Population pharmacokinetics and clinical outcome of nivolumab in Japanese patients with non-small cell lung cancer

M. Tohi [1], T. Mizuno [2, 3], K. Irie [1, 4], H. Okuyoshi [1], M. Hirabatake [1], H. Ikesue [1], N. Muroi [1], M. Eto [5], S. Fukushima [4], K. Tomii [6] and T Hashida [1]

[1] Department of Pharmacy, [5] Department of Clinical Laboratory Technology, [6] Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan.
[4] Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Kobe, Japan
[2] Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA [3] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Makiko Tohi, M.S.
E-mail：tohi-m@kcho.jp

BACKGROUND

- **Nivolumab is used at a fixed dose (240 mg every 2 weeks).**
- **Severe immune-related adverse events (irAE) (approx. 10 %), loss of response and the high cost of medication are major hurdles in the nivolumab therapy, suggesting the necessity of personalized dosing.**
- **Nivolumab PK and the exposure-response relationship has not been studied well in a real-world setting.**

OBJECTIVE

To characterize the nivolumab PK and examine the PK-clinical outcome relationship in patients with NSCLC using the data obtained during routine clinical care.

METHOD

- **Study design:** single center prospective observational study.
- **Patients** treated with nivolumab monotherapy at 240 mg every 2 weeks were enrolled.
- **Opportunistic PK sampling** resulted in 223 plasma samples.
- **LC-MS/MS assay** was used to determine plasma nivolumab concentrations[1)]
- **Population PK analysis** was performed using NONMEM. Only clearance was estimated with the other parameters adapted from the literature[3)] as most samples were pre-dose.

RESULT

Table 1. Demographic characteristics

	N=34, median (range)
Age, years	69 (38-83)
Body weight, kg	62.7 (36.8-80.5)
Height, cm	163.8 (146.6-180.1)
BSA, m^2	1.67 (1.24-1.94)
eGFR, mL/min/1.73m^2	70 (29-144)
ALB, g/L	3.6 (2.5-4.8)
NLR	2.79 (1.27-16.36)

	N=34, n (%)
Sex	Male: 25 (73.5), Female: 9 (26.5)
Tumor type	Adenocarcinoma: 22 (64.7), Squamous cell carcinoma: 11 (32.4), Not otherwise specified: 1 (2.9)
Stage	3: 5 (14.7), 4: 22 (64.7), Unknown: 7 (20.6)
PS	0: 10 (29.4), 1: 22 (64.7), 2: 1 (2.9), Unknown: 1 (2.9)

Table 2. Pop PK parameter estimates and comparison with previous reports

Parameters	Current study		G Bajaj.[2)]	M Osawa.[3)]	Hurkmans. [4)]
	Estimate	RSE (%)			
CL (mL/h)	**5.8**	**6**	8.2 * (mL/h/63kg)	9.8 * (mL/h/63kg)	7.5 * (mL/h/1.67m^2)
IIV of CL (CV %)	**22.0**	**38**	35.1	30.7	30.7
CL_ALB	**-1.89**	**25**	-	-	-1.34
CL_eGFR	**0.553**	**21**	0.186	0.151	-
V1 (L/80kg)	**4.46 (FIX)[3)]**	-	3.63	4.46	3.46 (L)
V2 (L)	**2.52 (FIX) [3)]**	-	2.78	2.52	3.46
Q (mL/h)	**26 (FIX) [3)]**	-	32.1	26	20
ε1 (CV %)	**22.0**	**15**			

$$Nivolumab\ CL\left(\frac{mL}{h}\right) = 5.8 \times \left(\frac{ALB}{3.6}\right)^{-1.89} \times \left(\frac{eGFR}{70}\right)^{0.553}$$

The validity of the final model was confirmed by Bootstrap. * Adjusted for our study population.

Fig 1. Treatment period and nivolumab clearance

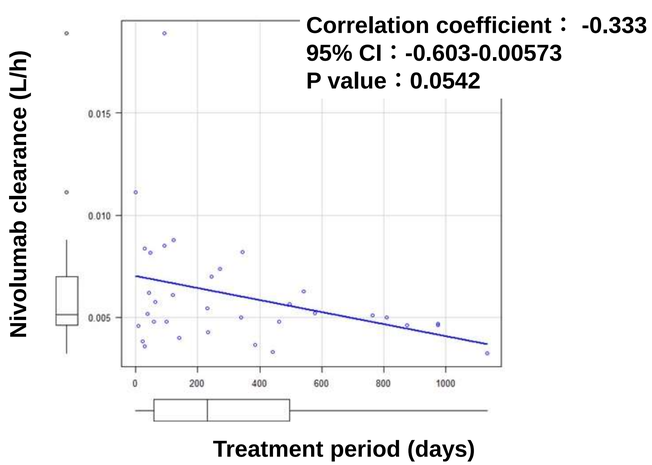


Fig 2. Effect of significant covariates on Nivo clearance

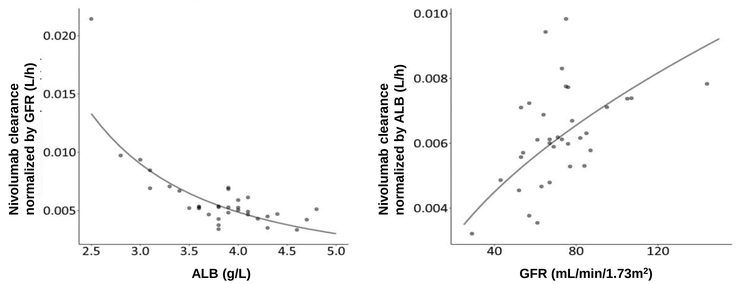
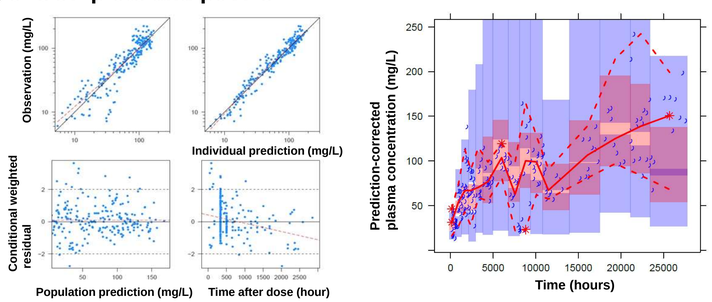


Fig 3. GOF plots and pcVPC



CONCLUSION

- **The mean clearance was slightly lower than the previous reports.**
- **The serum albumin and eGFR were found to be significant covariates on clearance.**
- **Our results indicate that the higher nivolumab clearance may be associated with the poor durability of nivolumab treatment.**

REFERENCE

1. K. Irie et al, Ther Drug Monit, 2018; 40: 716–724.
2. Bajaj G et al, CPT Pharmacometrics Syst Pharmacol, 2017 Jan;6(1):58-66.
3. M. Osawa et al, Cancer Chemotherapy and Pharmacology 2019; 83: 705-715.
4. Hurkmans DP et al, J Immunother Cancer. 2019 Jul 19;7(1):192.