

Pharmacometric Evaluation of Patient-Reported Symptom Burden in Anticancer Therapy With Axitinib and Cabozantinib Using Minimal Continuous-time Markov Models

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Introduction

The patient perspective is becoming increasingly important in the assessment of adverse drug events (ADEs), as measured by the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [1]. Predicting patient-reported symptom burden may help to optimize therapeutic interventions in anticancer treatment in a more individualized and targeted manner. Minimal continuous-time Markov models (mCTMM) are well suited to describe toxicity-covariate relationships in combination with pharmacometric models [2].

Aim

This project aimed to develop Markov models to describe the time course of selected patient-reported ADEs in patients with renal cell carcinoma receiving either axitinib or cabozantinib treatment within the ON-TARGET study [3].

Summary and Conclusions

- The development of mCTMMs in combination with PRO-CTCAE symptom scores was feasible.
- The hand-foot syndrome model was improved by the inclusion of clearance.
- This is a first step towards using Markov models to consider ADEs in precision dosing.
- Including biomarkers and evaluating alternative model structures could provide additional insights to enable more accurate patient-specific prediction of ADE occurrence and severity.

Methods

Study centers

Documentation of:
dose, plasma concentrations and
Comedications

Patients

Documentation of:
• daily intake of drugs
• ADEs in monthly PRO-CTCAE
Questionnaires

February 2021 to December 2024

40 Patients

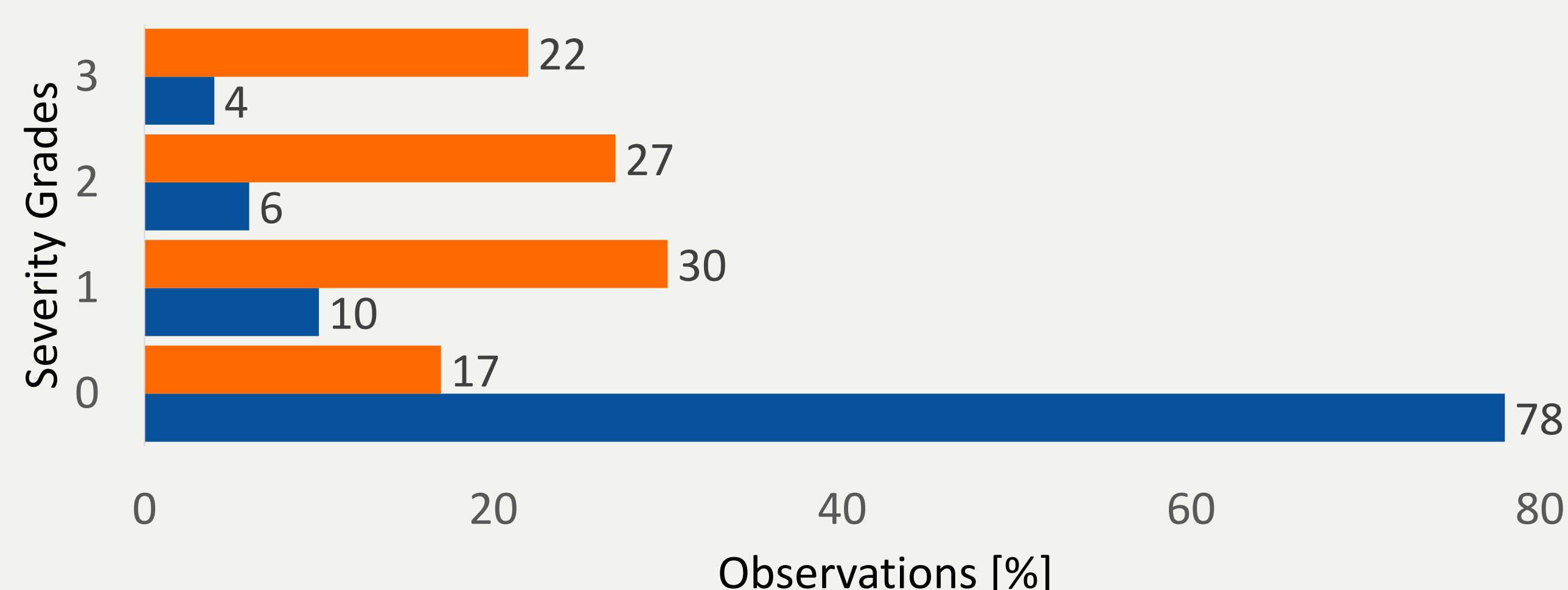
181 Axitinib Questionnaires
211 Cabozantinib Questionnaires

Modelling

- mCTMMs were developed to describe the severity of 14 PRO-CTCAE symptoms.
- Severity grades 2 and 3 were combined for modeling purposes, as severity grade 3 was reported very rarely.
- Covariate influences were tested on the intercept of the logit probability of severity grade 1 α_1 .
- Covariates were selected via forward inclusion (p value ≤ 0.05) and subsequent backward exclusion (p value ≤ 0.01).

Results for the patient-reported hand-foot syndrome

Frequency of the observed severity grades



Cabozantinib

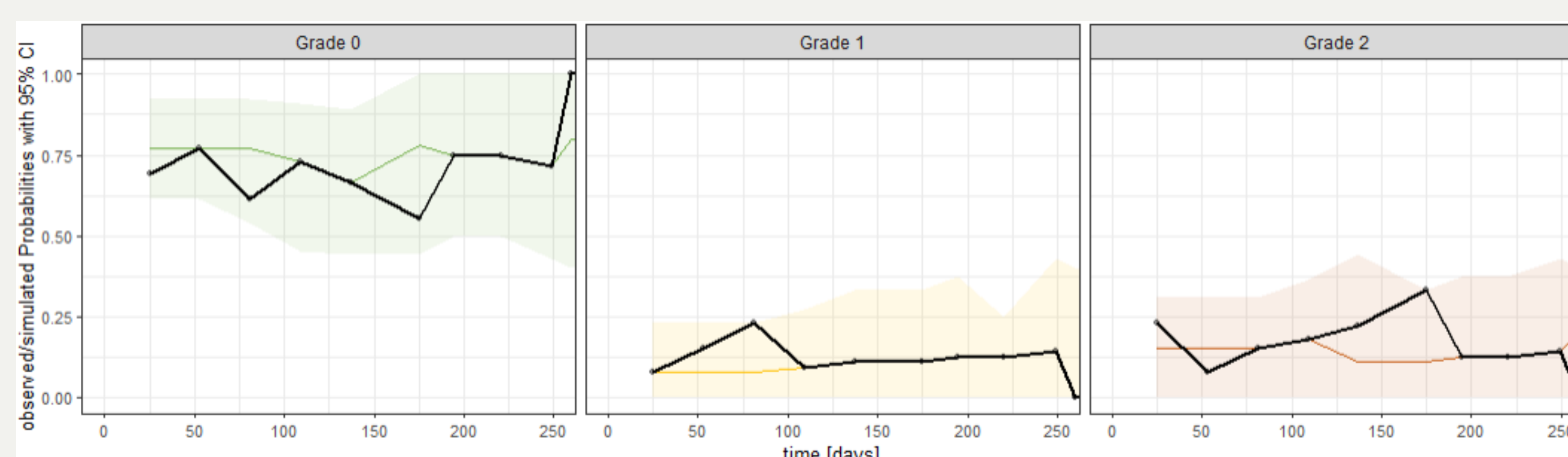
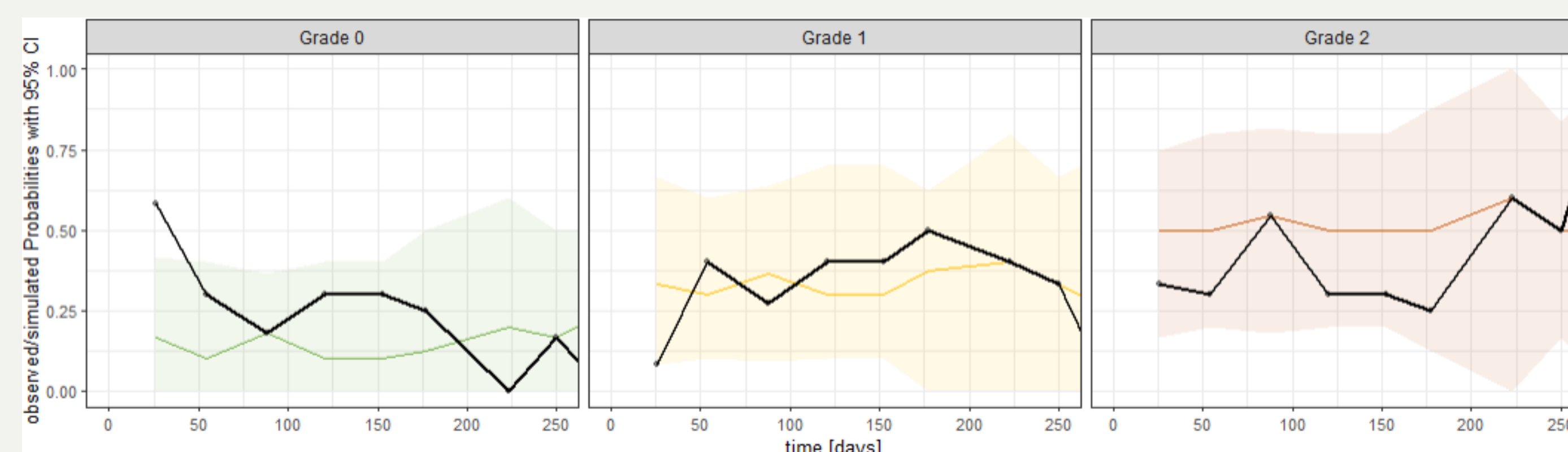
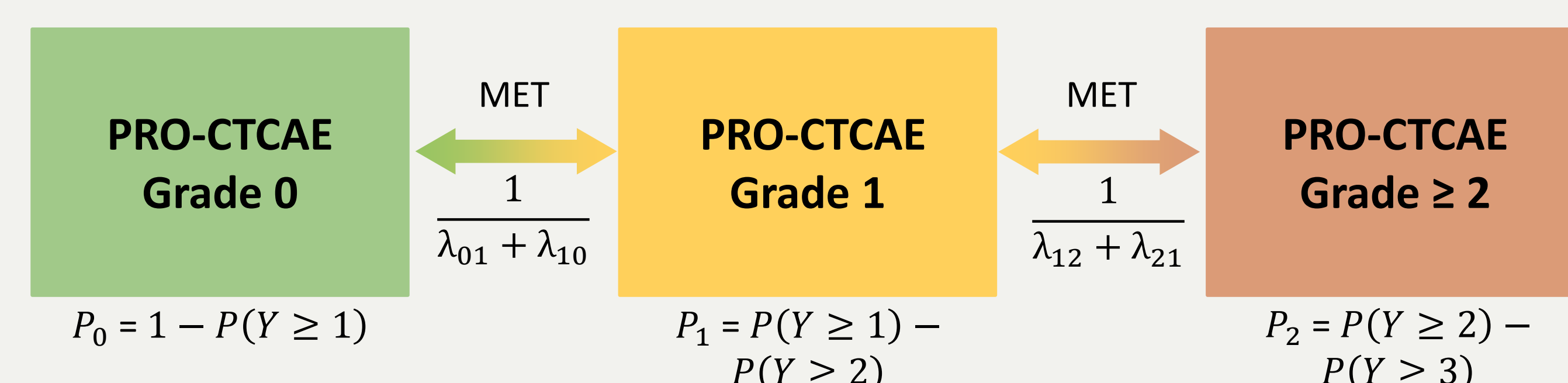
Parameter	Estimate	Bootstrap Median	Bootstrap 95 % CI
α_1	1.56	1.43	0.05 – 2.50
b_2	- 1.64	- 1.77	- 2.67 – - 0.95
<i>MET (days)</i>	11.30	11.21	4.71 – 45.03
$\theta_{\text{clearance}}$	- 0.03	- 0.01	-1.41 – 0.38

Axitinib

Parameter	Estimate	Bootstrap Median	Bootstrap 95 % CI
α_1	- 2.66	- 2.67	- 5.42 – - 1.13
b_2	- 0.76	- 0.77	- 2.92 – - 0.07
<i>MET (days)</i>	16.00	13.3	2.12 – 94.79
$\theta_{\text{clearance}}$	- 0.19	- 0.20	- 0.56 – - 0.06

α_1 , Intercept parameter for Hand-foot syndrome grade 1 on the logit scale, b_n parameter for grade n such that $\alpha_n = \alpha_{n-1} + b_n$, MET mean equilibration time, $\theta_{\text{clearance}}$ effect size of individual clearance as covariate on the logit scale

Minimal continuous-time Markov Model



Observed values: black line, median of the predicted values: colored line, 95 % confidence interval of the simulated values: colored areas

References

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Acknowledgements

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