Population Pharmacokinetics (PK) and Exposure-Efficacy Analyses of Nivolumab in Subjects with Advanced Hepatocellular Carcinoma (HCC)

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Objectives: Nivolumab, a PD-1 receptor-blocking antibody, has demonstrated overall survival benefit in several tumor types using a dosing regimen of 3 mg/kg every two weeks (Q2W). Nivolumab also demonstrated durable response and disease stabilization in HCC subjects in a phase I/II study. The aims of these analyses were to characterize nivolumab PK and the exposure-efficacy relationship with respect to objective response (OR) in previously treated subjects with HCC.

Methods: Nivolumab was administered, in escalation (dose range: 0.1 mg/kg to 10 mg/kg Q2W) or expansion (3 mg/kg Q2W) phases, to 254 HCC subjects with one of the following etiologies: uninfected, HBV infected, or HCV infected. The PK in HCC subjects was characterized by population PK analysis of data from all HCC subjects, pooled with data from 863 subjects with NSCLC and other tumor types, with the effect of HCC tumor type assessed on drug clearance. The impact of liver impairment status and disease etiology were also investigated. Exposure-response of OR in 174 sorafenib treated subjects was characterized using a logistic regression model, with the effect of etiology assessed.

Results: Nivolumab PK was well characterized with a linear, zero-order input, two-compartment model with time-varying clearance, with no effect of HCC tumor type (98.74%, 95% CI: 90.94%-107.21%). Nivolumab exposures (Cavg at steady state) were similar (< 20% different) in HCC patients regardless of etiology or hepatic impairment status (mild or moderate). Nivolumab exposures (Cavg over the first dosing interval) and etiology were not significant predictors of the probability of OR (95% CI of the odds ratio included 1) in HCC subjects who had been previously treated with sorafenib.

Conclusions: The PK of nivolumab is similar in HCC and NSCLC subjects. Etiology and mild/moderate liver impairment status did not have an impact on nivolumab exposures. Consistent with other tumor types, nivolumab has a flat exposure-efficacy relationship in HCC subjects. Etiology did not have an impact on this relationship.