Joint modeling of time-evolving tumor load and survival: an approach to rationally design treatment sequencing, staging, and dosing strategies for oncology combinations

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Background and Objective: Longitudinal tumor burden has long been used for the clinical diagnosis, staging, prognosis and treatment of non-small cell lung cancer (NSCLC). Tumor burden and growth rate correlate directly with survival and RECIST (measurement of tumor) is widely used as a surrogate endpoint but poorly correlates with survival, especially in IO therapies. Surrogate endpoints such as progression-free survival (PFS) or dichotomous RECIST-based overall response rate (ORR) allow early assessment of efficacy based on reduced study population size. Unfortunately, ORR and PFS are poorly predictive of OS in NSCLC. This well-known loss of information during categorization indicates emphasizes the potential benefits of continuous tumor load modeling.

Methods: This research provides a statistically valid basis for modeling and interpretation of longitudinal response dynamics, in the context of time-to-event (survival) censoring, through development of a joint longitudinal/event model. Using clinical data from the Phase 3 IPASS study (NCT00322452) of Iressa (gefitinib), we build a generalizable model relating tumor load dynamics to a time-evolving hazard of progression.

Results: Figure 1 shows the hazard of progression for EGFR-mutated subjects in IPASS, as well as those in the IFUM gefitinib follow-up study. The model shows that EGFR-mutated patients on gefitinib have stable hazard of progression for about 8 months, as which point hazard increases rapidly. EGFR-mutated patients treated with carboplatin/paclitaxel started with a 72% higher initial progression hazard which then increased rapidly after 4 months. The joint model built from IPASS closely matches IFUM, demonstrating generalizability.

Conclusions: Because of their continuous-in-time nature, joint longitudinal/event models provide a basis for exploring the complex timing issues in oncology treatment sequencing, treatment staging strategies for combinations, and dosing regimes.


Figure 1