Joint modeling of overall survival (OS) and tumor size for patient-level predictions of survival in non-small cell lung cancer (NSCLC)

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Objectives: To obtain and validate patient-level predictions of OS in NSCLC based on a joint model of OS and longitudinal tumor size.

Methods: Clinical data from the IPASS gefitinib Phase 3 study in NSCLC (NCT00322452) were used to fit a joint model of tumor size dynamics and OS. Model covariates were selected based on their statistical significance for the event hazard and longitudinal sub-models.

The survival estimation method was implemented in the R package JM [1]. Model validation was performed on follow-up study data (IFUM, Phase 4, NCT01203917). Using clinical trial simulations, we assessed the simulated mean survival times for individual subjects and compared to the observed data. We compared survival predictions for those patients who share common demographic and disease state covariates, i.e., patients whose differences in survival estimates would have been caused by differences in tumor size dynamics only (Figure 1). In a follow-up study, among subjects whose predicted probabilities of survival after time $t$ were larger or equal than $p$, we computed the proportion $\pi(t, p)$ of those subjects who actually survived beyond $t$.

Results: The fitted model accurately estimated patient survival based on an early, e.g. 3 months, data cut-off for tumor assessments. Treatment, EGFR mutation status and ECOG performance status were evaluated as significant covariates for the joint model. Associations between tumor dynamics (size and time derivative) and time-to-death were statistically significant (p-values < 0.05).

Model predictions at subject level were accurate, in that the function $\pi(t, p)$ was monotonically increasing as $p$ approached 0.5 - i.e., the individual median survival was accurately predicted by the model.

Conclusions: Joint modeling of tumor size dynamics and OS in NSCLC allows for effective simulation of clinical trials and accurate personalized predictions of survival.

Figure 1. Comparison of subject-level survival predictions