

PKPD Vs AI for Preclinical Tumour Xenograft Extrapolation

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Background:

- Patient-derived xenograft (PDX) models are the gold standard for evaluating the preclinical efficacy of oncology drug candidates.
- These experiments are time-consuming & costly.
- ML statistical forecasting methods are applied to pharmacometrics for the first time to extrapolate data from PDX experiments, with the goal of reducing the time required to obtain meaningful insight.

Objectives:

- To compare the extrapolation capacities of the pharmacokinetic-pharmacodynamic (PKPD) and machine learning (ML) forecasting models on PDX data, & hence to quantify whether there is a potential to reduce preclinical development time-lines.

Methods and Datasets:

- PDX data [1] [2] for 3 molecules: ribociclib, binimetinib, & buparlisib
- 6 cancer types
- For each molecule, the parameters were estimated on the complete dataset (300 days) and different early time windows ranging from 20 to 50 days. The parameters re-estimated on early data were used to simulate for the complete time series.
- 3 ML models from StatsForecast in Python: exponential smoothing (ETS) [4], complex exponential smoothing (CES) [4], and Theta [3]
- ML trained on early time windows (20-50 days) to make forecasts until for the remaining part of the complete time.

Discussion:

- The performance of selected PKPD models (exponential growth for ribociclib, proliferative rim for binimetinib and Gompertz for buparlisib) remains stable across different time windows.
- ML models provide an adequate overall description of tumour dynamics, however, fail to provide precise individual forecasts.
- ML forecast methods are more sensitive to training window size than PKPD.
- AI statistical forecast models have the potential to reduce the timelines of PDX experiments, however further evaluation is needed and more sophisticated models to be tested prior to their application in model-informed drug development.

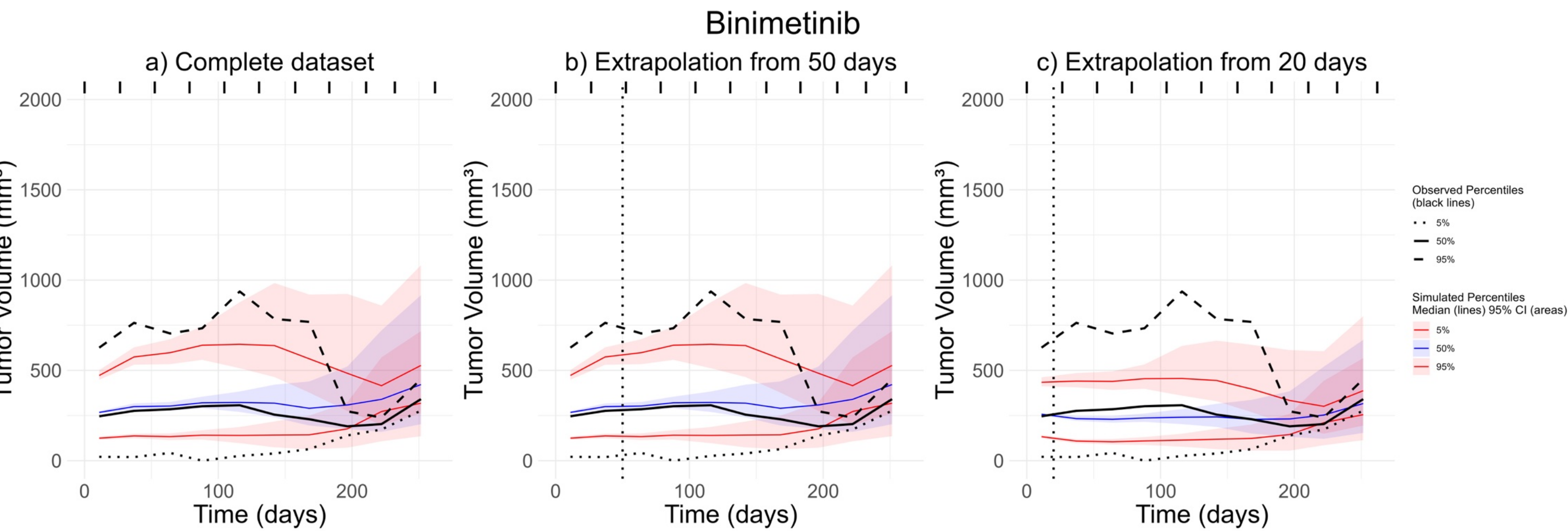


Figure 1. Visual predictive checks of longitudinal tumour size for PDX treated with binimetinib based on model parameters estimated on the complete dataset (a), the first 50 days (b), or the first 10 days (c). Bootstrap was repeated 1000 times and the confidence intervals of 95% of the predictions were calculated.

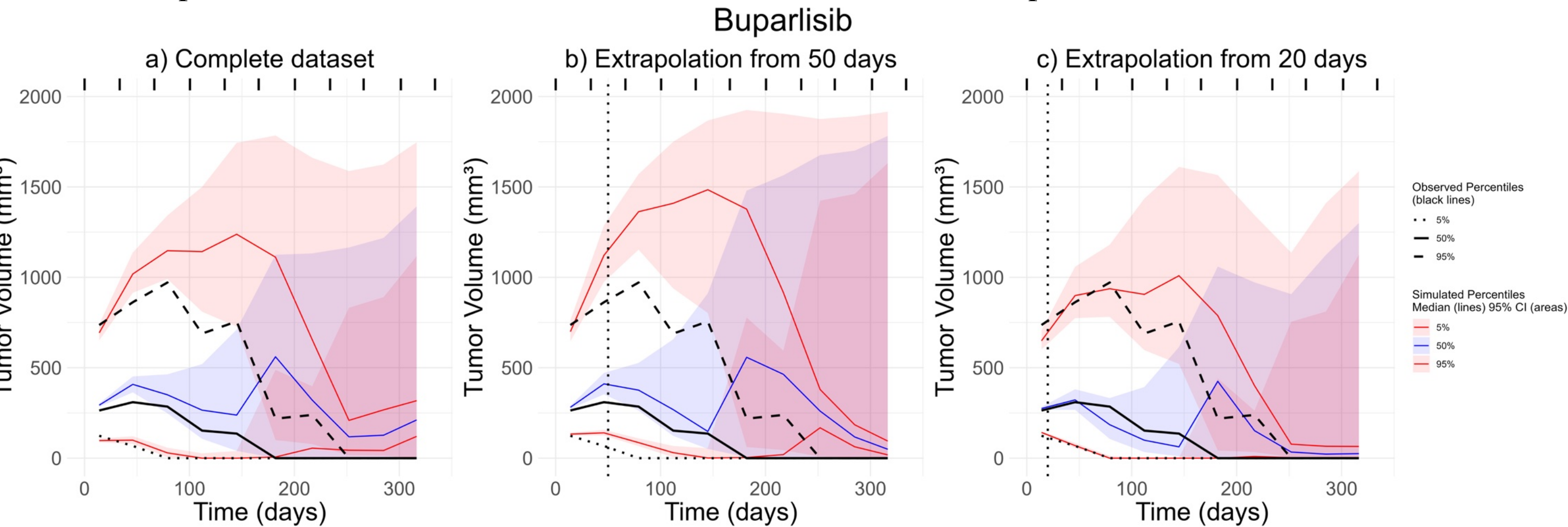


Figure 2. Visual predictive checks of longitudinal tumour size for PDX treated with buparlisib based on model

parameters estimated on the complete dataset (a), the first 50 days (b) or on the first 10 days (c). Bootstrap was repeated 1000 times and the confidence intervals of 95 % of the predictions were calculated.

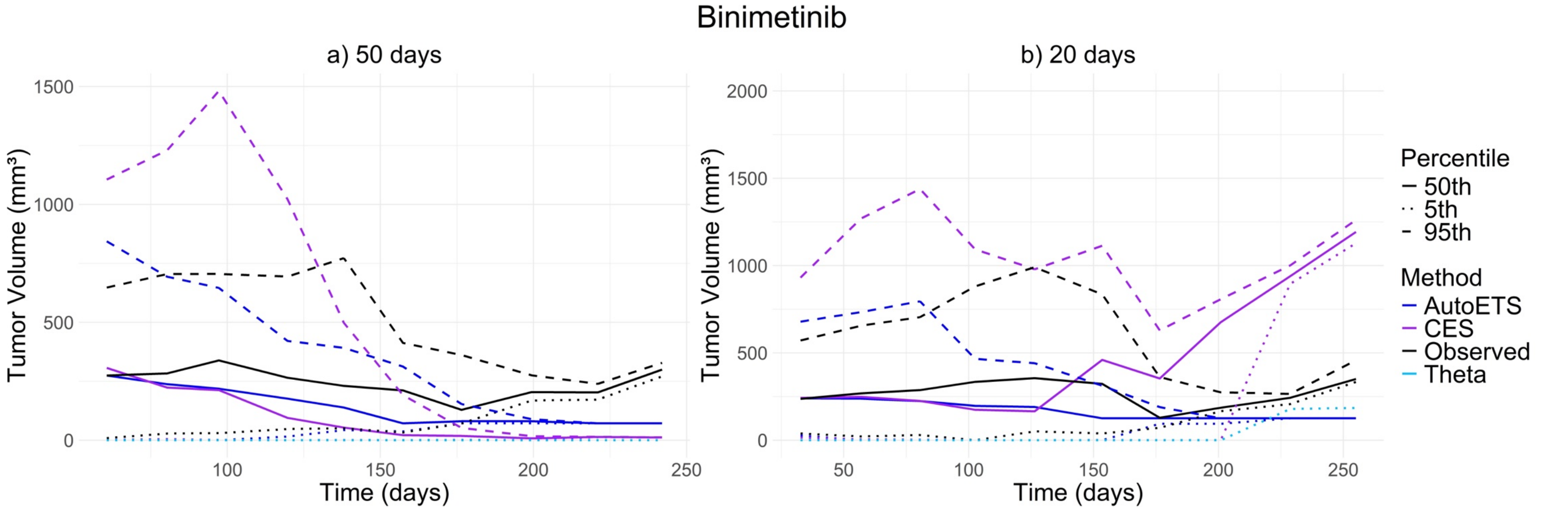


Figure 3. Median, 5th and 95th percentile of longitudinal tumour size forecast by AutoETS, CES, and Theta models compared to the observed data for PDX treated with binimetinib based on training on a time windows of 50 (a), and 20 days (b).

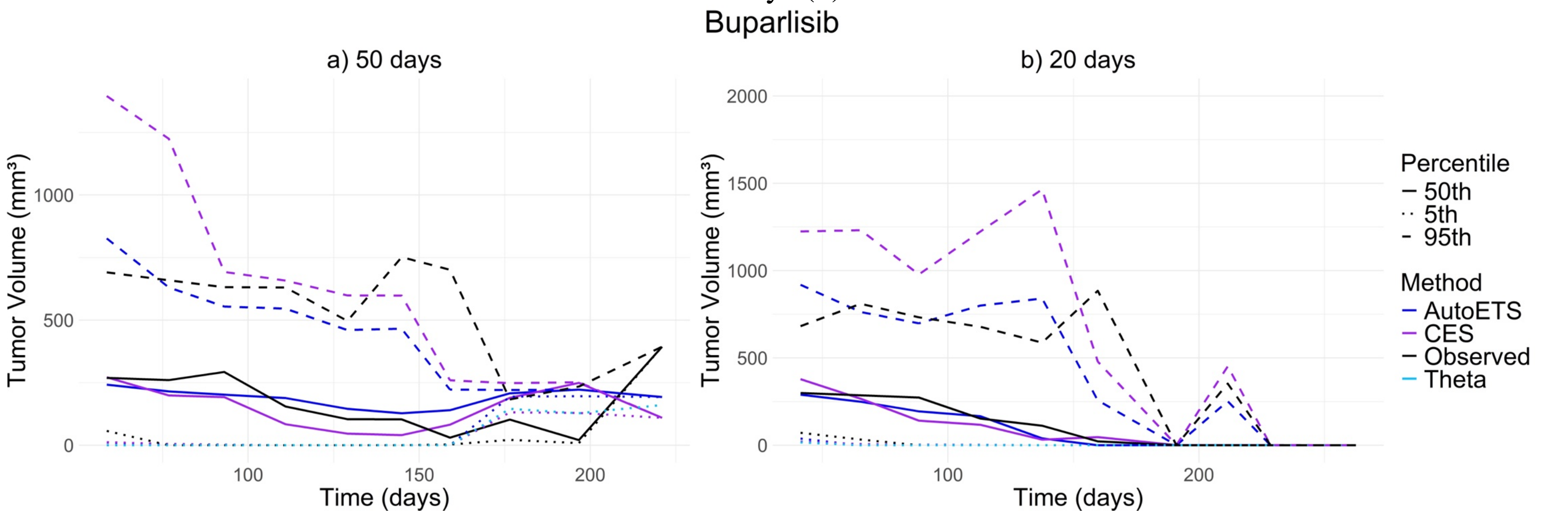


Figure 4. Median, 5th and 95th percentile of longitudinal tumour size forecast by AutoETS, CES, and Theta models compared to the observed data for PDX treated with buparlisib based on training on a time windows of 50 (a), and 20 days (b).

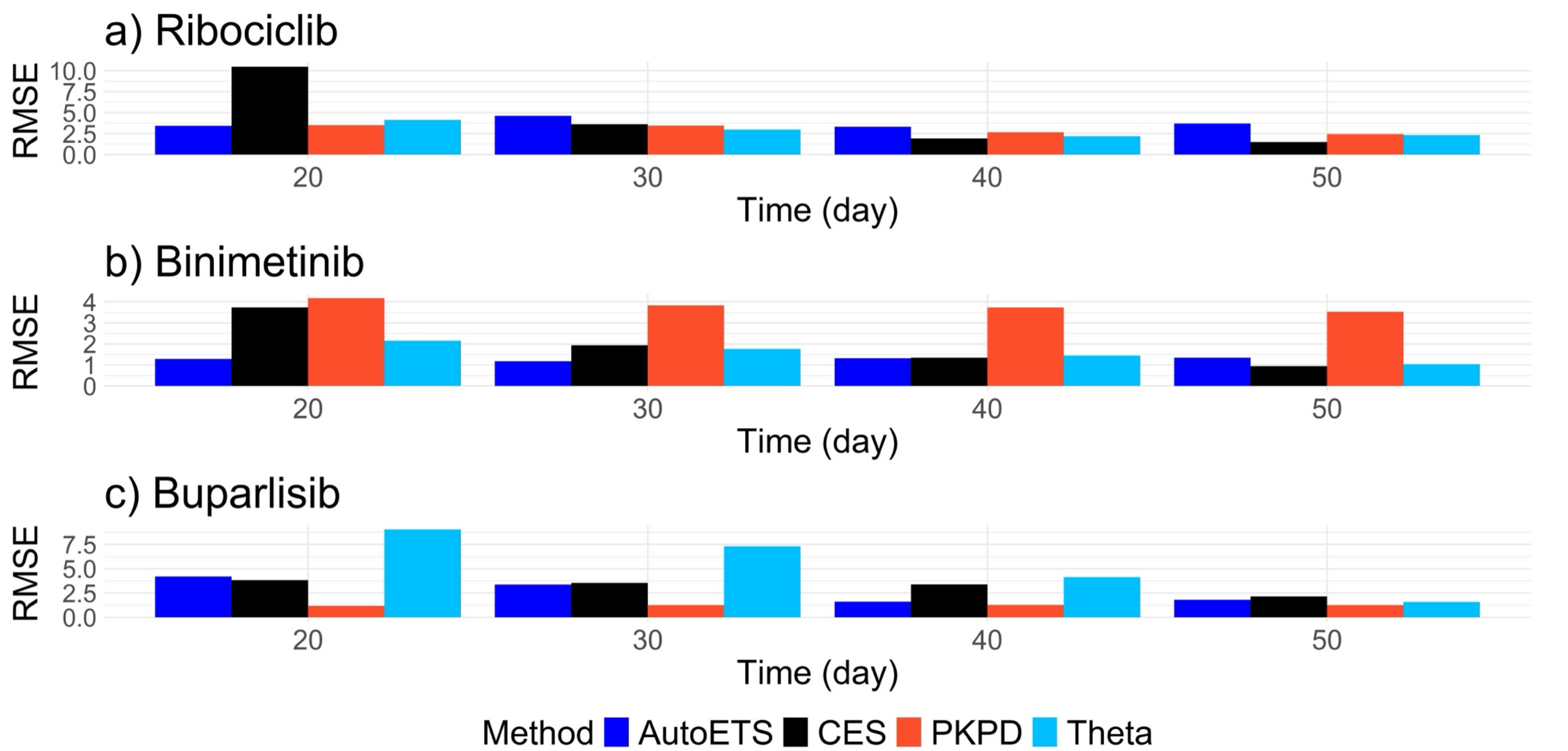


Figure 5. Accuracy of PKPD, AutoETS, CES and Theta for time windows of 20, 30, 40, and 50 days for a) ribociclib, b) binimetinib, and c) buparlisib.

References

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- [3] F. Petropoulos and K. Nikolopoulos. “Optimizing Theta model for monthly data”. English. In: *ICAART 2013 - Proceedings of the 5th International Conference on Agents and Artificial Intelligence*. ICAART 2013 - Proceedings of the 5th International Conference on Agents and Artificial Intelligence, 5th International Conference on Agents and Artificial Intelligence, ICAART 2013 ; Conference date: 15-02-2013 Through 18-02-2013. May 2013, pp. 190–195.
- [4] I. Svetunkov, N. Kourentzes, and J. K. Ord. “Complex exponential smoothing”. en. In: *Nav. Res. Logist.* 69.8 (Dec. 2022), pp. 1108–1123.