Leveraging Longitudinal Tumor Data for Prediction of Overall Survival from I-O therapy: A Proof of Concept with Quantitative Models and External Validation

Satyendra Suryawanshi¹*, CJ Godfrey², Amit Roy¹, Katy Simonsen¹, Jonathan French², Manish Gupta¹

¹Bristol-Myers Squibb, Princeton, USA ; ²Metrum Research Group, CT, USA

Objective: To identify and validate a summary measure of tumor-response (TM) that is predictive of clinical efficacy in patients with solid tumors treated with ipilimumab (IPI).

Methods: The estimation dataset included all available overall survival (OS) and longitudinal tumor data from 351 IPI treated advanced melanoma patients from 3 Phase 2 studies (CA184007, 008 and 022). The validation dataset included similar data from 395 IPI treated advanced melanoma patients from Phase 3 study (MDX01020). Previously-reported tumor growth dynamic model was used to derive following TMs for individual patients: Maximum predicted tumor shrinkage (TS_{max}), predicted tumor response at week 16 and week 8 (TS_{wk16} and TS_{wk8}), Tumor growth rate (TGR) and time to tumor growth (TTG).¹ Each TM was tested as predictor of OS by a Cox Proportional Hazard model, after accounting for the effect of known prognostic factors. Cross validation and bootstrap-based VPC were performed to evaluate model performance, and determine order of TMs as a predictor of OS. External validation was performed to evaluate discrimination and calibration ability of final OS models for survival probability in different risk group based on weighted sum of prognostic variables.

Results: Individual tumor response data was best described using mono-exponential shrinkage and linear growth rate. TMs were incorporated as nonlinear predictors of log hazard for OS. TS_{max}, TS_{wk16} and TS_{wk8} were most favourable predictors of survival based on cross validation and VPC. TGR and TTG did not demonstrate satisfactory performance. Final OS models provided good discrimination between risk groups in new dataset when PIs were constrained to similar range as estimation data. Final OS models tended to over predict survival probability to a modest extent in the validation dataset.

Conclusions: This analysis provided robust evaluation of tumor response metrics as predictors of survival in patients receiving IPI I-O therapy.

References:
1. Feng Y et al, ASCO, 2014, Chicago, IL.