A M&S Framework for Exposure-Response Analysis in Oncology: Comparison and Considerations of Multiple Methodologies

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Objectives: There is a need for dose optimization in oncology drug development. Typical M&S framework for this application focuses around exposure-response (ER) analysis with direct or indirect (e.g., via tumor growth inhibition (TGI)) ER for progression free survival (PFS) and overall survival (OS). ER assessments in oncology are frequently confounded by multiple prognostic factors and alternated dosing history, necessitating multiple methodological considerations. Here, we propose and discuss a M&S framework for ER analysis in oncology with a case example to compare different aspects of multiple direct ER methodologies.

Methods: The direct ER approaches are exemplified using data from an oncology Phase 3 trial with methods including: 1) stratified Kaplan-Meier (KM) estimates by exposure quartiles, 2) Cox proportional hazards (CPH) analysis with covariate adjustment, 3) case matching (CM) to address confounding effects on ER, and 4) parametric survival modeling (PS) for extrapolation to other dosing regimens.

Results: CPH, while allowing direct ER assessment, relies on assumptions about the relationship of covariates with outcome and exposure. Recent publications from FDA reviewers proposed matching methods easing these assumptions [1], but ER assessment is no longer directly addressed as in such approaches as in CPH. A doubly robust ER using CPH within CM on strata of exposure is demonstrated, guarding against either poor matching or model misspecification. In addition to TGI, PS gives another longitudinal approach to evaluate the ER relationship for dose/regimen optimization if deemed desirable based on CPH and/or CM ER.

Conclusions: Universal discussion and adoption of a general ER framework will expedite trial design and analysis. We propose and discuss one possible ER M&S framework that guards against model mispecification, provides a clear strategy for dose optimization if indicated, and to addresses regulatory review questions.

References: