Dynamic Risk Prediction for Disease Control with Nivolumab in Advanced or Recurrent Non-Small Cell Lung Cancer Patients: A Prospective observational study (NewEpoch)

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DISCLOSURES

共同演者の先生方のCOI確認

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Background

- Immune checkpoint inhibitors (ICI) have been widely used for treatment of advanced or recurrent non-small cell lung cancer (NSCLC).
- After randomized phase III trials in patients with advanced NSCLC,[1, 2)] nivolumab was approved as second or subsequent line of therapy in Japan in December 2015.
- The PD-1 inhibitor produced durable response in approximately 20% of NSCLC patients, although 30% to 40% had no response.[1-3)]
- However, prediction of their efficacy remains difficult before and at early phases of therapy.

[1)] Brahmer J, et al. NEJM 2015;373:123-135.
[2)] Borghaei H, et al. NEJM 2015;373:1627-1639.
[3)] Horn L, et al. JCO 2017:Jco2017743062.

Purpose

- We aimed to clarify early clinical predictors for disease control in patients with NSCLC treated with nivolumab.

  - **Primary endpoint**:
    - Disease control rate (DCR) at 25 weeks after the start of nivolumab

  - **Secondary endpoint**: Dynamic risk prediction for
    - Overall response rate (ORR)
    - Overall survival (OS)
    - Clinical factors predicting 2-year survival
    - QOL by EQ-5D-5L

Methods

- We prospectively collected a cohort of patients with advanced or recurrent NSCLC who received nivolumab every two weeks as second or third-line treatment at 32 medical institutions in Japan.
- Disease control was defined as continuing CR/PR/SD according to the RECIST at 25 weeks after the start of nivolumab.
- QOL score by EQ-5D-5L was collected at baseline and at weeks 5, 9, 13 and 25 (after 12 cycles).
- Potential clinical biomarkers included patient characteristics, laboratory data, performance status (PS) and QOL score before and at nivolumab week 9 (after 4 cycles), and immune-related adverse event (irAE) at week 9.

Consort

- ✓ Advanced or recurrent NSCLC patients
- ✓ Received nivolumab every two weeks
- ✓ As second or third-line treatment
- ✓ From July 2016 to December 2017

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Obtained consent, n=244

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Nivolumab treatment, n=243 → At two years after the start of the last registered case
Continued treatment, n=14
Discontinued, n=229
- Disease progression, n=176
- Adverse events, n=43
- Others, n=10

↓

Full analysis set, n=243
After 9th weeks, n=231
After 25th weeks, n=152

Patient Characteristics and Clinical Data at Baseline

		n	%
Gender	Mele / Female	193 / 50	79 / 21
PS	0 / 1 2 / 3 / 4	72 / 149 19 / 3 / 0	30/ 61 8 / 1 / 0
Smoking status	Never / Former / Current	30 / 204 / 9	12 / 84 / 4
Co-morbidity	ILD / COPD Liver disease	8 / 74 5	3.3 / 30.5 2.1
Stage	Advanced / Recurrent	183 / 60	75 / 25
Histology	Ad / Sq NOS / Others	148 / 80 10 / 5	61 / 33 4 / 2
PD-L1	≥50% / 1-49% / <1% Unknown	14 / 41 / 28 61	10 / 29 / 19 42
Treatment line	2^{nd} / 3^{rd}	175 / 67	72.3 / 27.7
Stage, TNM	I / II / III / IV	6 / 6 / 63 / 137	3 / 3 / 26 / 56

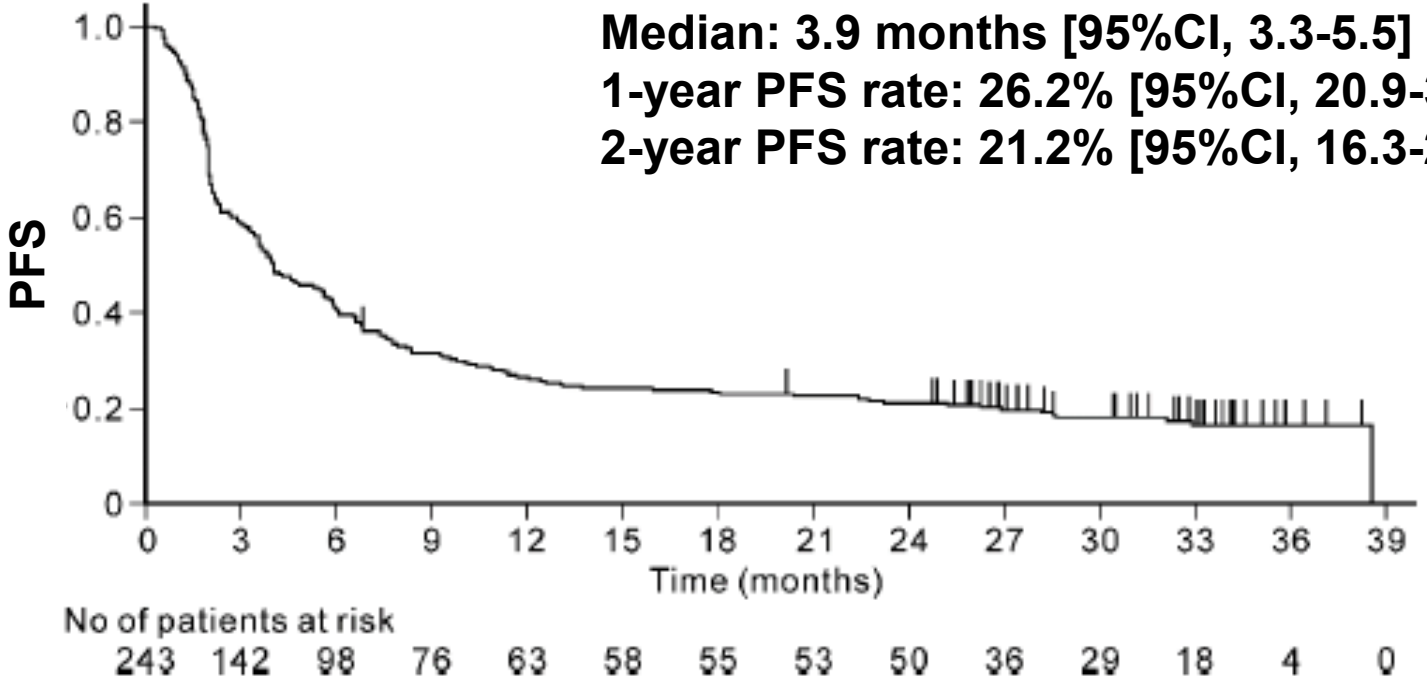
	mean	SD	min	max
Age, years	67.7	9.5	32	85
Hight, cm	163.1	8.2	139	183
Body weight, kg	58.9	11.3	32	96
BMI	18	3.1	11	28
WBC, /μL	6856	2575	2500	22810
Lymphocyte, /μL	1406	770	210	6850
Alb, g/dL	3.6	0.6	1.4	4.9
ALT, U/L	243	18	4	111
ALP, U/L	304	188	76	1943
Cr, mg/dL	0.84	0.31	0.43	4.39
LDH, U/L	248	124	46	1109
CRP, mg/dL	2648	4.5	0.01	29.7

Response According to the RECIST

n (% [95%CI])	CR	PR	SD	PD	NE
9 weeks (5 cycles)	1 (0.4)	42 (17.3)	97 (39.9)	68 (28.0)	35 (14.4)
25 weeks (13 cycles)	3 (1.2)	42 (17.3)	55 (22.6)	71 (29.2)	72 (29.6)
1 year (25 cycles)	4 (1.6)	37 (15.2)	30 (12.3)	40 (16.5)	132 (54.3)

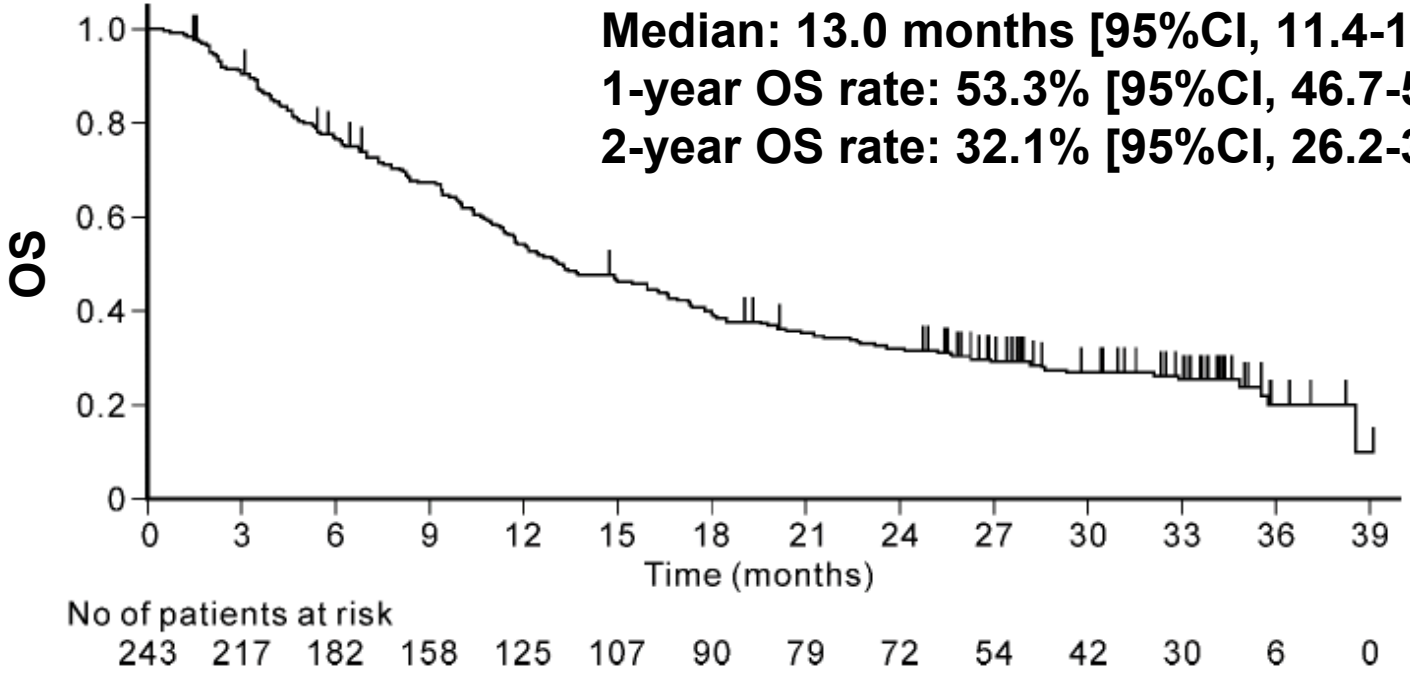
ORR	DCR
n=43 (17.7% [13.1-23.1])	n=140 (57.6% [51.1-63.9])
n=45 (18.5% [13.8-24.0])	n=100 (41.2% [34.9-47.6])
n=41 (16.9% [12.4-22.2])	n=71 (29.2% [23.6-35.4])

Progression Free Survival (PFS), n=243



Median: 3.9 months [95%CI, 3.3-5.5]
1-year PFS rate: 26.2% [95%CI, 20.9-31.9]
2-year PFS rate: 21.2% [95%CI, 16.3-26.6]

Overall Survival (OS), n=243



Association Between Disease Control at Week 25 and Patient Characteristics / Clinical Data at Baseline

Logistic regression	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Gender, female vs male	0.35	0.19-0.66	0.0013	0.29	0.13-0.65	0.0027
Age	0.995	0.97-1.02	0.73	-	-	-
BMI	1.11	1.02-1.21	0.018	0.98	0.88-1.09	0.72
PS, 1 vs. 0	0.45	0.24-0.84	0.85	0.54	0.26-1.10	0.60
PS, ≥2 vs. 0	0.18	0.06-0.49	0.0048	0.42	0.12-1.49	0.33
Smoking, yes vs. no	2.06	0.95-4.45	0.066	-	-	-
Co-morbidity, yes vs. no	0.63	0.37-1.57	0.45	-	-	-
Radiotherapy, yes vs. no	1.19	0.70-2.00	0.52	-	-	-
Line, 3rd vs. 2nd	1.02	0.57-2.82	0.95	-	-	-
Lymphocyte, /μL	2.64	1.61-4.33	0.0001	1.65	0.80-3.42	0.18

Association Between Disease Control at Week 25 and Patient Characteristics / Clinical Data at Week 9

Logistic regression	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Gender, female vs male	0.51	0.25-1.05	0.067	-	-	-
Lymphocyte, /μL	2.47	1.41-4.31	0.0015	1.03	0.38-3.00	0.91
Alb, g/U/L	1.00	0.98-1.02	0.91	-	-	-
ALT, U/L	0.999	0.998-1.00	0.13	-	-	-
Cr, mg/dL	0.99	0.986-0.996	0.0003	0.995	0.99-1.003	0.24
LDH, U/L	0.85	0.76-0.97	0.013	0.98	0.78-1.22	0.82
CRP, mg/dL	1.05	0.74-1.49	0.79	-	-	-
irAEs, yes vs. no	1.45	0.85-2.48	0.17	-	-	-
RECIST, CR/PR vs.SD/PD/NE	9.09	3.99-20.69	<0.0001	-	-	-
RECIST, CR/PR/SD vs. PD/NE	40.07	15.3-105.2	<0.0001	11.8	3.4-40.7	<0.0001

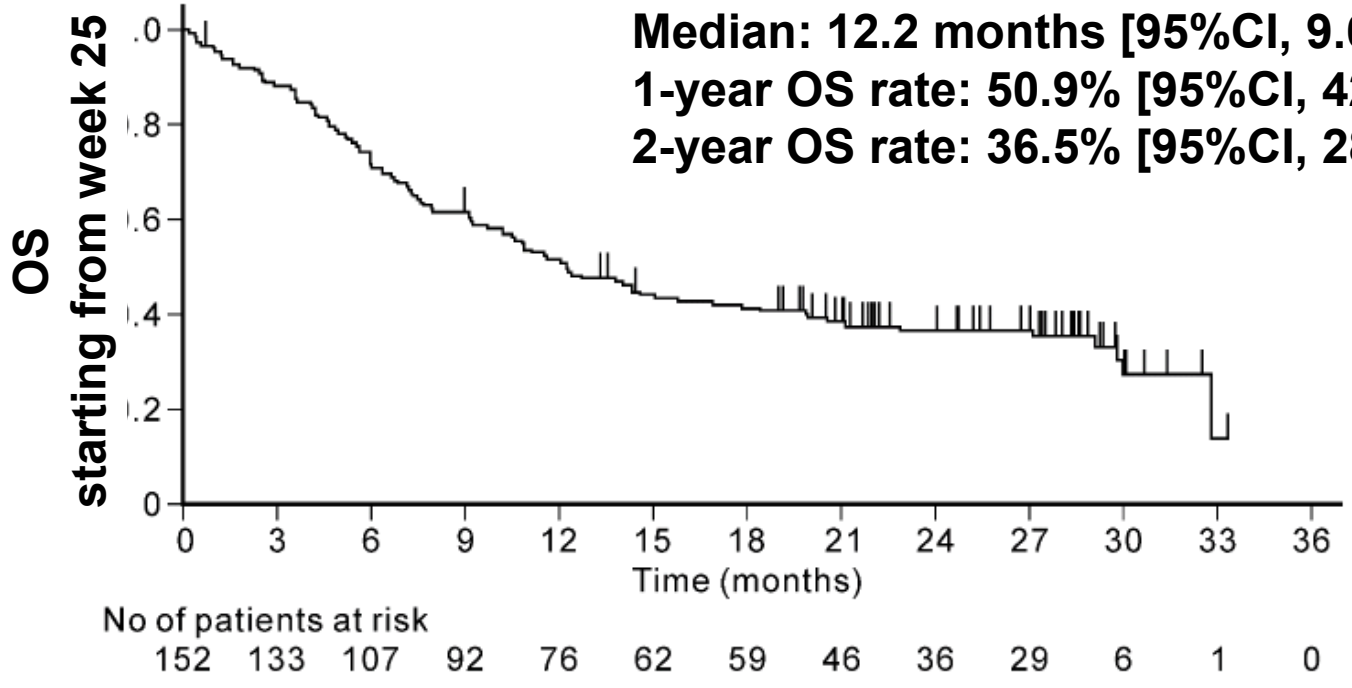
Association Between Tumor Response at Week 25 and Patient Characteristics / Clinical Data at Baseline

Logistic regression	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Gender, female vs male	0.37	0.15-0.92	0.032	0.41	0.16-1.04	0.060
Age	0.99	0.96-1.02	0.36	-	-	-
BMI	1.08	0.98-1.18	0.14	-	-	-
PS, 1 vs. 0	0.39	0.21-0.72	0.47	-	-	-
Smoking, yes vs. no	3.13	0.91-10.7	0.069	-	-	-
Line, 3rd vs. 2nd	0.79	0.40-1.55	0.49	-	-	-
Lymphocyte, /μL	2.87	1.55-5.33	0.0008	2.28	1.08-4.81	0.03
Alb, g/U/L	1.02	0.997-1.04	0.093	-	-	-
ALT, U/L	0.996	0.993-0.999	0.021	0.998	0.995-1.001	0.18
Cr, mg/dL	0.999	0.997-1.002	0.60	-	-	-

Association Between Tumor Response at Week 25 and Patient Characteristics / Clinical Data at Week 9

Logistic regression	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Gender, female vs male	0.26	0.077-0.89	0.031	0.51	0.099-2.57	0.41
Lymphocyte, /μL	4.44	2.03-9.73	0.0002	6.63	1.43-30.8	0.016
Alb, g/U/L	1.01	0.991-1.04	0.26	-	-	-
ALT, U/L	0.999	0.997-1.001	0.20	-	-	-
Cr, mg/dL	0.991	0.98-0.998	0.0077	0.99	0.98-0.999	0.028
LDH, U/L	0.78	0.62-0.97	0.028	1.09	0.76-1.55	0.64
CRP, mg/dL	0.98	0.64-1.52	0.94	-	-	-
irAEs, yes vs. no	1.16	0.59-2.27	0.66	-	-	-
RECIST, CR/PR vs.SD/PD/NE	64.9	25.0-168.4	<0.001	68.3	19.4-240.8	<0.0001
RECIST, CR/PR/SD vs. PD/NE	21.9	5.17-93.0	<0.001	-	-	-

Landmark Analysis of OS Starting from Week 25, n=152



Median: 12.2 months [95%CI, 9.6-16.8]
1-year OS rate: 50.9% [95%CI, 42.6-58.5]
2-year OS rate: 36.5% [95%CI, 28.7-44.3]

Association Between OS from Week 25 and Patient Characteristics / Clinical Data at Week 25

Cox proportional hazard model	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Gender, female vs male	1.97	1.19-3.25	0.0087	5.64	1.46-21.9	0.012
Age	0.99	0.97-1.02	0.44	-	-	-
BMI	0.97	0.90-1.05	0.42	-	-	-
Smoking, yes vs. no	0.93	0.50-1.73	0.81	-	-	-
Co-morbidity, yes vs. no	1.08	0.73-1.59	0.71	-	-	-
Radiotherapy, yes vs. no	0.91	0.61-1.35	0.63	-	-	-
Line, 3rd vs. 2nd	1.61	1.05-2.45	0.029	5.50	1.71-17.7	0.0042
PS at week 25, 1 vs. 0	2.05	1.08-3.69	0.028	1.55	0.55-4.41	0.41
PS at week 25, ≥2 vs. 0	22.1	9.54-51.0	<0.0001	56.6	3.36-954.0	0.0051

(Continued)

Association Between OS from Week 25 and Patient Characteristics / Clinical Data at Week 25

Cox proportional hazard model	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Lymphocyte, /μL	0.16	0.087-0.28	<0.0001	0.50	0.17-1.35	0.17
Alb, g/U/L	0.94	0.91-0.98	0.0016	0.97	0.92-1.02	0.20
ALT, U/L	1.005	1.001-1.008	0.054	1.002	0.998-1.007	0.29
Cr, mg/dL	1.007	1.003-1.011	0.0002	1.006	0.997-1.014	0.19
LDH, U/L	1.26	1.17-1.36	<0.0001	1.07	0.84-1.37	0.59
CRP, mg/dL	0.15	0.020-1.18	0.072	-	-	-
RECIST, CR/PR vs.SD/PD/NE	0.24	0.14-0.41	<0.0001	-	-	-
RECIST, CR/PR/SD vs. PD/NE	0.30	0.20-0.44	<0.0001	0.19	0.066-0.55	0.0023

(Continued)

Association Between OS from Week 25 and Patient Characteristics / Clinical Data at Week 25

Cox proportional hazard model	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
QOL MO, yes vs. no	1.99	1.55-2.55	<0.0001	1.29	0.61-2.75	0.50
QOL SC	2.74	1.92-3.92	<0.0001	1.18	0.40-3.43	0.77
QOL UA	1.93	1.54-2.42	<0.0001	0.48	0.14-1.59	0.23
QOL PD	2.12	1.71-2.64	<0.0001	2.85	1.31-6.23	0.0086
QOL AD	1.88	1.41-2.51	<0.0001	2.65	1.67-5.15	0.0039
QOL, health	0.98	0.96-0.99	0.0003	1.03	0.99-1.08	0.13

Imunne-related Adverse Events (irAE) of Nivolumab

	Grade 3		Grade 4	
	n	%	n	%
Any	21	8.6	1	0.4
Pulmonary toxicity	11	4.5	1	0.4
Diarrhea	5	2.1	0	0
Rash	4	1.6	0	0
Thyroid dysfunction	3	1.2	0	0
Type 1 diabetes	1	0.4	0	0
Others	19	7.8	2	0.8

irAE
Anyの数値を確認

Association Between Pulmonary Toxicity and Patient Characteristics / Clinical Data at Baseline

	Univariate			Multivariate		
	OR	95%CI	p*	OR	95%CI	p*
Gender, female vs male	0.33	0.19-2.35	0.52	-	-	-
Age	0.99	0.95-1.04	0.71	-	-	-
BMI	1.16	1.00-1.35	0.049	1.22	1.04-1.43	0.017
PS, 1 vs. 0	1.14	0.42-3.10	0.95	-	-	-
Smoking, yes vs. no	2.84	0.37-22.0	0.32	-	-	-
Co-morbidity, yes vs. no	3.74	1.43-9.77	0.007	4.63	1.70-12.61	0.003
Line, 3rd vs. 2nd	0.86	0.30-2.47	0.78	-	-	-
Lymphocyte, /μL	1.65	0.69-3.93	0.26	-	-	-
LDH, U/L	0.99	0.88-1.10	0.79	-	-	-
CRP, mg/dL	0.56	0.06-5.04	0.61	-	-	-

Conclusions

- Male gender, high lymphocyte count and low serum creatinine at week 9 may be clinical predictors for nivolumab efficacy in patients with advanced or recurrent NSCLC.
- Body mass index and co-morbidity such as interstitial lung disease, chronic obstructive pulmonary disease and liver disease at baseline were independently associated with pulmonary toxicity by nivolumab.
- In addition, patient reported outcomes may be independent prognostic factors.
- Construction of a prediction model using these factors as candidates will be considered in the future.