W-050

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

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Introduction

- Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that selectively binds to the programmed death-1 (PD-1) membrane receptor[1]
- PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death-ligand 1 (PD-L1) and 2 (PD-L2), results in the downregulation of lymphocyte activation[1]
- Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self antigens[1]
- Nivolumab 3 mg/kg, or an equivalent 240-mg dose, once every 2 weeks (Q2W) was approved for melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, head and neck cancer, classical Hodgkin lymphoma, urothelial carcinoma, and colorectal cancer in the United States and other countries[2]
- Nivolumab also demonstrated durable response and disease stabilization in patients with advanced HCC who have been previously treated with sorafenib in a phase 1/2 study (CA-209040), and has been recently approved for this indication by the US FDA

Objectives

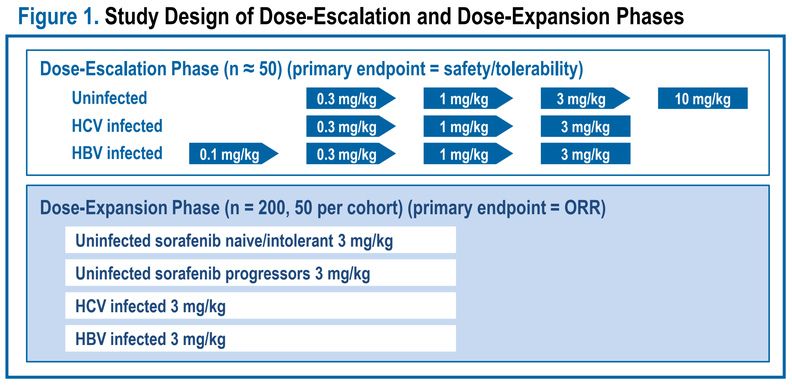
- To characterize the PK of nivolumab in patients with advanced HCC, and to determine the effect of key covariates on nivolumab PK and exposure
- To characterize the relationship between nivolumab exposure and efficacy (as measured by objective response) in patients with advanced HCC who have been previously treated with sorafenib

Methods

Study design

- Data in HCC patients were collected from part of a phase 1/2 dose-escalation and dose-expansion study of nivolumab in patients with advanced HCC (including both sorafenib naive and sorafenib treated) with or without chronic viral hepatitis
- In the escalation phase, a 3 + 3 design was used, with a starting dose of 0.3 mg/kg Q2W in the patients with uninfected and HCV-infected etiology. A starting dose of 0.1 mg/kg Q2W was used for patients with HBV-infected etiology. Maximum dose investigated in the escalation phase was 10 mg/kg Q2W in the uninfected patients (**Figure 1**)
- Dose-limiting toxicity was determined based on the incidence and intensity of adverse events (AEs) that occurred in the first cycle (42 days)
- In the expansion phases, nivolumab 3 mg/kg Q2W was selected for patients with HCC with one of the above etiologies based on the similar safety profile observed across etiologies in the escalation phase (**Figure 1**)

Figure 1. Study Design of Dose-Escalation and Dose-Expansion Phases



Sample collection and assay

- Intensive serial blood samples were collected for PK analysis after first dose (cycle 1) and at steady state (cycle 3) in the escalation phase. Additional trough samples were collected up to cycle 6 and at 2 follow-up visits for both escalation phase and expansion phase
- Blood serum samples were analyzed for nivolumab concentration using a validated ligand-binding electrochemiluminescence immunosorbent assay

Population PK (PPK) analysis

- The PK in patients with HCC was characterized by PPK analysis of data from all patients with HCC (N = 254) pooled with data from 863 patients with NSCLC and other tumor types
- The effect of HCC tumor type on nivolumab clearance was assessed by covariate analysis. The impact of liver impairment status and disease etiology were evaluated graphically
- A previously developed nivolumab PPK model with time-varying clearance (CL) was used as the base model. Tumor type and baseline albumin on nivolumab CL, tumor type on maximum change of CL (Emax), and tumor type on time to achieve 50% of the maximum change in CL (T50) were assessed in the full model
- The final model was derived by performing a stepwise backward elimination from the full model based upon Bayesian information criterion (BIC) calculated using the following equation: $BIC = -2LL + k\,ln(n)$

Exposure-response (ER) efficacy analysis

- ER efficacy analysis was performed on blinded independent central review (BICR)–assessed objective response (OR) from 174 sorafenib-treated patients, with average concentration after the first dose (Cavg1) used as the measure of exposure. OR was defined as a Best Overall Response of complete or partial response by RECIST Criteria
- The relationship of ER with regard to OR was described by a logistic regression model. The modulatory effect of covariates (etiology, extrahepatic spread/vascular invasion [EHS/VI], alpha-fetoprotein [AFP]) was assessed as well
- The ER efficacy model was developed in 3 steps. The base model characterized the marginal effect of nivolumab exposure on the probability of OR
- The effect of etiology, EHS/VI, AFP, and baseline CL was assessed in the full model. The final model was derived by performing a stepwise backward elimination from the full model based on BIC

Results

PPK

- Nivolumab PK was described by a linear 2-compartment model with time-varying CL such that CL decreased with time (≈ 26%) (**Table 1**)
- The PK parameters for patients with HCC were summarized in **Table 2.**
- HCC tumor type did not have a significant effect on nivolumab CL relative to NSCLC 2L+ tumor type (the 95% CI included 1) (**Figure 2**)
- Etiology did not have a clinically relevant effect on nivolumab CL and exposures (average concentration at steady state [Cavgss]) (**Figure 3**)
- Mild and moderate hepatic impairment did not appear to affect nivolumab CL and exposures (Cavgss) vs normal (**Figure 4**)

Table 1. Parameter Estimates of the Final PPK Model

	Final Parameter Estimate		Interindividual Variability[a]/ Residual Variability	
	Estimate	%RSE	Estimate	%RSE
CL: Clearance (mL/h)[b]	11.6	4.36	0.103	8.95
CL: Power of BBWT on CL[c]	0.529	11.4		
CL: Power of GFR on CL[c]	0.158	29.9		
CL: Sex effect on CL[d]	−0.208	14.8		
CL: PS effect on CL[d]	0.0747	33.3		
CL: Tumor type (other) effect on CL[d]	0.0642	49.0		
CL: Race (Asian) effect on CL[d]	−0.0630	60.2		
CL: Tumor type (HCC) effect on CL[d]	−0.0211	203		
CL: Baseline albumin effect on CL[c]	−0.800	11.9		
VC: Central volume (L)[b]	4.27	1.36	0.0938	18.1
VC: Power of BBWT on VC[c]	0.734	6.63		
VC: Sex effect on VC[d]	−0.142	19.1		
Q: Intercompartmental CL (mL/h)	33.1	8.96	NE	NA
VP: Peripheral volume (L)	3.06	4.10	0.193	14.9
Emax: Time-varying CL	−0.302	21.1	0.165	26.6
T50: Time-varying CL (h)	1530	17.9	NE	NA
T50: Tumor type (HCC) effect on T50[d]	1.38	22.2		
HILL: Coefficient for time-varying CL	1.63	17.8	NE	NA
cov(IIV in VC, IIV in CL)[e]	0.0476	15.0	NA	NA
RV: Residual error (proportional)	NE	NA	0.0529	4.07

Minimum value of the objective function = 43638.77.

[a] ETA shrinkage: ETA_CL: 16.7%, ETA_VC: 19.8%, ETA_VP: 43.6%; ETA Emax; 47.1%; Epsilon shrinkage: 12.9%.

[b] CL_{REF} and VC_{REF} are typical values of CL and VC at the reference covariate values. Covariate effects were estimated relative to a reference patient who is male; weighs 80 kg; has estimated GFR of 90 mL/min/1.73 m^2, serum albumin of 4 g/dL, PS of 0, and tumor type of NSCLC 2L+; and is white or other, defined as not African American and not Asian. The reference values for continuous valued covariates were selected to be approximately the median of the covariate values in the analysis dataset.

[c] The typical value of CL and VC corresponding to continuous valued covariates of Patient I are modeled as:

$$CL_{TV,i} = CL_{REF} \times \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} \times \left(\frac{BGFR_i}{BGFR_{REF}}\right)^{CL_{BGFR}} \left(\frac{BALB_i}{BALB_{REF}}\right)^{CL_{BALB}}$$

$$VC_{TV,i} = VC_{REF} \times \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}}$$

[d] The typical value of CL, VC, and T50 corresponding to categorical valued covariates of Patient I are modeled as:

$$CL_{TV,i} = CL_{REF} \times \left(e^{CL_{PS}}\right)^{PS_i} \times \left(e^{CL_{HCC}}\right)^{HCC_i} \times \left(e^{CL_{OTHER}}\right)^{OTHER_i} \times \left(e^{CL_{SEX}}\right)^{SEX_i} \times \left(e^{CL_{RAAS}}\right)^{RAAS_i}$$

$$VC_{TV,i} = VC_{REF} \times \left(e^{VC_{SEX}}\right)^{SEX_i}$$

$$T50_{TV,i} = T50_{REF} \times \left(e^{T50_{HCC}}\right)^{HCC_i}$$

[e] The calculated correlation coefficient (r^2) of the off-diagonal omegas was 0.235 for cov(IIV in VC, IIV in CL); the highest correlation between parameters was 0.405.

Note: The condition number for the final model was 108.3, indicating there was no evidence for ill conditioning.

BALB = baseline albumin
BBWT = baseline body weight
BGFR = baseline glomerular filtration rate
CL = clearance
$CL_{TV,i}$ = typical value of clearance for subject i
Emax = maximum change of clearance
ETA = random effect
HCC = hepatocellular carcinoma
PS = performance status
RAAS = race of Asian
REF = reference
%RSE = percent relative standard error
SEX = sex
T50 = time to achieve 50% of the maximum change in CL
T50TV,i = typical value of T50 for subject i
VC = central volume of distribution
VP = peripheral volume of distribution
$VC_{TV,i}$ = typical value of central volume of distribution for subject i

Table 2. Summary Statistics of Individual PK Parameters for Patients With HCC (n = 254)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (min, max)
Baseline clearance, mL/h	11.3 (4.46)	10.6 (39.3)	10.7 (2.85, 33.9)
Clearance, ss, mL/h	9.74 (4.77)	8.88 (49)	8.77 (2.23, 41.5)
Volume of the central cmt, L	4.04 (1.03)	3.91 (25.6)	3.91 (1.95, 7.42)
Volume of the peripheral cmt, L	3.2 (0.681)	3.13 (21.3)	3.12 (1.08, 6.42)
Volume of distribution, L[a]	7.23 (1.35)	7.11 (18.6)	7.13 (3.49, 11.1)
Alpha half-life, h	34.8 (5.89)	34.3 (16.9)	34.6 (15.4, 52.9)
Beta half-life, d	26.1 (9.66)	24.5 (37)	24.7 (6.33, 76.1)

cmt = compartment, CV = coefficient of variation, SE = standard error, ss = steady state.
Note on reference values: etiology = uninfected, EHS/VI = not present, and baseline AFP ≤ 400 µg/L.

Figure 2. Effects of Covariates on Nivolumab PPK Parameters

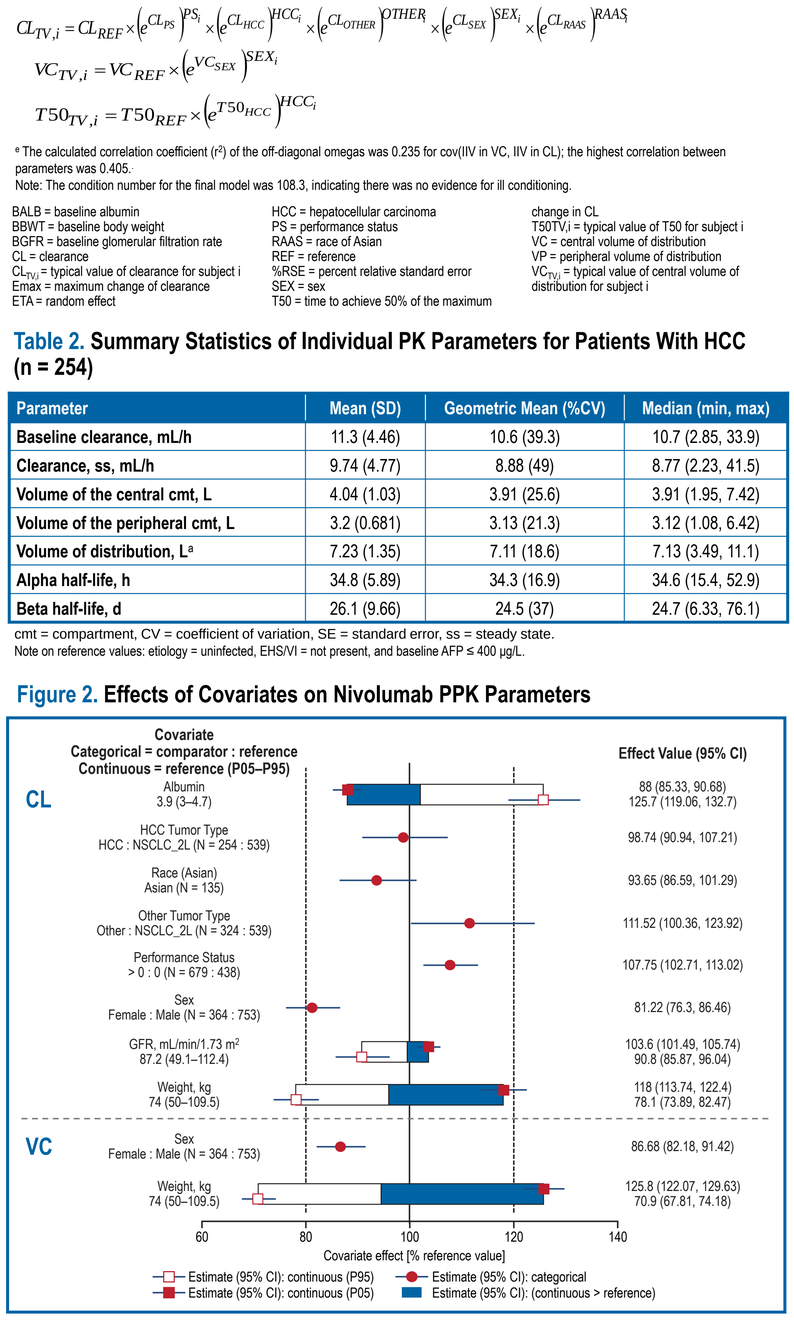


Figure 3. Effect of Etiology on CL and Dose-Normalized Cavgss

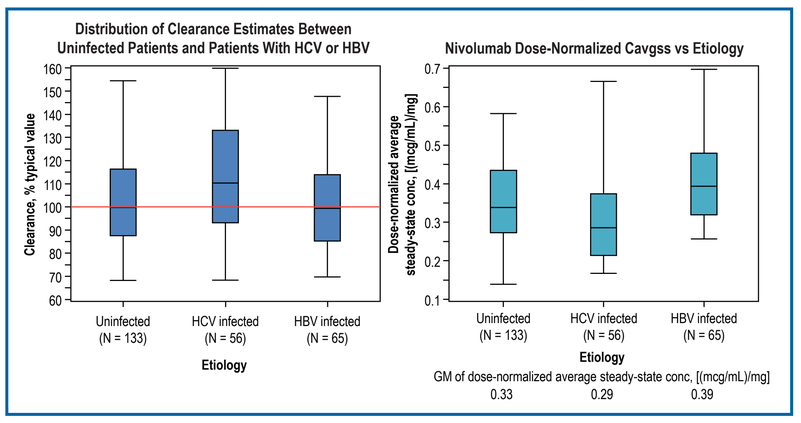
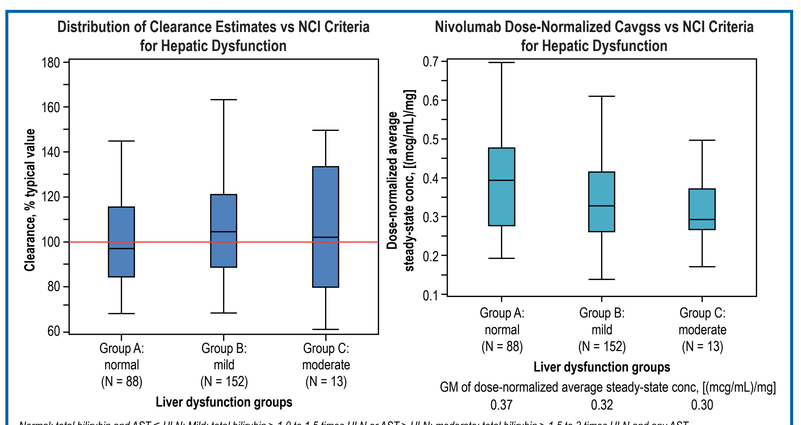


Figure 4. Effect of Hepatic Function on Nivolumab CL and Dose-Normalized Cavgss



Normal: total bilirubin and AST ≤ ULN; Mild: total bilirubin > 1.0 to 1.5 times ULN or AST > ULN; moderate: total bilirubin > 1.5 to 3 times ULN and any AST.
AST: aspartate aminotransferase; ULN: upper limit of normal.

OR ER Analysis

- Nivolumab exposure was not a significant predictor of BICR-assessed OR in sorafenib-treated patients with HCC (**Figure 5**)
- Baseline clearance, etiology, EHS/VI, and AFP were not significant predictors of probability of OR in patients with HCC (**Figure 5**)
- Only Cavg1 was retained in the final model, with 90% CI of its odds ratio including 1 (**Table 3**)

Figure 5. Effects of Covariates on Nivolumab ER

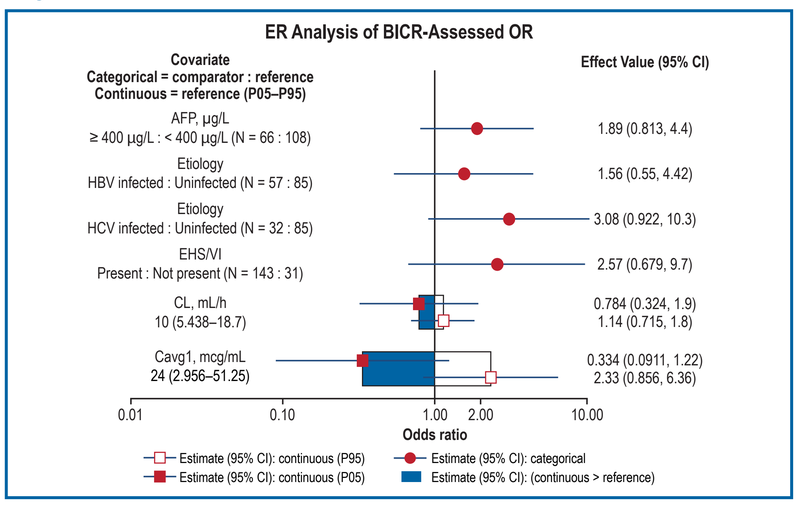


Table 3. Parameter Estimates of ER for OR

Predictor	Estimate	SE	%RSE	Odds Ratio (95% CI)
Cavg1, µg/mL	−0.034	0.02012	59.17	0.9666 (0.9292, 1.005)

Conclusions

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

References

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Acknowledgments

- The authors acknowledge the participation of patients in this study
- Professional editorial assistance was provided by Chrysalis Medical Communications, funded by Bristol-Myers Squibb

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Presented at the Eighth American Conference on Pharmacometrics (ACoP8); October 15–18, 2017; Fort Lauderdale, Florida

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