




# Nivolumab treatment of elderly Japanese patients with non-small cell lung cancer: subanalysis of a real-world retrospective observational study (CA209-9CR)

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## ABSTRACT

**Objectives** We conducted a subanalysis of data from the multicentre, retrospective observational Nivolumab Japan Real World (CA209-9CR) study to evaluate nivolumab effectiveness and safety in elderly patients (aged  $\geq 75$  years) with advanced/metastatic non-small cell lung cancer.

**Materials and methods** Medical record data of patients initiating nivolumab treatment between April 2016 and December 2016 were collected using electronic data capture from 23 cancer hospitals in Japan between March 2017 and August 2018. Nivolumab treatment data were collected to investigate the treatment patterns by age group ( $< 75$  and  $\geq 75$  years), and the effectiveness and safety of nivolumab treatment.

**Results** Of the 901 patients evaluated, 178 (19.8%) were aged  $\geq 75$  years. Overall, patients received a median of five nivolumab treatments regardless of age group. Comparable progression-free survival was observed, with a median of 2.1 months in patients aged  $< 75$  years and 2.1 months in patients aged  $\geq 75$  years ( $p=0.5441$ ). No significant differences were found in duration of response, overall response rate or disease control rate between the two age groups. Median overall survival in patients aged  $< 75$  and  $\geq 75$  years was 14.7 months and 12.3 months, respectively. Grade  $\geq 3$  adverse events (AEs) occurred in 29.2% and 28.1% of patients aged  $< 75$  and  $\geq 75$  years, respectively. Immune-related AEs decreased slightly with increasing age; time to onset and rates of improvement were similar for patients aged  $< 75$  and  $\geq 75$  years. The most common grade 3–4 AEs were interstitial lung disease in both age groups (4.0% in patients aged  $< 75$  years and 2.8% in those aged  $\geq 75$  years). Poor performance status was associated with worse outcomes in both age groups.

**Conclusion** Based on Japanese real-world data, the effectiveness and safety of nivolumab were confirmed regardless of age.

## Key question

### What is already known about this subject?

- As longevity of the Japanese population rises, elderly patients account for the majority of patients with non-small cell lung cancer (NSCLC) in Japan.
- Age has been found to be a major prognostic factor of survival in patients with NSCLC treated with conventional chemotherapies; however, a similar association between age and survival has not been fully determined in immune checkpoint inhibitors.

### What does this study add?

- This study assessed effectiveness and safety of nivolumab, the first approved immune checkpoint inhibitor in Japan, in elderly patients with NSCLC and found that safety and effectiveness were consistent among elderly (75 years old or more) and non-elderly (less than 75 years) patients. Instead of age, better performance status was associated with better outcomes regardless of age.

### How might this impact on clinical practice?

- This study suggests that age is not associated with the effectiveness or safety of nivolumab in a large Japanese population.
- Moreover, nivolumab treatment for elderly patients with good performance status may be a reasonable option.

## INTRODUCTION

Globally, lung cancer is the most commonly diagnosed cancer (11.6% of all cancers) and the leading cause of cancer deaths (18.4% of total cancer deaths).<sup>1</sup> It is a significant problem in Japan, affecting 15.0% ( $n=86\,700$ ) of men and 10.0% ( $n=42\,000$ ) of women, and resulting in 25.0% and 14.0% of cancer



deaths, respectively.<sup>2</sup> The age at diagnosis of Japanese patients with lung cancer is increasing, with a notable increase in incidence rate among patients aged  $\geq 70$  years in the past three decades.<sup>2</sup> According to epidemiological data,  $>80\%$  of all lung cancer cases are classified as non-small cell lung cancer (NSCLC).<sup>3,4</sup>

Programmed death-1 (PD-1) inhibitors, such as the immune checkpoint inhibitor nivolumab, have shown superiority over conventional therapy when used as monotherapy in patients with NSCLC, malignant melanoma, renal cell cancer, head and neck carcinoma and gastric cancer, and are now routinely used for the treatment of NSCLC.<sup>5</sup> In two phase III NSCLC studies conducted outside of Japan, nivolumab was shown to be superior to docetaxel in terms of overall survival (OS). In CheckMate 017,<sup>6</sup> in patients with squamous cell NSCLC who received nivolumab or docetaxel as second-line therapy after platinum treatment, the median OS was 9.2 months with nivolumab versus 6.0 months with docetaxel. In CheckMate 057,<sup>7</sup> in patients with non-squamous cell NSCLC, the median OS was 12.2 months with nivolumab versus 9.4 months with docetaxel. The efficacy and safety of nivolumab have also been confirmed in two phase II Japanese studies in patients with NSCLC. In ONO-4538-05 (squamous cell)<sup>8</sup> and ONO-4538-06 (non-squamous cell),<sup>9</sup> the median OS with nivolumab was 16.3 months and 17.1 months, respectively. Based on these results, in December 2015, nivolumab was approved for the treatment of previously treated, unresectable, locally advanced or metastatic NSCLC regardless of histological type or programmed death ligand 1 (PD-L1) mutation presence. Nivolumab is the first approved PD-1 inhibitor in Japan.

Although age has been identified as a major prognostic factor of survival in patients with lung cancer receiving conventional therapy,<sup>10</sup> a similar association has not yet been determined for PD-1 or immunotherapy. Nevertheless, because elderly patients comprise the largest proportion of patients with lung cancer, both in Japan<sup>2</sup> and in Western countries,<sup>11–13</sup> treatment and management of patients with lung cancer may need to be optimised according to age.<sup>14</sup> Furthermore, it is clear that the prevalence of multimorbidity increases substantially with age<sup>15</sup> and concurrently, physiological function gradually decreases with age.<sup>16</sup> However, historically, patients aged 75 years and over have been excluded from clinical trials in Japan.<sup>17</sup> Eastern Cooperative Oncology Group Performance Status (ECOG PS) has also been reported as a prognostic factor of survival in pharmacotherapy,<sup>18,19</sup> however, for this reason, reports of effectiveness by ECOG PS in Japanese elderly patients were insufficient.

According to the Japanese Lung Cancer Society Guideline for NSCLC, stage IV<sup>17</sup> elderly patients are defined as those aged  $\geq 75$  years, and the recommended treatment method can differ according to age. In CheckMate 017<sup>6</sup> and CheckMate 057,<sup>7</sup> the proportions of patients aged  $\geq 75$  years were limited to 11% (29 patients) and 7% (43 patients), respectively. For this reason, the efficacy and safety data of immune checkpoint inhibitors, including

nivolumab, in this population are limited. Therefore, real-world large-cohort data are needed.

The multicentre, retrospective, observational Nivolumab Japan Real World (CA209-9CR) study was designed to evaluate the effectiveness, safety and treatment patterns of nivolumab in Japanese patients with NSCLC.<sup>18</sup> Herein, we describe a subanalysis of elderly patients (aged  $\geq 75$  years) with advanced/metastatic NSCLC treated with nivolumab to evaluate nivolumab effectiveness and safety in this age group.

## MATERIALS AND METHODS

### Study design, data collection, treatment and ethical considerations

The full details of the study design were recently reported.<sup>19</sup> This was a multicentre, non-interventional, retrospective medical chart review study (trial registration NCT03273790) in which medical record data (collected by participating investigators using electronic data capture; Mebix, Inc, Tokyo, Japan) from 23 cancer hospitals in Japan were analysed.

The study was conducted from 1 April 2017 to 31 December 2018. Data recorded prior, during and after nivolumab treatment were collected to investigate the treatment trends before and after nivolumab treatment, and the safety and effectiveness of nivolumab treatment.

The study protocol was approved by the Ethics Committees or Independent Review Committees of each participating site. The study was conducted in accordance with Ethical Guidelines for Medical and Health Research Involving Human Subjects,<sup>20</sup> and all other applicable national and international guidelines. Informed consent was not required owing to the retrospective nature of this study, although patients were allowed to opt out from study participation.

### Study population

The study population has been described.<sup>19</sup> Previously treated advanced/metastatic patients with NSCLC who initiated nivolumab treatment between April 2016 and December 2016 were included, with the exception of patients who participated in the postmarketing surveillance of nivolumab and patients who participated in any clinical studies prior to or after nivolumab treatment.

### Endpoints and assessments

For this subanalysis, the population was stratified into two groups:  $<75$  years and  $\geq 75$  years. OS, progression-free survival (PFS), duration of response (DOR) and best overall response (objective response rate (ORR) and disease control rate (DCR)) were calculated. For a supplementary effectiveness analysis, the population was stratified into three groups:  $<75$  years, 75 to  $<80$  years and  $\geq 80$  years. The outcomes included clinical usage and treatment patterns by age group (ie, dosage, median number of treatments, median treatment duration, treatment line and reasons for discontinuation from nivolumab treatment).

Overall effectiveness of nivolumab was investigator assessed. Tumour evaluation was performed according to the methodology described in the Response Evaluation Criteria in Solid Tumors (V.1.1). OS was defined as the date of first nivolumab administration to the date of death from any cause. PFS was defined as the date of first nivolumab administration to the date of disease progression or death. DOR was defined as the time from first response to death or progression. ORR was defined as the number of patients achieving complete response (CR) or partial response (PR), and DCR was the proportion of patients achieving CR, PR or stable disease.

The OS, PFS and best overall response in elderly patients (aged  $\geq 75$  years) by ECOG PS were also calculated. In addition, response was evaluated according to serum albumin and body mass index (BMI), with responders defined as patients whose best overall response was CR or PR.

The safety of nivolumab, including incidence and severity of adverse events (AEs) and treatment-related AEs (immune-related AEs (irAEs)), was also investigator assessed. The severity of AEs was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events Grading System, V.4.0.<sup>21</sup>

### Statistical methods

Study calculations have been reported.<sup>19</sup> All eligible patients enrolled in the study were included in the analyses. For this subanalysis, the effectiveness and safety of nivolumab were assessed in patients aged  $\geq 75$  years and compared with patients aged  $< 75$  years; for the supplementary analysis, effectiveness outcomes were assessed in patients aged  $< 75$  years, 75 to  $< 80$  years and  $\geq 80$  years. Summary statistics (median (range)) were used for continuous variables, and frequency and percentage were used for categorical or ordinal variables. For OS and PFS, median and 95% CIs were estimated using the Kaplan-Meier method. Differences were considered statistically significant at  $p$  values  $< 0.05$ . Statistical analysis was performed using SAS V.9.4 (SAS Institute Inc, Cary, North Carolina, USA).

## RESULTS

### Patients

Overall, medical record data of 901 patients were collected from 23 cancer hospitals in Japan.<sup>19</sup> The major baseline characteristics and clinical background according to age group ( $< 75$  years and  $\geq 75$  years) are shown in [table 1](#). Of the 901 patients evaluated, 178 (19.8%) were aged  $\geq 75$  years. Most patients aged  $< 75$  years had an ECOG PS of 1 (54.4%), adenocarcinoma (67.7%), and presence of metastases (77.5%).

Most baseline characteristics were comparable between the two age groups. However, the incidences of ECOG PS 3 and 4, squamous cell carcinoma and concomitant hypertension were numerically higher in patients aged  $\geq 75$  years. The incidences of brain metastasis and adrenal

metastasis were significantly lower in patients aged  $\geq 75$  years compared with patients aged  $< 75$  years (brain,  $p=0.0006$ ; adrenal glands,  $p=0.0303$ , [table 1](#)). Serum albumin levels were significantly lower in patients aged  $\geq 75$  years compared with those aged  $< 75$  years ( $p=0.0300$ ).

### Nivolumab use and treatment patterns

Most patients aged  $\geq 75$  years received nivolumab as second-line treatment (55.6%), followed by third-line treatment (21.3%). The use of nivolumab was similar for patients aged  $< 75$  years ([table 2](#)). The median number of nivolumab doses per patient was five (both for the whole population and for both age groups). The proportions of patients receiving post-nivolumab treatment were 44.4% and 34.3% in the  $< 75$  and  $\geq 75$  age groups, respectively ( $p=0.0180$ ).

### Effectiveness of nivolumab according to age

Comparable PFS was observed in patients aged  $< 75$  years and  $\geq 75$  years (median PFS, 2.1 months vs 2.1 months;  $p=0.5441$ ). At 1 year, the PFS rate was 19.7% in patients aged  $< 75$  years and 15.8% in patients aged  $\geq 75$  years ([figure 1A](#)). There was no significant difference in DOR between patients aged  $< 75$  and those aged  $\geq 75$  years ([figure 1B](#)). The ORR and DCR were similar in the two age groups ([figure 1C](#)). Median OS in patients aged  $< 75$  years and those aged  $\geq 75$  years was 14.7 months and 12.3 months, respectively ( $p=0.3272$ , [figure 1D](#)).

In the supplementary effectiveness analysis, median PFS was 2.1 months in all three age groups evaluated ( $< 75$  years, 75 to  $< 80$  years and  $\geq 80$  years, online supplementary figure S1A). The median DOR was not reached in patients aged 75 to  $< 80$  years, and was 4.7 months in those aged  $\geq 80$  years, compared with 13.1 months in the  $< 75$  years group (online supplementary figure S1B). ORR and DCR were comparable between the three age groups (online supplementary figure S1C), as was median OS (online supplementary figure S1D). Significance testing was not performed for these analyses.

### Effectiveness in patients aged $\geq 75$ years according to ECOG PS

There was a clear trend towards improved PFS according to ECOG PS ([figure 2A](#)). Significant differences were observed between ECOG PS 0 and PS 1 ( $p=0.0170$ ), PS 0 vs PS 2 ( $p=0.034$ ), PS 0 vs PS 3 and 4 ( $p<0.0001$ ) and PS 1 vs PS 3 or 4 ( $p=0.0092$ ). ORR and DCR by ECOG PS are shown in [figure 2B](#). More patients with ECOG PS 0 achieved CR or PR compared with other ECOG PS groups (41.9%). The ORR and DCR were highest in patients with ECOG PS 0 (41.9% and 74.2%, respectively), and lowest in patients with ECOG PS 3 and 4 (13.3% and 40.0%, respectively). There was also a trend towards improved OS according to ECOG PS ([figure 2C](#)).

### Effectiveness in patients aged $\geq 75$ years according to serum albumin, C-reactive protein and BMI

When evaluated according to BMI, patients aged  $\geq 75$  years with a median BMI of 22.3 (21.5–23.6)  $\text{kg}/\text{m}^2$

**Table 1** Patient demographics and clinical background by age group

Variable	All patients	<75 years	≥75 years	Difference <75 years vs ≥75 years
Patients, n (%)	901 (100.0)	723 (100.0)	178 (100.0)	–
Gender, n (%)				
Male	651 (72.3)	519 (71.8)	132 (74.2)	0.5754*
Female	250 (27.7)	204 (28.2)	46 (25.8)	
Age (years), median (range)	67.0 (30.0–90.0)	65.0 (30.0–74.0)	78.0 (75.0–90.0)	–
BMI (kg/m <sup>2</sup> ), median (range)	21.4 (12.9–36.9)	21.4 (12.9–36.9)	21.3 (13.6–30.7)	0.4087†
Disease stage at diagnosis of NSCLC, n (%)				
IA–IIIA	302 (33.5)	232 (32.1)	70 (39.3)	0.1625*
IIIB	102 (11.3)	86 (11.9)	16 (9.0)	
IV	497 (55.2)	405 (56.0)	92 (51.7)	
ECOG PS, n (%)				
0	193 (21.4)	162 (22.4)	31 (17.4)	0.0253*‡
1	490 (54.4)	379 (52.4)	111 (62.4)	
2	109 (12.1)	93 (12.9)	16 (9.0)	
3 and 4	48 (5.3)	33 (4.6)	15 (8.4)	
Missing	61 (6.8)	56 (7.7)	5 (2.8)	
Histological type, n (%)				
Squamous cell carcinoma	221 (24.5)	159 (22.0)	62 (34.8)	0.0017*
Adenocarcinoma	610 (67.7)	505 (69.8)	105 (59.0)	
Other	28 (3.1)	21 (2.9)	7 (3.9)	
Unclassified	42 (4.7)	38 (5.3)	4 (2.2)	
Other primary malignant tumours, n (%)	100 (11.1)	77 (10.7)	23 (12.9)	0.4238*§
Smoking history, n (%)				
Current smoker	308 (34.2)	253 (35.0)	55 (30.9)	0.5549*
Former smoker	412 (45.7)	328 (45.4)	84 (47.2)	
Never smoker	181 (20.1)	142 (19.6)	39 (21.9)	
EGFR mutation, n (%)				
Yes	116 (12.9)	94 (13.0)	22 (12.4)	0.8963*§
No	641 (71.1)	524 (72.5)	117 (65.7)	
Unknown	144 (16.0)	105 (14.5)	39 (21.9)	
EGFR mutation subtype n (%)				
TKI sensitive (L858R or Del19)	94 (10.4)	76 (10.5)	18 (10.1)	0.5183*
TKI non-sensitive	16 (1.8)	14 (1.9)	2 (1.1)	
ALK mutation, n (%)				
Yes	11 (1.2)	7 (1.0)	4 (2.2)	0.1194*§
No	603 (66.9)	496 (68.6)	107 (60.1)	
Unknown	287 (31.9)	220 (30.4)	67 (37.6)	–
Metastasis, n (%)	698 (77.5)	569 (78.7)	129 (72.5)	0.0883*§
Metastasis location, n (%)				
Liver	104 (11.5)	82 (11.3)	22 (12.4)	0.6954*
Lung	244 (27.1)	195 (27.0)	49 (27.5)	0.9250*
Bone	256 (28.4)	213 (29.5)	43 (24.2)	0.1654*
Brain	201 (22.3)	178 (24.6)	23 (12.9)	0.0006*

Continued

**Table 1** Continued

Variable	All patients	<75 years	≥75 years	Difference <75 years vs ≥75 years
Adrenal glands	83 (9.2)	74 (10.2)	9 (5.1)	0.0303*
Other	309 (34.3)	262 (36.2)	47 (26.4)	0.0136*
Concomitant disease, n (%)				
Any	647 (71.8)	505 (69.8)	142 (79.8)	0.0091*
COPD	109 (12.1)	81 (11.2)	28 (15.7)	0.1227*
Pulmonary infection	22 (2.4)	18 (2.5)	4 (2.2)	1.0000*
Interstitial lung disease	47 (5.2)	34 (4.7)	13 (7.3)	0.1861*
Autoimmune disease	16 (1.8)	14 (1.9)	2 (1.1)	0.7509*
Hypertension	316 (35.1)	231 (32.0)	85 (47.8)	0.0001*
Diabetes	155 (17.2)	116 (16.0)	39 (21.9)	0.0756*
Dyslipidaemia	122 (13.5)	100 (13.8)	22 (12.4)	0.7138*
Albumin (g/dL), median (range)	3.7 (1.5–4.8)	3.7 (1.5–4.8)	3.6 (1.9–4.6)	0.0300†

\*Fisher's exact test.

†Wilcoxon rank-sum test.

‡0 vs 1 vs 2 vs (3 and 4).

§Yes/positive vs no/negative.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

were more likely to be responders (patients whose best overall response was CR or PR) compared with patients <75 years ( $p=0.040$ ). The serum albumin levels of responders were significantly higher than non-responders in patients ≥75 years, while there were no significant difference in patients <75 years (online supplementary table S1). The median levels of CRP of responders were 0.65 and 1.20 (mg/dL) for patients aged ≥75 and <75 years, respectively. There were no significant difference between patients with responder and with non-responder in both age groups (online supplementary table S1).

### Safety of nivolumab according to age

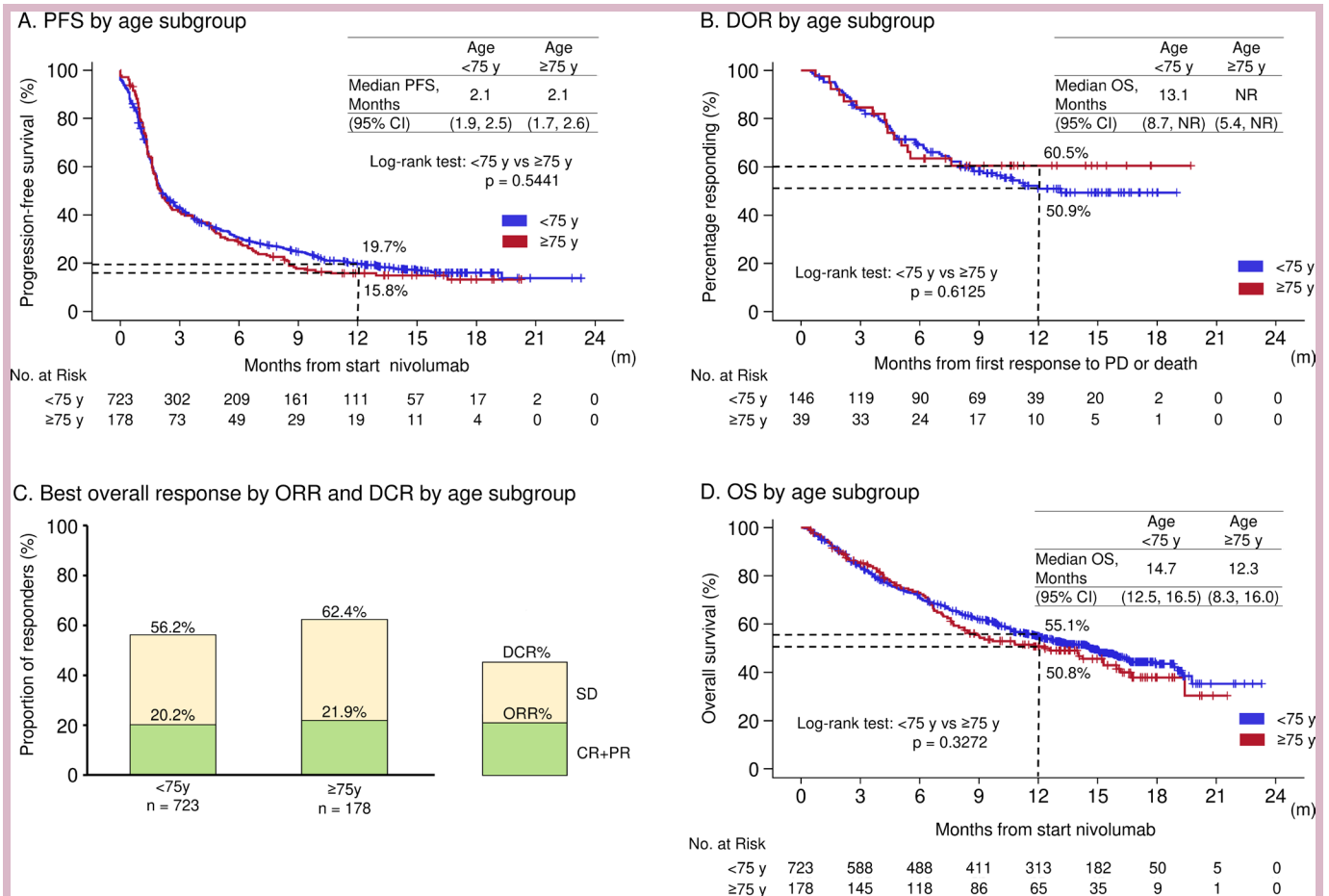
In general, the overall incidence of AEs in each age group was comparable (67.4% in patients aged <75 years and 64.0% in patients aged ≥75 years). Similarly, the incidences of grade ≥3 AEs were comparable between both age groups (29.2% in patients aged <75 years and 28.1% in those aged ≥75 years, [table 3](#)). The rates of nivolumab discontinuation due to AEs were 15.4% and 13.5% in patients aged <75 and ≥75 years, respectively. Regarding irAEs, the incidence rates were generally similar between age groups, with a trend towards a lower incidence as age increased ([table 3](#)). The time to onset of irAEs and the

**Table 2** Treatment patterns of nivolumab by age group

	All patients (n=901)	<75 years (n=723)	≥75 years (n=178)	Difference <75 years vs ≥75 years
Treatment line, n (%)				
Median (range)	2.0 (1.0–12.0)	3.0 (1.0–12.0)	2.0 (1.0–9.0)	
1	38 (4.2)	33 (4.6)	5 (2.8)	0.0666*†
2	422 (46.8)	323 (44.7)	99 (55.6)	
3	239 (26.5)	201 (27.8)	38 (21.3)	
≥4	202 (22.4)	166 (23.0)	36 (20.2)	
Number of doses, median (range)	5.0 (1.0–44.0)	5.0 (1.0–44.0)	5.0 (1.0–43.0)	0.5074‡
Treatment duration, median (range)	59.0 (1.0–693.0)	59.0 (1.0–693.0)	70.5 (1.0–602.0)	0.4974‡
Patients who continued nivolumab after the study, n (%)	129 (14.3)	101 (14.0)	28 (15.7)	0.5511*

\*Fisher's exact test.

†1 vs 2 vs 3 vs ≥4.



**Figure 1** PFS (A), DOR (B), best overall response by ORR and DCR (C) and OS (D) by age subgroup. CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; M, months.

rate of recovery and improvement were similar in the groups aged <75 years and ≥75 years (online supplementary table S2). Most irAEs resolved or improved, with the exception of endocrine, nervous and renal reactions.

The most frequently reported AEs of any grade in patients aged <75 years were interstitial lung disease (10.0%), diarrhoea (9.7%), thyroid dysfunction (6.6%) and hepatic dysfunction (5.8%). In patients aged ≥75 years, the most frequently reported AEs were diarrhoea (6.7%), hepatic and thyroid dysfunction (5.1% each) and interstitial lung disease (4.5%). In both age groups, the most common grade 3–4 AEs were interstitial lung disease (4.0% in patients aged <75 years and 2.8% in those aged ≥75 years, online supplementary table S3).

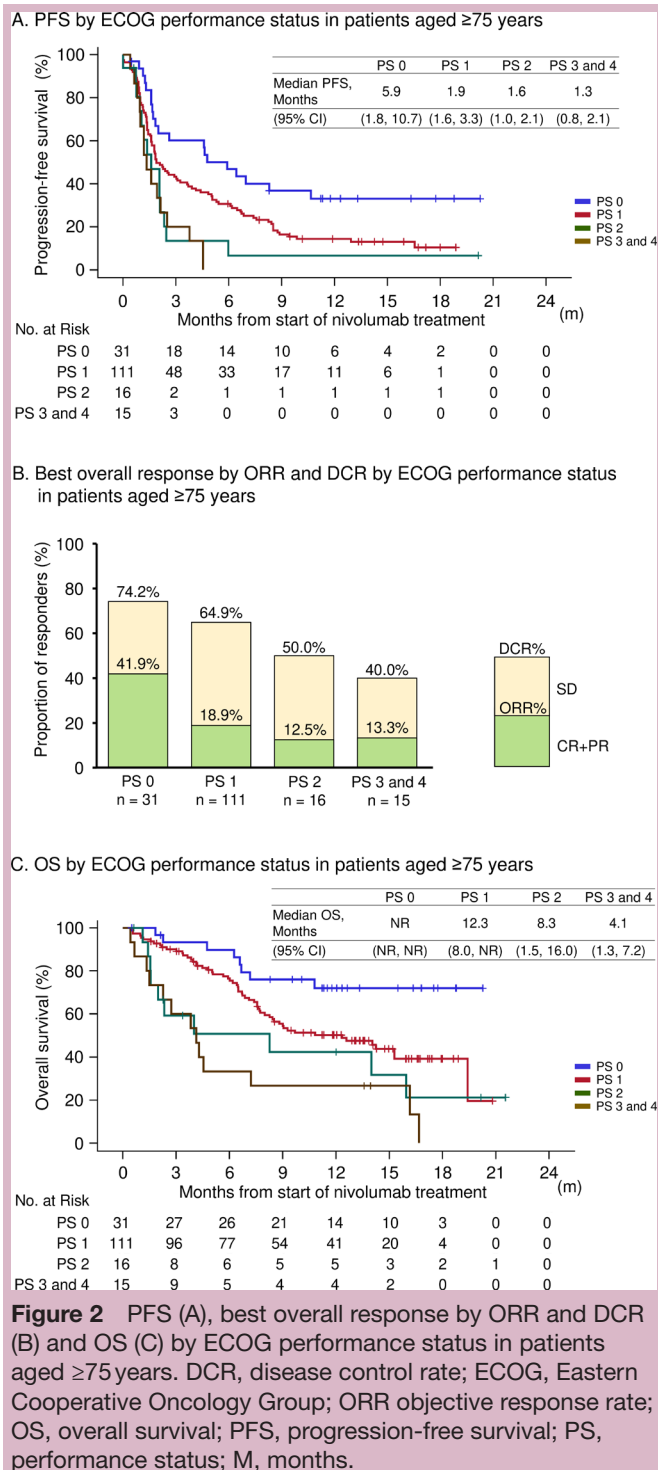
AEs including irAEs were evaluated from the start of nivolumab administration initiation up to the last administration. If there was no subsequent treatment, AEs were included up to 100 days from the last administration of nivolumab.

## DISCUSSION

Although Japanese treatment guidelines indicate that treatment for NSCLC may need to be varied according

to age,<sup>17</sup> there are limited efficacy and safety data available for newly approved treatments, such as nivolumab, in Japanese patients aged ≥75 years. In the absence of prospective clinical trial data, retrospective real-world cohort studies can fill this evidence gap and may inform clinical treatment decisions. This subanalysis of the Nivolumab Japan Real World (CA209-9CR) study,<sup>19</sup> evaluated data collected from 901 Japanese patients with NSCLC who received nivolumab, with the aim of investigating the safety and effectiveness outcomes according to age.

When study patients were categorised according to age (<75 and ≥75 years), there were few significant baseline differences between groups, with the exception of higher incidences of ECOG PS 3 and 4, squamous cell carcinoma and concomitant hypertension in patients aged ≥75 years vs <75 years. The overall incidence of concomitant disease in our study was significantly higher in patients aged ≥75 years (79.8%) compared with patients aged <75 years (69.8%;  $p < 0.05$ ). Treatment patterns of nivolumab and administration of subsequent treatment after nivolumab were similar in the two age groups.



It has long been recognised that patients with NSCLC aged  $\geq 80$  years, when carefully selected according to clinical factors and medical history, can not only tolerate chemotherapy but also benefit from it.<sup>22</sup> However, it is important to obtain real-world efficacy and safety data from patients with NSCLC aged  $\geq 80$  years receiving immunotherapies, since data from elderly patients treated with immunotherapies have been relatively scarce in the clinical trial publications to date. The results of our study are in line with those reported from the Italian cohort

of an expanded access programme in patients with squamous NSCLC receiving nivolumab,<sup>13</sup> in which the median OS was lower in patients aged  $\geq 75$  years (5.8 months) compared with patients aged  $< 65$  years (8.6 months), but PFS, ORR and DCR rates were similar for all age groups. The Italian EAP (expanded access programme) real-life experiences with nivolumab also focuses on elderly patients,<sup>12, 23</sup> the ORR was similar among patients aged  $< 65$ ,  $65$ – $< 75$  and  $\geq 75$  years (18%, 18% and 19%, respectively) with a similar safety profile for each age group. However, the median OS was shorter in patients aged  $\geq 75$  years (8.6 months, 8.0 months and 5.8 months, respectively).<sup>12</sup> In non-squamous cells, the ORR and OS were comparable between patients aged  $\geq 75$  years and the overall population (ORR: 25% and 18%; Median OS: 12.0 and 11.3 months), with similar safety profiles.<sup>23</sup> Considering that non-squamous cells were accounted for in the main population in patients aged  $\geq 75$  years in this study, the results of the Italian EAP real-life experiences were similar to the results of this study. Other real-world studies in patients of different ethnicities have also shown the value of nivolumab in treating elderly patients with NSCLC. In an Israeli study of nivolumab in advanced NSCLC,<sup>24</sup> the median OS and PFS for the whole population were 5.9 and 2.8 months, and there was no significant difference in OS between patients older than 75 years and those younger than 75 years. In a French study of patients aged  $\geq 70$  years with NSCLC treated with nivolumab (median age 75.2 years), the median OS and PFS were 7.1 and 3.3 months, respectively.<sup>25</sup> Taken together, our data, and those of other real-world studies indicate that there are no significant differences in the effectiveness of nivolumab between patients aged  $< 75$  and  $\geq 75$  years, and that nivolumab treatment should be considered in all appropriate patients with NSCLC, regardless of age.

In general, the safety profile of nivolumab was favourable and no new safety concerns were observed in either age group. This is consistent with the data in the literature and the safety data of the 2-year outcomes of CheckMate 017 and CheckMate 057.<sup>26</sup> Most of the irAEs observed were similar to those previously reported; the majority recovered or improved, regardless of patient age, and were manageable. Of note, the most frequent grade  $\geq 3$  AE was interstitial lung disease in both age groups, which indicates that interstitial lung disease must be cautiously monitored in NSCLC treatment with nivolumab. This result is similar to that reported in a real-world data study of elderly patients with NSCLC treated with nivolumab in which the frequency of irAEs was similar in both older and younger patients.<sup>25</sup>

As might be expected, in the subgroup analysis of effectiveness, response to nivolumab treatment among patients aged  $\geq 75$  years was associated with ECOG PS; these results are in line with those previously reported for the overall population.<sup>18</sup> This finding suggests that nivolumab treatment should be based on patient ECOG PS and not age. A previous publication has suggested that PS 2 and symptomatic brain metastases are factors associated with poor

**Table 3** Summary of AEs and irAEs by age group

	All patients (n=901)	<75 years (n=723)	≥75 years (n=178)
AE reported, n (%)	601 (66.7)	487 (67.4)	114 (64.0)
AE of grade 3 or 4, n (%)	261 (29.0)	211 (29.2)	50 (28.1)
Discontinuation due to AE, n (%)	135 (15.0)	111 (15.4)	24 (13.5)
irAE reported, n (%)	413 (45.8)	335 (46.3)	78 (43.8)
irAE category, n (%)			
Endocrine disorders	76 (8.4)	66 (9.1)	10 (5.6)
Skin toxicity	151 (16.8)	114 (15.8)	37 (20.8)
Pulmonary toxicity	94 (10.4)	82 (11.3)	12 (6.7)
Liver toxicity	46 (5.1)	36 (5.0)	10 (5.6)
Gastrointestinal toxicity	98 (10.9)	81 (11.2)	17 (9.6)
Nervous system disorders	22 (2.4)	21 (2.9)	1 (0.6)
Renal toxicity	20 (2.2)	17 (2.4)	3 (1.7)

AEs, adverse events; irAEs, immune-related adverse events.

response to nivolumab.<sup>27</sup> In addition, real-life data from patients with NSCLC treated with nivolumab in Israel,<sup>24</sup> and clinical trial data from the Checkmate 153 study,<sup>28</sup> have both reported that PS $\geq$ 2 was associated with poor prognosis.

Serum albumin is a well-known indicator of nutritional status among patients with cancer.<sup>29–31</sup> Poor nutrition in patients with cancer can lead to poor quality of life and activities of daily living. Moreover, a low serum albumin level was found to be an independent poor prognostic factor in patients with advanced NSCLC, and it was associated with reduced response rates and reduced survival time.<sup>32</sup> In our study, although serum albumin levels were significantly lower in patients aged  $\geq$ 75 years ( $p=0.0300$ ), there was no correlation between serum albumin and nivolumab effectiveness in elderly patients, suggesting that nivolumab activity may not be affected by serum albumin levels in elderly patients.

In this study, BMI was correlated with response to nivolumab treatment in patients aged  $\geq$ 75 years, but BMI and response were not correlated in patients aged <75 years. Patients aged  $\geq$ 75 years with a median BMI of 22.3 kg/m<sup>2</sup> and a range from normal (21.5 kg/m<sup>2</sup>) to overweight (23.6 kg/m<sup>2</sup>) according to the Japanese guidelines,<sup>33</sup> were more likely to respond (ie, achieve a best overall response of CR or PR) to nivolumab treatment compared with younger patients in the present study. This finding is consistent with the results of recent studies showing that patients with cancer and with low BMI have poor treatment outcomes compared with patients with high BMI.<sup>34</sup> Specifically, in patients with metastatic NSCLC treated with nivolumab and pembrolizumab, low BMI was associated with shorter OS and high BMI, with longer OS.<sup>35</sup> Another retrospective study on patients with NSCLC, melanoma, renal cell carcinoma and other cancers who were being treated with pembrolizumab, nivolumab or atezolizumab reported that in univariate

and multivariate analyses, the median OS and PFS were significantly longer in overweight/obese patients.<sup>36</sup>

We acknowledge that the present study has several limitations which must be considered when evaluating the data. These include the retrospective design and the fact that a review of medical records is subject to data variability from site to site or incompleteness of the clinical data recorded. Similarly, the retrospective design limits the collection of safety data, and it may be more difficult to determine which AEs may have been linked to study treatment. Finally, differences in PD-L1 expression or presence/type of epidermal growth factor receptor mutations may influence treatment efficacy.

## Conclusions

Based on Japanese real-world data, the safety and effectiveness of nivolumab were confirmed regardless of age (<75 or  $\geq$ 75 years). PS was a factor influencing outcomes in patients aged  $\geq$ 75 years, with worse PS associated with worsening outcomes. Effectiveness in patients aged  $\geq$ 80 years was similar to that in patients aged <75 years. No new safety concerns were observed in either age group.

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