

# Elderly Subset Analysis of Randomized Phase III Study Comparing Pemetrexed Plus Carboplatin with Docetaxel Plus Carboplatin as First-Line Treatment for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer

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## Abstract

**Background** Many physicians consider platinum-doublet chemotherapy inappropriate for elderly patients, regardless of their medical fitness.

**Objective** This was a retrospective subgroup analysis of data from a multicenter, randomized, phase III clinical trial evaluating pemetrexed + carboplatin versus docetaxel + carboplatin in elderly chemo-naïve patients with advanced, nonsquamous non-small cell lung cancer (NSCLC).

**Methods** Data from elderly patients (aged  $\geq 65$  years and  $\geq 70$  years) were evaluated using the same statistical methods as those used in patients aged  $< 70$  years and qualified intent-to-treat (Q-ITT) populations. The primary objective of the clinical trial was comparison of pemetrexed + carboplatin with docetaxel + carboplatin in terms of survival without grade 3 or 4 toxicity in chemo-naïve NSCLC patients.

**Results** The  $\geq 65$ - and  $\geq 70$ -year age groups had 68 and 37 patients, respectively. Among patients aged  $\geq 65$  years, the adjusted hazard ratio (HR) for survival without grade 3–4 toxicity (HR 0.40, 95 % confidence interval [CI] 0.23–0.70) favored pemetrexed + carboplatin; this was similar to the HRs in patients aged  $\geq 70$  years (HR 0.43, 95 % CI 0.20–0.92), patients aged  $< 70$  years (HR 0.44, 95 % CI 0.32–0.62), and the Q-ITT population (HR 0.45, 95 % CI 0.34–0.61). The median values for overall survival (OS) and progression-free survival (PFS) were similar across all age-group subsets and the Q-ITT population. The HRs for OS and PFS were similar for all age-group subsets, except for the  $\geq 70$ -year age group, which favored pemetrexed + carboplatin to a greater extent. The toxicity profile was similar across age groups, with the exception of diarrhea, mucosal inflammation, and grade 3–4 neutropenia and leukopenia, which were slightly more common in elderly patients in both treatment arms. Between-arm differences in the toxicity profiles for the  $\geq 65$ -,  $\geq 70$ - and  $< 70$ -year age subgroups were similar to those in the Q-ITT population. There were no on-study deaths or unexpected toxicities.

**Conclusion** The benefits of pemetrexed + carboplatin were maintained, and toxicity was manageable in both elderly subgroups. The favorable risk–benefit profile of pemetrexed + carboplatin makes it an appropriate first-line treatment option for elderly patients with advanced nonsquamous NSCLC.

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## 1 Introduction

Lung cancer predominantly affects the elderly; the median age of patients with non-small cell lung cancer (NSCLC) is 71 years [1]. Platinum-based doublets are the cornerstone

of treatment for advanced NSCLC patients with a good performance status. Although these produce a survival benefit in elderly patients, only 30 % receive this treatment, often because of physician concerns regarding anticipated age-related toxicity.

To mitigate toxicity, alternative agents have been incorporated into platinum-based backbones. Pemetrexed has been incorporated into first-line doublets [2–4], and carboplatin has been used instead of cisplatin [5, 6]. In a phase III trial, pemetrexed + carboplatin had a more favorable risk–benefit ratio than docetaxel + carboplatin [2]. This exploratory analysis evaluated the efficacy and safety of pemetrexed + carboplatin in elderly patients.

## 2 Patient and Methods

This was a retrospective subset analysis of a phase III trial comparing pemetrexed + carboplatin and docetaxel + carboplatin as first-line treatment in advanced nonsquamous NSCLC [2]. Data from elderly patients were evaluated in separate analyses (of patients aged  $\geq 65$  and  $\geq 70$  years) from the analyses of 20- to  $<70$ -year-old patients (i.e. patients aged  $<70$  years).

Patients were administered the study drugs in an intravenous infusion on day 1 of each 21-day cycle, up to a maximum of six cycles. Pemetrexed ( $500 \text{ mg/m}^2$ ) or docetaxel ( $75 \text{ mg/m}^2$ ), and carboplatin (area under the curve:  $5 \text{ mg/mL} \times \text{min}$ ) were administered. Patients in the pemetrexed + carboplatin group were supplemented with at least five daily doses of oral folic acid ( $350\text{--}1,000 \mu\text{g}$  once daily) within 7 days of the first dose of pemetrexed and were required to take daily folic acid supplements for 21 days following treatment; an intramuscular injection of vitamin B<sub>12</sub> ( $1,000 \mu\text{g}$ ) was given within 7 days of the first dose of pemetrexed and once every three cycles thereafter; and oral dexamethasone ( $4 \text{ mg}$  twice daily) was required the day before, the day of, and the day after administration of pemetrexed [2]. Patients in the docetaxel + carboplatin group received supplementation with oral dexamethasone ( $8 \text{ mg}$  twice daily) the day before, the day of, and the day after administration of docetaxel.

Time-to-event endpoints were analyzed using Cox proportional hazard models adjusted for Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2), disease stage (IIIB versus IV), ethnicity (East Asian versus others), gender (male versus female), and smoking status (never versus ever). The between-arm tumor response and disease control rates were compared using multivariate logistic regression models adjusted for the same covariates. Toxicities were compared using Fisher's exact test.

## 3 Results

### 3.1 Study Population

The  $<70$ -,  $\geq 65$ -, and  $\geq 70$ -year age groups had 174, 68, and 37 patients, respectively, with median ages of 57.5, 70.3, and 73.1 years, respectively. Between-arm imbalances in the  $<70$ -,  $\geq 65$ -, and  $\geq 70$ -year age groups favored the docetaxel + carboplatin arm among women (pemetrexed + carboplatin 39.3, 28.6, and 41.2 %, respectively, versus docetaxel + carboplatin 51.8, 51.5, and 55.0 %, respectively) and never smokers (pemetrexed + carboplatin 34.8, 14.3, and 17.6 %, respectively, versus docetaxel + carboplatin 38.8, 33.3, and 40.0 %, respectively) [Table 1].

#### 3.1.1 Treatment Delivery

The six-cycle completion rates in the  $<70$ -,  $\geq 65$ -, and  $\geq 70$ -year age groups were as follows: pemetrexed + carboplatin 58.4, 57.1, and 52.9 %, respectively; docetaxel + carboplatin 44.7, 54.5, and 60.0 %, respectively. Among the qualified intent-to-treat (Q-ITT) population, the six-cycle completion rates were pemetrexed + carboplatin 57.5 % and docetaxel + carboplatin 47.6 % [2]. Dose reductions in the  $<70$ -,  $\geq 65$ -, and  $\geq 70$ -year age groups were experienced by 9.0, 2.9, and 5.9 % of pemetrexed + carboplatin-treated patients, respectively, and by 23.5, 39.4, and 40.0 % of docetaxel + carboplatin-treated patients, respectively; in the Q-ITT population, dose reductions were experienced by 8.5 % of pemetrexed + carboplatin-treated patients and by 26.7 % of docetaxel + carboplatin-treated patients [2]. All dose reductions were due to adverse events (AEs). The median relative dose intensities for pemetrexed + carboplatin in the  $<70$ -,  $\geq 65$ -, and  $\geq 70$ -year age groups were as follows: pemetrexed 95.0, 95.4, and 95.5 %, respectively; carboplatin 92.4, 94.6, and 94.1 %, respectively; and those for docetaxel + carboplatin were as follows: docetaxel 96.4, 89.7, and 89.1 %, respectively; carboplatin 89.9, 84.4, and 82.9 %, respectively. Among Q-ITT patients, the median relative dose intensities for pemetrexed + carboplatin were 95.3 % for pemetrexed and 92.7 % for carboplatin, and those for docetaxel + carboplatin were 95.0 % for docetaxel and 88.7 % for carboplatin [2].

### 3.2 Survival Without Toxicity

Survival without grade 3 or 4 toxicity was significantly improved in pemetrexed + carboplatin-treated patients in all age groups (Table 2). The adjusted hazard ratio (HR) for the  $<70$ -year age group (median 3.4 months for pemetrexed + carboplatin versus 0.7 months for



Table 2 Efficacy

Patient number	Q-ITT population		<70-year age group		≥65-year age group		≥70-year age group	
	Pemetrexed + carboplatin, N = 128	Docetaxel + carboplatin, N = 132	Pemetrexed + carboplatin, N = 89	Docetaxel + carboplatin, N = 85	Pemetrexed + carboplatin, N = 35	Docetaxel + carboplatin, N = 33	Pemetrexed + carboplatin, N = 17	Docetaxel + carboplatin, N = 20
SWT grade 3–4 [mo; median (95% CI)]	3.2 (2.1–3.7)	0.7 (0.5–1.2)	3.4 (2.3–4.6)	0.7 (0.5–1.2)	1.7 (1.1–2.6)	0.6 (0.4–1.2)	1.6 (0.8–3.0)	0.7 (0.4–1.6)
HR (95% CI) <sup>a</sup>	0.45 (0.34–0.61); p < 0.001		0.44 (0.32–0.62); p < 0.001		0.40 (0.23–0.70); p = 0.002 <sup>b</sup>		0.43 (0.20–0.92); p = 0.029	
SWT grade 4 [mo; median (95% CI)]	12.2 (8.4–14.9)	2.0 (1.6–3.8)	11.9 (8.0–14.9)	2.6 (1.6–4.5)	14.8 (6.1–19.3)	1.7 (0.6–2.7) <sup>b</sup>	14.8 (4.1–NA)	1.2 (0.5–10.1)
HR (95% CI) <sup>a</sup>	NR		0.54 (0.38–0.77); p < 0.001		0.34 (0.18–0.65); p < 0.001		0.19 (0.07–0.50); p ≤ 0.001	
SWT clinically important grade 3–4 [mo; median (95% CI)]	3.6 (3.0–8.0)	1.3 (1.1–1.9)	4.4 (3.2–8.6)	1.3 (1.1–2.0)	2.6 (1.5–9.2)	1.2 (0.5–1.7) <sup>b</sup>	2.9 (1.2–14.8)	0.9 (0.4–2.3)
HR (95% CI) <sup>a</sup>	NR		0.56 (0.40–0.78); p < 0.001		0.44 (0.25–0.77); p = 0.004		0.29 (0.13, 0.64); p = 0.002	
OS [mo; median (95% CI)]	14.9 (12.2–19.0)	14.7 (10.8–19.8)	14.8 (10.5–18.8)	14.9 (10.2–19.8)	15.1 (10.5–20.0)	17.9 <sup>b</sup> (10.1–23.1)	15.1 (6.6–NA)	12.6 (8.4–NA)
HR (95% CI) <sup>a</sup>	0.93 (0.66–1.32); p = 0.698		0.98 (0.67–1.42); p = 0.909		0.92 (0.48–1.77); p = 0.801		0.56 (0.20–1.53); p = 0.259	
PFS [mo; median (95% CI)]	5.8 (4.8–6.4)	6.0 (4.8–6.6)	5.8 (4.7–6.4)	6.0 (4.0–6.6)	6.9 (4.6–9.7)	7.3 <sup>b</sup> (4.9–9.4)	6.1 (3.0–14.8)	5.8 (4.4–11.2)
HR (95% CI) <sup>a</sup>	0.91 (0.67–1.23); p = 0.534		0.99 (0.71–1.39); p = 0.975		0.99 (0.55–1.76); p = 0.963		0.48 (0.19–1.21); p = 0.121	
DoR [mo; median (95% CI)]	5.5 (4.0–8.1)	5.4 (4.4–6.7)	4.7 (4.0–7.4)	5.0 (4.2–5.7)	8.8 (4.0–13.2)	7.1 (4.4–NA) <sup>c</sup>	10.3 (3.2–14.5)	9.0 (8.5–9.4)
HR (95% CI) <sup>a</sup>	0.83 (0.46–1.51); p = 0.549		0.86 (0.45–1.65); p = 0.658		1.57 (0.42–5.89); p = 0.502		0.00 (0.00–NA); p = 0.997	
ORR [% (95% CI)]	34.0 (25.0–43.8)	22.9 (15.2–32.1)	32.6 (23.0–43.3)	24.7 (16.0–35.3)	40.0 (23.9–57.9)	21.2 (9.0–38.9) <sup>b</sup>	41.2 (18.4–67.1)	15.0 (3.2–37.9)
OR (95% CI) <sup>a</sup>	1.68 (0.91–3.10); p = 0.095		1.46 (0.74–2.86); p = 0.273		2.15 (0.69–6.71); p = 0.189		4.27 (0.71–25.63); p = 0.113	
DCR [% (95% CI)]	74.5 (65.1–82.5)	64.8 (54.8–73.8)	76.4 (66.2–84.8)	63.5 (52.4–73.7)	71.4 (53.7–85.4)	63.6 (45.1–79.6)	64.7 (38.3–85.8)	70.0 (45.7–88.1)
OR (95% CI) <sup>a</sup>	1.68 (0.91–3.10); p = 0.095		1.91 (0.97–3.79); p = 0.063		1.33 (0.43–4.05); p = 0.619 <sup>b</sup>		0.88 (0.20–3.82); p = 0.860	

CI confidence interval, DCR disease control rate, DoR duration of response, ECOG Eastern Cooperative Oncology Group, HR hazard ratio, N population size, NA not assessable, NR not reported, OR odds ratio, ORR overall response rate, OS overall survival, PFS progression-free survival, Q-ITT qualified intent-to-treat population, SWT survival without toxicity

<sup>a</sup> HR or OR (pemetrexed + carboplatin versus docetaxel + carboplatin) adjusted for ECOG performance status (0 or 1 versus 2), disease stage (IIIB versus IV), ethnicity (East Asian versus others), gender (male versus female), smoking status (never versus ever)

<sup>b</sup> p value based on Wald's test at a 2-sided significance level of 0.05

<sup>c</sup> p value based on normal approximations for the difference between rates at a 2-sided significance level of 0.05

docetaxel + carboplatin; adjusted HR 0.44, 95 % confidence interval [CI] 0.32–0.62;  $p < 0.001$ ) was consistent with those in the  $\geq 65$ -year age group (median 1.7 months for pemetrexed + carboplatin versus 0.6 months for docetaxel + carboplatin; adjusted HR 0.40, 95 % CI 0.23–0.70;  $p = 0.002$ ), the  $\geq 70$ -year age group (median 1.6 months for pemetrexed + carboplatin versus 0.7 months for docetaxel + carboplatin; adjusted HR 0.43, 95 % CI 0.20–0.92;  $p = 0.029$ ) [Table 2] and the Q-ITT population [2]. Survival without grade 4 toxicity and survival without clinically important grade 3 or 4 toxicity were also significantly improved in the pemetrexed + carboplatin treatment arm for all age subgroups (Table 2). The magnitude of the HR change favoring pemetrexed + carboplatin was greater for the  $\geq 70$ -year age group than for the  $< 70$ -year age group with respect to survival without grade 4 toxicity and survival without clinically important grade 3 or 4 toxicity (Table 2).

### 3.3 Efficacy

Among elderly patients, there were no statistically significant between-treatment group differences in overall survival (OS) or progression-free survival (PFS) [Table 2]. The median values were similar across all age-group subsets. The HRs were similar for all age-group subsets except for the  $\geq 70$ -year age group, which favored pemetrexed + carboplatin to a greater extent (Table 2). The tumor response rate favored the pemetrexed + carboplatin arm across all age groups and, similarly to OS and PFS, the magnitude of benefit increased for the elderly subsets (Table 2).

### 3.4 Safety

Fewer PCb-treated patients experienced  $\geq 1$  drug-related Grade 3 or 4 treatment-emergent adverse event (TEAE) than DCb-treated patients ( $\geq 65/\geq 70$ ) (PCb, 54.3 %/58.8 %; DCb, 81.8 %/85.0 %;  $p = 0.020/p = 0.136$ ), but the proportions of patients experiencing  $\geq 1$  drug-related TEAE of any grade were similar ( $< 70/\geq 65/\geq 70$ ): (PCb, 79.8 %/88.6 %/82.4 %; DCb, 90.6 %/87.9 %/90.0 %;  $p = 0.056/p = 1.000/p = 0.644$ ). Discontinuations due to possibly drug-related serious AEs occurred in two  $\geq 65$ -year-old patients in each arm (pemetrexed + carboplatin: 1 anemia and 1 decreased platelet count; docetaxel + carboplatin: 2 febrile neutropenia) and in one  $\geq 70$ -year-old patient in each arm (pemetrexed + carboplatin: anemia; docetaxel + carboplatin: febrile neutropenia). Notably, there were no on-therapy deaths in either treatment arm in elderly patients, patients aged  $< 70$  years, or the Q-ITT population.

In patients aged  $\geq 65$  years, there were significantly lower incidences of all-grade drug-related neutropenia, leukopenia, febrile neutropenia, alopecia, and diarrhea in the pemetrexed + carboplatin arm than in the docetaxel + carboplatin arm (Table 3). Docetaxel + carboplatin-treated patients aged  $\geq 65$  years may be more likely to suffer febrile neutropenia than the docetaxel + carboplatin-treated Q-ITT population. Additionally, in patients aged  $\geq 65$  years, the incidences of grade 3 or 4 neutropenia, leukopenia, and febrile neutropenia were significantly lower in the pemetrexed + carboplatin arm.

In general, the between-arm trends and incidences of possibly drug-related treatment-emergent AEs were similar in patients aged  $\geq 65$  years and the Q-ITT population. There were some differences within the  $\geq 70$ -year age group, perhaps because of the small sample size. Nonetheless, regardless of treatment, elderly patients may be more likely to suffer diarrhea, constipation, abdominal pain (except in docetaxel + carboplatin-treated patients  $\geq 70$  years), and mucosal inflammation than patients aged  $< 70$  years and the Q-ITT population (Table 3).

A summary of dose reductions due to AEs in the safety population age-group subsets ( $< 70$  years,  $\geq 65$  years, and  $\geq 70$  years) demonstrated that significantly more patients in the docetaxel + carboplatin arm than in the pemetrexed + carboplatin arm had at least one dose reduction due to AEs: pemetrexed + carboplatin 9.0, 2.9, and 5.9 %, respectively; docetaxel + carboplatin 23.5, 39.4, and 40.0 %, respectively;  $p = 0.013, 0.001, \text{ and } 0.023$ , respectively). Notably, this difference was driven predominantly by neutropenia in the docetaxel + carboplatin arm, which led to at least one dose reduction due to an AE significantly more often in each of the age-group subsets: pemetrexed + carboplatin 2.2, 0.0, and 0.0 %, respectively; docetaxel + carboplatin 17.6, 24.2, and 25.0 %, respectively;  $p < 0.001, 0.002, \text{ and } 0.050$ , respectively).

### 3.5 Post-Discontinuation Anti-Cancer Therapy

Within the  $< 70$ -,  $\geq 65$ -, and  $\geq 70$ -year age-group subsets, 62.9, 40.0, and 17.6 % of pemetrexed + carboplatin-treated patients, respectively, and 48.2, 48.5, and 55.0 % of docetaxel + carboplatin-treated patients, respectively, received post-study therapy. Among the Q-ITT patients, 55.7 % of pemetrexed + carboplatin-treated patients and 49.5 % of docetaxel + carboplatin-treated patients received post-discontinuation therapy [2]. Within the  $< 70$ -,  $\geq 65$ -, and  $\geq 70$ -year age-group subsets, the most common post-discontinuation chemotherapeutic agent used in pemetrexed + carboplatin-treated patients was docetaxel (used in 23.6, 11.4, and 5.9 %, respectively), and in docetaxel + carboplatin-treated patients it was pemetrexed (14.1, 12.1, and 15.0 %, respectively). Within the  $< 70$ -

**Table 3** Frequency of drug-related treatment-emergent adverse events (all grades occurring in  $\geq 5\%$  of the whole study population and clinically important grade 3–4)<sup>a,b</sup>

	Q-ITT population			<70-year age group			≥65-year age group			≥70-year age group		
	Pemetrexed + carboplatin, N = 106	Docetaxel + carboplatin, N = 105	p value	Pemetrexed + carboplatin, N = 89	Docetaxel + carboplatin, N = 85	p value	Pemetrexed + carboplatin, N = 35	Docetaxel + carboplatin, N = 33	p value	Pemetrexed + carboplatin, N = 17	Docetaxel + carboplatin, N = 20	p value
<b>Hematological events [n (%)]</b>												
Neutropenia	42 (39.6)	76 (72.4)	<0.001	34 (38.2)	59 (69.4)	<0.001	16 (45.7)	26 (78.8)	0.006	8 (47.1)	17 (85.0)	0.032
Grade 3–4 neutropenia <sup>c</sup>	35 (33.0)	68 (64.8)	<0.001	27 (30.3)	52 (61.2)	<0.001	14 (40.0)	25 (75.8)	0.004	8 (47.1)	16 (80.0)	0.047
Leukopenia	32 (30.2)	56 (53.3)	<0.001	28 (31.5)	42 (49.4)	0.020	10 (28.6)	20 (60.6)	0.014	4 (23.5)	14 (70.0)	0.008
Grade 3–4 leukopenia <sup>c</sup>	17 (16.0)	42 (40.0)	<0.001	14 (15.7)	30 (35.3)	0.005	7 (20.0)	18 (54.5)	0.005	3 (17.6)	12 (60.0)	0.018
Anemia	33 (31.1)	16 (15.2)	0.009	29 (32.6)	11 (12.9)	0.002	9 (25.7)	6 (18.2)	0.563	4 (23.5)	5 (25.0)	1.000
Grade 3–4 anemia <sup>c</sup>	13 (12.3)	2 (1.9)	0.006	10 (11.2)	1 (1.2)	0.010	4 (11.4)	1 (3.0)	0.357	3 (17.6)	1 (5.0)	0.315
Lymphopenia	4 (3.8)	17 (16.2)	0.003	4 (4.5)	13 (15.3)	0.021	1 (2.9)	6 (18.2)	0.051	0 (0.0)	4 (20.0)	0.109
Thrombocytopenia	15 (14.2)	6 (5.7)	0.064	13 (14.6)	5 (5.9)	0.081	5 (14.3)	3 (9.1)	0.710	2 (11.8)	1 (5.0)	0.584
Grade 3–4 thrombocytopenia <sup>c</sup>	10 (9.4)	3 (2.9)	0.082	9 (10.1)	3 (3.5)	0.133	3 (8.6)	1 (3.0)	0.614	1 (5.9)	0 (0.0)	0.459
Febrile neutropenia	0 (0.0)	9 (8.6)	0.002	0 (0.0)	6 (7.1)	0.012	0 (0.0)	5 (15.2)	0.023	0 (0.0)	3 (15.0)	0.234
Grade 3–4 neutropenia <sup>c</sup>	0 (0.0)	9 (8.6)	0.002	0 (0.0)	6 (7.1)	0.012	0 (0.0)	5 (15.2)	0.023	0 (0.0)	3 (15.0)	0.234
<b>Nonhematological events [n (%)]</b>												
Nausea	40 (37.7)	34 (32.4)	0.471	33 (37.1)	28 (32.9)	0.634	14 (40.0)	11 (33.3)	0.621	7 (41.2)	6 (30.0)	0.512
Grade 3–4 nausea <sup>c</sup>	1 (0.9)	1 (1.0)	1.000	1 (1.1)	1 (1.2)	1.000	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Alopecia	9 (8.5)	45 (42.9)	<0.001	9 (10.1)	37 (43.5)	<0.001	2 (5.7)	15 (45.5)	<0.001	0 (0.0)	8 (40.0)	0.004
Decreased appetite	21 (19.8)	26 (24.8)	0.412	17 (19.1)	24 (28.2)	0.211	7 (20.0)	6 (18.2)	1.000	4 (23.5)	2 (10.0)	0.383
Vomiting	16 (15.1)	20 (19.0)	0.470	12 (13.5)	18 (21.2)	0.229	5 (14.3)	6 (18.2)	0.749	4 (23.5)	2 (10.0)	0.383
Grade 3–4 vomiting <sup>c</sup>	1 (0.9)	2 (1.9)	0.621	1 (1.1)	2 (2.4)	0.614	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Asthenia	16 (15.1)	19 (18.1)	0.584	14 (15.7)	19 (22.4)	0.334	5 (14.3)	4 (12.1)	1.000	2 (11.8)	0 (0.0)	0.204
Fatigue	12 (11.3)	17 (16.2)	0.325	9 (10.1)	12 (14.1)	0.489	5 (14.3)	6 (18.2)	0.749	3 (17.6)	5 (25.0)	0.701
Diarrhea	7 (6.6)	21 (20.0)	0.004	5 (5.6)	13 (15.3)	0.046	4 (11.4)	11 (33.3)	0.041	2 (11.8)	8 (40.0)	0.073
Grade 3–4 diarrhea <sup>c</sup>	1 (0.9)	4 (3.8)	0.212	1 (1.1)	1 (1.2)	1.000	1 (2.9)	3 (9.1)	0.349	0 (0.0)	3 (15.0)	0.234
Peripheral sensory neuropathy	6 (5.7)	12 (11.4)	0.148	5 (5.6)	11 (12.9)	0.118	2 (5.7)	4 (12.1)	0.421	1 (5.9)	1 (5.0)	1.000
Grade 3–4 peripheral sensory neuropathy <sup>c</sup>	2 (1.9)	1 (1.0)	1.000	2 (2.2)	1 (1.2)	1.000	1 (2.9)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	NA
Stomatitis	9 (8.5)	9 (8.6)	1.000	7 (7.9)	9 (10.6)	0.606	4 (11.4)	2 (6.1)	0.674	2 (11.8)	0 (0.0)	0.204
Grade 3–4 stomatitis <sup>c</sup>	1 (0.9)	0 (0.0)	1.000	1 (1.1)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Dysgeusia	7 (6.6)	11 (10.5)	0.336	6 (6.7)	8 (9.4)	0.585	2 (5.7)	3 (9.1)	0.668	1 (5.9)	3 (15.0)	0.609
Rash	8 (7.5)	7 (6.7)	1.000	7 (7.9)	7 (8.2)	1.000	2 (5.7)	2 (6.1)	1.000	1 (5.9)	0 (0.0)	0.459
Constipation	9 (8.5)	6 (5.7)	0.594	6 (6.7)	4 (4.7)	0.747	5 (14.3)	5 (15.2)	1.000	3 (17.6)	2 (10.0)	0.644
Abdominal pain	2 (1.9)	10 (9.5)	0.019	1 (1.1)	8 (9.4)	0.016	1 (2.9)	6 (18.2)	0.051	1 (5.9)	2 (10.0)	1.000
Mucosal inflammation	7 (6.6)	4 (3.8)	0.538	3 (3.4)	2 (2.4)	1.000	6 (17.1)	3 (9.1)	0.478	4 (23.5)	2 (10.0)	0.383

N population size, n number in group, NA not assessable, Q-ITT qualified intent-to-treat

<sup>a</sup> Considered by the investigator to be possibly related to the study treatment

<sup>b</sup> Classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

<sup>c</sup> Clinically important

$\geq 65$ -, and  $\geq 70$ -year age-group subsets, post-study epidermal growth factor receptor tyrosine kinase inhibitors were received by 22.5, 14.3, and 11.8 % of pemetrexed + carboplatin-treated patients, respectively, and by 28.2, 27.3, and 20.0 % of docetaxel + carboplatin-treated patients, respectively. Post-study radiotherapy was received by 21.3, 8.6, and 0.0 % of pemetrexed + carboplatin-treated patients, respectively, and by 22.4, 21.2, and 25.0 % of docetaxel + carboplatin-treated patients, respectively.

#### 4 Discussion and Conclusion

Retrospective studies suggest that elderly patients can receive a clinical benefit from platinum-based chemotherapy similar to that seen in younger patients; toxicity may be increased in this population but is still generally acceptable. Nevertheless, physicians still hesitate to use these regimens in elderly patients [7, 8]. Mortality rates for elderly patients with lung cancer have increased over the decades [9]. This could be partly related to lower chemotherapy usage in the elderly [10].

We performed a retrospective analysis of elderly patient subsets (aged  $\geq 65$  and  $\geq 70$  years) within a phase III trial evaluating pemetrexed + carboplatin and docetaxel + carboplatin in advanced nonsquamous NSCLC [2]. Elderly patients treated with pemetrexed + carboplatin tolerated slightly higher dose intensities and experienced fewer dose reductions than elderly patients treated with docetaxel + carboplatin. The benefits of pemetrexed + carboplatin were maintained in elderly patients with advanced NSCLC. As seen in the Q-ITT population and the  $< 70$ -year age group, elderly pemetrexed + carboplatin-treated patients experienced longer survival without toxicity than docetaxel + carboplatin-treated patients did. There were no statistically significant between-treatment arm differences in OS, PFS, or the response rate among elderly patients, among patients aged  $< 70$  years, and in the Q-ITT population; however, the response rate was numerically higher in pemetrexed + carboplatin-treated patients than in docetaxel + carboplatin-treated patients, and the between-arm response differences appeared greater in elderly patients than in the those aged  $< 70$  years and the Q-ITT population. This might be a reflection of greater variability due to the smaller number of patients in the  $\geq 70$ -year age group.

The retention of pemetrexed + carboplatin-related benefits in elderly patients is likely due to this regimen's favorable AE profile. Elderly patients treated with pemetrexed + carboplatin experienced lower rates of most hematological AEs (i.e., neutropenia, leukopenia, lymphopenia, febrile neutropenia) than elderly patients treated with docetaxel + carboplatin. Moreover, there were

reduced rates of alopecia and diarrhea among elderly patients treated with pemetrexed + carboplatin. In both arms, the AE trends in the elderly mostly mirrored those of the Q-ITT population and the  $< 70$ -year age group. Importantly, there were no unexpected AEs in either treatment arm, nor were there on-study deaths among elderly patients. The between-arm toxicity profile difference was consistent across all age-group subsets. There was a slight increase in selected toxicities (mucosal inflammation, diarrhea, neutropenia, and leukopenia) in the elderly age groups compared with the  $< 70$ -year age-group subset, regardless of the treatment arm. This may have contributed to the improved survival without grade 4 toxicity and survival without grade 3 or 4 clinically important toxicity differences observed with respect to the magnitude of the HR in favor of pemetrexed + carboplatin.

Subset analyses of pemetrexed registration trials showed that the benefit of pemetrexed is maintained in elderly advanced NSCLC patients without compromising tolerability [11, 12]. In elderly first-line NSCLC patients treated with pemetrexed + cisplatin, the rates of neutropenia, thrombocytopenia, and febrile neutropenia appeared to increase with age [11]. However, in all age groups, the  $< 70$ -year age group, the  $\geq 65$ -year age group, and  $\geq 70$ -year age group in our trial, the rates of neutropenia (39.6, 38.2, 45.7, and 47.1 %, respectively), thrombocytopenia (14.2, 14.6, 14.3, and 11.8 %, respectively), and febrile neutropenia (0, 0, 0, and 0 %, respectively) were approximately the same in pemetrexed-treated patients. Differences between trials could possibly be attributed to the use of carboplatin; however, this seems unlikely because carboplatin is associated with lower rates of nausea, vomiting, and nephrotoxicity, but a higher rate of thrombocytopenia, relative to cisplatin [5, 6].

In this exploratory analysis, defining  $\geq 65$  years as 'elderly' allowed for sufficient patient numbers to be included in the main subgroup. Further analysis of  $\geq 70$ -year-old patients showed efficacy and safety similar to those in  $\geq 65$ -year-old patients, but the former was limited by a small population size, yielding more variable results. Our study underscores that NSCLC patients, regardless of age, benefit from appropriate treatment [13], and supports the idea that treatment selection in the elderly should not be based solely on chronological age.

This exploratory analysis suggests that the outcomes of elderly patients with nonsquamous NSCLC are consistent with those in the  $< 70$ -year age group and the Q-ITT population with respect to dose intensity, efficacy, and tolerability. Therefore, with few limitations, elderly patients with advanced nonsquamous NSCLC and good performance status should be treated similarly to younger patients. We and others have shown that platinum-based doublet therapy is a tolerable, viable option for elderly

advanced NSCLC patients [11, 12, 14]. However, our conclusions are hypothesis generating, as this retrospective analysis had a small sample size and unbalanced between-arm patient characteristics. The limitations of retrospective elderly patient studies include potential differences between chronological age and medical fitness, elderly population heterogeneity, arbitrary age cut-offs, and age-associated co-morbidities. Our selection criteria of fit elderly patients may not have been applicable to the general elderly population. Therefore, a prospective clinical trial involving a carefully controlled group of elderly patients is warranted.

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