Characterization of the Pharmacokinetics and Exposure-Response Relationship for Nivolumab in Patients with Previously Treated or Untreated Advanced Melanoma

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**Background:** Nivolumab is a fully human immunoglobulin-G4 (IgG4) monoclonal antibody (mAb) that selectively binds to programmed death-1 (PD-1) membrane receptor, to promote antitumor immune responses. Nivolumab, 3 mg/kg every 2-weeks (Q2W), is approved for treatment in patients with advanced melanoma who progressed post anti-CTLA-4 (aCTLA4) therapy. The purpose of this analysis is to assess relationship between nivolumab exposure and overall survival (OS) in both previously treated (PT) and untreated (UT) advanced melanoma (MEL) patients, after accounting for the potential effect of other covariates, to support the dose recommendation in both PT/UT MEL patients.

**Methods:** Nivolumab pharmacokinetics (PK) was characterized by a linear 2-compartment population PK (PPK) model with serum concentration data from 1087 patients with solid tumors. The exposure-response (E-R) analysis relating PPK model derived Cavgss to OS in PT/UT MEL patients (N=399) was conducted by a Cox Proportional-Hazards model. The effect of covariates: prior-treatment, prior-aCTLA-4 treatment, sex, ECOG status, baseline body-weight (BBW), nivolumab clearance (CL), age, week-8 tumor-shrinkage (W8TS), tumor size, baseline lactate dehydrogenase (BLDH), were evaluated. M-stage, PD-L1, and BRAF-mutant status were also tested by sensitivity analyses. E-R model of OS was evaluated by visual predictive check comparing the 90% model-predicted cumulative time-to-event distributions with the corresponding distribution determined by non-parametric Kaplan-Meier analysis.

**Results:** Nivolumab Cavgss produced by 1 - 10 mg/kg Q2W was not a significant predictor of OS in PT/UT MEL patients after accounting for the potential effect of other covariates. The predictor variables with significant effect on OS in the full model were W8TS, CL, BLDH, BBW and age. BLDH and W8TS were the only significant predictors in sensitivity analyses when M-stage, BRAF-mutation, and PD-L1 status were included in the model.

**Conclusion:** The efficacy of nivolumab is similar over the range of exposure produced by 1 - 10 mg/kg Q2W in patients with PT/UT MEL patients.