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Augmented Clearance of Nivolumab Is Associated with Renal Functions in Chronic Renal Disease Model Rats

Kazuaki Taguchi,[1] Yukitaka Hayashi,[1] Mayu Ohuchi,[1] Hotaka Yamada, Shigehiro Yagishita, Yuki Enoki, Kazuaki Matsumoto, and Akinobu Hamada

Faculty of Pharmacy, Keio University of Pharmacy, Tokyo, Japan (K.T., Y.H., H.Y., Y.E., K.M.); Division of Molecular Pharmacology, National Cancer Center Research Institute, Tokyo, Japan (M.O., S.Y., A.H.); and Department of Medical Oncology and Translational Research, Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan (M.O., A.H.)

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ABSTRACT

The clinically approved dose of nivolumab is 240 mg every 2 weeks. However, previous studies have shown that baseline nivolumab clearance (CL) is associated with treatment outcomes in patients with solid cancers, thus motivating researchers to identify prognostic factors and indices influencing nivolumab CL. This study used chronic kidney disease model rats to investigate whether chronic renal impairment affected nivolumab CL and explored the surrogate markers associated with nivolumab CL. We observed that the total CL for nivolumab (CL_{tot}) was approximately 1.42 times higher in chronic kidney disease model rats than that in sham rats with an increased urinary excretion. Additionally, CL_{tot} showed positive correlation with renal CL for nivolumab (CL_R) but not with extrarenal CL. Furthermore, the baseline levels of creatinine, blood urea nitrogen, creatinine CL, and urinary albumin/creatine ratio based on laboratory data were also significantly correlated with CL_R. Our findings suggest that nivolumab CL increases as renal function deteriorates because of an increased excretion of nivolumab in the urine; additionally, laboratory data reflecting renal function may be a feasible index to qualitatively estimate nivolumab CL prior to nivolumab treatment under conditions of renal impairment.

SIGNIFICANCE STATEMENT

This study demonstrated that nivolumab was rapidly eliminated from the circulation in chronic kidney disease model rats compared with sham rats with an increased urinary nivolumab excretion. Moreover, nivolumab clearance was significantly correlated with the baseline levels of certain laboratory parameters reflecting renal functions. These results indicate the potential applicability of baseline renal function as a prognostic index to qualitatively estimate nivolumab clearance prior to nivolumab treatment under conditions with renal impairment.

Introduction

Nivolumab, a fully human monoclonal immunoglobulin G_4, is an immune checkpoint inhibitor that targets programmed cell death receptor 1. The therapeutic efficacy of nivolumab alone or in combination with ipilimumab has been validated in patients with various solid cancers, such as melanoma (Robert et al., 2015), advanced gastric or gastroesophageal junction cancer (Kang et al., 2017), advanced renal cell carcinoma (Motzer et al., 2015), advanced non–small-cell lung cancer (Borghaei et al., 2015), recurrent squamous cell carcinoma of the head and neck (Ferris et al., 2016), Hodgkin lymphoma (Younes et al., 2016), and colorectal cancer (Azad et al., 2020). For nivolumab monotherapy in clinics, irrespective of the patient's physical conditions and underlying disorders, the fixed approved dose is 240 mg every 2 weeks. Few clinical studies have shown that patients with a high baseline nivolumab clearance (CL) exhibit lower overall survival than patients with a low baseline nivolumab CL (Feng et al., 2017; Wang et al., 2019, 2020), indicating that nivolumab exposure is associated with treatment outcomes. Thus, the dosage adjustment of nivolumab that reflected baseline nivolumab CL may contribute to the improvement of therapeutic outcomes of nivolumab treatment. However, information on the factors that influence baseline nivolumab CL is limited.

Recently, Bajaj et al. (2017) reported a pivotal population pharmacokinetic analysis that used integrated data obtained from 11 clinical studies of nivolumab conducted in patients with solid cancers. This study clearly showed that the final population pharmacokinetic model included baseline estimated glomerular filtration as a covariant of

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[1]K.T., Y.H., and M.O. contributed equally to this work.

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ABBREVIATIONS: AUC_{all}, area under the blood concentration-time curve; BUN, blood urea nitrogen; CKD, chronic kidney disease; CL, clearance; CL_{cr}, creatinine clearance; CL_{eR}, extrarenal clearance; CL_R, renal clearance; CL_{tot}, total clearance; CRE, creatinine; m/z, mass-to-charge ratio.

nivolumab CL, estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. Additionally, another population pharmacokinetic analysis of nivolumab in patients with gastric or gastroesophageal junction cancer also included estimated glomerular filtration as a covariant of nivolumab CL (Osawa et al., 2019). Although these findings indicate that nivolumab CL is more or less affected by renal functions, the direct impact of renal impairment on nivolumab CL is unclear because a small number of patients with renal impairment have been enrolled in clinical trials and most of them presented with mild to moderate renal impairment.

Therefore, to elucidate the influence of renal impairment on nivolumab CL, we conducted pharmacokinetic experiments in sham and chronic kidney disease (CKD) model rats and compared the blood retention and urinary excretion of nivolumab between the two groups. Furthermore, we also investigated the clinically available laboratory data associated with nivolumab CL under conditions with renal impairment.

Materials and Methods

Chemicals and Reagents. Nivolumab (Opdivo) was purchased from Ono Pharmaceutical Co., Ltd. (Osaka, Japan), and trastuzumab (Herceptin) was purchased from Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan). nSMOL Antibody BA Kit was purchased from Shimadzu Co., Ltd. (Kyoto, Japan). LBIS Rat Albumin ELISA Kit was obtained from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). All other reagents and solvents were obtained from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan), Nacalai Tesque (Kyoto, Japan), or Sigma-Aldrich (St. Louis, MO).

Surgical Preparation of CKD Model Rats. In total, 11 Sprague-Dawley rats (male, 6 weeks old, 181.2 ± 9.5 g) were purchased from Sankyo Labo Service (Tokyo, Japan). All animals were housed in a temperature-controlled conventional room with a 12-hour light/dark cycle, and they were provided with food and water ad libitum. Under conditions of subjection to isoflurane anesthesia, nephrectomized model rats (n = 6), which are generally used as CKD model rats, were surgically prepared by resecting two-thirds of the right kidney and the whole left kidney, as per methods previously reported (Shimoishi et al., 2007; Kadowaki et al., 2009). In sham rats (n = 5), the kidneys were taken out from the abdominal cavity, and then the kidneys were returned without resection. All CKD model rats were used for pharmacokinetic studies at 4 weeks after the left kidney resection. All animal experiments were reviewed and approved by the Animal Care and Use Committee of Keio University [approval number: 18069-(0)].

Pharmacokinetic Study. A day before the commencement of the pharmacokinetic study, a cannula filled with heparin solution was fixed (100 IU/ml) into the right jugular vein of all rats for nivolumab administration and blood collection. Blood samples were collected to determine plasma baseline levels of creatinine (CRE), blood urea nitrogen (BUN), and albumin, and urine samples were collected from rats in a metabolic cage at 24 hours for calculation of creatinine clearance (CLcr) and quantification of baseline urinary albumin levels. Sham-operated (body weight: 436.4 ± 26.6 g, CRE: 0.17 ± 0.02 mg/dl, BUN: 15.3 ± 2.6 mg/dl) and CKD rats (body weight: 343.1 ± 54.4 g, CRE: 0.67 ± 0.32 mg/dl, BUN: 50.2 ± 16.1 mg/dl) were subjected to continuous administration with nivolumab solution (10 mg/kg) using a syringe pump for 60 minutes. After 1, 2, 4, 6, 24, 48, and 72 hours of administration, venous blood samples (0.3 ml) were collected from a fixed cannula using a heparinized syringe. Blood samples were centrifuged at 1200 rpm for 10 minutes to collect the plasma samples. All rats were housed in metabolic cages to collect urine samples until they were sacrificed. Urine samples were collected, and the volume was measured every 24 hours. All plasma and urine samples were stored at −80°C until use. All surgical procedures were performed under conditions of subjection to isoflurane anesthesia.

The area under the blood concentration-time curve (AUC_{all}) from 0 to 72 hours after nivolumab administration was analyzed using a noncompartmental model with the Phoenix WinNonlin software program (Version 8.0; Certara LP, Princeton, NJ). The apparent half-life was estimated from the elimination rate constant using the 24- to 72-hour time points. Total clearance (CL_{tot}), renal clearance (CL_R), extrarenal clearance (CL_{eR}), and renal excretion ratio for nivolumab were calculated using the following equations:

$$CL_{tot} = Dose/AUC_{all}$$

$$CL_R = X(u)_{0\rightarrow 72}/AUC_{all}$$

$$CL_{eR} = CL_{tot} - CL_R$$

$$\text{Renal excretion ratio } (\%) = CL_R/CL_{tot}*100,$$

where $X(u)_{0\rightarrow 72}$ represents the cumulative excreted amount of nivolumab in urine from 0 to 72 hours after nivolumab administration.

Clinical Biochemistry Assessments in Plasma and Urine. Plasma concentrations of BUN, CRE, and albumin and the urine concentration of CRE were analyzed using Fuji DRI-CHEM 7000Z (FUJIFILM Wako Pure Chemical Corp., Tokyo, Japan). Urine microalbumin levels were determined using the LBIS Rat Albumin ELISA Kit. CLcr was calculated based on the CRE levels in plasma and in 24-hour cumulative urine before nivolumab administration.

Quantification of Nivolumab Concentration in Plasma and Urine Using Liquid Chromatography–Mass Spectrometry. Nivolumab concentrations in plasma and urine were quantified using the target signature peptides ASQSVSSYLAWYQQKPGQAPR (mass-to-charge ratio (m/z): 785.0 > 940.2) and LLIYDASNR (m/z: 532.9 > 838.2), respectively, using liquid chromatography–electrospray ionization–mass spectrometry with a triple quadrupole mass spectrometer (Nexera ×2 and LCMS-8050, Shimadzu), as per previously reported protocols (Ohuchi et al., 2021). These signature peptides were extracted from plasma and urine samples using the nSMOL Antibody BA Kit as follows: the plasma and urine samples were filtered using Ultrafree-MC SV (Merck Millipore, Billerica, MA) and centrifuged at 1800*g* for 5 minutes. Subsequently, the supernatant (5 μl of plasma or 40 μl of urine) was subjected to treatments using the nSMOL Antibody BA Kit according to the nSMOL proteolysis method. As an internal standard, trastuzumab signature peptides IYPTNGYTR (543.3 > 404.8) and FTISADTSK (485.2 > 721.1) were used for nivolumab quantification in plasma and urine, respectively. The optimized analytical conditions of mass spectrometry for each peptide are listed in Supplemental Table 1. The urinary selectivity and reproducibility of nivolumab and trastuzumab surrogate peptides are shown in Supplemental Fig. 1 and Supplemental Table 2.

Statistical Analysis. All data are expressed as means ± S.D. Statistical analyses were performed using the unpaired Student's t test or Welch t test. Pearson's test was used for conducting correlation analyses. Data analysis was performed using the GraphPad Prism version 8.4.2 (GraphPad, San Diego, CA). Statistical significance was set at $P < 0.05$.

Results

Plasma Concentration and Pharmacokinetic Parameters of Nivolumab in Sham and CKD Model Rats. Figure 1 and Supplemental Fig. 2 show the time course of nivolumab plasma concentration in sham and CKD model rats after the performance of a continuous

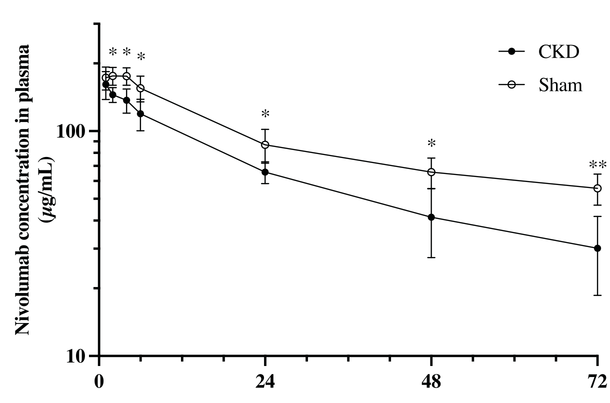

Fig. 1. The semilogarithmic plot of the time course for the plasma concentration of nivolumab after a continuous intravenous administration to sham (open circle) and CKD model rats (closed circle) at a dose of 10 mg/kg. Sham (n = 5) and CKD rats (n = 6). Data were analyzed using an unpaired t test. *P < 0.05, **P < 0.01 vs. sham rats.

TABLE 1

Pharmacokinetic parameters of nivolumab in sham and CKD model rats

AUC_{all} and CL_{tot} were analyzed using an unpaired t test. $X(u)_{0\rightarrow72}$, CL_R, and renal excretion ratio were analyzed using a Welch t test.

	Sham (*n* = 5)	CKD (*n* = 6)
AUC_{all} (h*µg/ml)	6411 ± 639	4585 ± 746**
$X(u)_{0\rightarrow72}$ (µg)	8.34 ± 6.37	958 ± 444**
CL_{tot} (ml/h/kg)	1.57 ± 0.16	2.23 ± 0.38**
CL_R (ml/h/kg)	0.003 ± 0.003	0.71 ± 0.45**
CL_{eR} (ml/h/kg)	1.57 ± 0.15	1.53 ± 0.21
Apparent half-life (h)	122.8 ± 119.6	47.5 ± 25.6
Renal excretion ratio (%)	0.19 ± 0.15	29.9 ± 15.5**

**$P < 0.01$ vs. sham rats.

intravenous administration (60 minutes) of nivolumab at a dose of 10 mg/kg (a semilogarithmic plot and a linear plot, respectively), and Table 1 lists the pharmacokinetic parameters calculated based on the plasma concentration curve. Nivolumab was rapidly cleared from the circulation in CKD model rats compared with sham rats. Along with the changes in plasma concentration, CL_{tot} was approximately 1.42 times higher in CKD model rats than that in sham rats, and AUC_{all} and estimated half-life was approximately 0.72 times and 0.39 times lower in CKD model rats than that in sham rats, respectively.

Relationship between Nivolumab CL and Renal Functions. As shown in Fig. 1 and Supplemental Fig. 2, the ingravescence of renal function influences nivolumab CL. Correlations between CL_{tot} for nivolumab and plasma CRE or BUN concentration were analyzed to further assess the association of nivolumab CL with renal functions. We observed that nivolumab CL_{tot} was positively correlated with the baseline plasma levels of CRE (Fig. 2A; r = 0.782, P = 0.0045) and BUN (Fig. 2B; r = 0.826, P = 0.0017), indicating that nivolumab CL increased as the renal functions deteriorated. In contrast, the plasma baseline levels of albumin, which is a covariant of nivolumab CL in population pharmacokinetic analysis conducted for patients with solid tumors (Osawa et al., 2019), were not correlated with CL_{tot} for nivolumab (Fig. 2C; r = −0.367, P = 0.266).

Urinary Excretion of Nivolumab. The urinary excretion of nivolumab every 24 hours was compared between the sham and CKD model rats. The results showed that nivolumab excretion every 24 hours significantly increased in CKD model rats compared with sham rats until 72 hours after nivolumab administration (Fig. 3A). Additionally, CL_R in the CKD model rats remarkably increased as compared with that in sham rats during the 72-hour observation period, whereas no significant change was observed in CL_{eR} between the two groups (Table 1). Furthermore, CL_{tot} for nivolumab was positively correlated with CL_R for nivolumab (Fig. 3B; r = 0.931, $P < 0.0001$); however, no correlation was observed between CL_{tot} and CL_{eR} (r = −0.018, P = 0.958).

Relationship between Nivolumab CL and Baseline Urinary Parameters. In addition to the plasma laboratory data reflecting renal impairment, as shown in Fig. 2, the relationship between nivolumab CL and urinary parameters reflecting renal function was also evaluated. We observed that CL_{tot} for nivolumab decreased as the baseline CLcr calculated from the 24-hour–accumulated urine sample increased (Fig. 4A; r = −0.867, P = 0.0006). In addition to CLcr, urinary albumin/CRE ratio was also correlated with CL_{tot} for nivolumab (Fig. 4B; r = 0.847, P = 0.001).

Relationship between Nivolumab Renal CL and Relevant Parameters for Renal Function. The relationship between the CL_R for nivolumab and the plasma urinary parameters reflecting renal function was evaluated. The relationship between the CL_{tot} for nivolumab and the relevant parameters for renal function is shown in Figs. 2 and 4. The CL_R for nivolumab was markedly correlated with CRE (Fig. 5A; r = 0.905, P = 0.0001), BUN (Fig. 5B; r = 0.928, $P < 0.0001$), baseline CLcr (Fig. 5D; r = −0.852, P = 0.0009), and urinary albumin/CRE ratio (Fig. 5E; r = 0.871, P = 0.0005). However, the plasma baseline levels of albumin did not correlate with CL_R for nivolumab (Fig. 5C; r = −0.37, P = 0.262).

Discussion

This study reports two major novel findings regarding the pharmacokinetics of nivolumab. One finding indicates that renal impairment is an important factor influencing nivolumab CL due to an increased urinary excretion. Another finding indicates that nivolumab CL may be qualitatively estimated using plasma and urinary laboratory data reflecting renal functions prior to nivolumab treatment.

Previous studies have suggested that nivolumab exhibited long retention time in blood circulation (CL in human: 7.9–9.5 ml/h) with a linear elimination (0.1–10 mg/kg), as well as endogenous IgG and other IgG preparations (Kontermann, 2011; Desnoyer et al., 2020). This is because IgG preparations, including nivolumab, can be salvaged from intracellular catabolic degradation by lysosomes via actions of the neonatal Fc receptor (Ryman and Meibohm, 2017; Datta-Mannan, 2019). Additionally, proteins with molecular mass greater than 50 kDa, such as nivolumab (molecular mass: approximately 145 kDa), block glomerular filtration due to histologic characteristics of the kidney, such as size and charge barrier (Tryggvason and Wartiovaara, 2005). However, the enhanced plasma retention of nivolumab could not be observed in the CKD model rats compared with the sham rats (Fig. 1; Supplemental Fig. 2; Table 1). It is known that structural disruptions of glomeruli with a loss of size and charge barrier occur when renal impairment is induced, resulting in the facilitation of protein leakage into the urine. In fact, it has been reported that high-molecular-weight protein preparations and dimerized albumin (molecular mass > 130 kDa) are excessively and rapidly excreted into the urine under conditions of renal impairment (Taguchi et al., 2010). In this study, the urinary excretion of nivolumab was significantly higher in the CKD model rats compared with the sham rats (Fig. 3A). Additionally, CL_R for nivolumab, but not CL_{eR}, was significantly correlated with CL_{tot} for nivolumab (Fig. 3B), indicating that nivolumab CL was dependent on CL_R under conditions of renal impairment. Taken together, the findings suggest that the facilitation of renal elimination rather than catabolic degradation may mainly

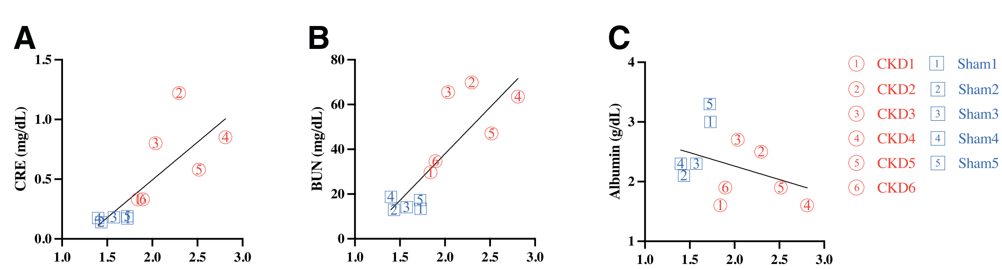

Fig. 2. Correlation between CL_{tot} for nivolumab and (A) baseline CRE levels in plasma, (B) baseline BUN levels in plasma, and (C) baseline albumin levels in plasma. Blue squares and red circles indicate data obtained from the analysis using sham and CKD model rats, respectively. Linear regression was calculated using Pearson's test. (A) $y = 0.632x - 0.77$, r = 0.782, P = 0.0045; (B) $y = 41.6x - 45.2$, r = 0.826, P = 0.0017; (C) $y = -0.451x + 3.162$, r = −0.367, P = 0.267).

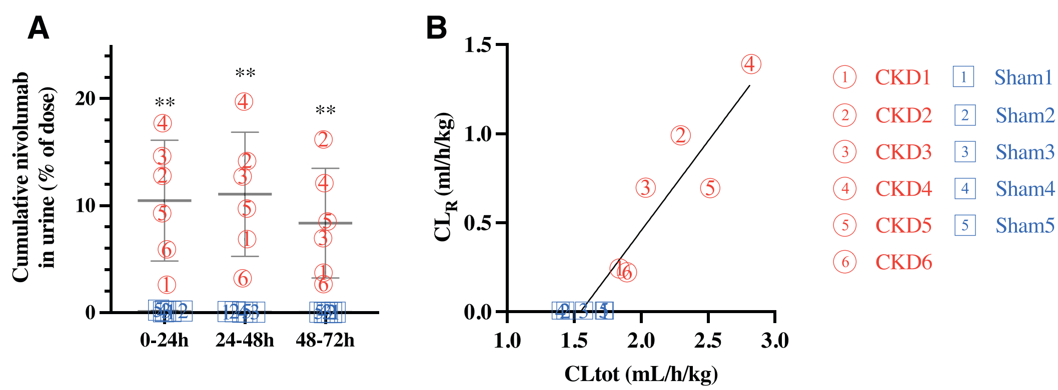

Fig. 3. (A) Cumulative nivolumab excretion in urine every 24 hours after nivolumab administration to sham (blue square) and CKD model rats (red circle). Gray bars indicate the average values of each group. Data were analyzed using an unpaired *t* test. $^{**}P < 0.01$ vs. sham rats. (B) Correlation between CL_{tot} and CL_R for nivolumab. Open and closed dots indicate data obtained from the analysis using sham and CKD model rats, respectively. Linear regression was calculated using Pearson's test ($y = 1.007x - 1.558$, $r = 0.931$, $P < 0.0001$).

contribute to the loss of blood retention of nivolumab in CKD model rats.

Determination of nivolumab CL before the conduction of nivolumab-based therapy is clinically useful for dosage adjustment in patients with renal impairment because CL_{tot} for nivolumab is dependent on the extent of renal impairment. However, it is difficult to determine baseline nivolumab CL in individual patients without conducting post-treatment pharmacokinetic analysis. Thus, it is clinically important to identify the baseline levels of feasible clinical parameters that may enable the estimation of nivolumab CL. In this study, the baseline levels of plasma laboratory data (CRE and BUN) and urinary parameters (CLcr calculated based on the 24-hour urinary accumulation and albumin/CRE ratio) showed remarkable correlation with CL_{tot} and CL_R for nivolumab (Fig. 2, A and B, Fig. 4, and Fig. 5, A, B, D, and E), suggesting that these parameters might be potential indicators for estimating nivolumab CL prior to nivolumab administration. Unfortunately, the plasma levels of CRE and BUN are influenced not only by renal functions but also by other factors, such as muscle mass and meals. Furthermore, the 24-hour urinary accumulation occurring before nivolumab treatment is a big burden from the perspective of improving the quality of life of patients. These findings suggest that the data on laboratory parameters are clinically unavailable and unfeasible for the estimation of nivolumab CL. However, the value of urinary albumin/CRE ratio can be determined without the 24-hour urinary accumulation. It substantially reflects the renal functions without any interference from the pathophysiological factors. Therefore, the urinary albumin/CRE ratio before the nivolumab administration is a potential clinical indicator for estimating the nivolumab CL.

It has been reported that the plasma levels of albumin can be considered as a biomarker to estimate nivolumab CL in patients with solid tumors (Bajaj et al., 2017; Hirsch et al., 2020). Since hypoalbuminemia occurs as renal injury progresses, it is expected that baseline plasma albumin levels may be a feasible biomarker for the estimation of nivolumab CL under conditions with renal impairment. Contrary to our expectations, no correlation was observed between plasma baseline albumin levels and CL_{tot} and CL_R for nivolumab in this study (Fig. 2C and Fig. 5C). Based on previous findings, it has been hypothesized that high protein turnover, which is induced by cancer cachexia, is related to high CL of monoclonal antibody preparations (Bajaj et al., 2017). Additionally, cancer cachexia is frequently accompanied by hypoalbuminemia due to catabolic drive (Evans et al., 2008). Thus, hypoalbuminemia is associated with high nivolumab CL due to a high catabolic drive in cancer cachexia. Further studies using cachexia animal models are warranted to elucidate the mechanism.

In conclusion, for the first time, the present study showed that nivolumab CL increased in the CKD model rats compared with sham rats, and the baseline urinary albumin/CRE ratio might be a potential indicator to estimate nivolumab CL prior to nivolumab treatment under conditions of renal impairment. Although it has been recommended that no dosage adjustment of nivolumab is necessary in patients with cancer with renal impairment (Sheng et al., 2017), our findings suggest that dosage adjustment of nivolumab may be performed depending on the patients' pathophysiological conditions. However, our findings are limited to a small number of CKD model rats investigated herein. The clearance of other antibody drugs (bevacizumab and panitumumab) was similar between the subjects with normal renal function and patients with end-stage renal disease (Garnier-Viougeat et al., 2007; Krens et al., 2018). The difference in the outcomes between the present study and that from the previous study could be attributed to the presence of different types of CKD etiology or pathophysiology, such as the patients with end-stage renal disease undergoing hemodialysis being anuric.

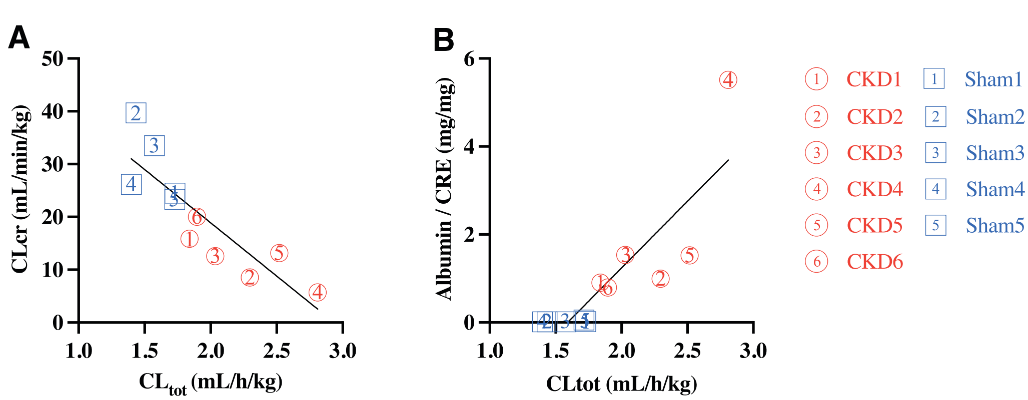

Fig. 4. Correlation between CL_{tot} for nivolumab and (A) baseline CL_{cr} or (B) baseline urinary albumin/CRE ratio. Blue squares and red circles indicate data obtained from the analysis using sham and CKD model rats, respectively. CL_{cr} was calculated based on the CRE levels in plasma and in 24-hour cumulative urine before nivolumab administration. Linear regression was calculated using Pearson's test. (A) $y = -20.2x + 59.3$, $r = -0.867$, $P = 0.0006$; (B) $y = 3.03x - 4.81$, $r = 0.847$, $P = 0.001$.

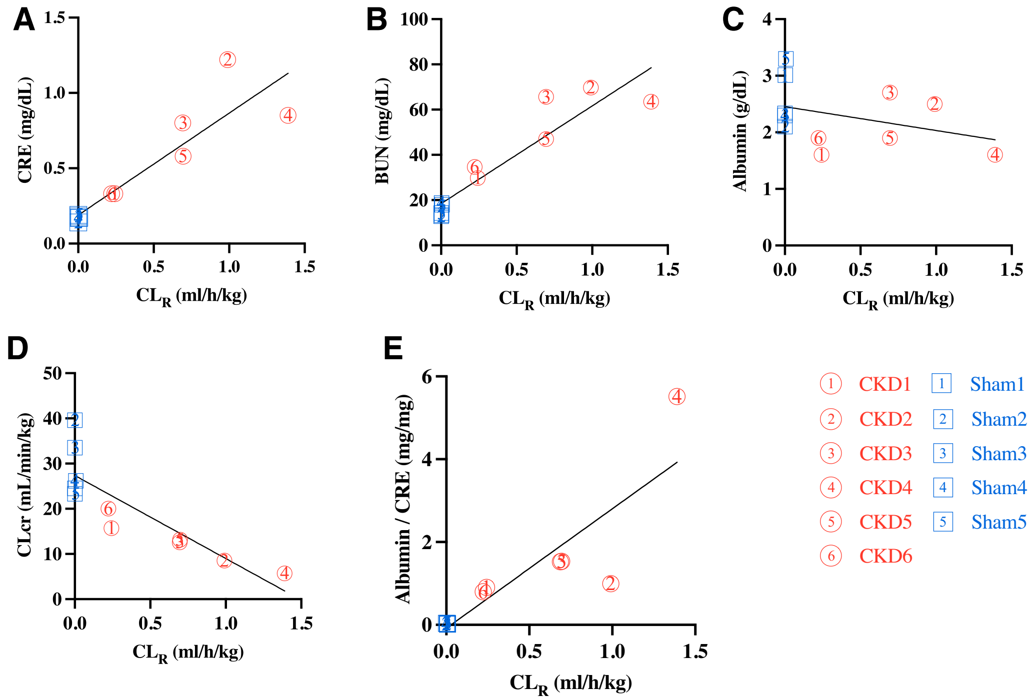

Fig. 5. Correlation between CL_R for nivolumab and (A) baseline CRE levels in plasma, (B) baseline BUN levels in plasma, (C) baseline albumin levels in plasma, (D) baseline CL_{cr}, and (E) baseline urinary albumin/CRE ratio. Blue squares and red circles indicate data obtained from sham and CKD model rats, respectively. CL_{cr} was calculated based on the CRE levels in plasma and in 24-hour cumulative urine before nivolumab administration. Linear regression was calculated using Pearson's test. (A) $y = 0.677x + 0.189$, $r = 0.905$, $P = 0.0001$; (B) $y = 43.2x + 18.4$, $r = 0.928$, $P < 0.0001$; (C) $y = -0.421x + 2.45$, $r = -0.37$, $P = 0.262$; (D) $y = -18.4x + 27.4$, $r = -0.852$, $P = 0.0009$; (E) $y = 2.88x - 0.0798$, $r = 0.871$, $P = 0.0005$).

Thus, further animal experiments with different acute and chronic kidney injury models are warranted.

Authorship Contributions

Participated in research design: Taguchi, Matsumoto, Hamada.

Conducted experiments: Taguchi, Hayashi, Yamada, Enoki.

Contributed new reagents or analytic tools: Hayashi, Ohuchi, Yamada, Yagishita, Hamada.

Performed data analysis: Taguchi, Ohuchi.

Wrote or contributed to the writing of the manuscript: Taguchi, Ohuchi, Matsumoto, Hamada.

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Address correspondence to: Akinobu Hamada, Division of Molecular Pharmacology, National Cancer Center Research Institute, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: akhamad@ncc.go.jp