



The tumor time-course predicts the overall survival in non-small cell lung cancer patients treated with atezolizumab in a large Phase I study: an evaluation of using different censoring times

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Introduction

- Interleukin 18 (IL-18), together with atezolizumab area under the curve (AUC) predicted tumor size (TS) changes in 88 non-small cell lung cancer (NSCLC) patients treated with atezolizumab [1]
- High values of the relative change from IL-18 baseline at day 21 ($RCFB_{IL-18,d21}$) predicted sustained tumor suppression
- A relationship between on-atezolizumab tumor growth rate and overall survival (OS) has been proposed [2].
- Analyses of OS may be influenced by confounding factors such as patients receiving a new treatment after progression or death not caused by cancer.

Objective

To evaluate IL-18, together with other model-derived variables, such as TS-related, as well as baseline covariates, as predictors of OS, using four different censoring strategies.

Methods and Results

The analysis was performed in NONMEM 7.4 [3] on NSCLC patients treated with 1-20 mg/kg atezolizumab every third week in the phase I study PCD4989g [4]. The workflow of the performed analysis is illustrated below. Descriptions of the final models are presented in Table 1.

- Re-estimate PK-IL18-TS model** (updated covariate values): Relationship between IL-18 and TS remained statistically significant
- Description of the baseline hazard** ($h_0(t)$) for distribution of event times (exponential, Weibull, Gompertz, log-normal and log-logistic) using four different censoring strategies

AAD	C2YE	C2YASOT	C5MALD
All available data (69 deaths)	Data censored no later than at a cut-off date set 2 years earlier than in AAD (56 deaths)	Data censored no later than 2 years after start of treatment for each individual patient (54 deaths)	Data censored a maximum of five months after last dose (28 deaths)

- Stepwise covariate modelling of baseline covariates** (p-value<0.05)
- Evaluation of model-derived variables as predictors of OS** (p-value<0.05)

Age	Lymphocyte count (LYM)	Atezolizumab, IL-18 and ITAC AUC	Time-varying until day 21, then carried forward
Albumin	Metastatic sites	IL-18 and ITAC $RCFB_{d21}$	0 until day 21, then carried forward
Alkaline phosphatase (ALP)	Neutrophil count	Tumor growth rate (log and normal)	
Alanine aminotransferase	Neutophil/Lymphocyte ratio (NLR)	Tumor size ratio week 6/12	Time-varying until week 6/12, then carried forward
Aspartate aminotransferase	Programmed death-ligand 1 expression (PD-L1)	Time to tumor growth	Time-varying until occurrence and then carried forward
Bilirubin	Platelet count	Time-course of TS RCFB ($RCFB-TS(t)$) and current rate of TS changes ($TS(t)$ -slope) (ext.)	Extrapolated based on EBEs after last observed tumor size measurement
Body weight	Race	RCFB-TS(t) and $TS(t)$ -slope (c-f.)	Carried forward 3 weeks after last dose
Brain, liver and visceral metastases	Sex		
ECOG status	Smoking		
Histology	Total protein		
IL-18	Tumor size		
Interferon-inducible T-cell alpha chemoattractant (ITAC)	Years since initial diagnosis		
Lactate dehydrogenase	Years since metastatic disease		
Line of treatment			

- Final backward deletion step** (p-value<0.05)
- Prediction of AAD.** Predict AAD from the final C2YE, C2YASOT and C5MALD models

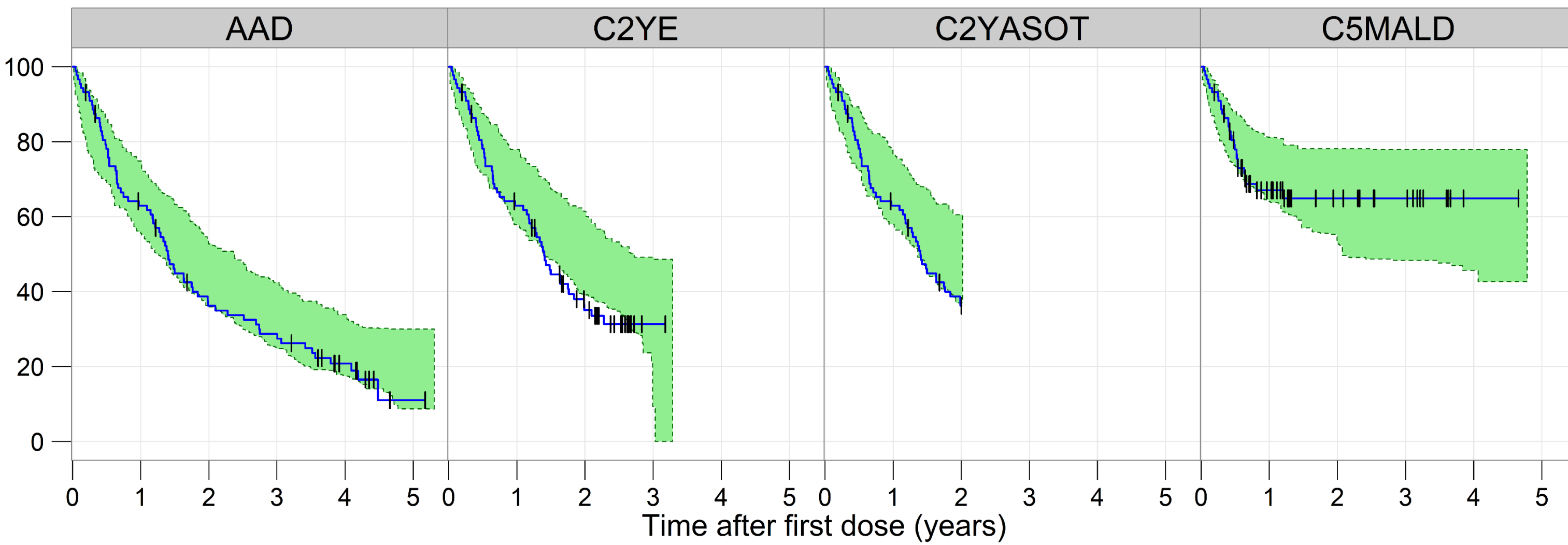


Figure 1 KMVPCs of the final models. The plots illustrate the observed Kaplan-Meier curve (blue line) in comparison to the 95% confidence interval, generated from 100 simulations (green shaded area). Black vertical lines indicate censored events.

Table 1 Description of the final models

	AAD	C2YE	C2YASOT	C5MALD
$h_0(t)$	Exponential	Exponential	Exponential	Gompertz
Predictors included in the final model	LYM ALP RCFB-TS(t) (c-f)	NLR ALP ¹ PD-L1 expression RCFB-TS(t) (ext.)	NLR ALP ¹ PD-L1 expression RCFB-TS(t) (ext.)	NLR ALP RCFB-TS(t) (ext.)

¹Parameterized as PD-L1+ immune cells/tumor mass <5% or PD-L1+ tumor cells/tumor mass <50% vs. PD-L1+ immune cells/tumor mass ≥5% or PD-L1+ tumor cells/tumor mass ≥50%

Conclusions

- The value of a relatively large Phase I data was demonstrated in this analysis, where the tumor time-course was identified as a predictor of OS, independently of censoring strategy.
- Final predictors were similar in all models.
- Shorter follow-up data could be used to predict longer follow-up outcome.

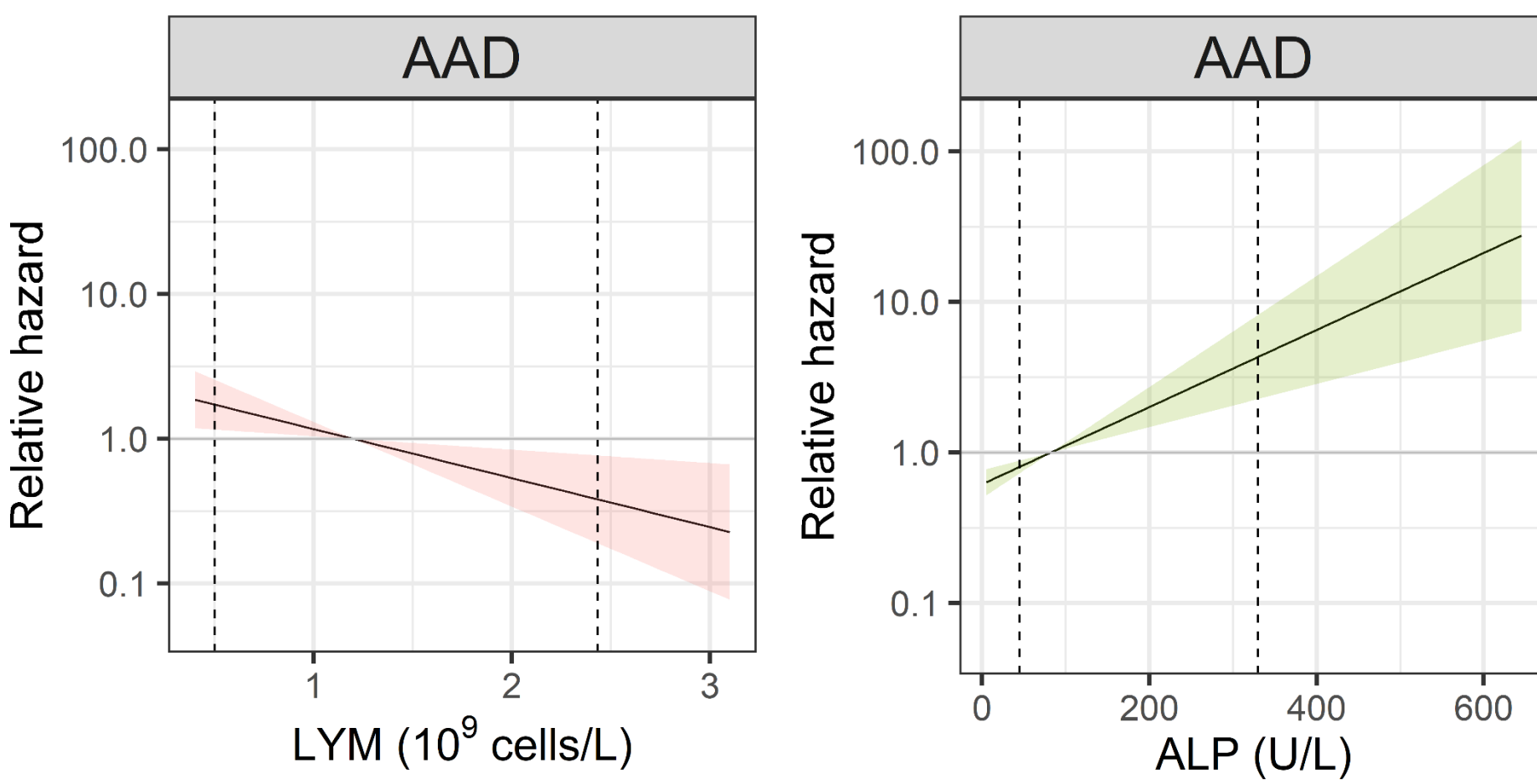


Figure 2 The solid black line represents the relative hazard (to the typical patient) versus the observed range of lymphocyte count (LYM) and alkaline phosphatase (ALP). Shaded areas represent the 95% confidence interval, given the corresponding standard error in the AAD model. Dashed vertical lines represent the 2.5th and 97.5th percentiles of the observed covariate value. The horizontal grey line indicates no change in relative hazard, i.e. a patient with median values of all covariates and no change from tumor size baseline.

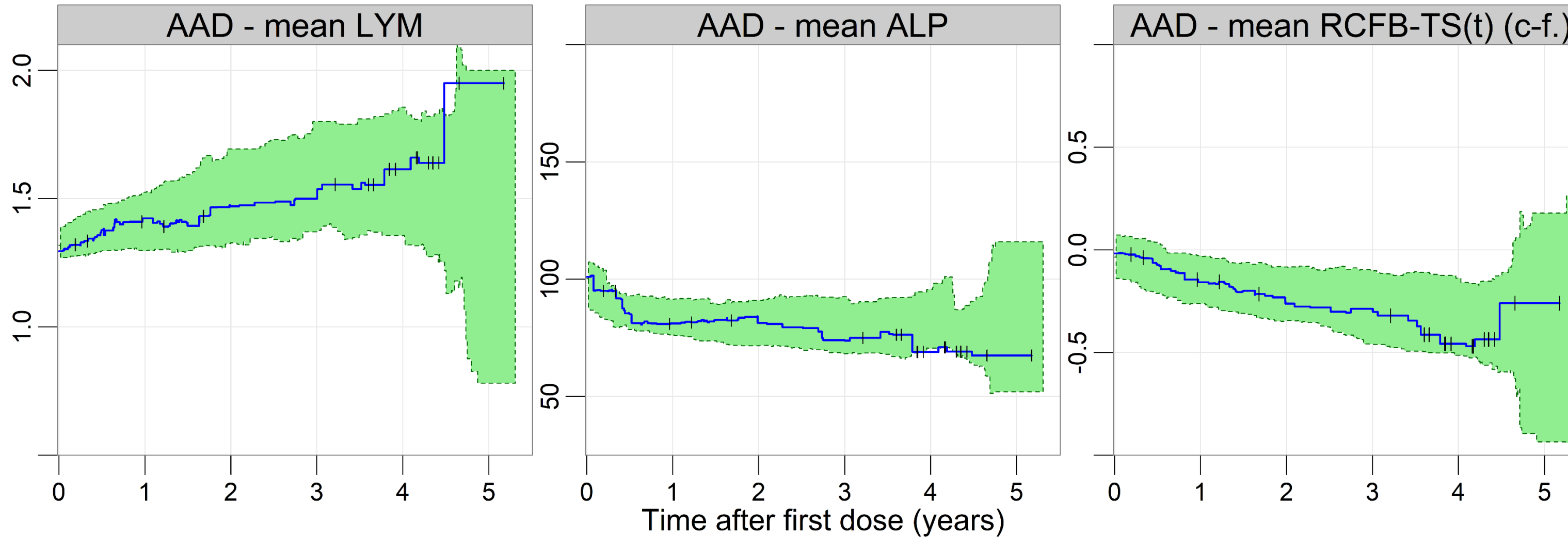


Figure 3 KMMCVCs of the final AAD model. The plots illustrate the observed mean of baseline lymphocyte count (left panel), baseline alkaline phosphatase (middle panel) and time course of tumor size relative change from baseline, carried forward 3 weeks after last dose ($RCFB-TS(t)$ (c-f); right panel) of patients remaining in the study (blue line) in comparison to the 95% confidence interval, generated from 100 simulations (green shaded area). Black vertical lines indicate censored events.

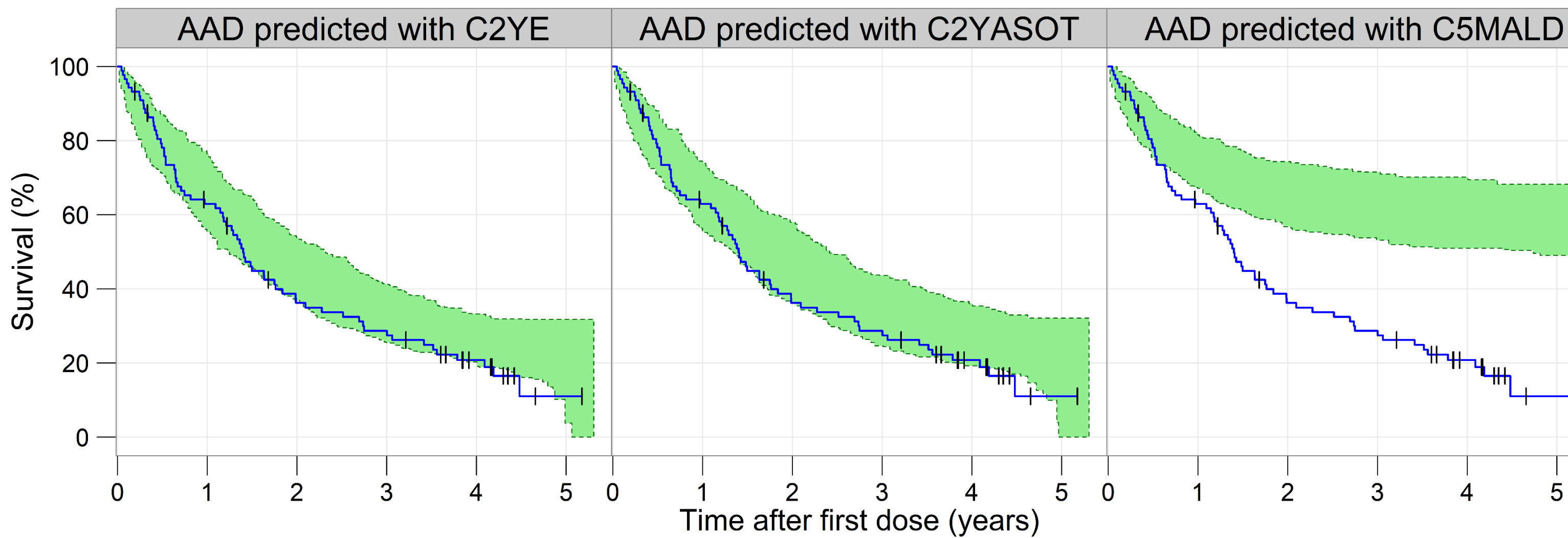


Figure 4 KMVPCs of AAD predicted with C2YE, C2YASOT and C5MALD. The plots illustrate the observed Kaplan-Meier curve (blue line) in comparison to the 95% confidence interval, generated from 100 simulations (green shaded area). Black vertical lines indicate censored events.

- Kaplan-Meier visual predictive checks (KMVPCs) of the final models illustrated a good model fit of the distribution of event times (**Figure 1**).
- Higher values of NLR and ALP and lower values of LYM, as well as low PD-L1 expression were related to a higher hazard (illustrated in **Figure 2** for the AAD model).
- All model-derived variables related to TS, but none of the IL-18, ITAC or atezolizumab variables, provided p-values<0.05 in the univariate analysis. Inclusion of a second model-derived resulted in model instability and a second model-derived variable was consequently not included.
- Evaluation of the adequacy of included predictors in the final AAD model (Kaplan-Meier mean covariate VPCs, KMMCVC [4]) revealed no misspecification (**Figure 3**). Evaluation of the other three models showed similar results (not presented).
- The C2YE and C2YASOT models predicted the AAD well, while misspecification was observed for the C5MALD model (**Figure 4**).

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References

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