Analysis of Exposure-Response Relationships for Cobimetinib in Combination with Vemurafenib

Nageshwar R Budha, Mathilde Marchand, Laurent Claret, Christine Falcoz, Christine Garnett, Rene Bruno, Nalin Tikoo, Ilsung Chang, Susan Eng, Nicholas Choong, Mark Dresser, Luna Musib, Jin Y Jin

1Genentech Inc, South San Francisco, CA, 2Pharsight Consulting Services

Objectives: Cobimetinib, a potent and highly selective inhibitor of mitogen activated protein kinases, is currently being developed in combination with vemurafenib to treat patients with BRAFV600 mutation-positive melanoma. The aim of these analyses was to explore the exposure-response (E-R) relationships for cobimetinib in combination with vemurafenib in patients with melanoma and solid tumors.

Methods: Data from three clinical studies, MEK4592g (Phase I, n=114), NO25395 (Phase Ib, n=131), and GO28141 (Phase III, n=495) were used in the analysis. E-R relationships were assessed for efficacy endpoints, progression free survival (PFS) and objective response rate (ORR) and selected safety events. Binary endpoints i.e. proportion of responders and frequencies of safety events were explored by logistic regression. The time-to-event variable PFS was explored by Kaplan-Meier analysis and log rank test p-values by quartiles of exposure. Longitudinal tumor size data were analyzed using simplified tumor growth inhibition model. Concentration-QTc interval analyses were performed using linear mixed effects modeling.

Results: No E-R relationship was observed between PFS and cobimetinib exposure in the cobimetinib plus vemurafenib arm (log rank p = 0.98). Similarly, no E-R relationship was observed for ORR. No clinically significant trends of E-R relationship were observed for safety events following 60 mg QD dose of cobimetinib on a 21/7 schedule in combination with vemurafenib in Study GO28141. No E-R relationship was observed between tumor size ratio metrics and cobimetinib exposure. QTc interval is not related to cobimetinib exposure either as a single agent (MEK4592g) or in combination with vemurafenib (GO28141).

Conclusions: Overall, results from the E-R analysis suggest no relationship between cobimetinib exposure and efficacy or safety within the exposure range observed at 60 mg QD cobimetinib on a 21/7 schedule and that current cobimetinib dose in combination with vemurafenib for treatment of patients with advanced melanoma with BRAFV600 mutations is optimal.