Meta-Analysis of First-Line Pemetrexed Plus Platinum Treatment in Compared to Other Platinum-Based Doublet Regimens in Elderly East Asian Patients With Advanced Nonsquamous Non–Small-Cell Lung Cancer

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Abstract

We performed a meta-analysis with maximum individual patient data from three phase 3 trials with data available for an elderly East Asian population to compare therapy with a pemetrexed plus platinum doublet with other platinum-based doublets as first-line treatment for nonsquamous non–small-cell lung cancer patients. Consistent with all-age East Asians, better tumor response and tolerability supports a preference for pemetrexed/platinum in elderly East Asians.

Background: Pemetrexed plus platinum has become a standard of care in first-line treatment for patients with advanced nonsquamous non–small-cell lung cancer. However, elderly lung cancer patients are generally understudied and undertreated in clinical practice in East Asia because of safety concerns. This analysis aimed to provide a picture of the clinical benefit of pemetrexed/platinum in the first-line setting for elderly (age $\geq$ 65 years) East Asian patients. **Patients and Methods:** Individual patient data from 3 randomized controlled phase 3 trials that enrolled East Asian patients were analyzed in this meta-analysis. **Results:** In elderly East Asian patients (63 in the pemetrexed/platinum group and 42 in the control group), pemetrexed/platinum treatment achieved more benefits compared to other platinum-based doublets, including better overall response rate (32.8% vs. 7.5%), favorable progression-free survival (not statistically significant in adjusted hazard ratio), and significantly longer (3.15 vs. 1.54 months) survival without drug-related grade 3/4 toxicity. Overall survival was numerically prolonged (16.33 vs. 13.77 months; not statistically significant). These benefit trends were similar to those in all-age East Asian patients. In elderly East Asians, pemetrexed/platinum treatment was also associated with a lower incidence rate of drug-related grade 3/4 adverse events. The adverse event profile was similar to that in all-age East Asians. There were no unexpected adverse events. **Conclusion:** Pemetrexed/platinum had good efficacy and also resulted in better overall response and tolerability than other platinum-based doublets as first-line treatment in nonsquamous non–small cell lung cancer in elderly East Asians, which was consistent with data observed in all-age East Asians.

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Introduction

Platinum-based doublet chemotherapy has been widely studied and is currently recommended as a standard of care in the first-line treatment setting for advanced-stage (IIIB and IV) non–small-cell lung cancer (NSCLC) in patients with good performance status.[1] Nevertheless, there are few data about the elderly in clinical trials. This is partially due to the compromised physiological conditions elderly patients have, such as organ functions, drug pharmacokinetics, and comorbidity, which are often assumed to be medical challenges.[2] In these patients, clinicians worry about the potential toxicity of active treatment, thus relying instead on monochemotherapy or best supportive care in real-world practice.[3] According to Surveillance Epidemiology, and End Results (SEER) program data, from 2007 to 2011, the median age of newly diagnosed patients with lung cancer in the United States was 70 years, and elderly ($\geq$ 65 years) patients comprised 68.5% of new cases.[4] Demographics, which are currently shifting toward an older population, suggest that oncologists and clinicians will be seeing more elderly patients with lung cancer in the years to come.

NSCLC histology subtype is proved to be a predictive factor of survival after chemotherapy with pemetrexed.[5] A preplanned subset analyses of a global randomized phase 3 trial demonstrated superior overall survival (OS) and better safety profile in nonsquamous (NSq) NSCLC patients treated with pemetrexed/cisplatin as first-line treatment compared to those treated with gemcitabine/cisplatin (here referred to as the Scagliotti trial).[5,6] The East Asian subgroup analysis of the Scagliotti trial[7] and a subsequent Chinese bridging trial with an almost identical design (here referred to as the Wu trial)[8] both suggested similar efficacy and a similar safety benefit of pemetrexed/cisplatin—efficacy superior to that of gemcitabine/cisplatin in East Asian patients with advanced NSq NSCLC. Another multicenter randomized phase 3 trial with East Asian enrollment primarily compared pemetrexed/carboplatin versus docetaxel/carboplatin for survival without treatment-emergent grade 3/4 toxicity (SWT) (here referred to as the Rodrigues-Pereira trial).[9] It also demonstrated a favorable risk–benefit profile of pemetrexed/carboplatin for chemonaive patients with advanced NSq NSCLC. Nevertheless, the data of pemetrexed plus platinum treatment for East Asian patients from clinical trials are limited, let alone data for elderly East Asian patients.

Meta-analysis using individual patient data (IPD) is regarded as the reference standard for systematic review, especially when time-to-event outcomes are evaluated.[10] It extracts and then analyzes individual-level raw data from several similar trials. We sought to discover whether the efficacy and safety data of pemetrexed/platinum in elderly East Asians are consistent with those in all-age East Asians through a meta-analysis including all available IPD data of first-line pemetrexed-treated East Asian patients and of elderly East Asian patients.

Materials and Methods

Selection Criteria

Phase 3 clinical trials were selected on the basis of the following criteria: (1) randomized controlled design; (2) pemetrexed/platinum doublet in comparison with other third-generation cytotoxic drug plus platinum doublet in the first-line setting; (3) enrolled East Asian patients; and (4) IPD available.

Patients

Individual data of baseline characteristics, efficacy measurements, adverse events (AE), and drug exposure were extracted from the Lilly internal database. Key eligibility criteria for patient enrollment in these 3 trials included NSCLC patients who were chemonaive, had IIIB or IV disease, and had good performance status (Eastern Cooperative Oncology Group performance status 0 or 1 in the Scagliotti and Wu trials, 0 to 2 in the Rodrigues-Pereira trial). Only patients with histologic or cytologic NSq NSCLC were enrolled onto the Wu and Rodrigues-Pereira trials. Because histology was not distinguished in the Scagliotti study design, only those NSq NSCLC patients in the Scagliotti trial were included in this meta-analysis. The East Asian data sets pooled for this meta-analysis were defined as patients enrolled in China, Taiwan, and Korea. Elderly was defined as age $\geq$ 65 years.

Chemotherapy

Enrolled patients were randomized in a 1:1 ratio to receive either pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2, or gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2 (in the Scagliotti and Wu trials), then were randomized 1:1 to pemetrexed 500 mg/m^2 + area under the curve (AUC) 5 carboplatin or docetaxel 75 mg/m^2 + AUC 5 carboplatin (Rodrigues-Pereira trial). Treatment regimens were repeated every 3 weeks for a maximum of 6 cycles. Within each 21-day cycle, patients received gemcitabine on days 1 and 8, while they received pemetrexed, docetaxel, cisplatin, or carboplatin on day 1. Gemcitabine/cisplatin and docetaxel/carboplatin were considered control doublets (vs. pemetrexed/cisplatin or carboplatin) in this analysis.

Outcome Measures

OS was measured from randomization to patient death, and progression-free survival (PFS) was measured from randomization to progressive disease or death. Tumor response was assessed by the Response Evaluation Criteria in Solid Tumors version 1.0. Toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (version 2.0 in Scagliotti trial). AE considered possibly caused by the study drug in the opinion of the investigator were reported as drug related. Survival without toxicity was defined as the time measured from randomization to the first treatment-emergent grade 3/4 AE that occurred during the study or within 30 days after the last treatment dose or death, whichever occurred first. OS, PFS, and SWT were analyzed in the complete intention-to-treat population. Overall response rate (ORR) and disease control rate (DCR) were calculated in the tumor-response-qualified (TRQ) population. Drug exposure and AE were studied in the safety population.

Statistical Analysis

For each single study, the hazard ratio was estimated from multivariate Cox proportional hazard model with corresponding covariates. The random effect model was then applied to estimate the combined hazard ratio of time-to-event end points and the 95% confidence intervals (CI). The I^2 value was provided to quantify the

heterogeneity. Median survival was estimated by the Kaplan-Meier method based on the pooled IPD. Tumor response rate and DCR were also estimated from the pooled data. The Fisher exact test was applied to compare rates between treatment and control arms.

Results

Studies

Considering IPD, Lilly in-house databases were queried and searched in 2014. Only 3 trials—that of Scagliotti et al (2008),[6] Rodrigues-Pereira et al (2011),[9] and Wu et al (2014)[8]—met the criteria and were included.

Patient Demographic and Baseline Disease Characteristics

A total of 437 East Asian patients (93 from the Scagliotti trial, 256 from the Wu trial, and 88 from the Rodrigues-Pereira trial) were included in this meta-analysis as the combined intention-to-treat population, of which 217 patients were treated with pemetrexed/platinum and 220 with other platinum-based doublets (Table 1). Among the East Asian population, 105 were elderly (≥ 65 years; 63 in the pemetrexed/platinum group and 42 in the control group). Patient demographic and baseline disease characteristics for each of the 3 trials are listed in Table 1.

Drug Exposure and Dose Adjustment

In all-age East Asian patients, a median of 6 cycles was administered to both the pemetrexed/platinum and control groups (214 patients in each; safety population). The percentages of patients who completed 4 or 6 cycles were comparable between the treatment and control groups (Table 2). However, in elderly East Asians (63 in the pemetrexed/platinum group and 42 in the control group), the median number of cycles of pemetrexed/platinum treatment was consistently 6, whereas it was only 4 cycles in the control group. In the pemetrexed/platinum group, 58.7% of patients completed 6 cycles of therapy, while only 35.7% in the control group completed 6 cycles of therapy (Table 2). The proportion of patients with dose reduction during the treatment was also significantly smaller in the pemetrexed/platinum group than in the control group (all age: 4.2% vs. 36.0%, $P < .001$; elderly: 7.9% vs. 33.3%, $P = .002$) (Table 2). Those with dose delay had similar findings (Table 2). The percentages of mean dose (actual/planned) reflected dose intensity achieved and were consistently over 90% in the pemetrexed/platinum groups in all 3 trials (Supplemental Table 1 in the online version).

Efficacy

In the TRQ population of all-age East Asians (406 patients), patients in the pemetrexed/platinum group had a significantly higher ORR than patients in the control group (32.9% vs. 19.6%, $P = .003$). In elderly East Asian patients, the pemetrexed/platinum group also showed a significantly higher ORR than the control group (32.8% vs. 7.5%, $P = .003$). DCR was similar between 2 treatment groups in both all-age and elderly East Asian patients (Table 3).

Median PFS of East Asian patients was 5.88 months in the pemetrexed doublet group and 5.82 months in the control group (Table 3). The adjusted hazard ratio (HR, 0.81; 95% CI, 0.56-1.17) of PFS in East Asian patients did not show statistical significance, although numerically, the pemetrexed doublet treatment was favored over other platinum doublets (Figure 1). In elderly East Asian patients, the median PFS was 6.47 months in the pemetrexed doublet group and 6.24 months in the control group. The adjusted HR of PFS in elderly patients was 0.73 (95% CI, 0.37-1.42) (Table 3). The adjusted HR of PFS in East Asian or elderly East Asian patients from each single study is plotted in Figure 1.

The SWT of East Asian patients in the pemetrexed doublet group (median, 5.95 months) was longer than that of the control group (median, 1.81 months) (Table 3). The adjusted HR (0.50; 95% CI, 0.31-0.81) favored the pemetrexed doublet (Figure 2). Furthermore, the SWT of elderly East Asian in the pemetrexed doublet group (median, 3.15 months) was also longer than that of the control group (median, 1.54 months), with an adjusted HR of 0.55 (95% CI, 0.30-1.02) (Table 3). The adjusted HR values of SWT in East Asian or elderly East Asian patients from each single study are plotted in Figure 2.

OS of all-age East Asian patients in the pemetrexed doublet group (median, 19.02 months) did not differ from that of the control group (median, 16.56 months) (Table 3). The adjusted HR was 0.99 (95% CI, 0.77-1.25). The OS of elderly East Asian did not differ (median, 16.33 months in the pemetrexed doublet group vs. 13.77 months in the control group; adjusted HR, 0.92; 95% CI, 0.49-1.70) (Table 3).

Adverse Events

Numbers of patients with and frequencies of drug-related CTCAE grade 3/4 AE are listed (> 3% in either group) in Table 4. In elderly East Asians, the most common drug-related grade 3/4 toxicities included anemia, neutropenia, febrile neutropenia, leukopenia, thrombocytopenia, vomiting, and fatigue. Besides anemia, there was also more anorexia observed in the pemetrexed/platinum group. The frequencies of those toxicities in elderly patients were comparable to those in the all-age East Asian population (Table 4). In general, elderly patients in the pemetrexed/platinum group experienced fewer drug-related grade 3/4 laboratory toxicities (42.9% vs. 57.1%) and fewer nonlaboratory toxicities (9.5% vs. 16.7%) than those in the control group.

Fewer growth factors (G-CSF/GM-CSF) were used in pemetrexed/platinum-treated elderly East Asian patients as supportive therapies (pemetrexed/platinum vs. control, 9.5% vs. 26.2%). The use of other concomitant medications (analgesics, antibiotics, and erythropoiesis-stimulating agents) were similar between the 2 groups (data not shown).

Discussion

The definition of "elderly" may vary among regulatory authorities and clinical societies.[11-13] Although debated, ages of ≥ 65 or ≥ 70 are currently 2 commonly accepted cutoffs in clinical trials. To permit a sufficient patient sample size to reach meaningful conclusions, we used a 65-year cutoff. On the basis of IPD data from 3 randomized controlled phase 3 trials, this meta-analysis provides some hint of the clinical benefit of pemetrexed/platinum in elderly East Asian patients with advanced NSq NSCLC in the first-line setting by comparing with other platinum-based doublets. East Asian patients enrolled onto the 3 trials included in this

Table 1 Demographic and Baseline Characteristics of East Asian Patients With Advanced Nonsquamous Non–Small-Cell Lung Cancer

Characteristic	Scagliotti (2008)[6]		Wu (2014)[8]		Rodrigues-Pereira (2011)[9]		Total	
	Pem + Cis (n = 47)	Gem + Cis (n = 46)	Pem + Cis (n = 126)	Gem + Cis (n = 130)	Pem + Carbo (n = 44)	Doc + Carbo (n = 44)	Pem Doublet (n = 217)	Control (n = 220)
Median Age	61.0	57.3	57.3	55.9	58.5	55.9	58.1	56.5
≥65 years, n (%)	17 (36.2)	10 (21.7)	35 (27.8)	22 (16.9)	11 (25.0)	10 (22.7)	63 (29.0)	42 (19.1)
<65 years, n (%)	30 (63.8)	36 (78.3)	91 (72.2)	108 (83.1)	33 (75.0)	34 (77.3)	154 (71.0)	178 (80.9)
Gender, %								
Male	57.4	47.8	56.3	54.6	65.9	50.0	58.5	52.3
Female	42.6	52.2	43.7	45.4	34.1	50.0	41.5	47.7
Male (in ≥65 years)	58.8	50.0	62.9	50.0	81.8	40.0	65.1	47.6
Female (in ≥65 years)	41.2	50.0	37.1	50.0	18.2	60.0	34.9	52.4
ECOG PS, %								
0	36.2	39.1	26.2	20.8	40.9	25.0	31.3	25.5
1	63.8	60.9	73.8	79.2	59.1	65.9	68.7	72.7
2	0	0	0	0	0	9.1	0	1.8
0 (in ≥65 years)	23.5	20.0	20.0	18.2	45.5	30.0	25.4	21.4
1 (in ≥65 years)	76.5	80.0	80.0	81.8	54.5	50.0	74.6	73.8
2 (in ≥65 years)	0	0	0	0	0	20.0	0	4.8
Stage, %								
IIIB	25.5	13.0	15.1	15.4	9.1	27.3	16.1	17.3
IV	74.5	87.0	84.9	84.6	90.9	72.7	83.9	82.7
IIIB (in ≥65 years)	17.6	0	17.1	4.5	0	20.0	14.3	7.1
IV (in ≥65 years)	82.4	100.0	82.9	95.5	100.0	80.0	85.7	92.9
Smoking Status, %[a]								
Never	59.6	60.9	54.8	55.4	38.6	52.3	52.5	55.9
Ever	38.3	39.1	45.2	44.6	61.4	47.7	47.0	44.1
Never (in ≥65 years)	47.1	70.0	45.7	63.6	9.1	50.0	39.7	61.9
Ever (in ≥65 years)	52.9	30.0	54.3	36.4	90.9	50.0	60.3	38.1

Abbreviations: Carbo = carboplatin; Cis = cisplatin; Doc = docetaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; Gem = gemcitabine; Pem = pemetrexed.
[a]One patient aged < 65 years from Scagliotti study, Pem + Cis arm, had unknown smoking status.

meta-analysis displayed similar demographic and baseline disease characteristics (Table 1). This is likely because of the similarity of study designs and the key inclusion/exclusion criteria used in these trials.[6,8,9]

This analysis further confirms that an advantage in ORR was achieved in patients treated with pemetrexed/platinum. ORR in elderly East Asian patients treated with pemetrexed/platinum (32.8%) was close to that of the all-age East Asian patients (32.9%) but was markedly decreased in elderly patients treated with other doublet regimens (7.5%) compared to their all-age East Asian counterparts (19.6%) (Table 3). Taking into consideration that patients often obtain a clinically significant symptomatic alleviation

Table 2 Drug Exposure and Dose Adjustment

Characteristic	All-Age East Asian		Elderly (≥65 Years) East Asian	
	Pem Doublet (n = 214)	Control (n = 214)	Pem Doublet (n = 63)	Control (n = 42)
No. of Cycles Completed (Median %)	6.0	6.0	6.0	4.0
Four	78.5	72.0	73.0	64.3
Six	60.7	51.9	58.7	35.7
No. of cycles, mean	4.8	4.5	4.7	4.1
Patients with dose reduction, %	4.2	36.0	7.9	33.3
Patients with dose delay, %	75.2	71.5	73.0	66.7

Abbreviation: Pem = pemetrexed.

Table 3 Summary of Tumor Response and Efficacy Results[a]

Patient Population	All-Age East Asian		Elderly (≥65 Years) East Asian	
	Pemetrexed Doublet	Control	Pemetrexed Doublet	Control
TRQ, n	207	199	61	40
ORR				
%	32.9 (26.5-39.7)	19.6 (14.3-25.8)	32.8 (21.3-46.0)	7.5 (1.6-20.4)
P	.003		.003	
DCR				
%	79.2 (73.1-84.5)	76.4 (69.9-82.1)	82.0 (70.0-90.6)	70.0 (53.5-83.4)
P	.550		.225	
ITT, n	217	220	63	42
PFS				
Median, months	5.88 (5.55-6.47)	5.82 (5.55-6.31)	6.47 (5.03-6.87)	6.24 (5.26-7.49)
Adjusted HR	0.81 (0.56-1.17)		0.73 (0.37-1.42)	
SWT				
Median, months	5.95 (4.21-8.64)	1.81 (1.15-2.56)	3.15 (2.56-9.20)	1.54 (0.59-2.69)
Adjusted HR	0.50 (0.31-0.81)		0.55 (0.30-1.02)	
OS				
Median, months	19.02 (14.85-22.11)	16.56 (13.80-19.91)	16.33 (12.94-23.98)	13.77 (11.63-19.91)
Adjusted HR	0.99 (0.77-1.25)		0.92 (0.49-1.70)	

Abbreviations: DCR = disease control rate; HR = hazard ratio; ITT = intention to treat; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SWT = survival without toxicity; TRQ = tumor-response qualified.
[a]Data are provided as median (95% confidence interval). *P* values for tumor response are from Fisher exact test. Efficacy outcomes are estimated from random effect model.

from tumor shrinkage, elderly East Asians may benefit more from pemetrexed/platinum than from other platinum-based doublet regimens.

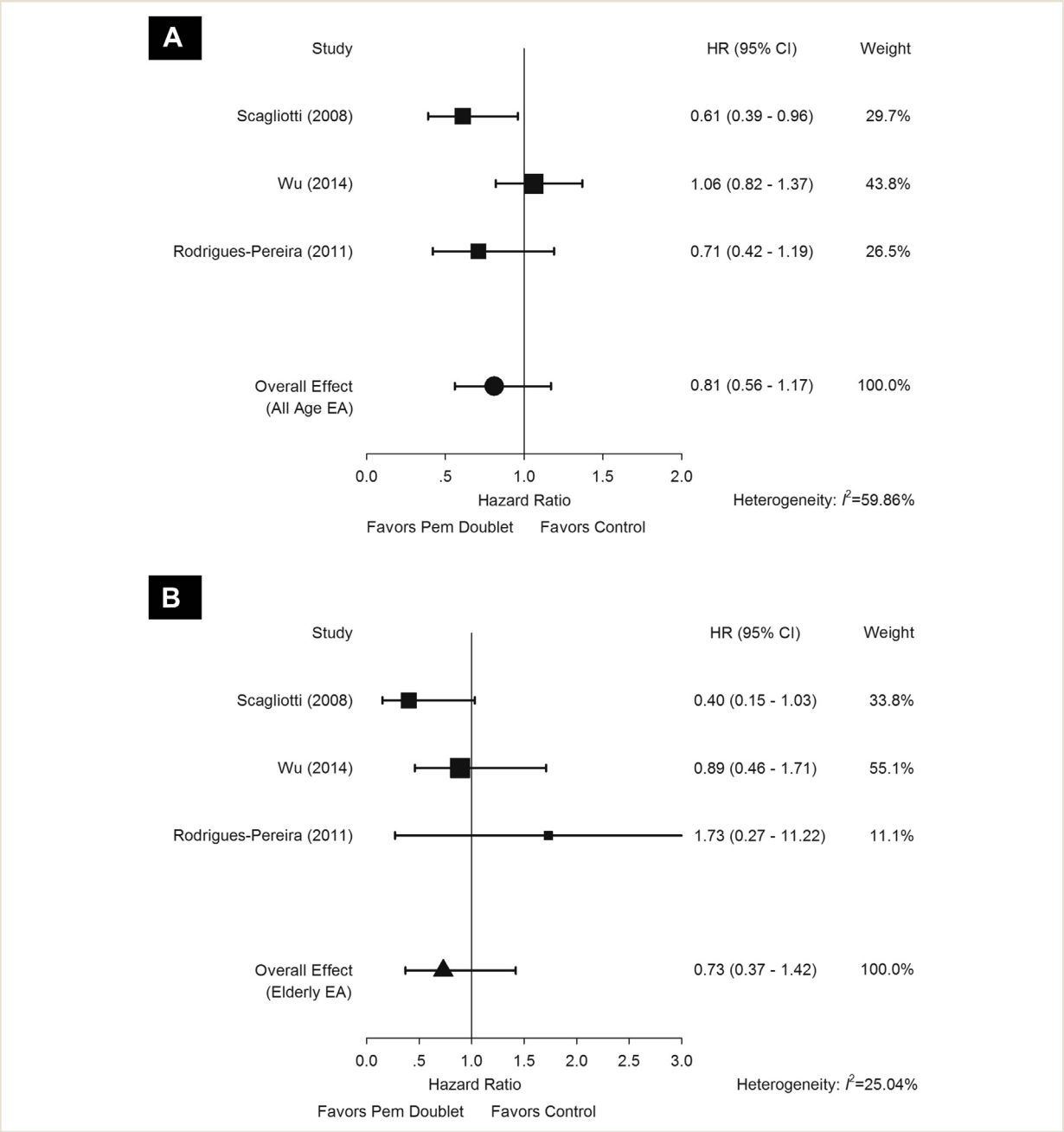
No statistical difference between treatments was observed in both survival outcomes (PFS and OS), though there was some indication in hazard ratios favoring pemetrexed/platinum over other platinum-based doublets in all-age and elderly East Asian patients (Figure 1, Table 3). These data showed a benefit HR trend in efficacy that is in line with the results previously reported in the entire NSq population of the Scagliotti trial: PFS, HR 0.90 (95% CI, 0.79-1.02), and OS, HR 0.81 (95% CI, 0.70-0.94).[5,6] The numerically prolonged median OS with pemetrexed/platinum treatment in both all-age and elderly East Asian patients was also consistent with other study reports.[14,15] No statistical significance between groups could be explained. First, given that the primary end point of the Rodrigues-Pereira trial was SWT,[9] the OS data from this trial were immature. Second, even though the maximum available IPD had been included, the total number of patients in this meta-analysis is still underpowered to detect any between-arm statistical difference in OS. Additionally, given the time frame of these 3 trials, some important factors such as *EGFR* mutation and *ALK* rearrangement status may not had been well balanced between treatment arms for the East Asian population in any of the 3 trials; this may be another confounding issue for our results.

This meta-analysis further demonstrated a longer SWT with an HR favoring pemetrexed/platinum in elderly East Asian patients as well as all-age East Asian patients (Figure 2, Table 3). Survival without grade 3/4 toxicity is a novel end point combining efficacy and safety outcomes. In special populations where less toxicity would be highly preferred, such as the elderly, this is reasonable and clinically relevant. This clinical risk–benefit outcome well characterized pemetrexed-based treatment for NSq NSCLC patients. Consistent results have been previously reported by other studies.[16-18]

As shown in Table 2, higher drug exposure was achieved with pemetrexed/platinum treatment in East Asian patients, including the elderly. In particular, elderly East Asian patients tolerated pemetrexed/platinum better than control subjects (median number of cycles, 6 vs. 4; dose reduction, 7.9% vs. 33.3%). This higher drug exposure could be explained by better efficacy and better toxicity profile of pemetrexed/platinum, which allowed better treatment compliance. Pemetrexed/platinum-treated elderly East Asians experienced lower rates of the most common grade 3/4 hematological AE, including neutropenia, leukopenia, lymphopenia, thrombocytopenia, and febrile neutropenia, than those treated with other platinum-based doublets (Table 4). Moreover, rates of vomiting and fatigue in pemetrexed/platinum-treated elderly East Asian patients were also reduced. The AE profile of the elderly East Asian patients is mostly similar to that of the all-age East Asian patients, and there was no unexpected AE in either treatment arm.

Although previous trials suggested that hematologic toxicity may be a primary concern when treating elderly patients, recent emerging evidence has suggested a treatment limitation in elderly NSCLC patients that must be considered.[19-23] The elderly could still benefit from chemotherapies and targeted therapies with acceptable toxicity.[3,24] A retrospective subpopulation analysis of elderly patients mostly consisting of non-Asians in the Scagliotti trial reported no significant compromise by aging in terms of consistent dose tolerance, OS benefit, and safety.[25] Similarly, benefits of pemetrexed/platinum were also maintained in the elderly

Figure 1 Adjusted Hazard Ratios of Progression Free Survival (PFS) for All-Age East Asians (A) and Elderly East Asians (B)

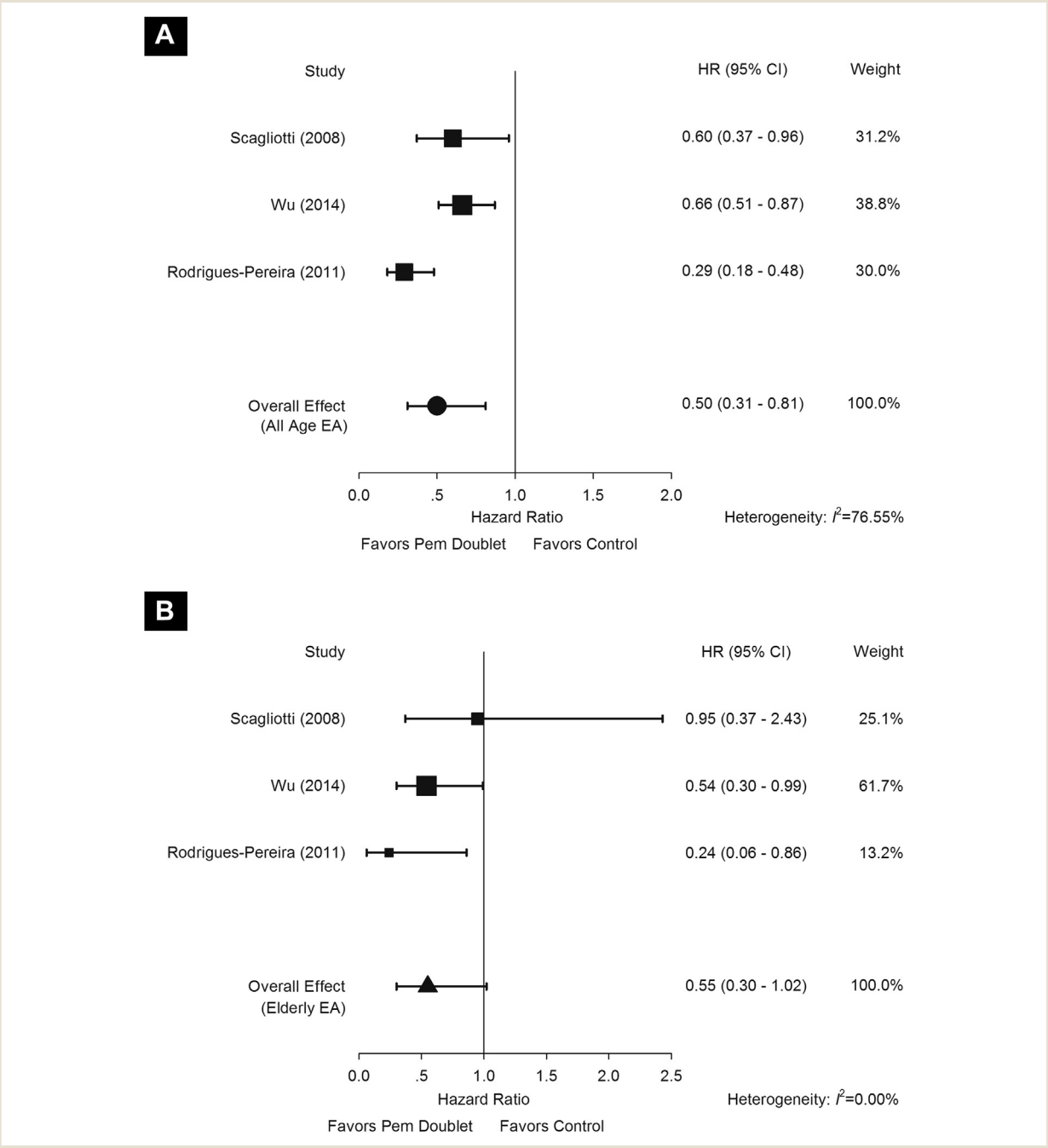


subpopulation of the Rodrigues-Pereira trial.[26] This meta-analysis demonstrated that the toxicities of pemetrexed/platinum in elderly East Asians were also manageable, reversible, and consistent with favorable safety profiles in previous studies.[15,25-27]

Conclusion

There are few data regarding pemetrexed-based doublet regimens as a first-line standard of care from clinical trials and in the literature about its use in elderly patients, East Asian patients, or both. To our knowledge, this is the first IPD meta-analysis and of the largest populations studied so far to compare pemetrexed/platinum with other platinum-based doublets in both East Asian and elderly East Asian patients with advanced NSq NSCLC. It showed superior ORR and SWT as well as better tolerability of pemetrexed/platinum than control doublets in elderly East Asian patients and in all-age East Asians. Hence, though with a few limitations, pemetrexed/platinum could be recommended as one of the standard-of-care options for elderly East Asians with advanced NSq NSCLC and

Figure 2 Adjusted Hazard Ratios of Survival Without Drug-Related Grade 3/4 Toxicity for All-Age East Asians (A) and Elderly East Asians (B)



good performance status. However, this meta-analysis is still underpowered for OS difference detection in either East Asians or elderly East Asians, and the survival data should be interpreted with caution. Considering the heterogeneity of the elderly population and the criteria applied in those trials, the selected population in this analysis may not fully represent the general elderly patients in clinical practice. Several prospective clinical trials with doublet or monochemotherapy in elderly patients including East Asians are ongoing.[28-30] In the future, clinical trials in elderly patients considering comprehensive geriatric assessment may be warranted.[31,32]

Clinical Practice Points

- Pemetrexed/platinum has become a standard of care in first-line treatment for patients with advanced NSq NSCLC in East Asia. However, elderly lung cancer patients are generally understudied

Table 4 Most Frequent (>3% in Either Group) Drug-Related Common Terminology Criteria for Adverse Event Grade 3/4 Toxicities

Characteristic	Grade 3/4 Toxicity, n (%), for:			
	All-Age East Asian		Elderly (≥65 Years) East Asian	
	Pemetrexed Doublet (n = 214)	Control (n = 214)	Pemetrexed Doublet (n = 63)	Control (n = 42)
Laboratory Toxicity				
Patients with any grade 3/4 laboratory toxicities	80 (37.4)	121 (56.5)	27 (42.9)	24 (57.1)
Neutropenia	63 (29.4)	91 (42.5)	24 (38.1)	18 (42.9)
Leukopenia	12 (5.6)	57 (26.6)	7 (11.1)	15 (35.7)
Anemia	10 (4.7)	14 (6.5)	7 (11.1)	3 (7.1)
Lymphopenia	6 (2.8)	13 (6.1)	1 (1.6)	3 (7.1)
Thrombocytopenia	5 (2.3)	18 (8.4)	3 (4.8)	3 (7.1)
Febrile neutropenia	0 (0.0)	7 (3.3)	0 (0.0)	3 (7.1)
Nonlaboratory Toxicities				
Patients with any grade 3/4 nonlaboratory toxicities	15 (7.0)	31 (14.5)	6 (9.5)	7 (16.7)
Vomiting	6 (2.8)	10 (4.7)	2 (3.2)	2 (4.8)
Fatigue	1 (0.5)	9 (4.2)	1 (1.6)	3 (7.1)
Anorexia	5 (2.3)	2 (0.9)	2 (3.2)	0 (0.0)

and undertreated in clinical practice because of safety concerns regarding the compromised physiologic conditions, such as organ functions, drug pharmacokinetics, and comorbidity, which are often assumed to be medical challenges.

- We performed a meta-analysis with maximum IPD from 3 randomized phase 3 trials by comparing pemetrexed/platinum doublet with other platinum-based doublets to provide clinical evidence of first-line treatment for elderly East Asian advanced NSq NSCLC patients.
- Better tumor response and tolerability, as well as a well-characterized clinical risk–benefit profile of the pemetrexed/platinum doublet, were seen compared to other platinum-based doublets in elderly East Asian patients, and findings were consistent with previous reports. However, survival outcome, especially OS, is still inconclusive because of some limitations of this analysis.
- This study supports the pemetrexed/platinum doublet as a standard-of-care option for elderly East Asians with advanced NSq NSCLC and good performance status.

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Supplemental Data

Supplemental table accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.cllc.2016.04.003.

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Supplemental Table 1 Dose Intensity Achieved

Regimen	Planned Mean Dose (Actual/Planned) (%) for:		
	Scagliotti (2008)[6]	Wu (2014)[8]	Rodrigues-Pereira (2011)[9]
Pemetrexed Doublet			
Pemetrexed	92.6	92.9	94.8
Cisplatin	92.6	92.6	—
Carboplatin	—	—	93.2
Control			
Gemcitabine	83.7	91.9	—
Docetaxel	—	—	88
Cisplatin	87.8	92.3	—
Carboplatin	—	—	83.8