Modeling of Tumor Kinetics and Overall Survival to Identify Prognostic and Predictive Biomarkers of Efficacy for Durvalumab

Yanan Zheng

FDA-ISOP Workshop: Model-Informed Drug Development in Oncology
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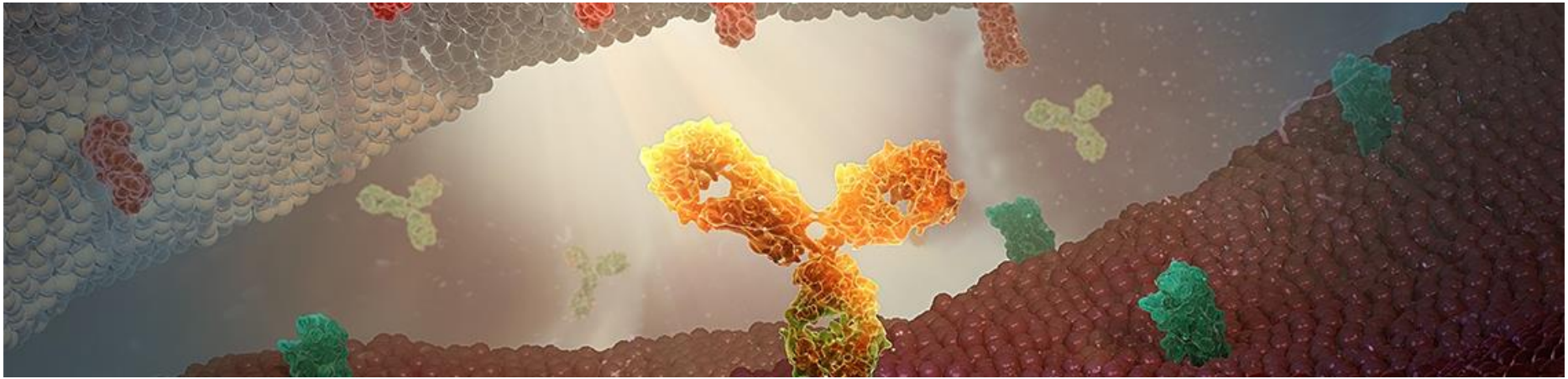
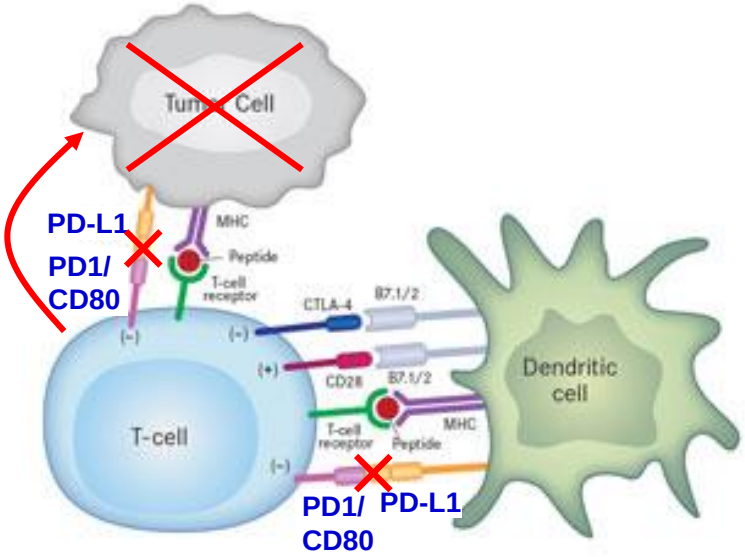


Durvalumab – an anti-PD-L1 Monoclonal Antibody for Cancer Immunotherapy

- Durvalumab is an anti-PD-L1 mAb that blocks the interaction between PD-L1 and its receptors (PD-1 and CD80)
- Blocking PD-L1 and PD-1/CD80 interaction by anti-PD-L1 results in enhanced T cell activity and T cell mediated tumor cell killing
- Durvalumab is approved for patients with locally advanced or metastatic urothelial carcinoma (UC) who have progressed following platinum containing chemotherapy

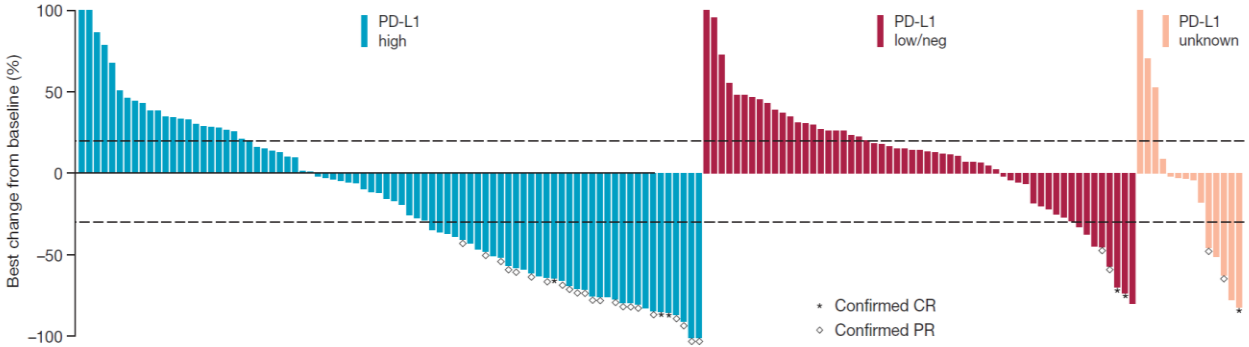


Ott, OncLive, 2014

Durvalumab Demonstrated Favorable Efficacy in UC Patients

Study 1108: a Phase 1/2 dose escalation/expansion study to evaluate the safety, tolerability, and PK of durvalumab in patients with advanced solid tumors (UC expansion cohort: 10 mg/kg Q2W)

Best Percentage Change from Baseline in Tumor Size by BICR
(Patients with Target Lesions at Baseline and ≥1 Post-baseline Scan)



	Total	PD-L1 high	PD-L1 low/negative
	N=191	N=98	N=79
Confirmed ORR, n (%) (95% CI)	34 (17.8) (12.7, 24.0)	27 (27.6) (19.0, 37.5)	4 (5.1) (1.4, 12.5)

Powles et al., JAMA Oncol. 2017 Sep 14;3(9):e172411

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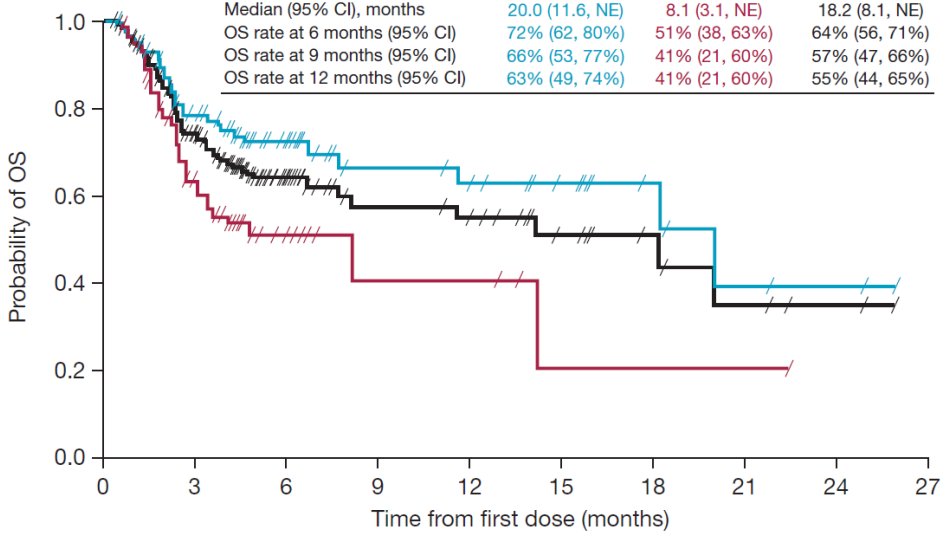
Overall Survival

	PD-L1 high	PD-L1 low/neg	Total
No. of patients (no. of events)	98 (30)	79 (35)	191 (68)
Median (95% CI), months	20.0 (11.6, NE)	8.1 (3.1, NE)	18.2 (8.1, NE)
OS rate at 6 months (95% CI)	72% (62, 80%)	51% (38, 63%)	64% (56, 71%)
OS rate at 9 months (95% CI)	66% (53, 77%)	41% (21, 60%)	57% (47, 66%)
OS rate at 12 months (95% CI)	63% (49, 74%)	41% (21, 60%)	55% (44, 65%)

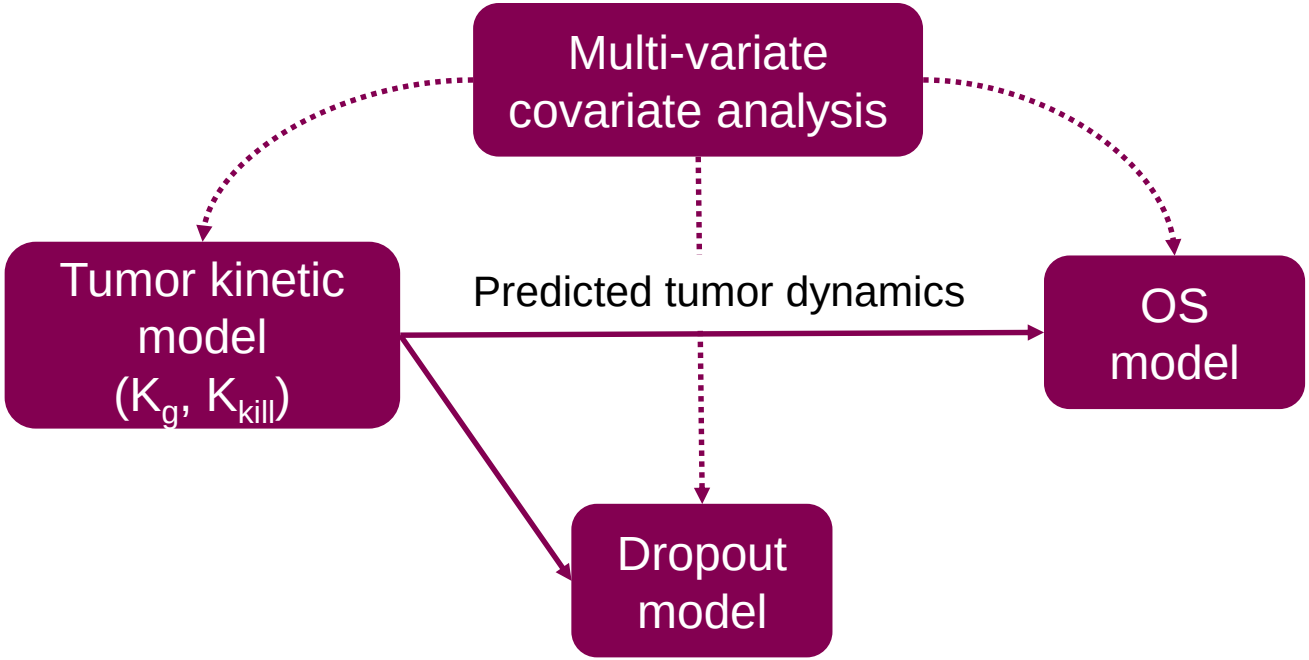


Powles et al., JAMA Oncol. 2017 Sep 14;3(9):e172411

Question

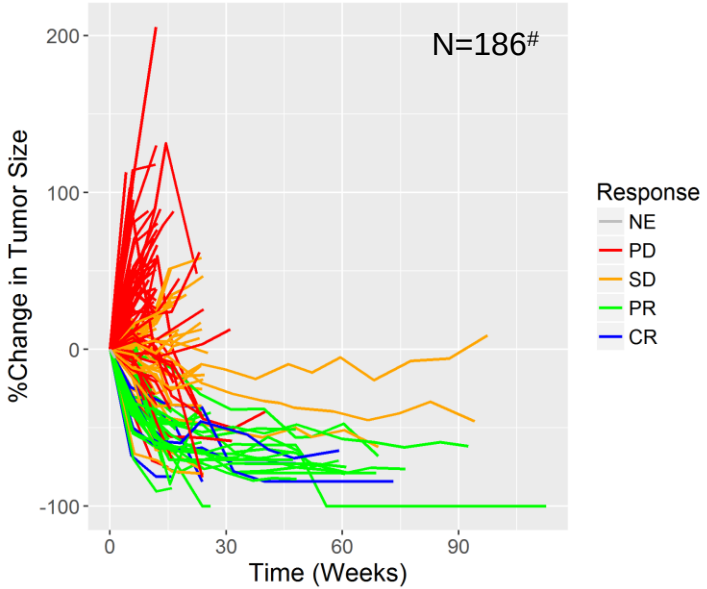
How can we best identify patients who are likely to respond to durvalumab treatment?

A Tumor Kinetic-OS Modeling Framework for IO Therapy

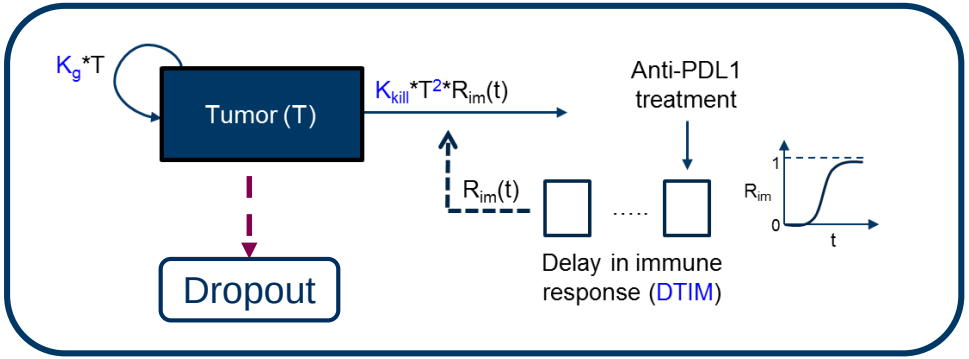


The Population Tumor Kinetic Model for Durvalumab

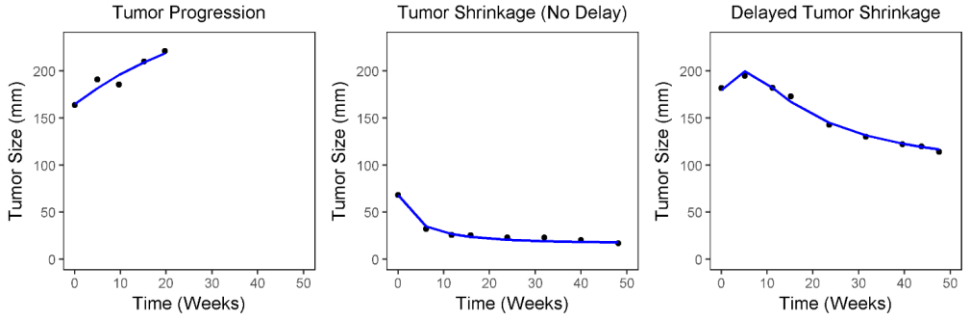
Observed individual tumor profiles*
in UC cohort from Study 1108



*Sum of longest diameter
#159 with post-bsln data



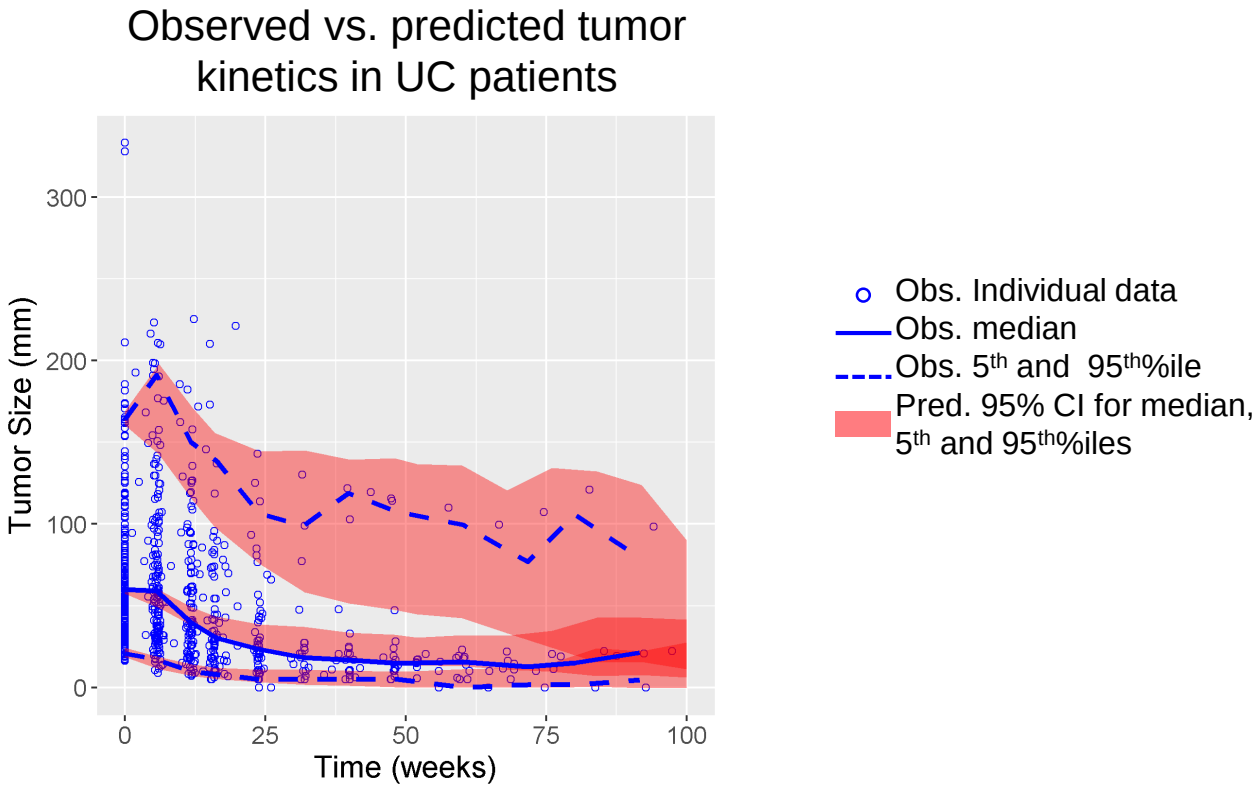
Typical types of tumor kinetic profiles



• Observed data — Individual model prediction

Zheng et al., Clin Pharmacol Ther. 2017 Dec 15 [Epub ahead of print]

The Population Tumor Kinetic Model for Durvalumab



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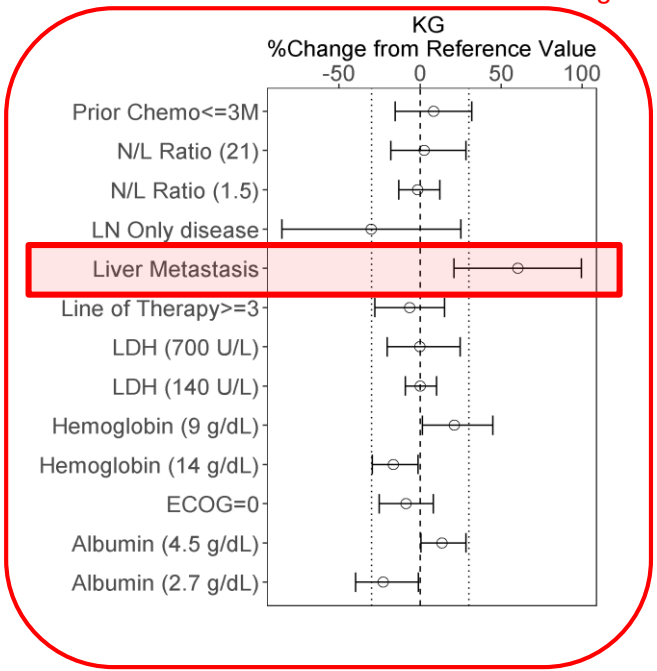
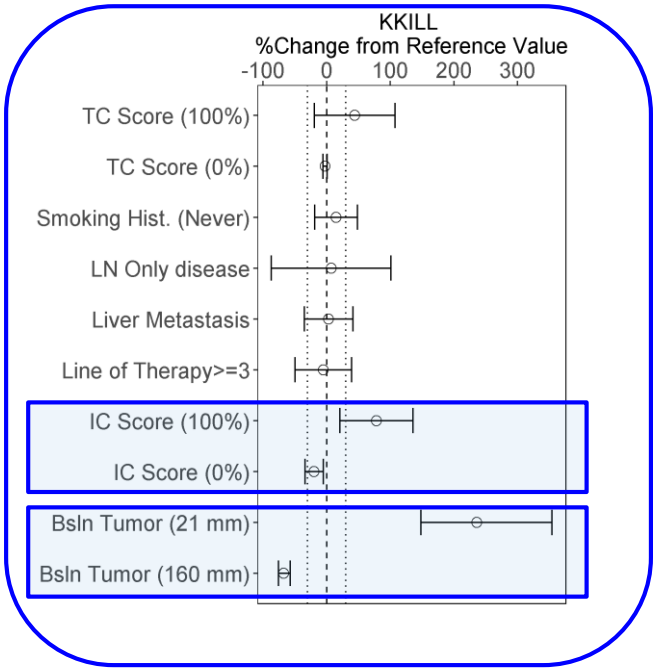
Model-Based Covariate Analysis Identified Potential Prognostic and Predictive Factors

Potential prognostic factors:
Impact tumor growth rate (K_g)



Potential predictive factors:
Impact tumor killing rate (K_{kill})



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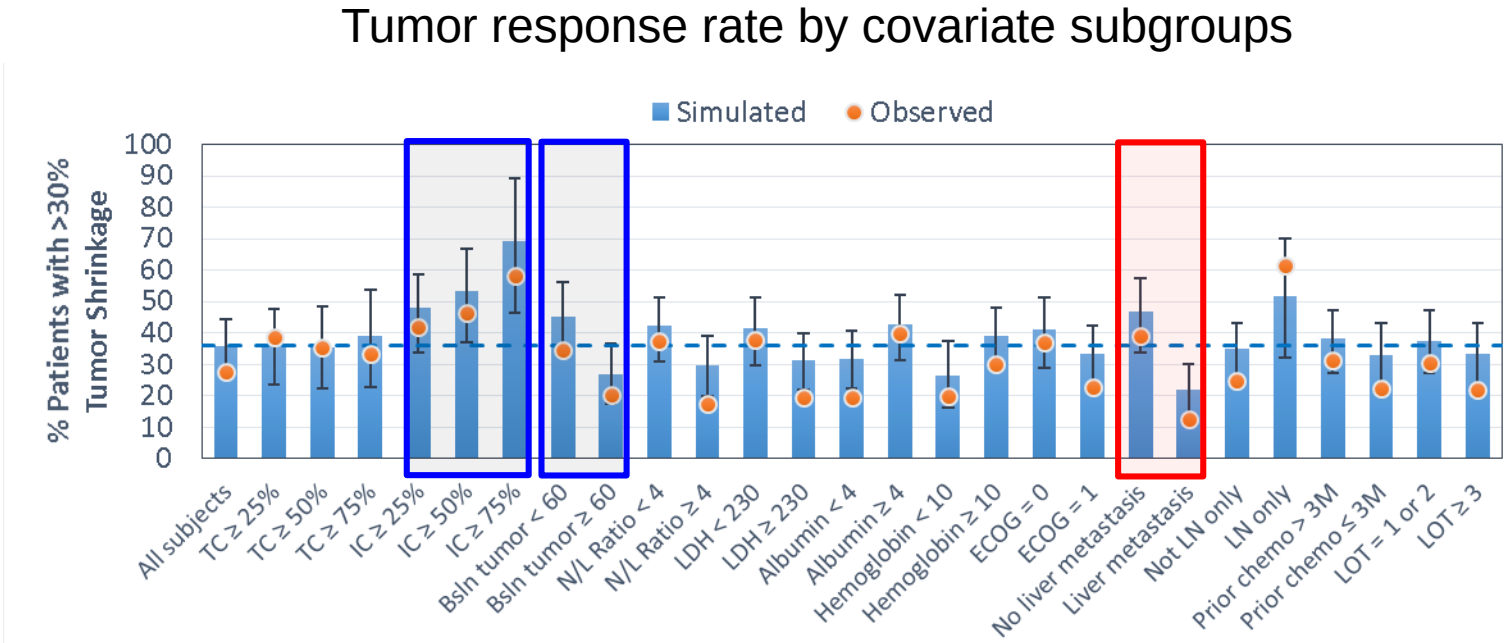
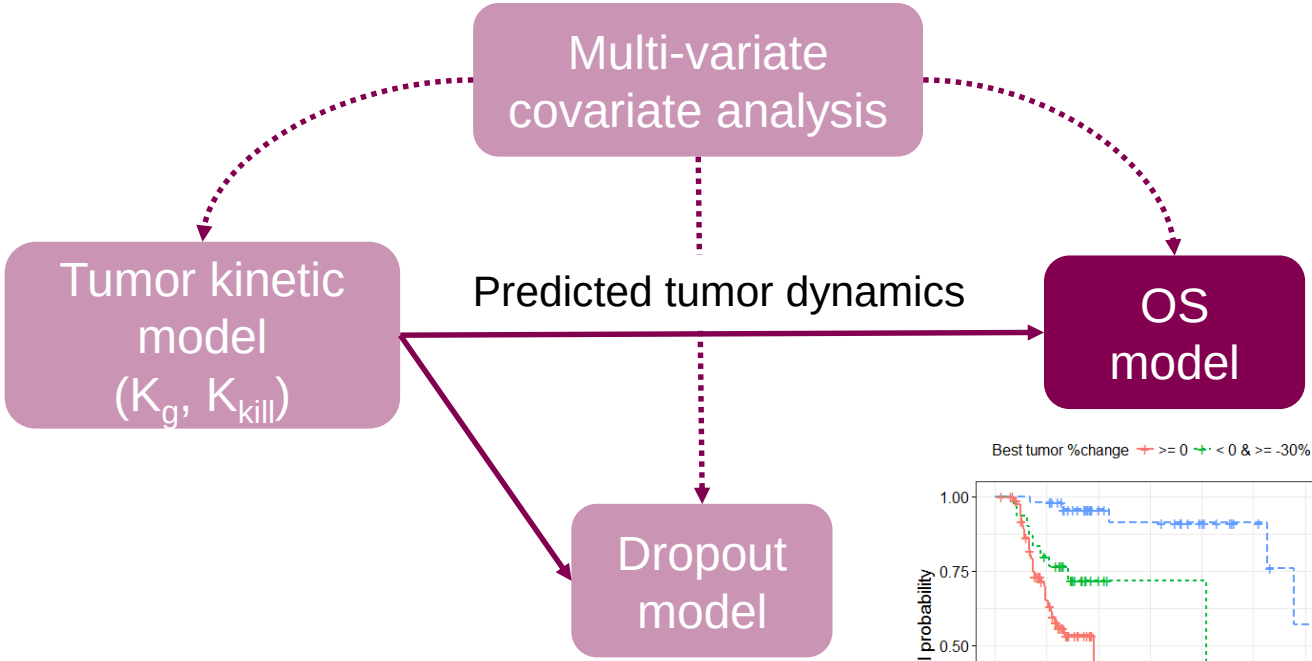
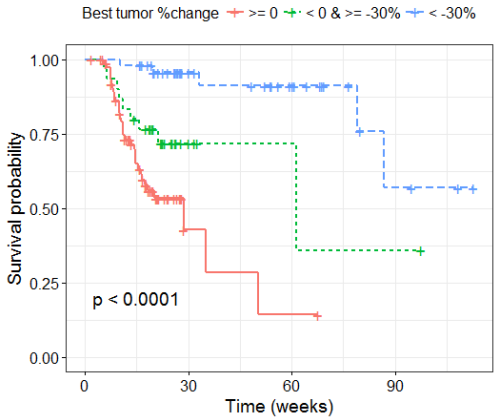
Model Simulations Predicted Tumor Response Rate in Various Patient Subgroups and Biomarker Cutoffs

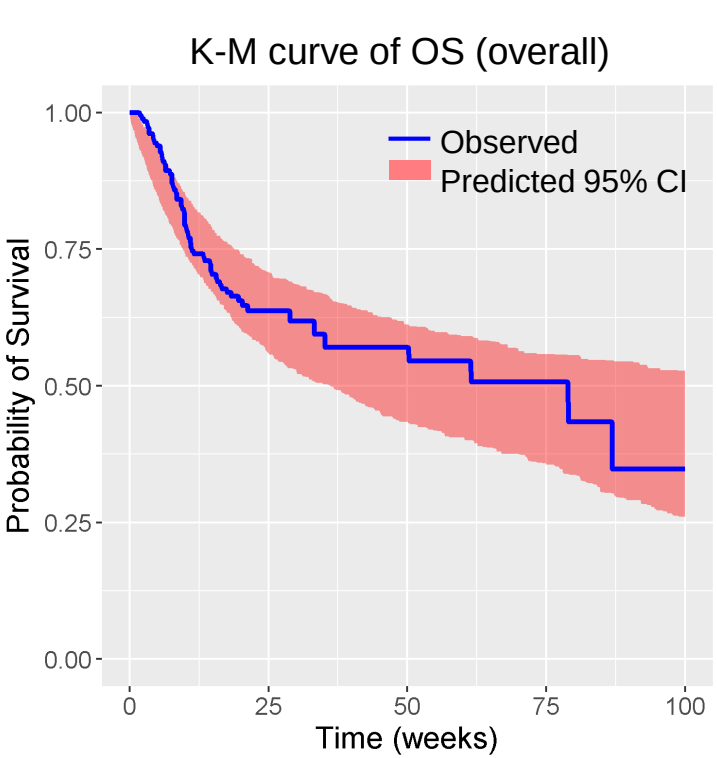


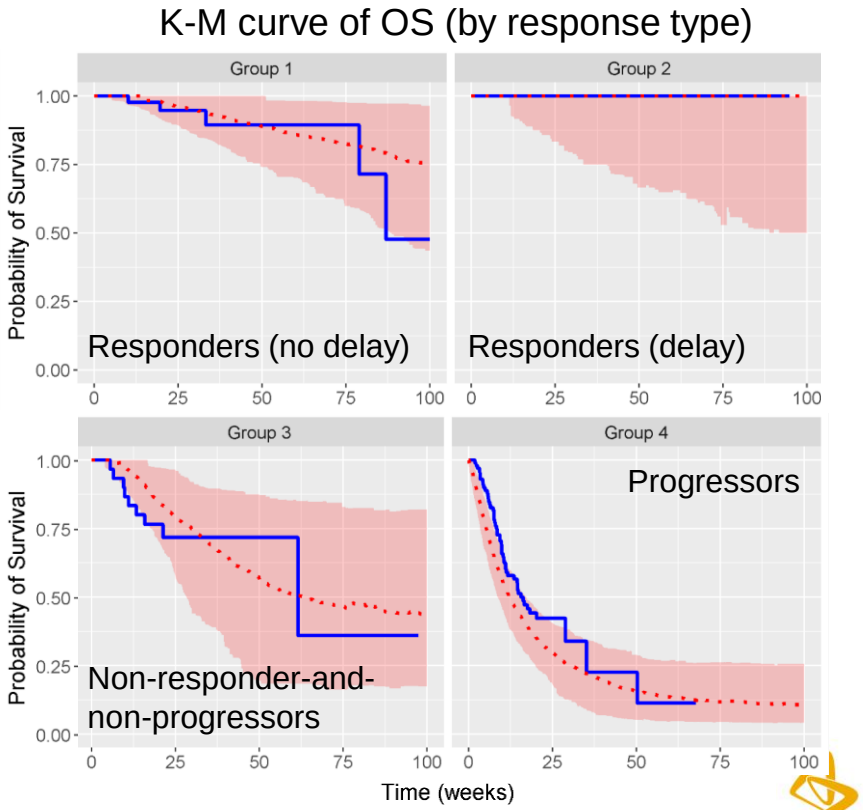
A Tumor Kinetic-OS Modeling Framework for IO Therapy





The Final OS Model Predicted the Observed Survival Curves from Study 1108 UC Cohort





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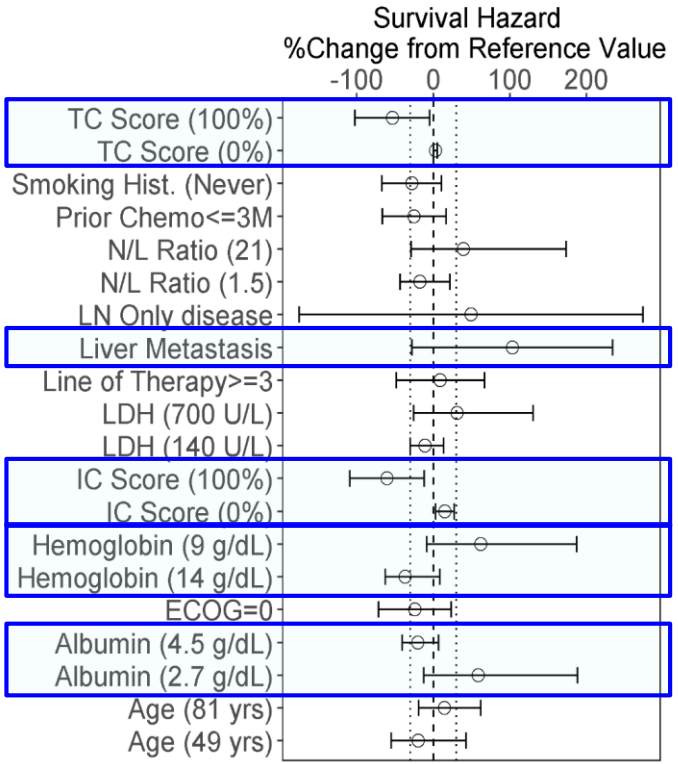
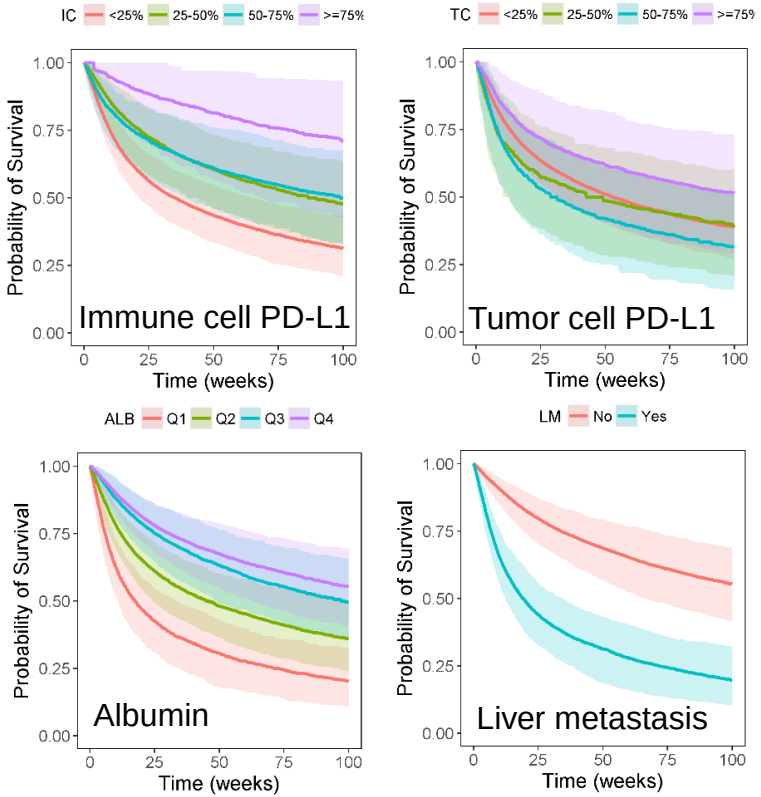
Covariate Analysis Using the OS Model Identified Significant Factors for Survival



Simulated OS curves by covariates



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Summary

- A population tumor kinetic – OS – dropout modeling framework is developed to describe the longitudinal change in tumor size and survival in cancer patients treated with durvalumab

- This modeling framework is a useful tool to study tumor response and its correlation with OS, in which the effect of multiple prognostic and predictive biomarkers can be evaluated in a multivariate analysis

- This modeling approach can be used to guide patient selection and enrichment strategies and to optimize clinical trial designs for IO therapies across various cancer indications

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