Modeling & Simulation Approaches To Support Development of Immuno-Oncology Drugs

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Quantitative Translational Approaches in Oncology
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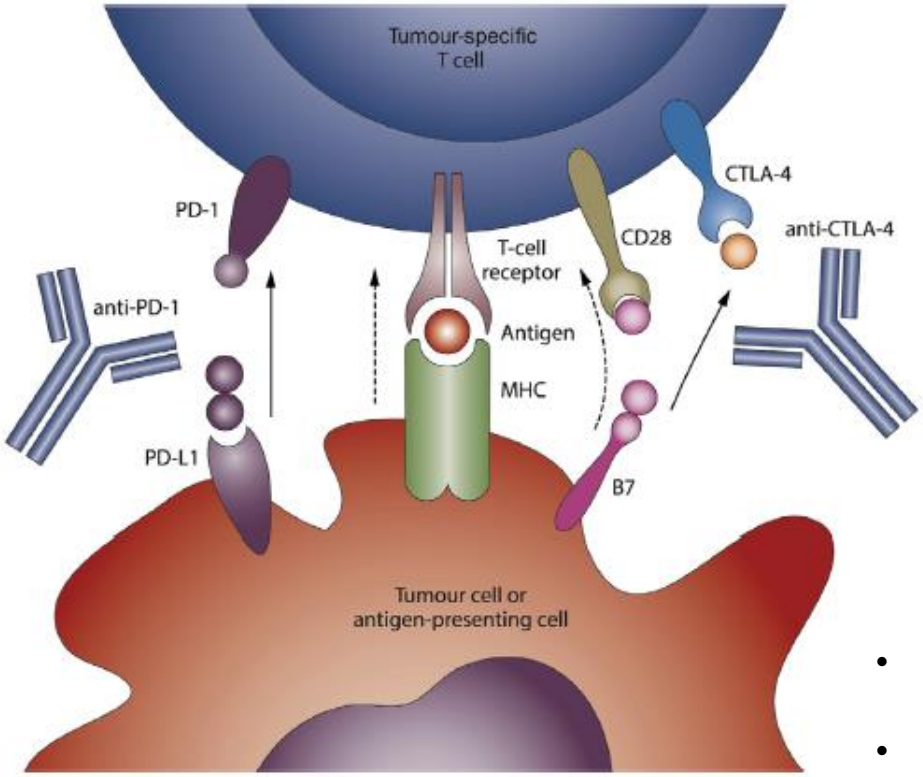
Goals of M&S in the Development of I-O Drugs

- Characterize clinical pharmacology profile
- Inform go/no-go decisions and dose selection
- Inform assessments of benefit-risk
- Support dose-optimization

Pharmacometric analyses should account for the unique attributes of I-O agents

Mechanism of Action of I-O Agents: Ipilimumab and Nivolumab



- Ipilimumab: fully human aCTLA-4 IgG1 mAb
- Nivolumab: fully human aPD-1 IgG4 mAb

I-O agents enable and enhance the ability of the immune system to recognize and eliminate tumor cells

- *Ipilimumab increases the number of activated T-cells*
- *Nivolumab prevents inactivation, and promotes re-activation of T-cells*

McDermott D, et al. (2014). Cancer Treatment Reviews, 40(9), 1056–1064

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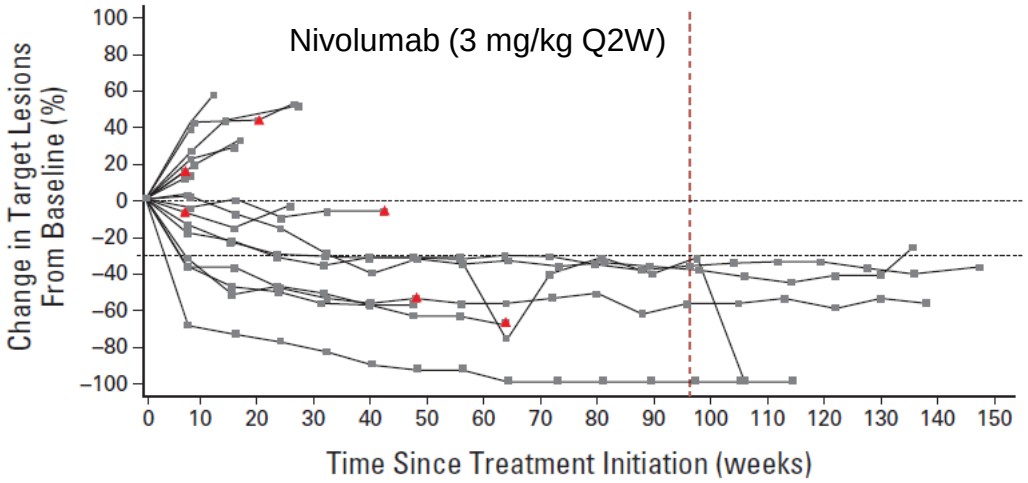
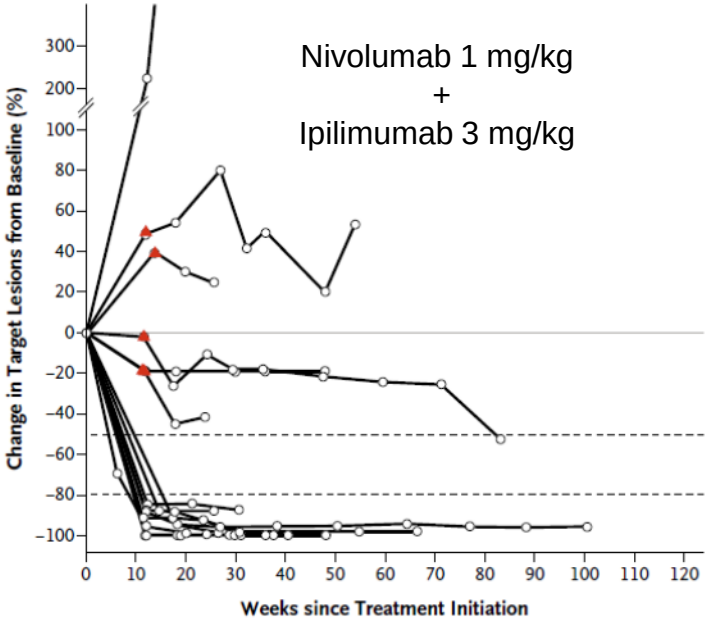
Time-Profile of Target Tumor Burden: Metastatic Melanoma Patients Treated with Nivolumab ± Ipilimumab



Topalian SL, et al. (2013), *Journal of Clinical Oncology*, *32*(10), 1020–1030



Wolchok JD, et al. (2013). New England Journal of Medicine, 369(2), 122–33.

Characteristics of tumor-response to I-O Agents

- ***Patients who do not progress tend to have durable disease control***
- ***Unconventional responses: reduction in target tumor burden despite appearance of new lesions***
- ***Distinct patterns of response particularly evident with combination therapy***

Red triangles: New lesions

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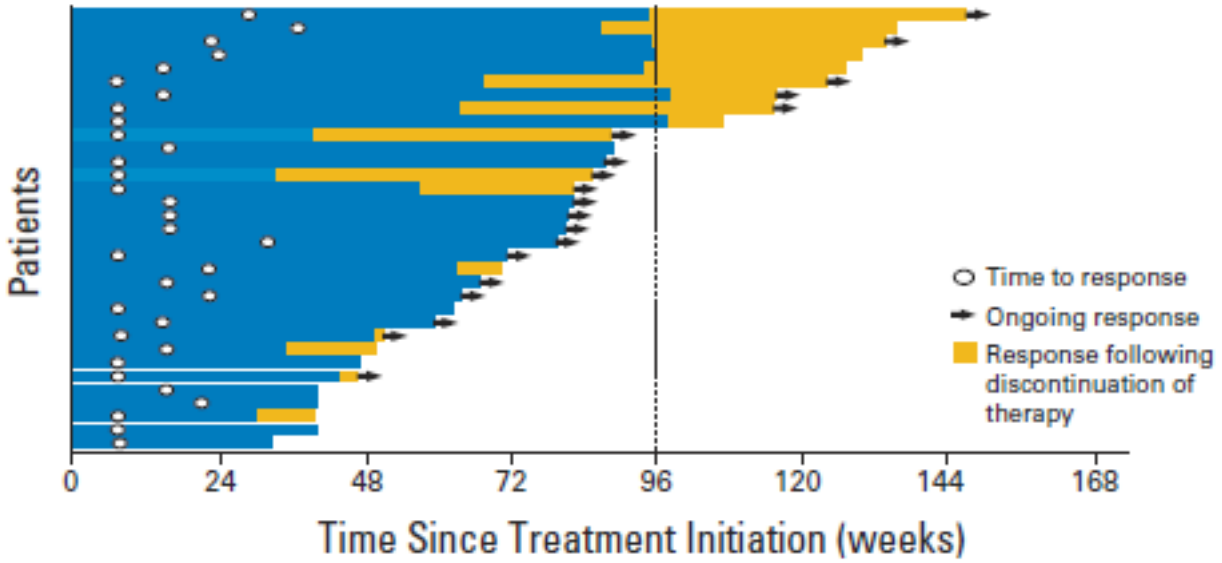
Onset and Durability of I-O Agent Induced Tumor Responses: Metastatic Melanoma

Treatment Duration and Tumor Response:
Advanced Melanoma Patients Treated with Nivolumab



- ***Tumor responses are maintained, despite discontinuation of therapy***
- ***The immune response may be self-sustaining***

Topalian SL, et al. (2013), *Journal of Clinical Oncology*, *32*(10), 1020–1030

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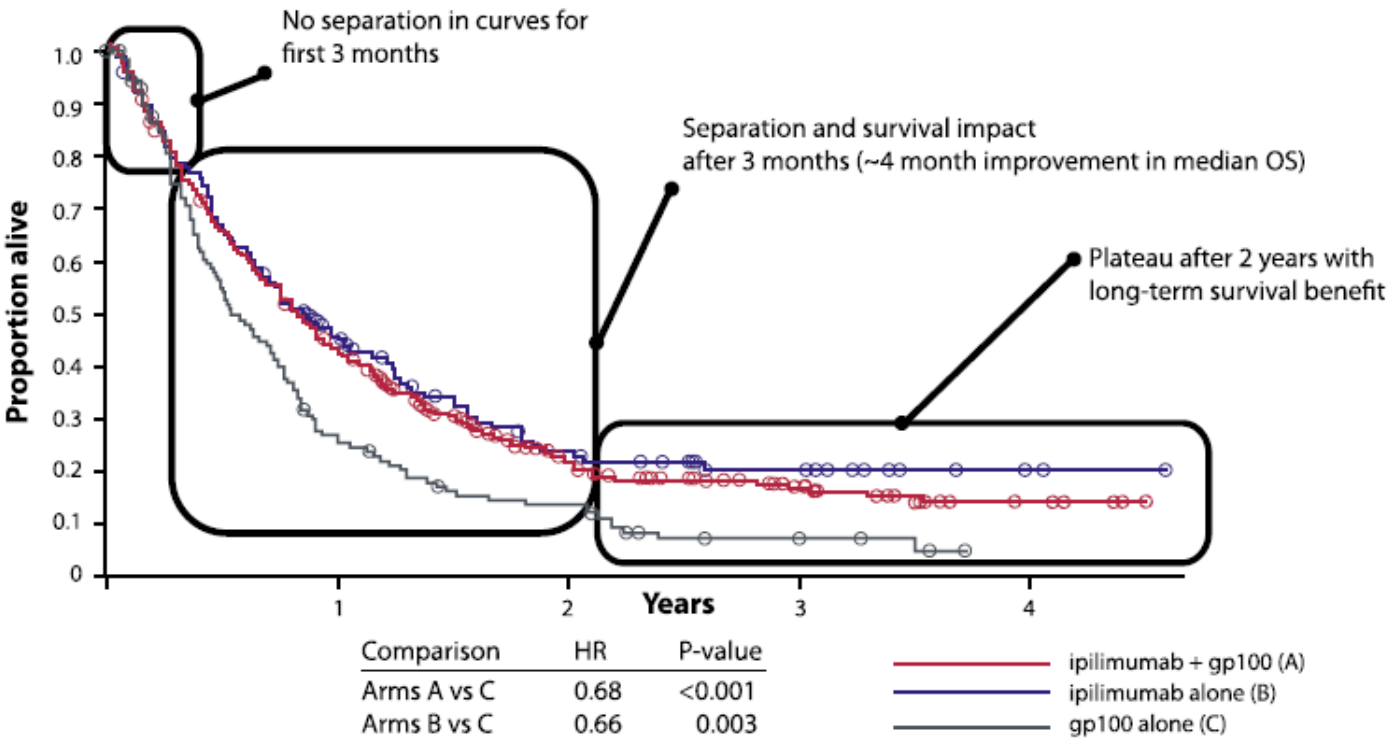
Long-Term Survival: Ipilimumab in Metastatic Melanoma



- ***Delayed separation of OS curves relative to non-IO agents***
- ***Median survival may not fully reflect clinical benefit***

McDermott D, et al. (2014). Cancer Treatment Reviews, 40(9), 1056–1064

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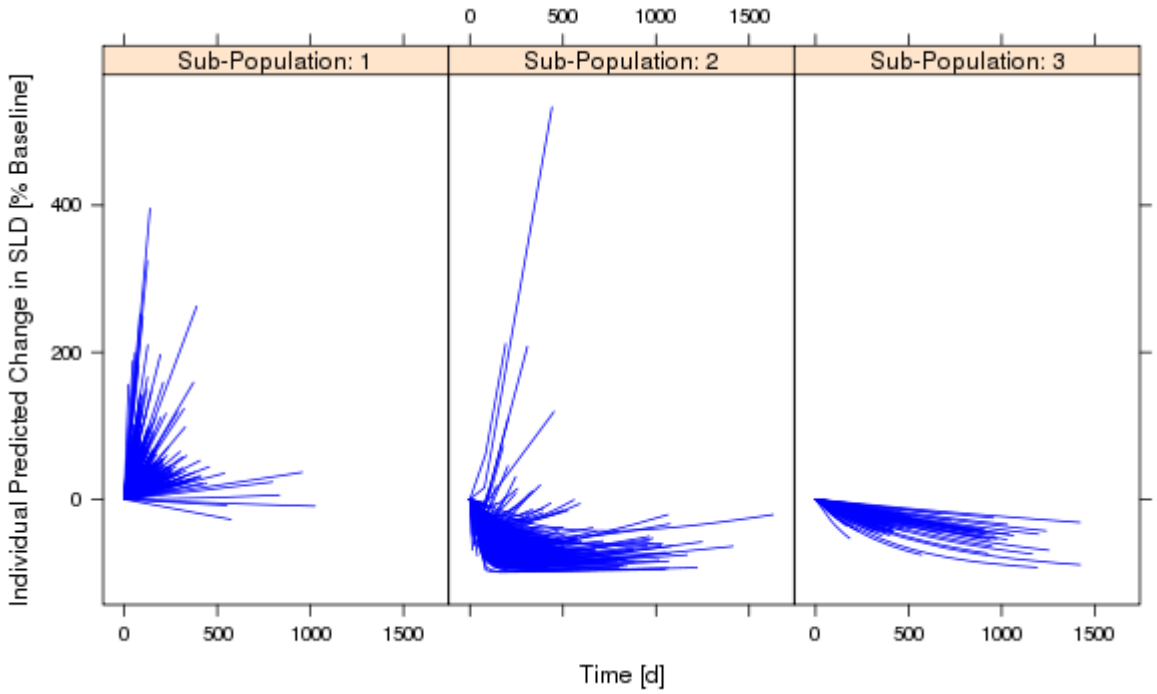
Model-Predicted* Tumor Growth Dynamics Following Treatment with I-O Agents (Ipilimumab and Nivolumab)

Predicted-Change in Target Tumor Burden vs Time,
By Mixture Model-Determined Sub-Populations



Mixture model of TGD describes patterns of tumor response

* Nonlinear mixed-effects mixture-model of TGD is based on structural model proposed by Wang et al, CPT (2009)

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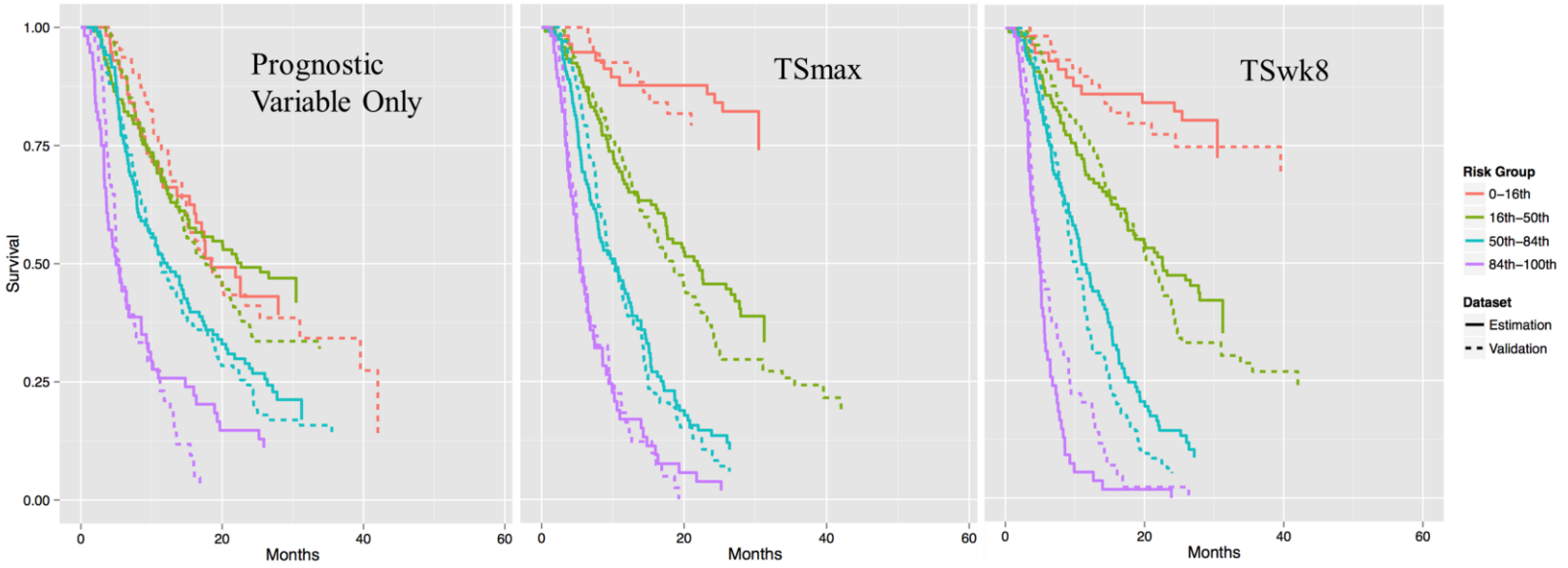
Utility of I-O Agent Induced Tumor Response to Predict Overall Survival: Ipilimumab in Advanced Melanoma

External Validation of Prognostic Variables and Tumor Shrinkage Measures to Predict OS



- ***OS model developed with data from Ph2 studies was validated with data from a Ph3 study***
- ***I-O agent induced tumor shrinkage is predictive of OS***

Suryawanshi et al., ACoP (2015)

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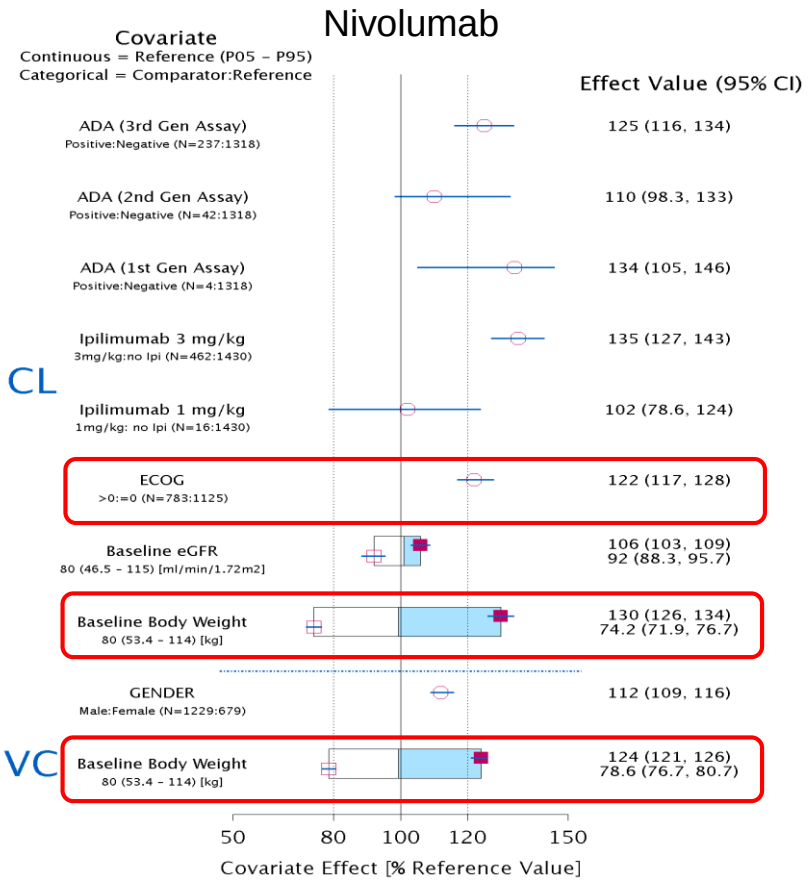
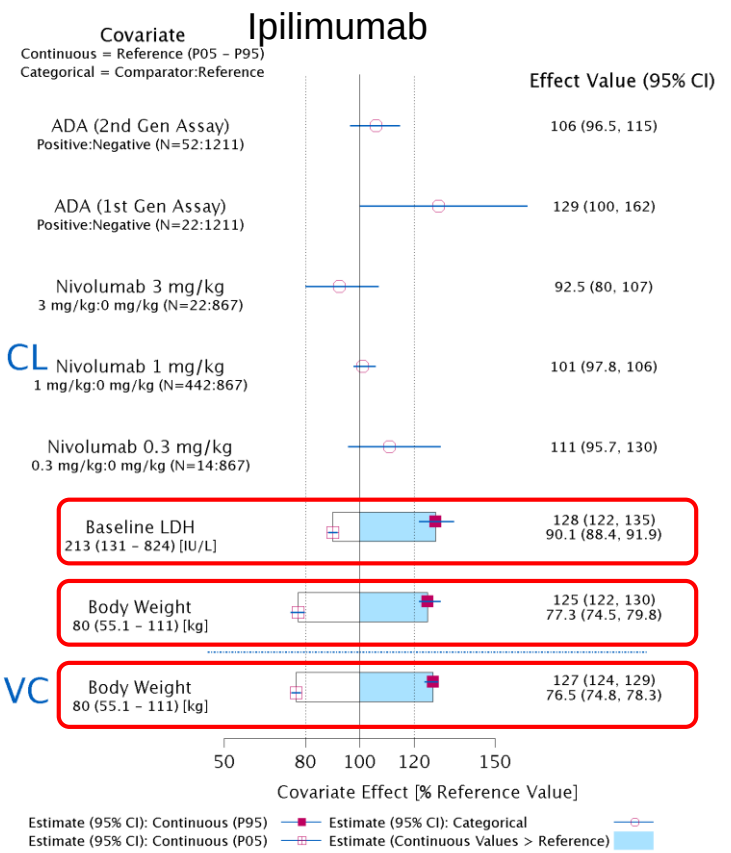
Pharmacokinetics of Nivolumab and Ipilimumab in Combination: Effects of Covariates on CL and VC*





*CL: Clearance, VC: Central compartment volume of distribution

Nivolumab and ipilimumab exhibit linear PK

- ***CL and VC increase with increasing body weight***
- ***CL is associated with disease severity (ECOG and LDH)***

Zhu L, et al, ASCPT (2016) [Poster PC-16 and PI-002]
Statkevich P, et al, ASCPT (2016) [Poster PC-17 and PI-126]

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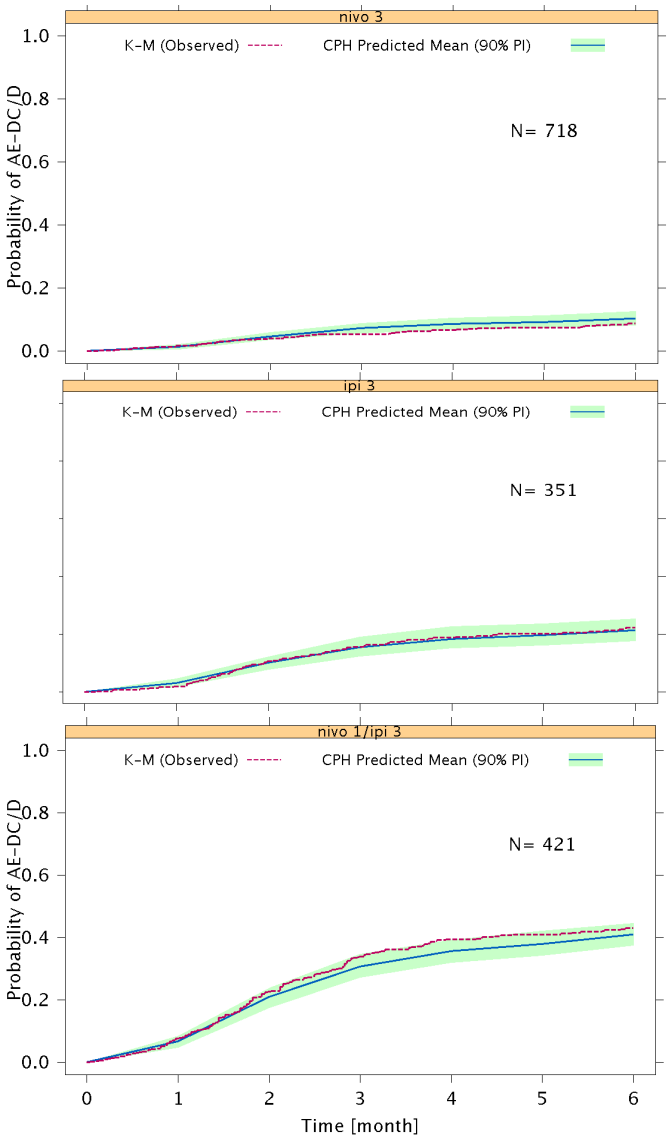
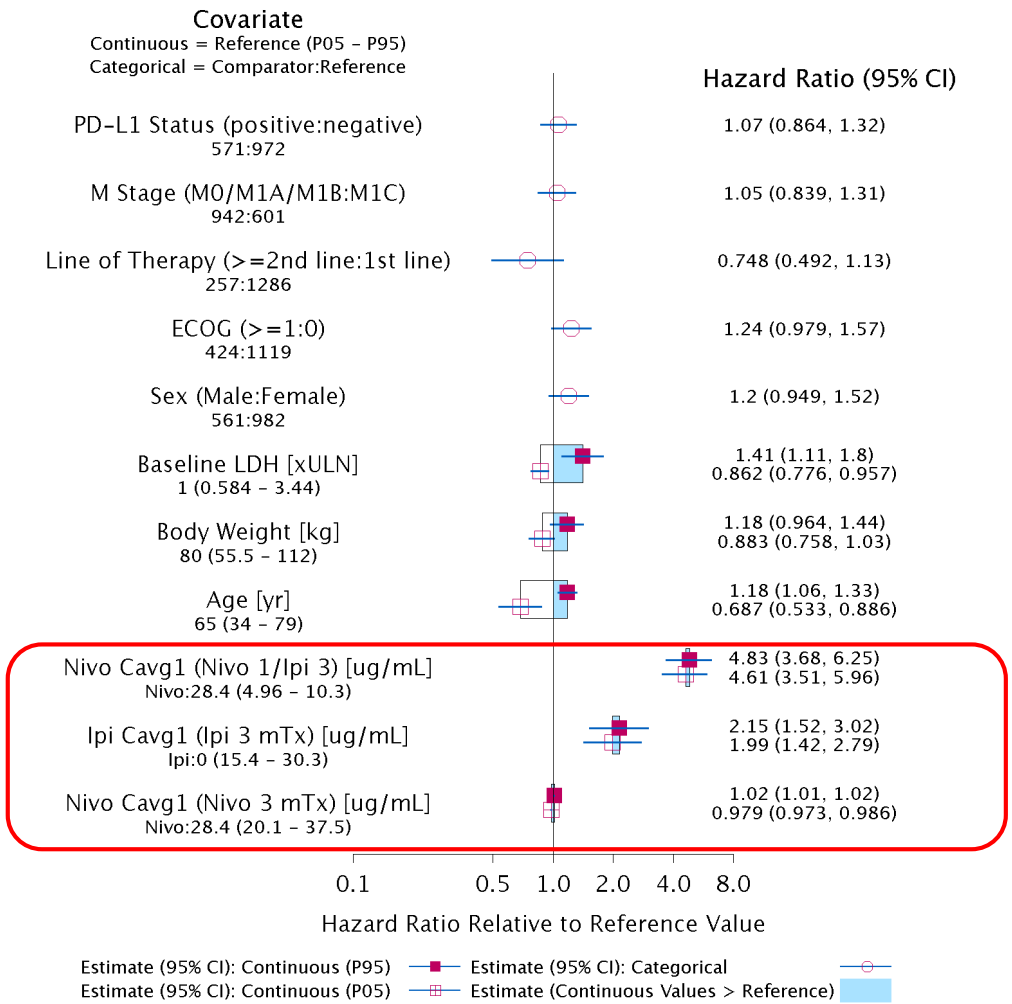
Exposure-Response of Safety (AEs DC/D)*: Nivolumab and Ipilimumab in Advanced Melanoma





Risk of AEs DC/D is higher with combination therapy (relative to NIVO 3 mg/kg)

*AEs leading to discontinuation or death

Wang X et al, ACoP (2015)

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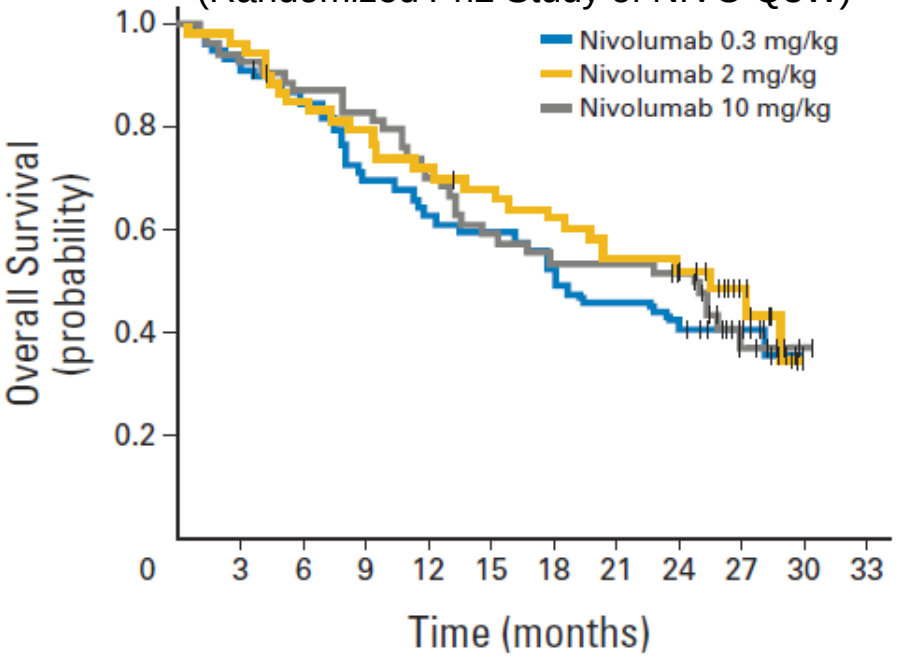
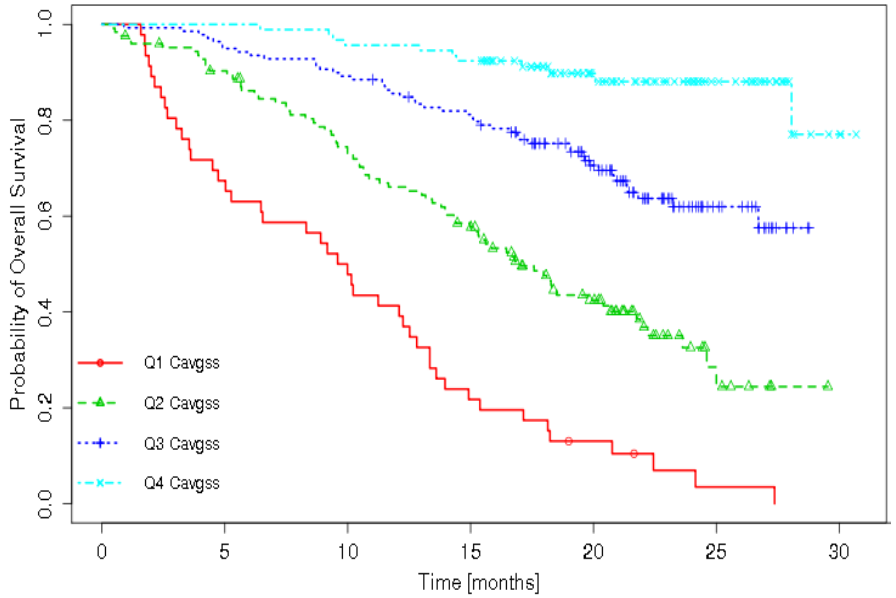
Nivolumab Dose/Exposure-Response of OS in Patients with 2L RCC

Kaplan-Meier of OS, Dose Level
(Randomized Ph2 Study of NIVO Q3W)



Kaplan-Meier of OS, by Exposure Quartiles
(Ph3 Study of NIVO 3 mg/kg Q2W)



Motzer RJ, et al. (2015). Journal of Clinical Oncology, 33(13), 1430-1437.

The modest dose-response is not consistent with the apparent exposure-response

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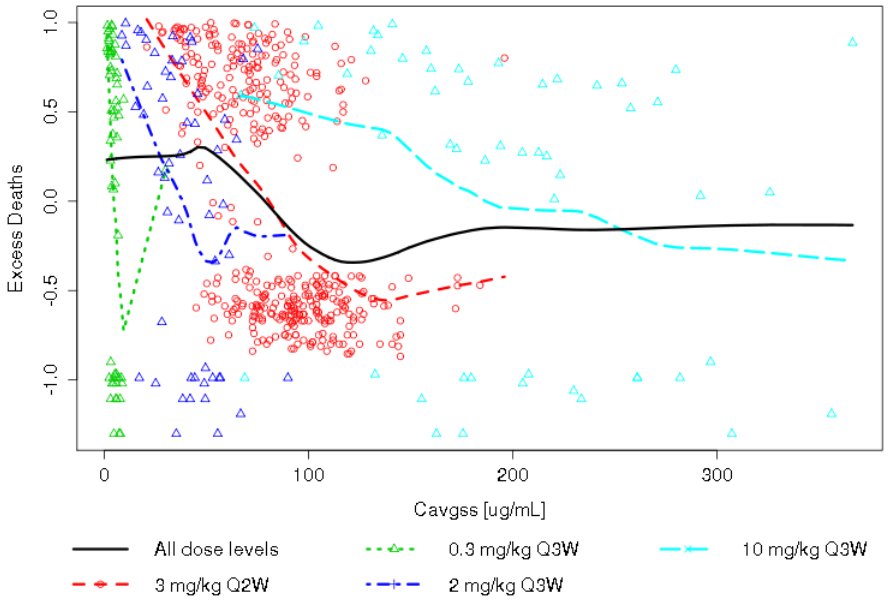
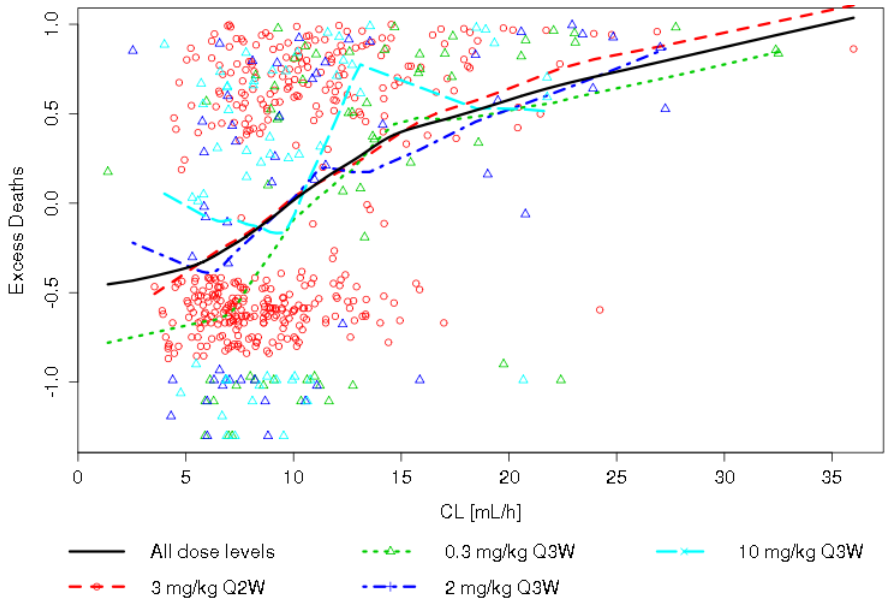
Functional Form of Cavgss and CL Relationship to Risk of Death

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



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



- ***Relationship of Cavgss to risk of death <u>is not</u> consistent across dose regimens***
- ***Relationship of CL to risk of death <u>is</u> consistent across dose regimens***

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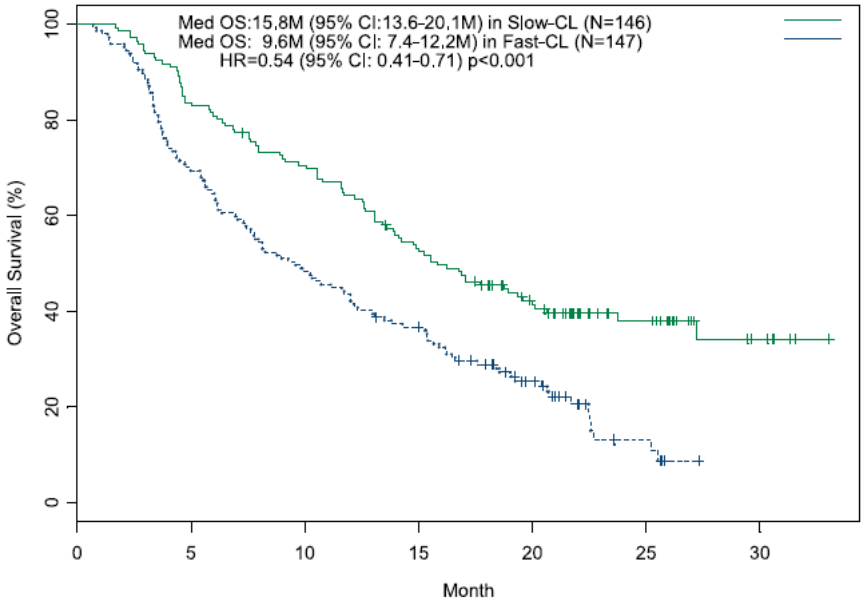
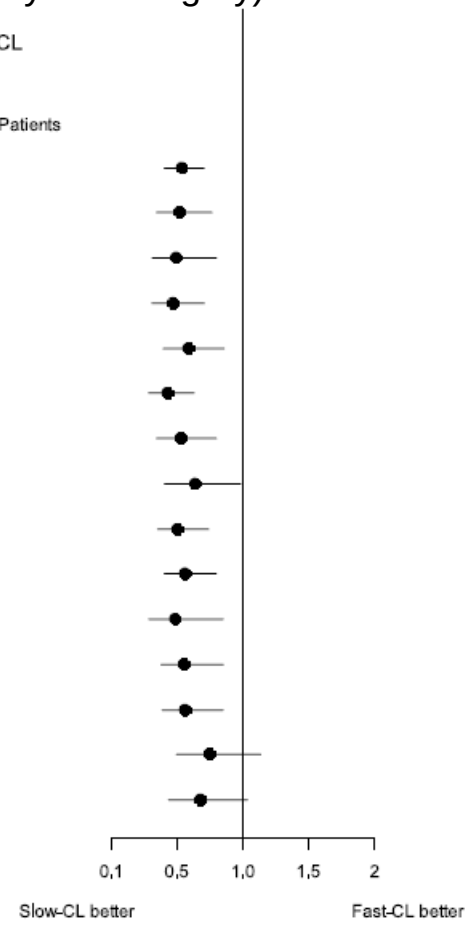
Another Example of the Association Between CL and OS: Tremelimumab Patients with Metastatic Melanoma

Kaplan-Meier of OS, by Exposure Quartiles
(Ph3 Study of TREME 15 mg/kg Q90D)



Hazard-Ratio of Death
(Sub-Group Analysis by CL category)

Subgroup	Slow-CL	Fast-CL
	No. of Patients	No. of Patients
All Patients	146	147
Male	57	113
Female	89	34
IgG <960 mg/dL	78	53
IgG =>960 mg/dL	68	94
CLcr<95,5 mL/min	91	50
CLcr=>95.5 mL/min	55	97
M0,M1a,M1b	74	52
M1c	72	95
ECOG=0	114	90
ECOG=1	32	57
LDH<0,85xULN	87	68
LDH=>0,85xULN	59	79
CRP<0.8xULN	110	54
CRP=>0,8xULN	36	93



- ***Magnitude of the effect of CL cannot be explained by lower exposure***
- ***OS of 15 mg/kg Q90D was better than 10 mg/kg Q28D (in Ph2 study)***
- ***Association between CL is independent of other risk factors***

Wang E., et al. (2014). Journal of Clinical Pharmacology, 54(10), 1108–1116.

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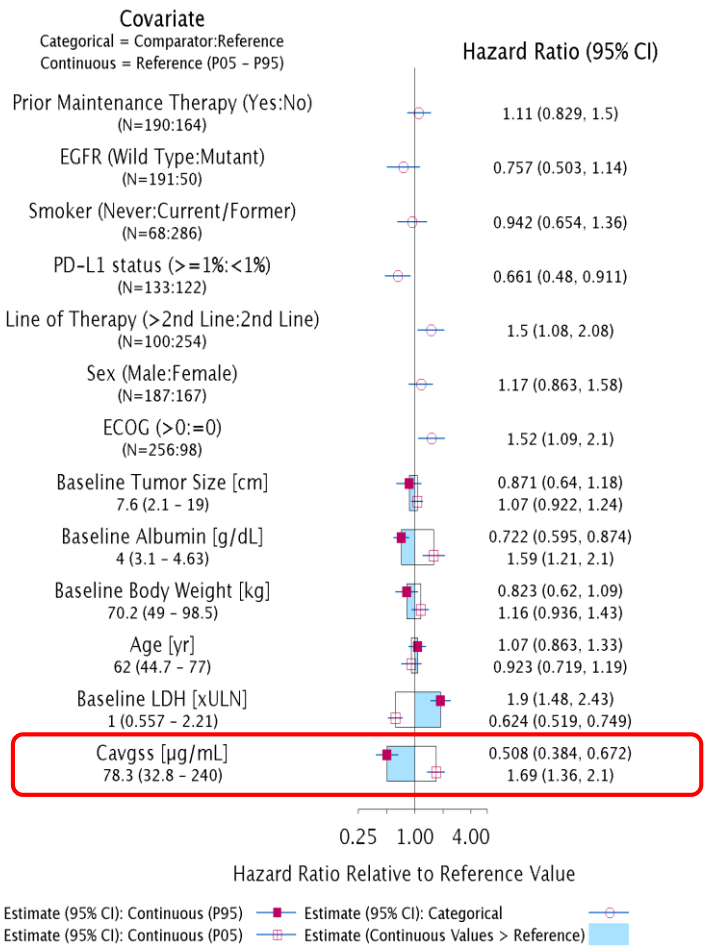
Potential Reasons for the Association Between CL of Anti-Cancer mAbs and Efficacy

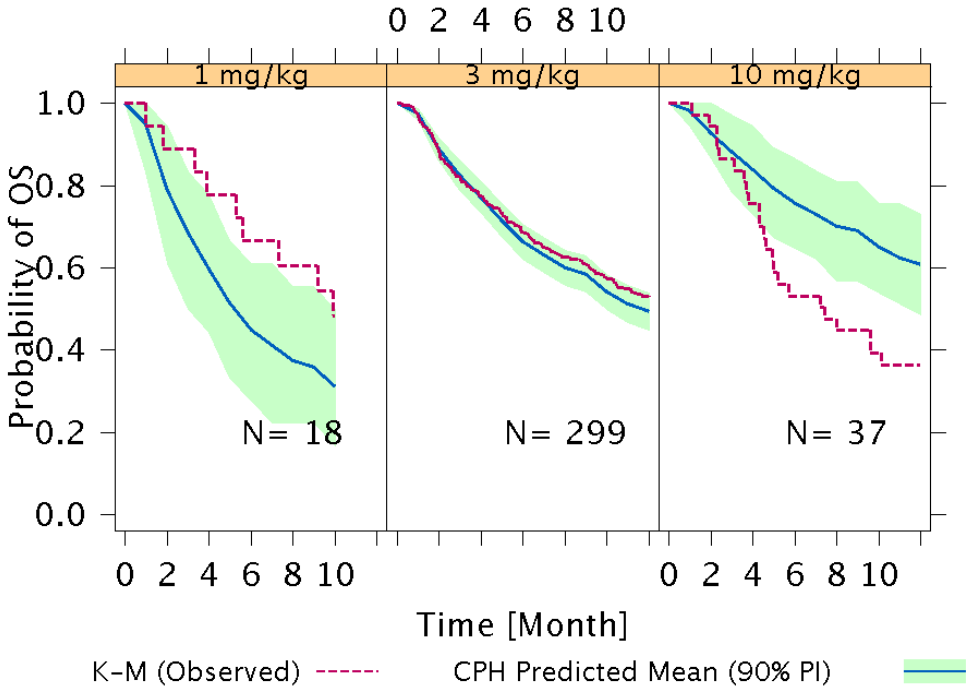
- CL of anti-cancer mAbs is associated with factors related to disease-severity (and poor prognosis)
- Observed prognostic factors only explain a portion of the higher risk
- CL may be a surrogate for unobserved risk factors

Potential Confounding Effect of CL on Exposure-Response of Efficacy (OS) in NSQ-NSCLC (1/2)

Effect of Covariates on Hazard of OS in NSQ-NSCLC
(Full Model without CL)



Visual Predictive Check of OS in NSQ-NSCLC, by Dose Level
(Full Model without CL)



Predictions of model without CL are not consistent with the observed data

Feng Y et al, ASCPT (2016) [Poster PC-10 and PI-098]

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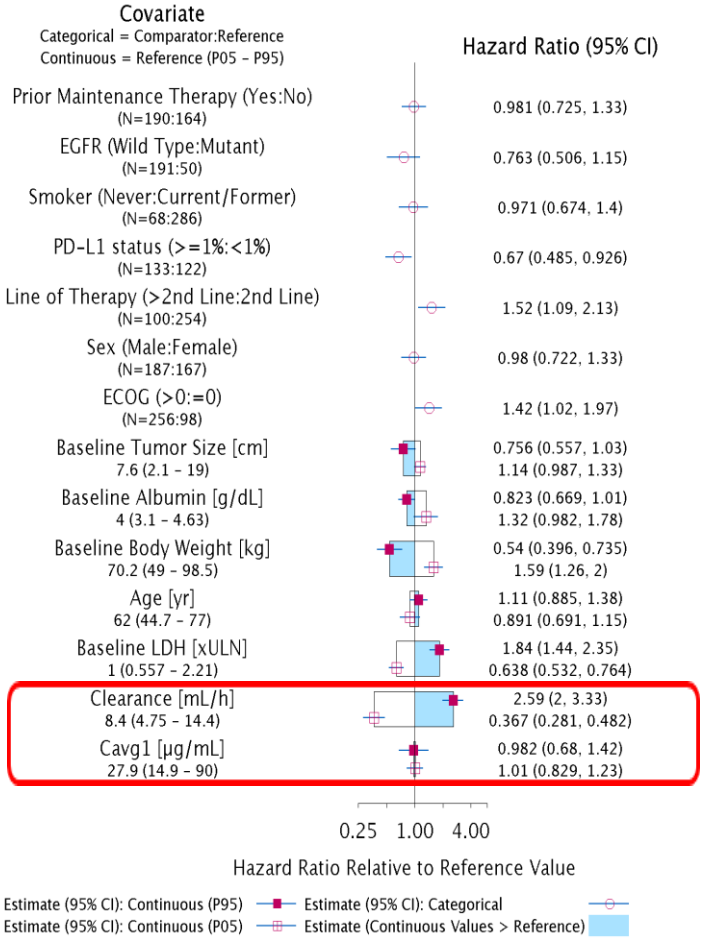
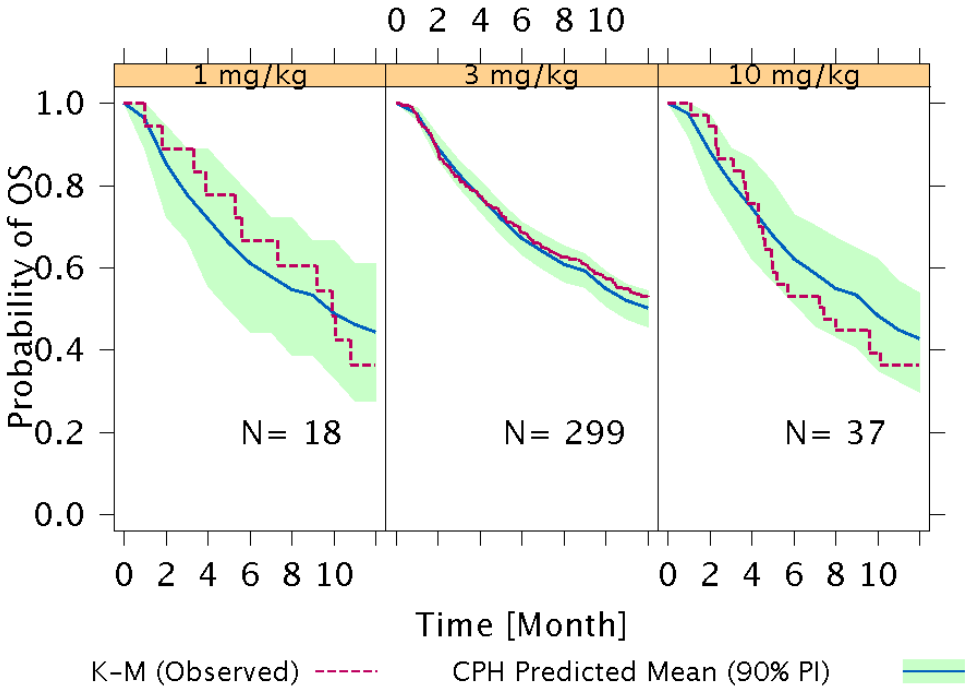
Potential Confounding Effect of CL on Exposure-Response of Efficacy (OS) in NSQ-NSCLC (2/2)

Effect of Covariates on Hazard of OS in NSQ-NSCLC
(Full Model with CL)



Visual Predictive Check of OS in NSQ-NSCLC, by Dose Level
(Full Model with CL)



Predictions of model with CL are consistent with observed data

Feng Y et al, ASCPT (2016) [Poster PC-10 and PI-098]

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Summary

- **I-O agents have unique attributes**
  - **Tumor growth may be controlled without achieving objective response (PR or CR) by RECIST criteria**
  - **Efficacy may be maintained long after drug wash-out**
- **CL of mAb agents may be associated with efficacy, independent of exposure**
  - **Subjects who have more severe disease may have higher CL**
  - **Exposure-response relationships determined with data from just a single dose level may show an artefactual relationship**
  - **Dose-response studies are recommended to generate data that can estimate the effects of both CL and exposure**

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