Survey of Methodologies for Exposure-Response Analysis of Oncology Drugs Approved in FDA from 2010 to 2015

Tong Lu¹, Dan Lu¹, Bert L. Lum¹, Mark Stroh¹, Priya Agarwal¹, Jin Y. Jin¹, Amita Joshi ¹*

¹Genentech, Inc., South San Francisco, CA

Objectives: Exposure-response (E-R) analysis is extensively used in drug development and regulatory decision-making, and is still a developing field in oncology. This survey will provide an overview and discussion of E-R methodologies used in FDA oncology approvals from 2010 to 2015.

Methods: 41 New Molecular Entity (NME) in oncology approved by FDA in 2010–2015 were surveyed [1]. Both exposure-efficacy (E-E) and exposure-safety (E-S) analyses were reviewed. Analyses that were not relevant to dose justification, as commented by the reviewers, were excluded from the summary. FDA’s methods were chosen when different from sponsors. Results were summarized as pie charts and as table with pros and cons and case examples.

Results: In 41 NMEs, 55 E-E and 49 E-S analyses were performed. Typical E-E analysis included Kaplan-Meier plots & Cox proportional hazard (Cox PH) model for time-to-event data (26 cases), and logistic plot & regression model for binary data (19 cases). For E-S, logistic analysis played the central role (29 cases); time-to-event analysis was also conducted but with much lesser extent (5 cases). The graphical evaluations (box, logistic and Kaplan-Meier plots) when used usually followed by modeling approaches (logistic regression and Cox PH models). Longitudinal plots were observed (1 case each for safety and efficacy) to assess the impact of exposure on time-profile of continuous outcomes. More advanced methodologies were presented for palbociclib, including parametric time-to-event model for PFS and longitudinal PK/PD model for neutrophil count. Additional methodologies not mentioned in FDA reviews but discussed will be longitudinal models for categorical data and case-matching analysis for survival data. These methodologies may be more robust to refine E-R relationship in oncology but need further evaluation.

Conclusions: This presentation summarized the E-R analysis for the recent FDA oncology approvals and outlines other potential useful advanced methodologies. It provides a framework for appropriate application and further advancement of E-R methodology to support dose justification and optimization in oncology.

References:

Figure 1: Summary of the E-R analysis approaches for the 41 drugs reviewed