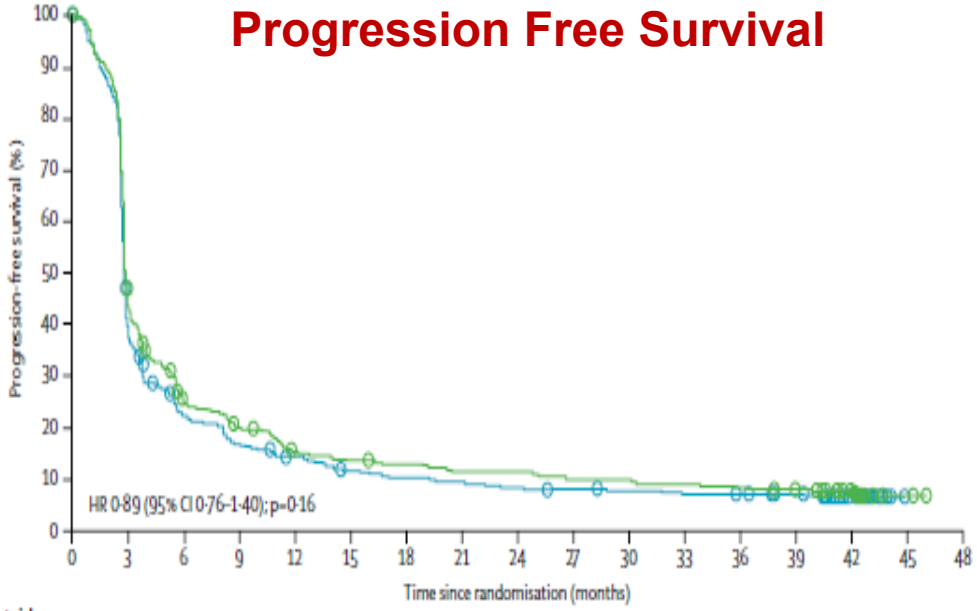
Long-term efficacy of ipilimumab does not depend upon maintenance of drug in circulation

Ascierto P, et al. (2017) *Lancet Oncology*

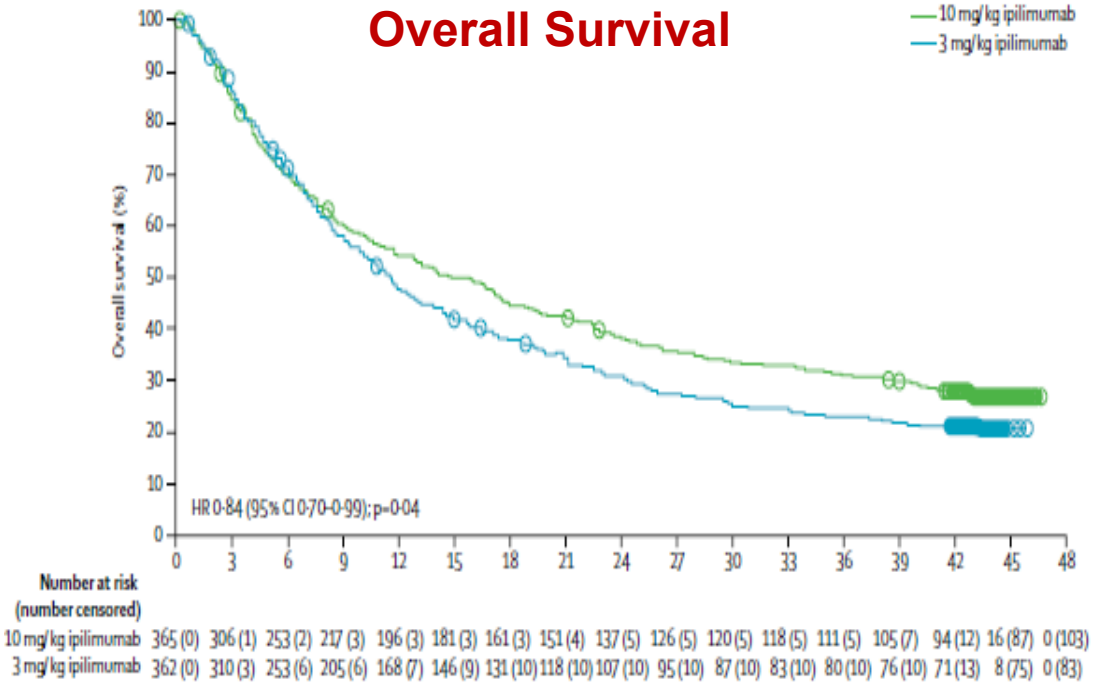
Confirmation of Ipilimumab E-R of OS in Adv Melanoma

PFS and OS in Advanced Melanoma: Ph3 Study of Ipilimumab 3 vs 10 mg/kg Q3W (4-doses)

Progression Free Survival



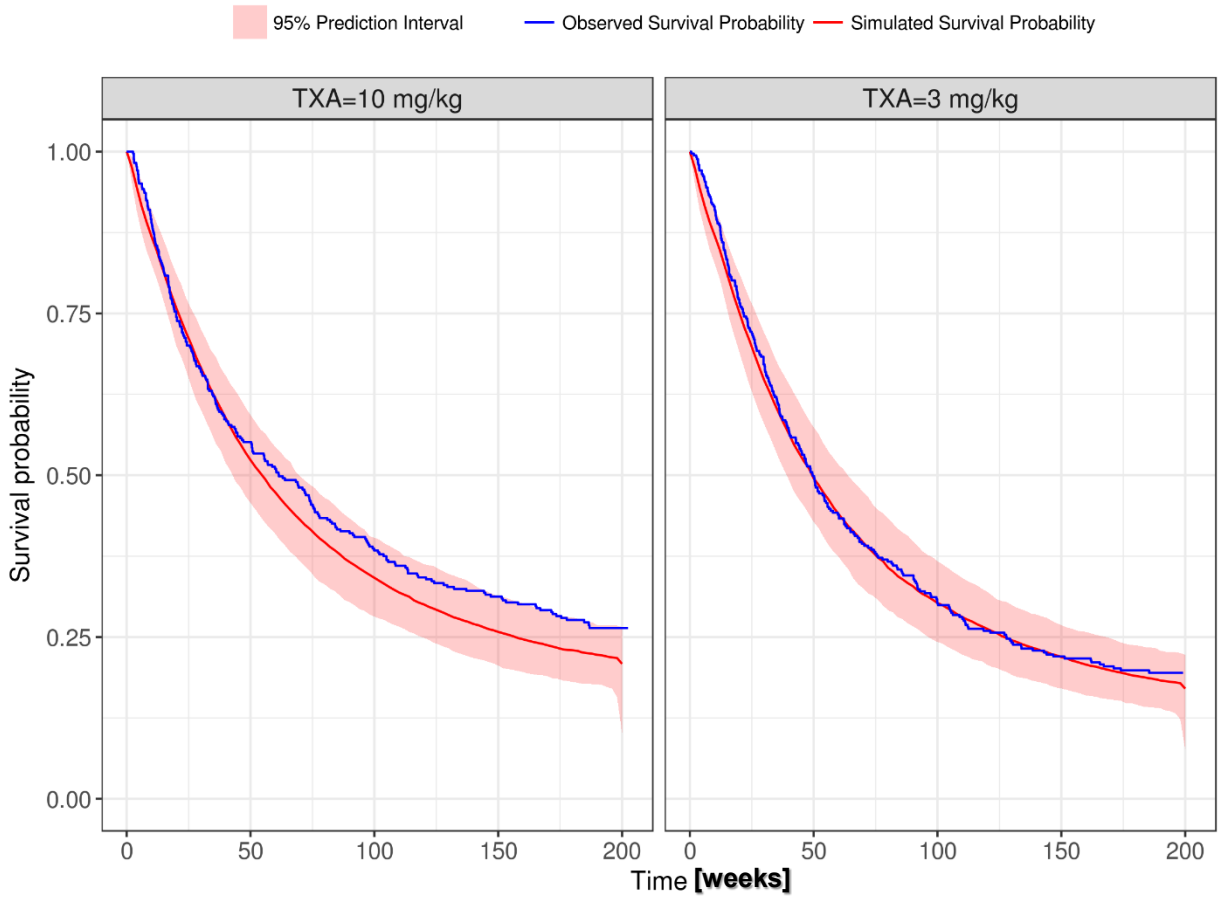
Overall Survival



- ***PFS was similar, but OS was better with 10 mg/kg***
- ***Long-term efficacy of ipilimumab does not depend upon maintenance of drug in circulation***

Ascierto P, et al. (2017) *Lancet Oncology*

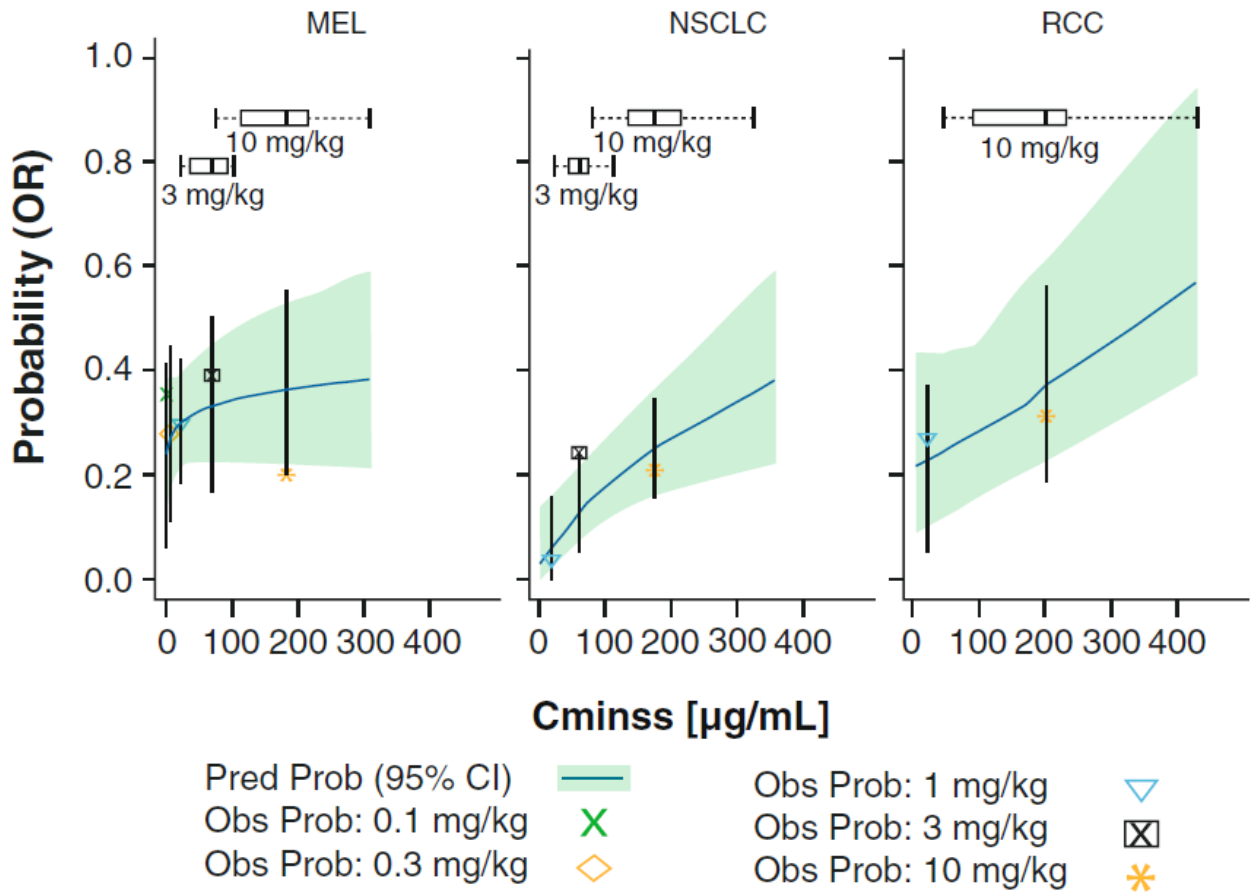
External Validation of a TGD-OS Model



TGD-OS model developed with nivolumab predicts OS with ipilimumab

Roy A, et al. (2018) *FDA Workshop of MIDD in Oncology*

Nivolumab Dose Selection: Preliminary E-R of Efficacy in Melanoma, NSCLC, and RCC

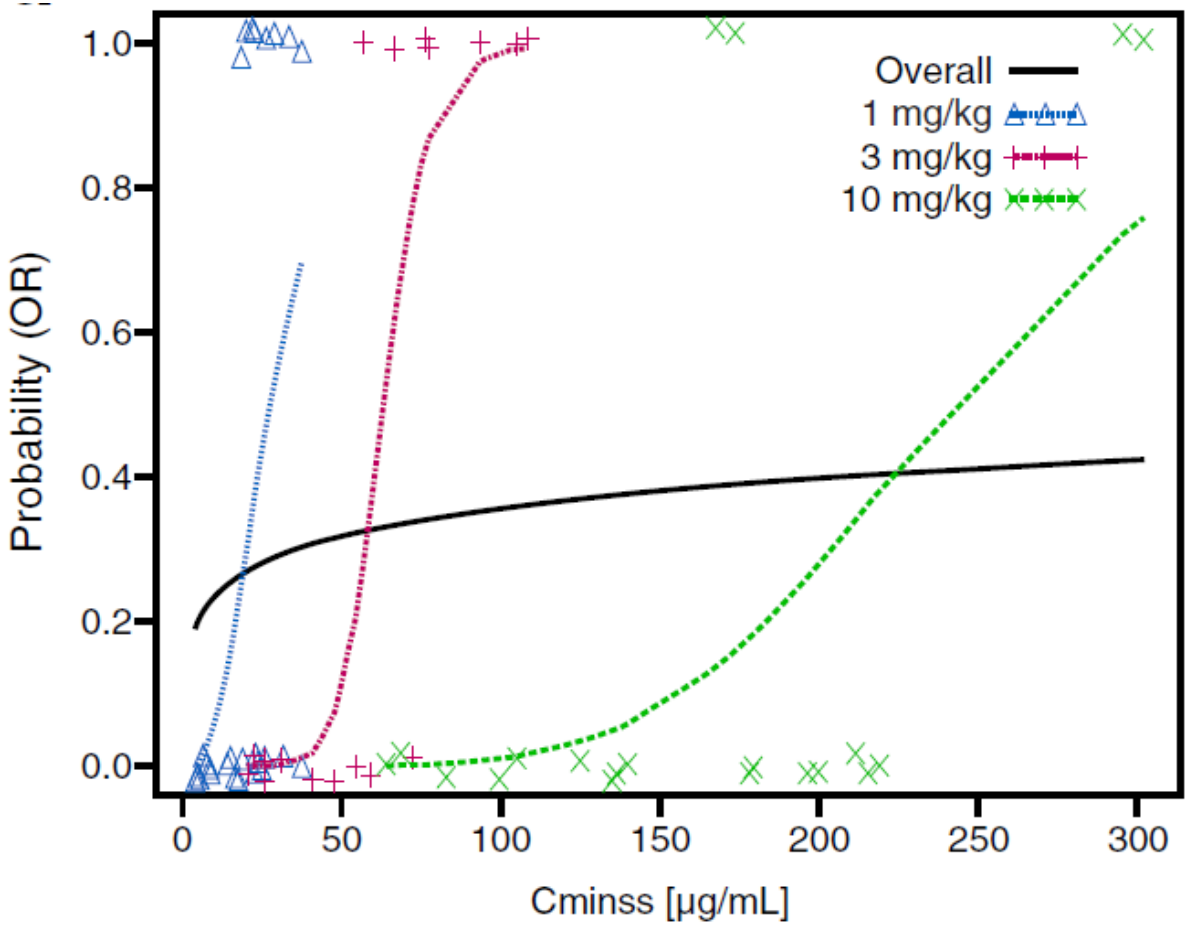


- ***Exposure-response appears to have an increasing trend***
- ***Observed response rate is maximal at 3 mg/kg Q2W***

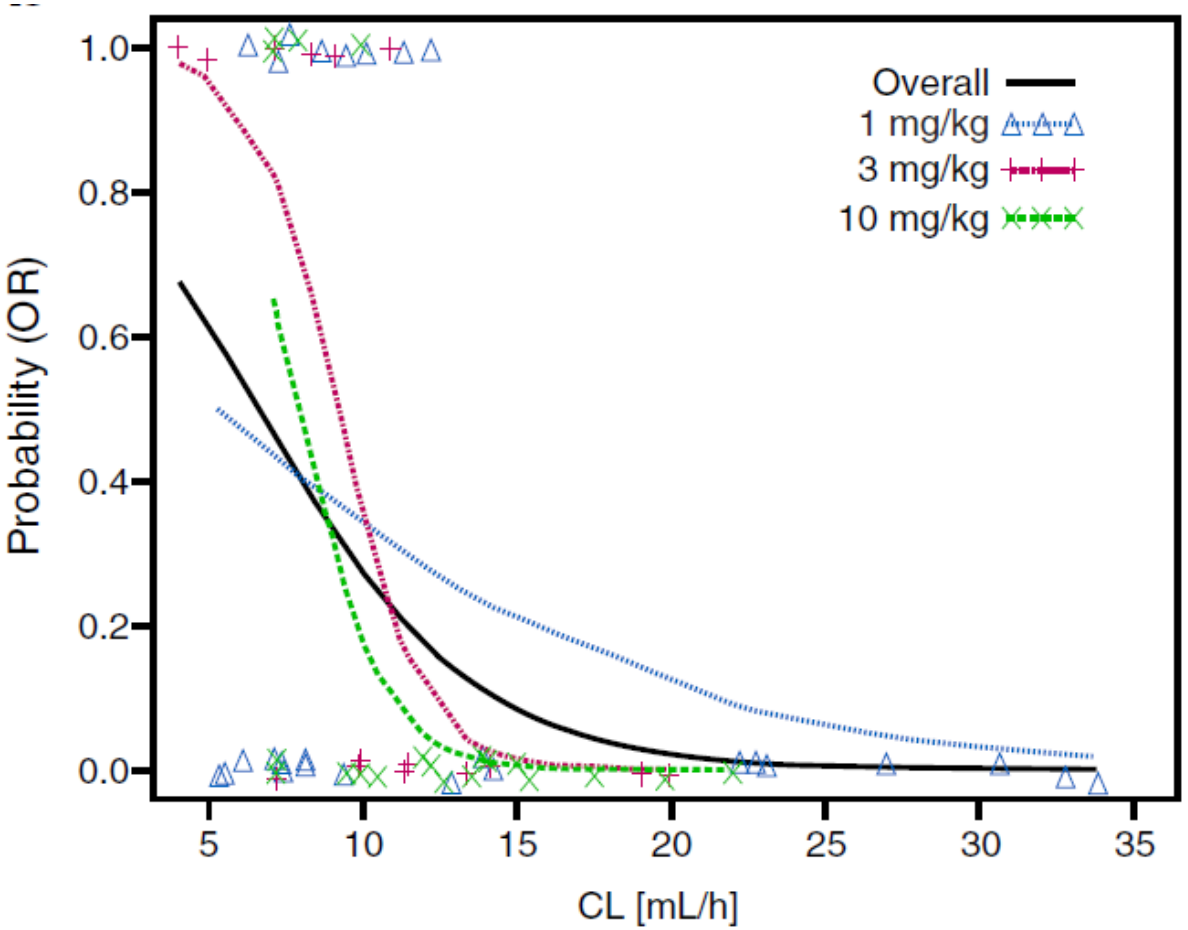
Agrawal S, et al. (2016) *J Immunotherapy Cancer*

Nivolumab Exploratory E-R of Efficacy (Melanoma)

Pr(Objective Response) vs Cminss, by Dose



Pr(Objective Response) vs CL, by Dose

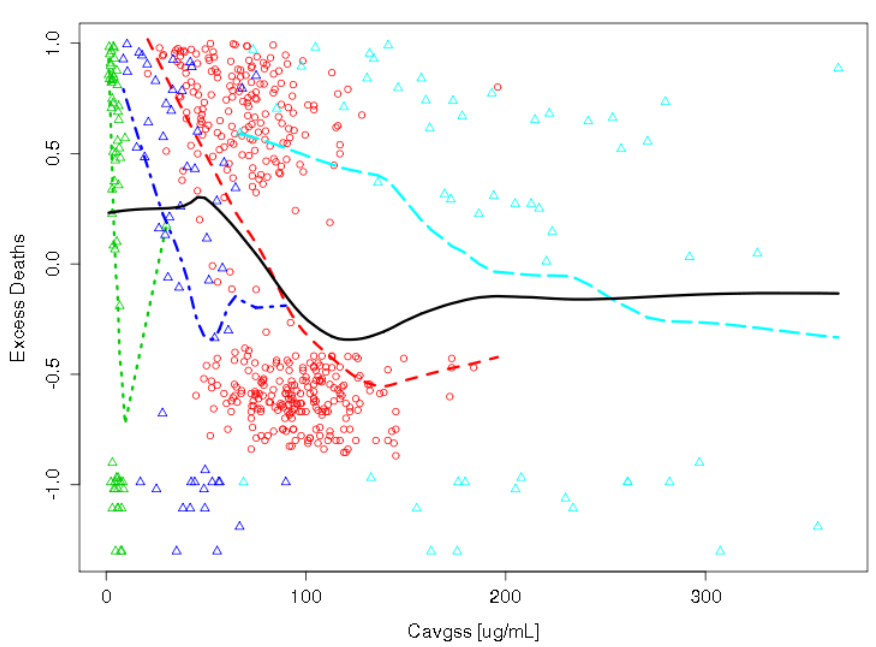


Subjects with higher CL have lower probability of responding

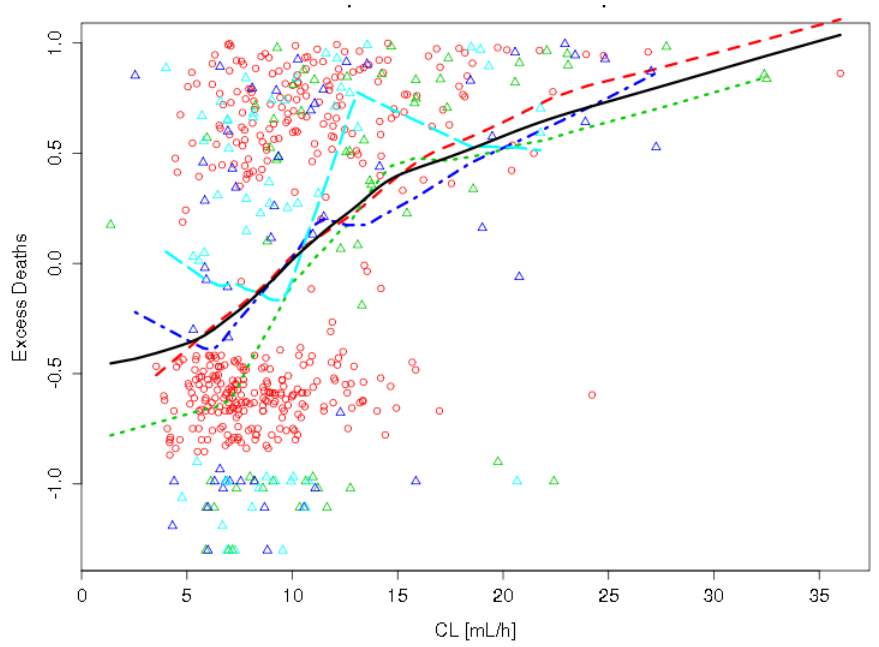
Agrawal S, et al. (2016) *J Immunotherapy Cancer*

Exploratory Nivolumab E-R of OS in RCC

Martingale Residuals versus Cavgss in 2L RCC, by Nivolumab Dosing Regimen



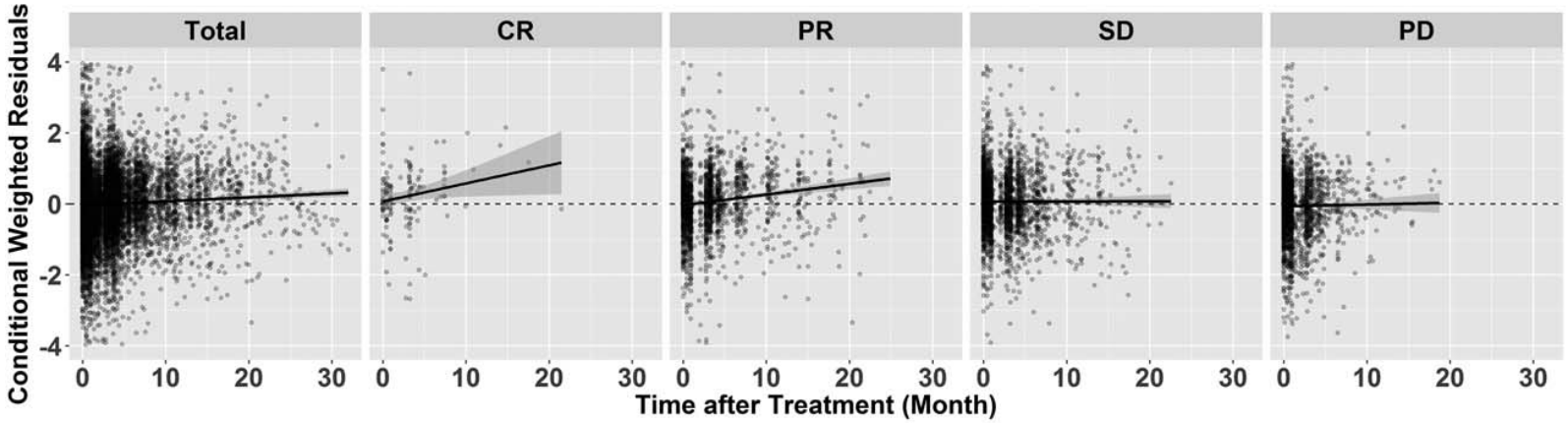
Martingale Residuals versus CL in 2L RCC, by Nivolumab Dosing Regimen

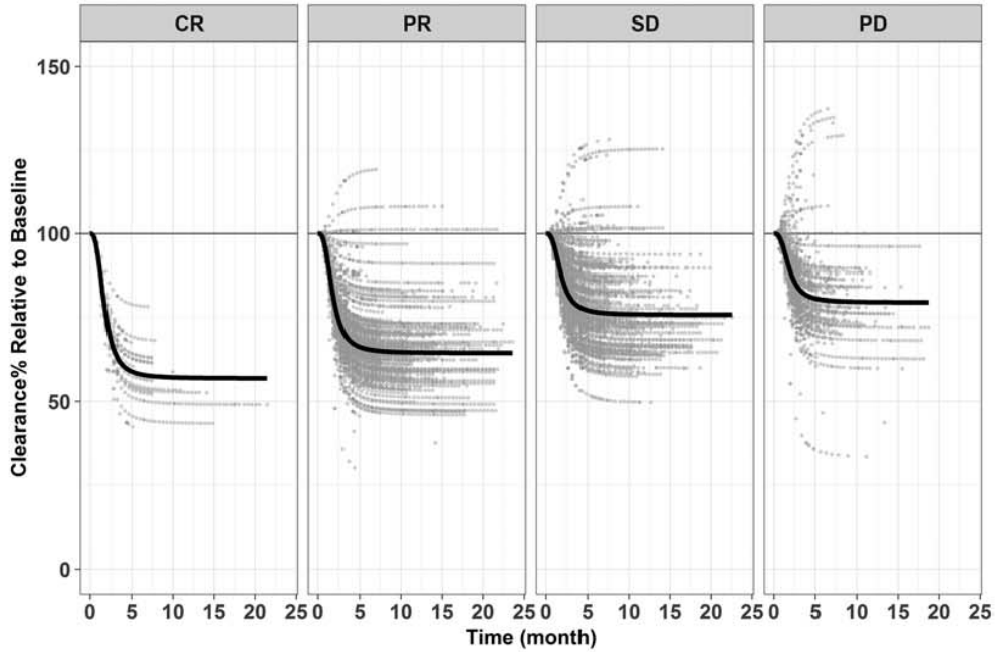


- ***Relationship of Cavgss to risk of death is not consistent across dose regimens***
- ***Relationship of CL to risk of death is consistent across dose regimens***

Roy A (2016) *ASCPT Pre-Conference Meeting*

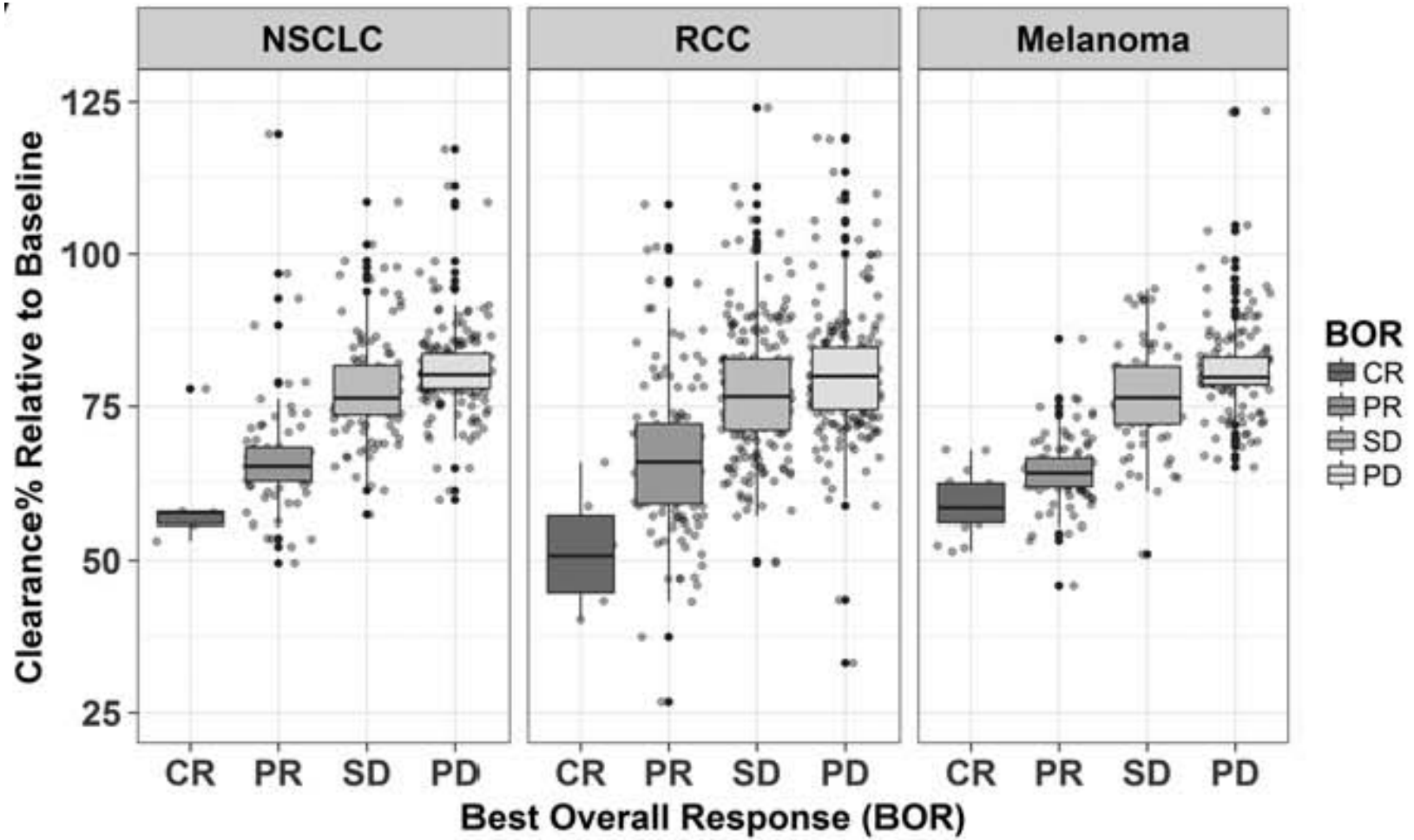
Discovery of Time-Varying Nivolumab CL





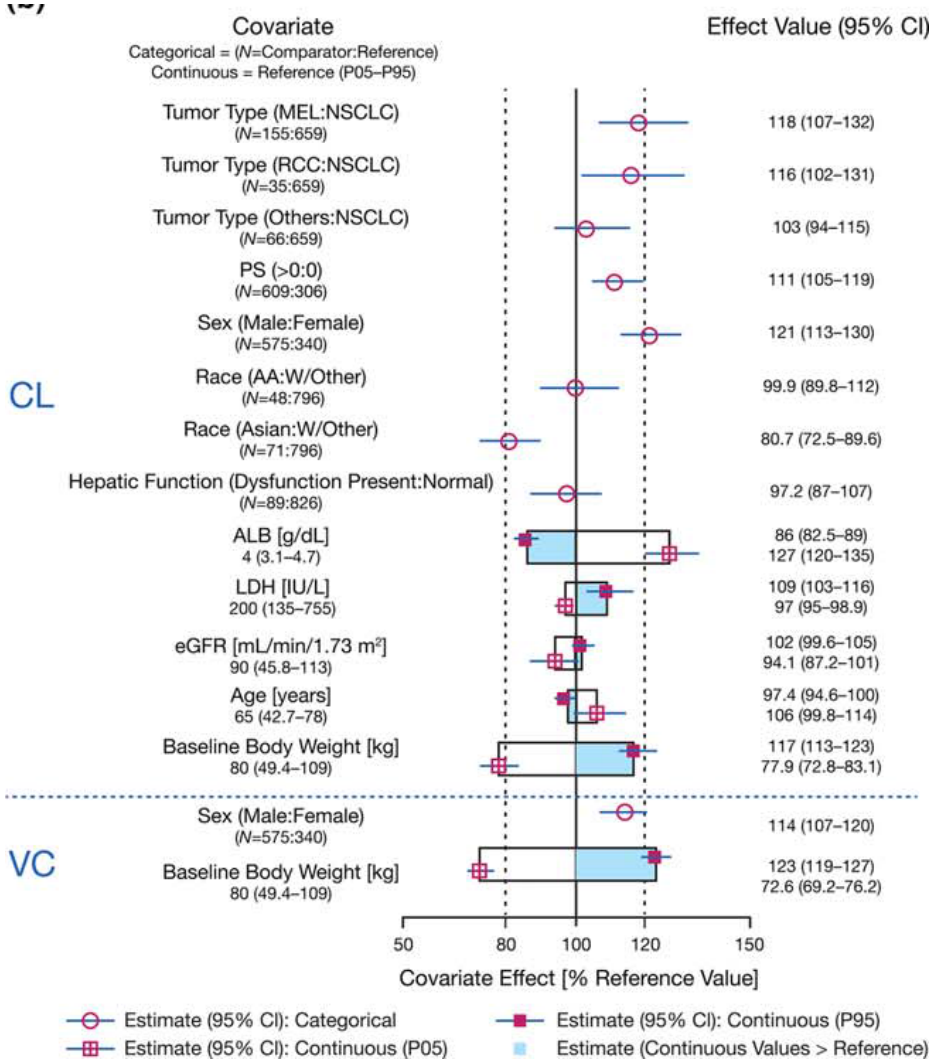
Liu C, et al. (2016) *CPT*

Association of CL and Efficacy (Best Overall Response): Melanoma, RCC, and NSCLC



Wang Y, et al. (2016) *CPT*

Covariate Effects on Nivolumab PK

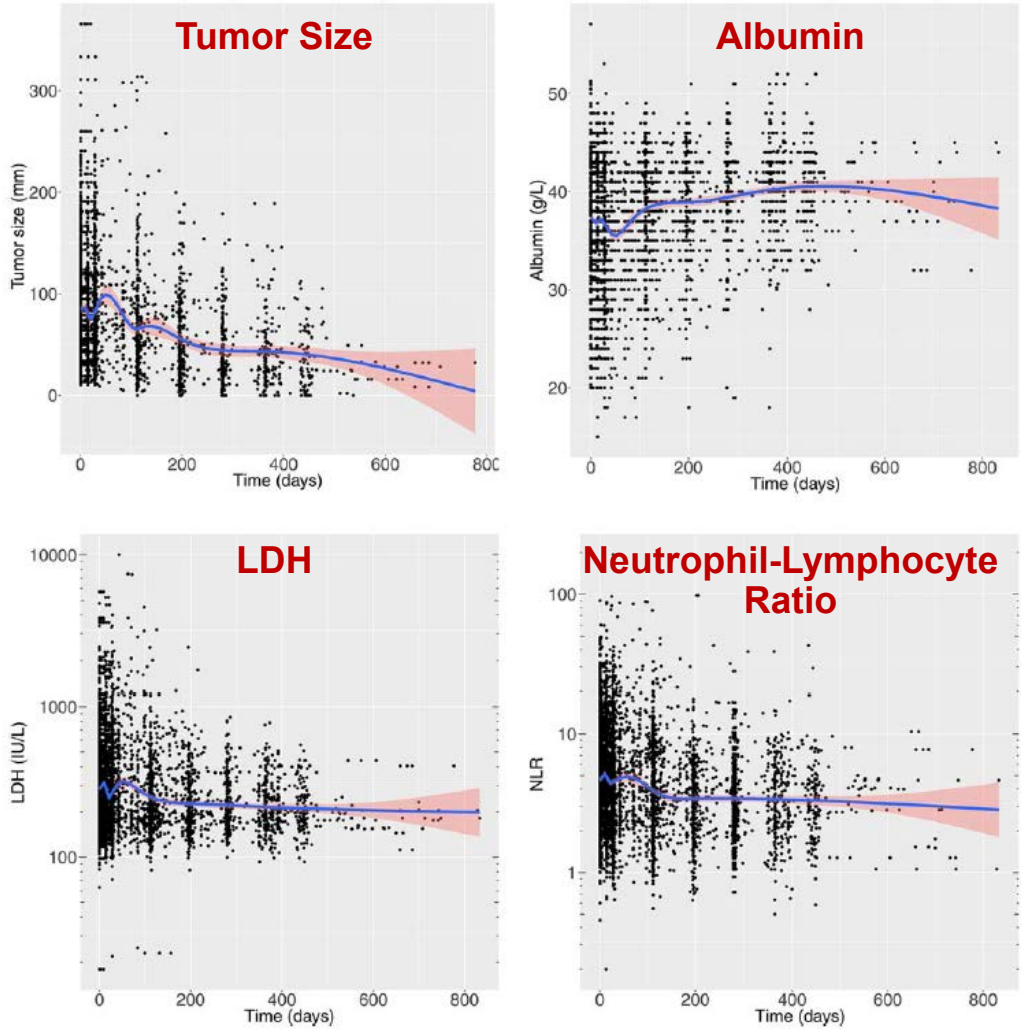


- CL was higher in patients who were: male, ECOG>0, lower serum albumin, higher BWT, higher LDH
- VC was higher in patients who were: male, higher BWT

- ***Covariates that affect nivolumab PK are similar to those of ipilimumab***
- ***Nivolumab CL may vary with tumor type***

Bajaj G, et al. (2016) *CPT:PSP*

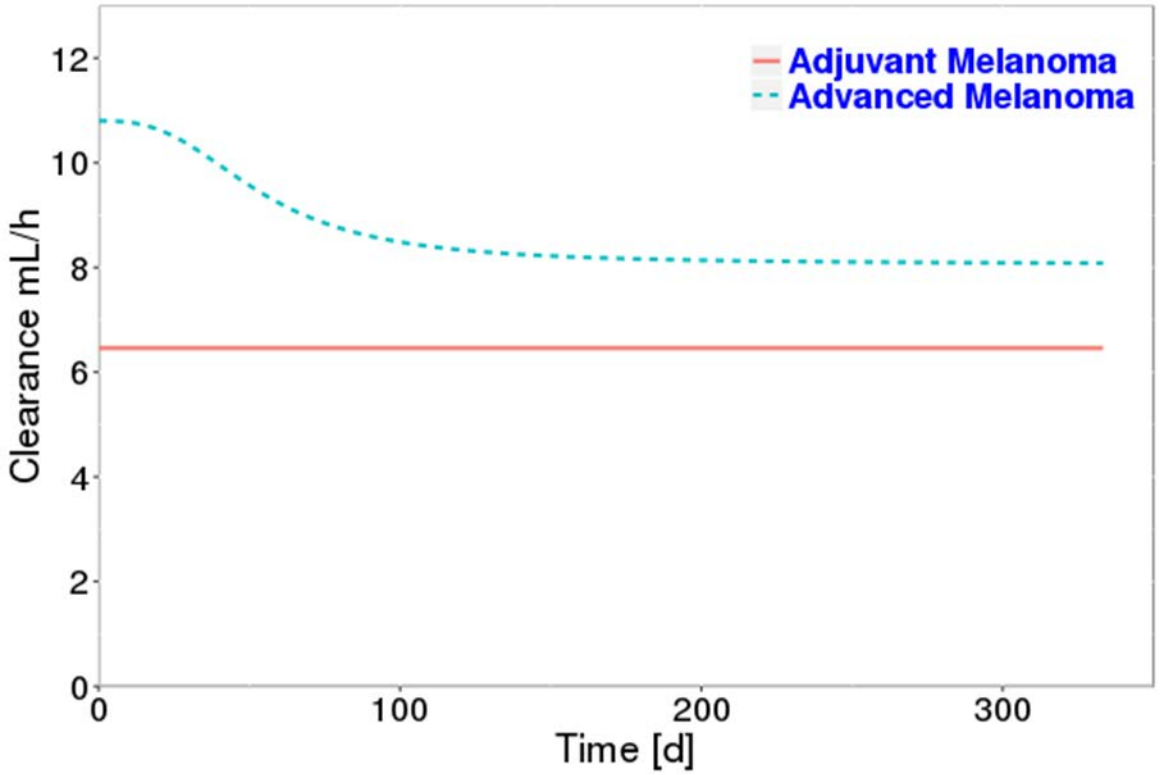
Durvalumab: Temporal Association of CL and Covariates



Temporal changes in CL correspond to temporal changes in covariates that are associated with disease

Baverel P, et al. (2018) *CPT*

Comparison of Nivolumab CL in Adjuvant and Advanced Melanoma

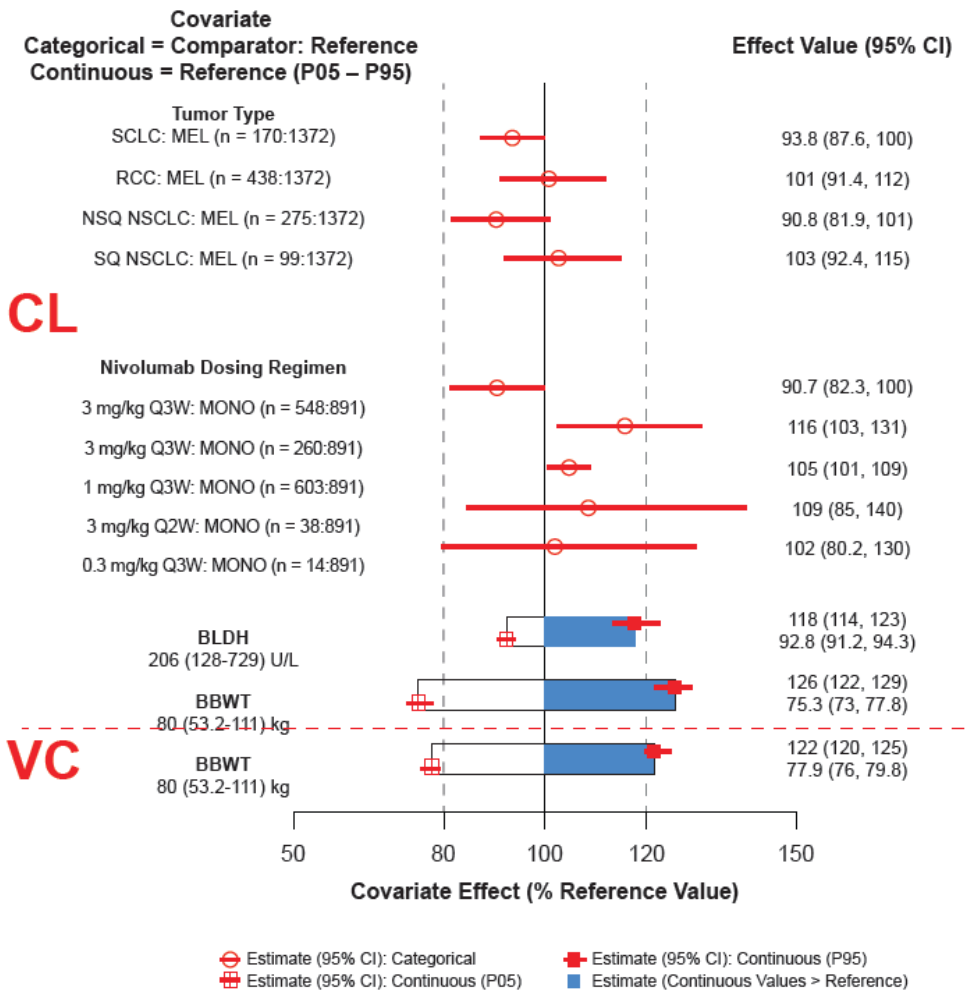


Nivolumab CL in adjuvant melanoma is constant, and consistently lower than in advanced melanoma

Hamuro L, et al. (2018) *ASCPT Meeting*

Clin Pharm Profiling of IO mAbs in Combination

Covariate-Effects on Ipilimumab PK (in Combination with Nivolumab)



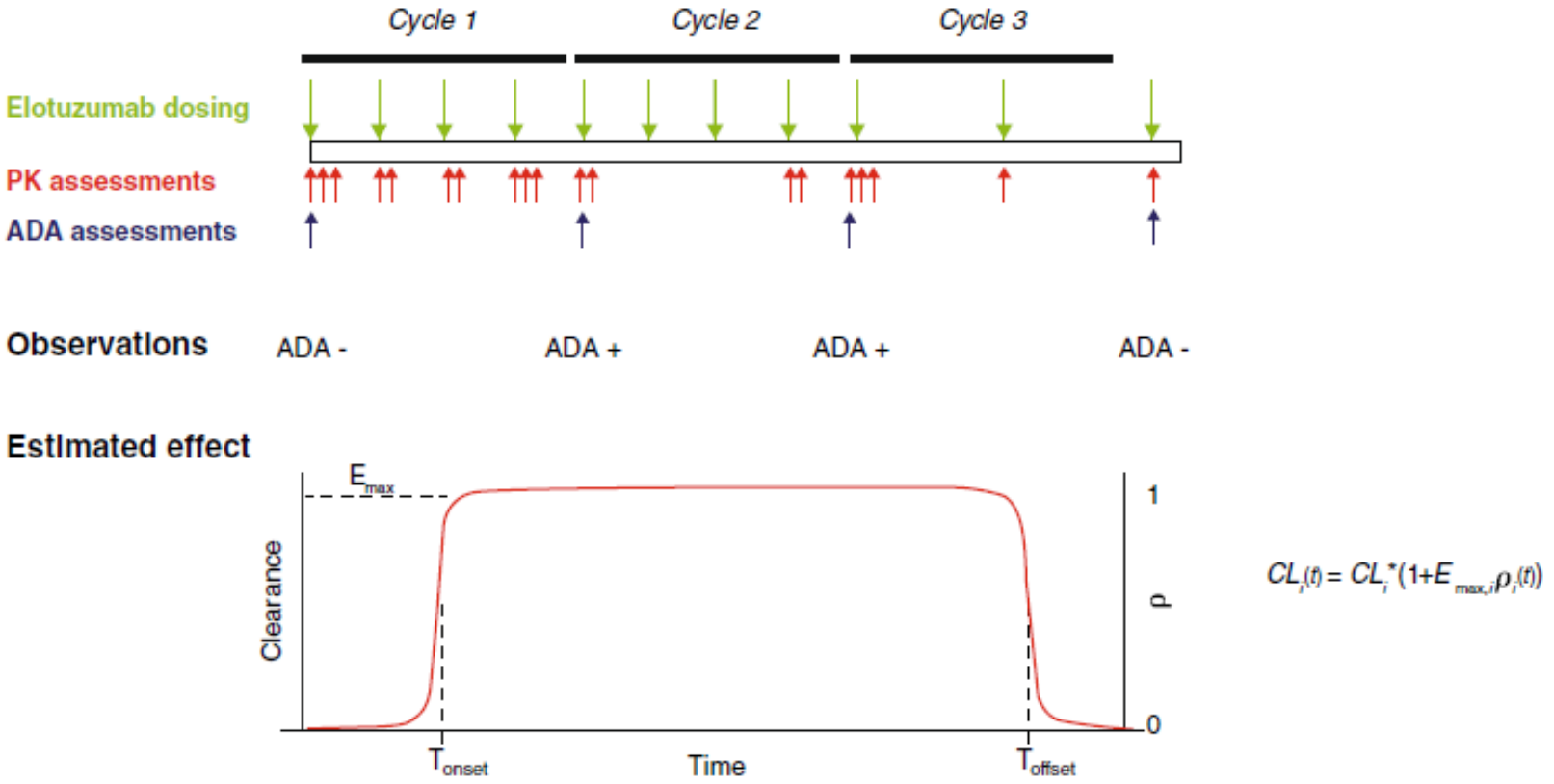
MONO = monotherapy

- ***Serum concentrations of mAb drugs << endogenous IgG***
- ***Linear component of mAb CL unlikely to be affected by combination therapy with another mAb***
- ***DDI assessment focused on effect of treatment, rather than concentration of interacting drug***
- ***Enables assessment of potential DDI due to both PK and PD related effects***
- ***E-R analyses of safety was performed by time-to-event analysis using time-varying exposure***

Sanghavi K, et al. (2017) *ACOP Meeting;* *Wang X, et al (2015) ACoP*

Assessment of Effect of Anti-Drug Antibodies (ADA) on CL

Effect of ADA on Elotuzumab CL
(Estimated by PPK Analysis)



$$CL_i(t) = CL_i^*(1+E_{max,i}\rho_i(t))$$

Assessment of ADA on PK should account for the time-varying nature of this covariate

Passey C, et al (2017) *AAPS J*

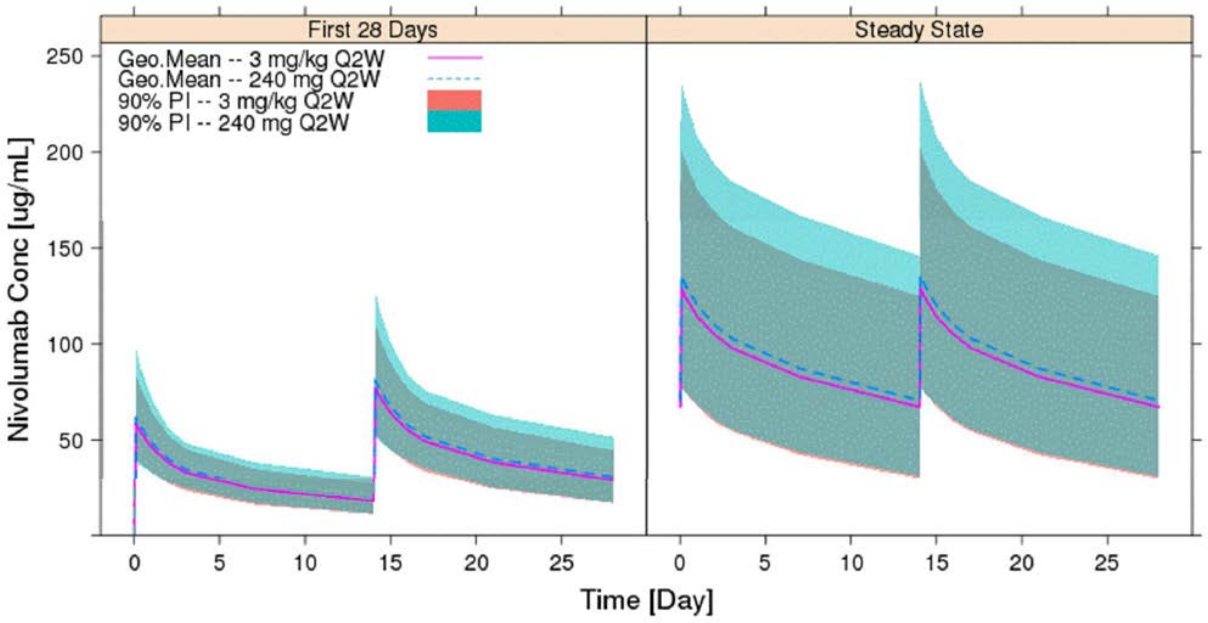
Model-Based Dose Optimization of Nivolumab

- Compare nivolumab exposures with 240 mg Q2W and 480 mg Q4W with that of 3 mg/kg Q2W and 10 mg/kg Q2W
  - 240 mg Q2W is equivalent to 3 mg/kg for an 80 kg patient (~ median weight)
  - 480 mg Q4W is expected to achieve the same Cavgss as that of 240 mg Q2W
  - Utilize a population pharmacokinetic (PPK) model to predict exposures
  - Quantify differences in summary measures of exposure
- Assess the impact of differences in exposure
  - Safety margin with respect to 10 mg/kg Q2W, shown to be safe and tolerable in Ph1 study
  - E-R of efficacy: Objective response rate (ORR), and overall survival (OS)
  - E-R of safety: Adverse events leading to discontinuation or death (AE-DC/D), Gr3+ AEs, and immune-mediated AEs
  - E-R of biomarkers: Intratumoral receptor occupancy (RO)

Roy A (2017) *ACCP Meeting*

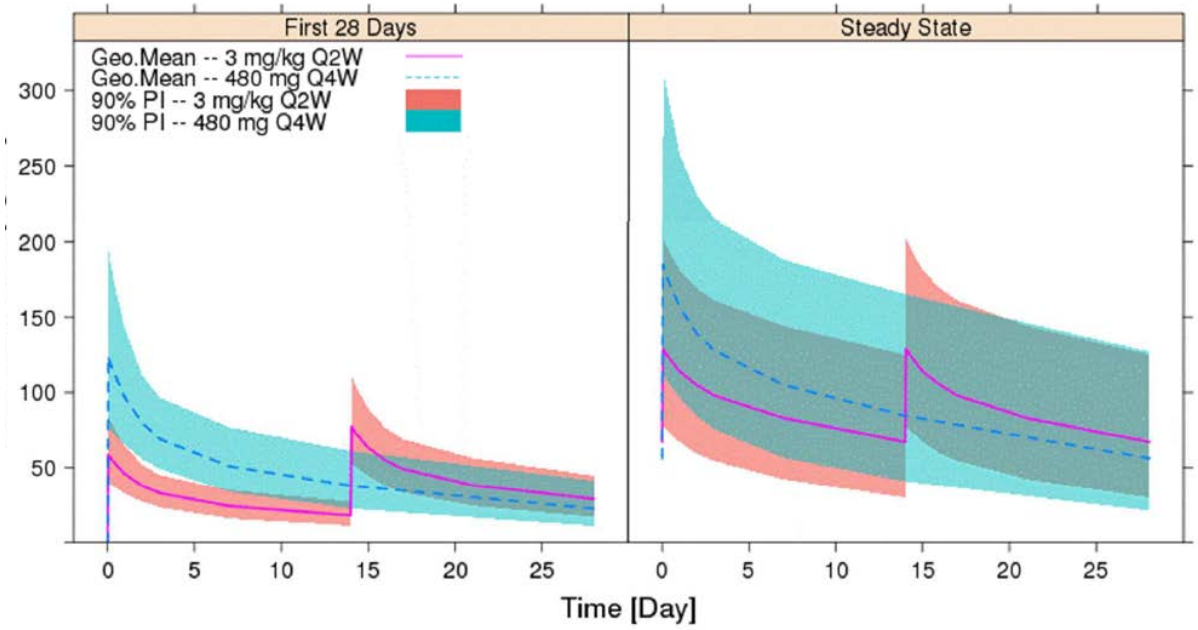
Comparison of Conc-Time Profiles, by Dosing Regimen

240 mg Q2W vs 3 mg/kg Q2W



Geo.Mean [ug/mL]	CAVGD28	CAVGSS
3 mg/kg Q2W	34.7	86.7
240 mg Q2W	36.5	91.2

480 mg Q4W vs 3 mg/kg Q2W



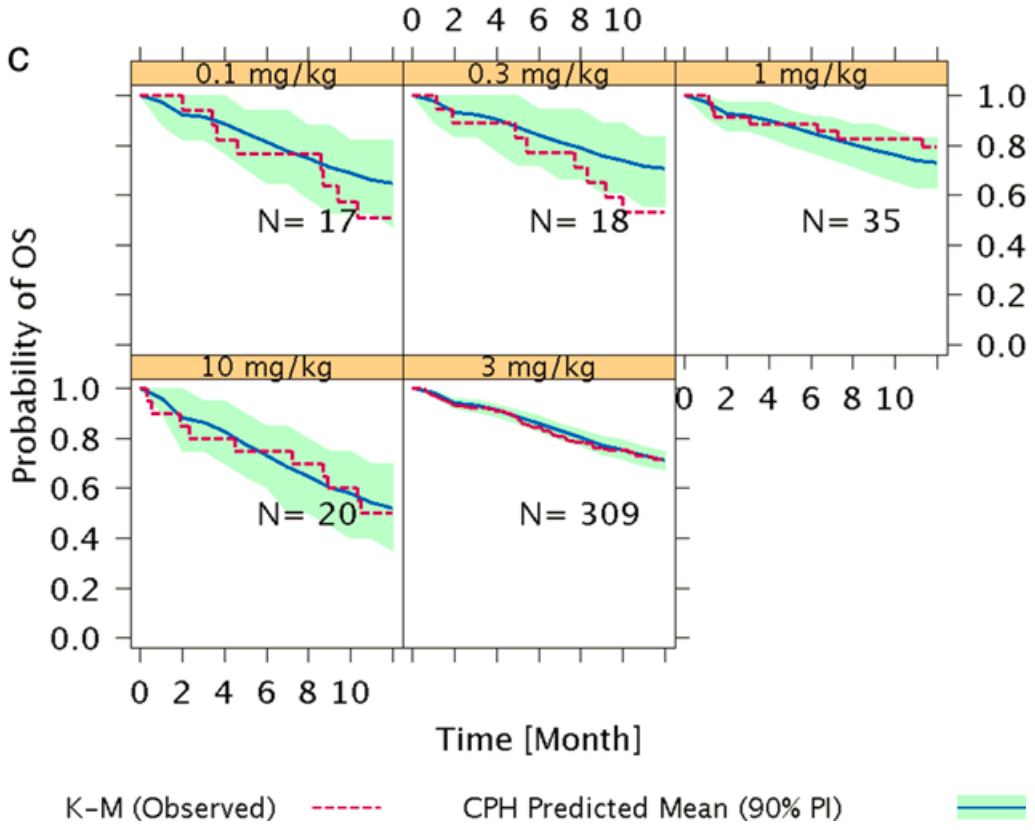
Geo.Mean [ug/mL]	CAVGD28	CAVGSS
3 mg/kg Q2W	34.7	86.7
480 mg Q4W	44	91.2

- ***Exposures are slightly more variable with flat dosing***
- ***Q4W dosing results in higher peak concentrations and lower trough concentrations than Q2W dosing***

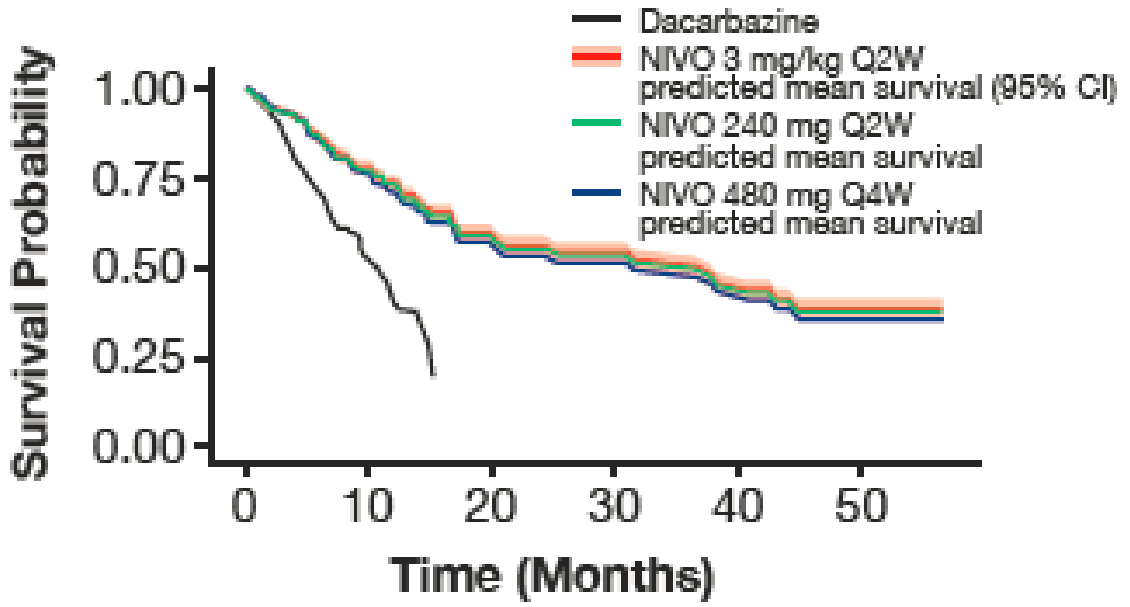
Zhao X, et al. (2017) *Oncologist ;* Zhao X, et al. (2017) *AACR Meeting*

Assessment of Dosing Regimen on OS (Melanoma)

E-R of OS in Advanced Melanoma (Visual Predictive Check)



Predicted OS in Previously Untreated Adv Melanoma, by Dosing Regimen



Bajaj G, et al (2017) *J Clin Pharm*; Zhao X, et al. (2017) *AACR Meeting*

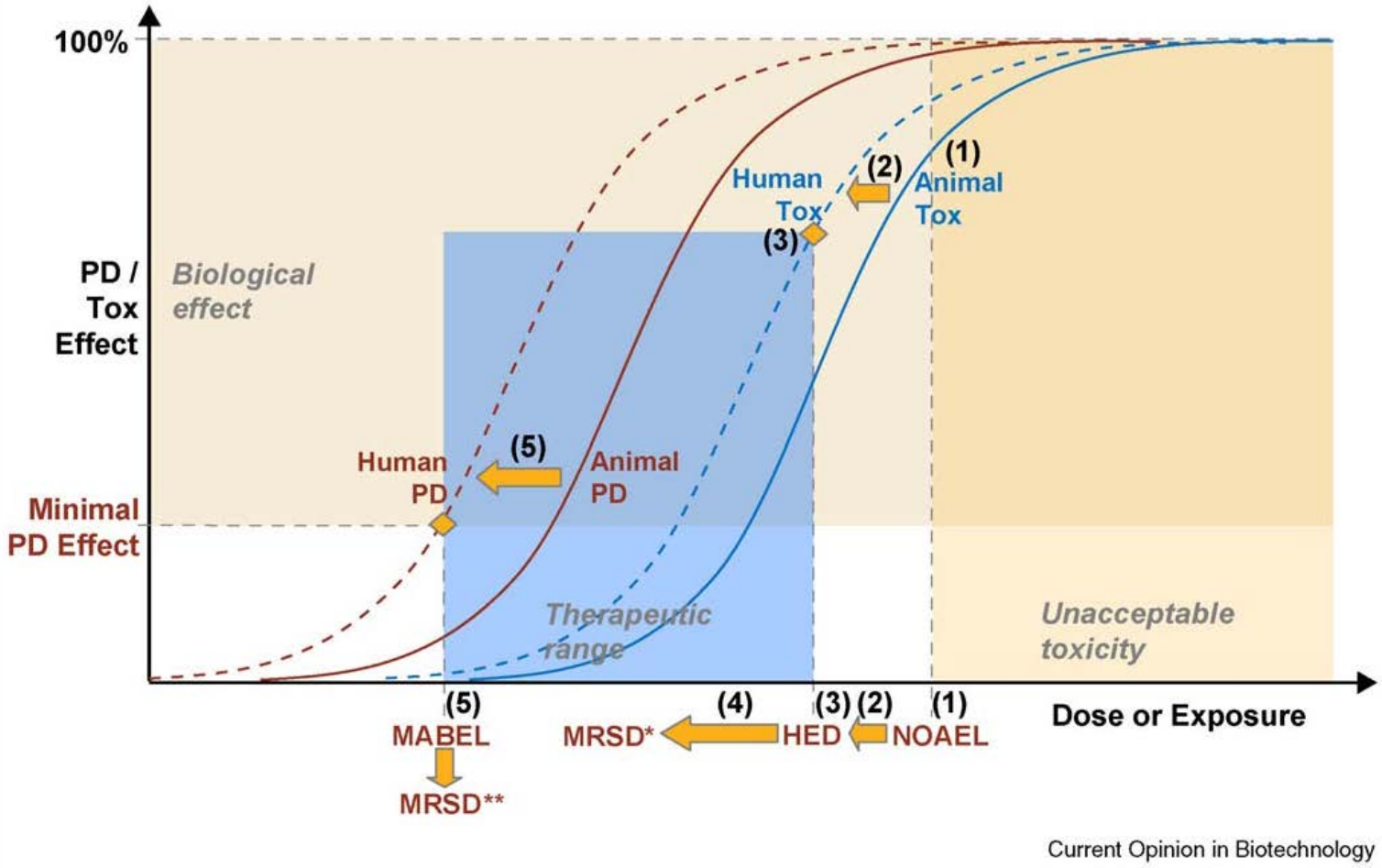
Translational Considerations for FIH Dose Selection

- Safety of subjects is a priority, but need to also consider the opportunity for clinical benefit for patient studies
- Identify risks and factors that mitigate risks: Consider the totality of the data
  - Mechanism-of-action:
    - Agonist/antagonist
    - Knowledge of the safety/activity of compounds with similar MoA
  - Relevance of animal model
  - Potential for adverse immune-reactions
    - Minimal anticipated biologically active level (MABEL)
    - Cytokine release assay

FIH dose selection should be based on the totality of the data

Saber H, et al. (2016) *Reg Tox Pharm*

Determination of Maximum Recommended Starting Dose

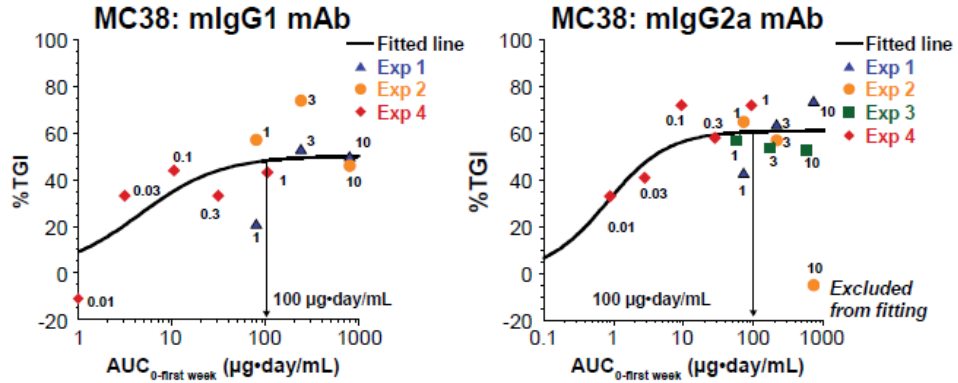


- ***MSRD is determined based on both NOAEL and MABEL***
- ***MABEL based MSRD is not expected to provide any clinical benefit***

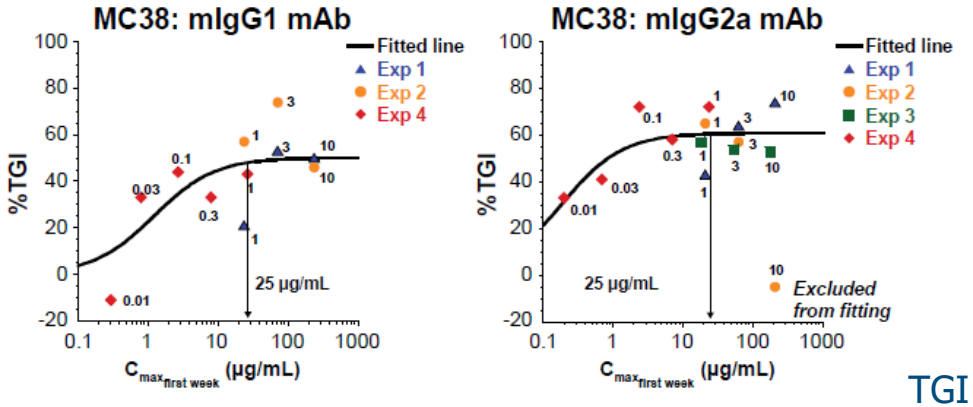
Muller PY, et al. (2009) *Curr Opin Biotech*

Translational PK-PD To Select FIH Starting Dose: Case Study with anti-OX40 mAb

Targeting $AUC_{0\text{-first week}}$ of 100 µg•day/mL for human efficacious dose projection



Targeting $C_{max_{first\ week}}$ of 25 µg/mL for human efficacious dose projection



Values in plots are the doses studied
Dosing regimens:
- Exp 1 & 2: every 6 days × 2
- Exp 3: every 7 days × 2[a]
- Exp 4: every 4 days × 2

TGI: Tumor Growth Inhibition

Human efficacious dose projected to be 1 mg/kg based on target AUC and Cmax

Huang C, et al. (2017) *SITC Meeting*

Comparison of Starting Dose Selected by Alternative Criteria

	PK/PD-based FIH starting dose	Toxicology-based FIH starting dose (one-sixth monkey HNSTD)	No effect level in dry-coat cytokine release assay[a]	Minimal vaccine-induced T-cell response in monkeys	Clinically tolerated exposure with previously reported anti-OX40 agonist[6]
Dose, mg/kg	0.25	17-20	1.3	4	2
C_{max}, µg/mL	6.3	425-500	33	78	80
C_{max} margin (vs PK/PD-based FIH starting dose)	NA	68-80×	5.3×	13×	2.5×[b]

NA = not applicable

[a]Drug concentration in the dry-coat cytokine release assay was approximated using the incubation volume (0.3 mL), and the human dose was calculated by multiplying the no-effect drug level by the plasma volume of 40 mL/kg

[b]Margin was calculated after normalization with differences in the binding EC_{50} values

FIH starting dose of aOX40 agents already in clinical development was ~10-fold lower

Huang C, et al. (2017) *SITC Meeting*

Learning Objectives

- What covariates should be assessed on PK parameters of anti-cancer mAbs?
- What is the association between disease severity and PK
- How should the effect of ADA be assessed?
- What measures of exposure should be utilized in exposure-response analyses
- How can E-R analyses be leveraged to address data gaps and inform drug development and regulatory decisions
- Considerations for FIH dose selection

Summary

- Clearance of I-O mAbs is associated with disease severity
  - Higher in patients with worse disease
  - Decreases with improvement of patient status
- Assessment of ADA should account for time-varying nature of covariate
- Exposure-response can inform regulatory decisions
  - Randomized dose-ranging studies are needed for robust characterization of E-R
  - Select early measure of exposure to avoid confounding of E-R relationship
  - TTE analyses are needed for endpoints affected by censoring
- Translational PK-PD modeling can inform FIH dose selection
  - Prioritize safety and consider the desire for potential clinical benefit
  - Identify potential risks and consider factors that mitigate risk

Acknowledgements

- Akintunde Bello
- Chaitali Passey
- Christine Huang
- Eric Masson
- Heather Vezina
- Kinjal Sanghavi
- Li Zhu
- Lora Hamuro
- Jason Zhang
- Jennifer Zhang
- Manish Gupta
- Paul Statkevich
- Rick Bertz
- Satyendra Suryawanshi
- Yan (Summer) Feng
- Xiaoning (Shelly) Wang
- Xiaochen (Molly) Zhao
- Zheng Yang

References (1/2)

- Agrawal, S., Feng, Y., Roy, A., Kollia, G., & Lestini, B. (2016). Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. Journal for ImmunoTherapy of Cancer, 4, 1–11. (https://doi.org/10.1186/s40425-016-0177-2)
- Ascierto, P. A., Vecchio, M. Del, Robert, C., Mackiewicz, A., Chiarion-sileni, V., Arance, A., … Maio, M. (2017). Ipilimumab 10 mg / kg versus ipilimumab 3 mg / kg in patients with unresectable or metastatic melanoma : a randomised , double-blind , multicentre , phase 3 trial. Lancet Oncology, 18, 611–622. (https://doi.org/10.1016/S1470-2045(17)30231-0)
- Bajaj, G., Wang, X., Agrawal, S., Gupta, M., Roy, A., & Feng, Y. (2016). Model-Based Population Pharmacokinetic Analysis of Nivolumab in Patients With Solid Tumors. CPT: Pharmacometrics and Systems Pharmacology, 4(December 2016), 58–66. (https://doi.org/10.1002/psp4.12143)
- Bajaj, G., Gupta, M., Feng, Y., Statkevich, P., & Roy, A. (2017). Exposure – Response Analysis of Nivolumab in Patients With Previously Treated or Untreated Advanced Melanoma. Journal of Clinical Pharmacology, 57(12), 1527–1533. (https://doi.org/10.1002/jcph.962)
- Baverel, P. G., Dubois, V. F. S., Jin, C. Y., Zheng, Y., Song, X., Jin, X., … Roskos, L. (2018). Population Pharmacokinetics of Durvalumab in Cancer Patients and Association With Longitudinal Biomarkers of Disease Status. Clinical Pharmacology and Therapeutics, 103(4), 631–642. (https://doi.org/10.1002/cpt.982)
- Feng, Y., Masson, E., Dai, D., Parker, S. M., Berman, D., & Roy, A. (2014). Model-based clinical pharmacology profiling of ipilimumab in patients with advanced melanoma. *British Journal of Clinical Pharmacology*, *78*(1), 106–117. (https://doi.org/10.1111/bcp.12323)
- Hamuro, L., Statkevich, P., Bello, A., Roy, A., & Bajaj, G. (2018). Nivolumab Clearance Is Time-Varying in Advanced Melanoma and Stationary in Adjuvant Melanoma. ASCPT. Orlando, FL
- Hodi, F. S., O'Day, S. J., McDermott, D. F., Weber, R. W., Sosman, J. a, Haanen, J. B., … Urba, W. J. (2010). Improved survival with ipilimumab in patients with metastatic melanoma. New England Journal of Medicine, 363(8), 711–723. (https://doi.org/10.1056/NEJMoa1003466)
- Huang, C., Feng, Y., Barnhart, B., Quigley, M., Huber, J., Bello, A., … Yang, Z. (2017). Selection of First-in-Human Starting Dose of Anti-OX40 Agonist Monoclonal Antibody BMS-986178 Using a Pharmacokinetic / Pharmacodynamic-Based Approach. SITC. National Harbor, MD.
- Liu, C., Yu, J., Li, H., Liu, J., Xu, Y., Song, P., … Wang, Y. (2017). Association of Time-Varying Clearance of Nivolumab With Disease Dynamics and Its Implications on Exposure Response Analysis. Clinical Pharmacology and Therapeutics, 101(5), 657–666. (https://doi.org/10.1002/cpt.656)
- Muller, P. Y., Milton, M., Lloyd, P., Sims, J., & Brennan, F. R. (2009). The minimum anticipated biological effect level (MABEL) for selection of first human dose in clinical trials with monoclonal antibodies. Current Opinion in Biotechnology, 20(6), 722–729. (https://doi.org/10.1016/j.copbio.2009.10.013)

References (2/2)

- Passey, C., Mora, J., Dodge, R., Gibiansky, L., Sheng, J., Roy, A., … Gupta, M. (2017). An Integrated Assessment of the Effects of Immunogenicity on the Pharmacokinetics, Safety, and Efficacy of Elotuzumab. AAPS Journal, 19(2), 557–567. (https://doi.org/10.1208/s12248-016-0033-9)
- Ramalingam, S. S., Kummar, S., Sarantopoulos, J., Shibata, S., LoRusso, P., Yerk, M., … Egorin, M. J. (2010). Phase I study of vorinostat in patients with advanced solid tumors and hepatic dysfunction: a National Cancer Institute Organ Dysfunction Working Group study. Journal of Clinical Oncology, 28(29), 4507–4512. (https://doi.org/10.1200/JCO.2010.30.2307)
- Roy, A. (2016). Modeling & Simulation Approaches To Support Development of Immuno-Oncology Drugs. ASCPT. San Diego, CA.
- Roy, A. (2017). Model-Based Analyses to Optimize Dosing Regimen of Biologics: During Development and Post-Approval. ACCP. San Diego, CA.
- Roy, A. (2018). Evaluation and Application of a Tumor Growth Dynamic-Overall Survival (TGD-OS) Model for Advanced Melanoma. In FDA-ISoP Public Workshop: Model Informed Drug Development (MIDD) for Oncology Products. Silver Spring, MD. (https://www.fda.gov/downloads/Drugs/NewsEvents/UCM608039.pdf)
- Saber, H., Gudi, R., Manning, M., Wearne, E., & Leighton, J. K. (2016). An FDA oncology analysis of immune activating products and fi rst-in-human dose selection. Regulatory Toxicology and Pharmacology, 81, 448–456. (https://doi.org/10.1016/j.yrtph.2016.10.002)
- Sanghavi, K., Roy, A., Dombrowsky, E., Bello, A., Statkevich, P., Agrawal, S., … Cl, S. E. (2017). Characterizing Time-Varying Clearance of Ipilimumab in Patients With Advanced Solid Tumors. ACoP. Fort Lauderdale, FL.
- Wang, Y., Booth, B., Rahman, A., Kim, G., Huang, S. M., & Zineh, I. (2017). Toward Greater Insights on Pharmacokinetics and Exposure – Response Relationships for Therapeutic Biologics in Oncology Drug Development. Clinical Pharmacology and Therapeutics, 101(5), 582–584. (https://doi.org/10.1002/cpt.628)
- Wang X, Feng Y, Statkevich P, and Roy A. (2015) Characterizing Exposure-Response (E-R) Relationship of Safety for Nivolumab in Combination With Ipilimumab in Patients With Previously Untreated Advanced Melanoma (MEL). ACoP, Crystal City, VA
- Zhao, X., Suryawanshi, S., Hruska, M., Feng, Y., Wang, X., Shen, J., … Agrawal, S. (2017). Assessment of nivolumab benefit – risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. Annals of Oncology, 28(8), 2002–2008. (https://doi.org/10.1093/annonc/mdx235)
- Xiaochen Zhao, Vijay Ivaturi, Mathangi Gopalakrishnan, Jun Shen, Yan Feng, Paul Statkevich, Eric Richards, Michelle Rashford, Vicki Goodman, Joga Gobburu, Akintunde Bello, Amit Roy, S. A. (2017). A Model-Based Exposure–Response (ER) Assessment of a Nivolumab (NIVO) 4-weekly (Q4W) Dosing Schedule Across Multiple Tumor Types. AACR. Washington, DC.