Longitudinal tumor dynamic modeling in non-small cell lung cancer (NSCLC) patients treated with gefitinib

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**Objectives:** Population modeling of tumor size dynamics has been emerged as an important tool in clinical research and oncology drug development. However, tumor size measurements are usually discontinued when disease progression is declared. The objective of this analysis was to develop a tumor dynamic model to capture treatment effect and predict tumor size changes that can be further applied in linking tumor size with other clinical endpoint, such as overall survival.

**Methods:** Clinical data from IPASS (NCT00322452) Phase 3 study of gefitinib in non-small cell lung cancer (NSCLC) patients were used to develop a tumor dynamic model. A total of 437 NSCLC patients (223 on gefitinib and 214 on carboplatin/paclitaxel doublet chemotherapy) and 2248 tumor measurements (single longest diameter) were included in the analysis. NONMEM 7.3 was used for modeling and simulation. Different tumor size models including considering sensitive and resistant tumor cell population were tested. The final model was applied to predict tumor dynamics up to overall survival for each patient.

**Results:** More complex model such as considering sensitive and resistance tumor population could describe the data but parameter identifiability could be an issue. Eventually, a parsimonious model with linear growth and exponential killing well characterized data from both chemotherapy and gefitinib treatment arms simultaneously. The estimated growth rate is 0.12 cm/week. Treatment group (gefitinib vs. chemotherapy) and EGFR mutation status has significant impact on tumor growth inhibition rate (Kd). The patients with EGFR negative status has significant lower Kd compared to those with EGFR positive status (0.0039 vs. 0.067 week⁻¹).

**Conclusions:** Different longitudinal tumor size models were evaluated. In addition to simultaneously described tumor size data from two treatment arms, the final model also successfully identified treatment effects between arms. The simulated individual tumor dynamic data after progression would be utilized to establish a joint longitudinal/event model with overall survival.