Improving interim and subgroup analyses of oncology trials with joint modeling of time-evolving tumor size and survival

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Background and Objective: The joint modeling approach allows a statistically valid analysis and interpretation of longitudinal tumor size dynamics and subject survival, in the context of time-to-event (survival) censoring of longitudinal dynamics and intrinsic time-dependent covariates in the Cox proportional-hazards model.¹ We applied joint modeling to a phase 3 oncology trial to establish the increased power to detect a treatment effect on the hazard of disease progression.

Methods: Using clinical data for 261 EGFR-positive subjects from the Phase 3 IPASS study (NCT00322452) of Iressa (gefitinib), we built modeled progression-free survival.

Results: Figure 1 (black line with dashed 95% CI) shows the resulting joint model time-dependent proportional hazard estimation incorporating both treatment, tumor size, and rate-of-change of tumor size. For comparison, the traditional Cox analysis is also shown (red line). Note the Cox hazard is flat, since it does not incorporate the time-dependent tumor size. After starting with similar hazard at times near zero, the joint model hazard estimate substantially increases through the trial period. This leads to significantly higher power to detect treatment differences in smaller studies, such as interim analysis or subgroup analysis.² The blue line shows the time-dependent joint model hazard time averaged over event times, which approximates the "average effect."³ This average effect also demonstrates a significantly larger detected signal.

Conclusions: We demonstrated significant potential gains in detecting treatment effect using a joint modeling approach. This benefit in study power may strengthen interim analyses and allow further exploration of subgroups.


Figure 1