Lung Cancer 135 (2019) 188–195

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1–positive advanced non–small-cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies

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ARTICLE INFO

Keywords:
Elderly
Pembrolizumab
Non–small-cell lung cancer
Chemotherapy
Pooled analysis
Phase 3

ABSTRACT

Objectives: Most lung cancer diagnoses occur in elderly patients, who are underrepresented in clinical trials. We present a pooled analysis of safety and efficacy in elderly patients (≥75 years) who received pembrolizumab (a programmed death 1 inhibitor) for advanced non–small-cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1)–positive tumors.

Methods: The pooled analysis included patients aged ≥18 years with advanced NSCLC with PD-L1–positive tumors from the KEYNOTE-010 (NCT01905657), KEYNOTE-024 (NCT02142738), and KEYNOTE-042 (NCT02220894) studies. In KEYNOTE-010, patients were randomized to pembrolizumab 2 or 10 mg/kg every 3 weeks (Q3W) or docetaxel, as second- or later-line therapy. In KEYNOTE-024 and KEYNOTE-042, patients were randomized to first-line pembrolizumab 200 mg Q3W or platinum-based chemotherapy. Overall survival (OS) was estimated by the Kaplan-Meier method, and safety data were summarized in elderly patients (≥75 years).

Results: The analysis included 264 elderly patients with PD-L1–positive tumors (PD-L1 tumor proportion score [TPS] ≥1%); among these, 132 had PD-L1 TPS ≥ 50%. Pembrolizumab improved OS among elderly patients with PD-L1 TPS ≥ 1% (hazard ratio [HR], 0.76 [95% CI, 0.56–1.02]) and PD-L1 TPS ≥ 50% (HR, 0.40 [95% CI, 0.25–0.64]). Pembrolizumab as first-line therapy also improved OS among elderly patients with PD-L1 TPS ≥ 50% (from KEYNOTE-024 and KEYNOTE-042) compared with chemotherapy (HR, 0.41 [95% CI, 0.23–0.73]). Pembrolizumab was associated with fewer treatment-related adverse events (AEs) in elderly

Abbreviations: AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance score; ESMO, European Society for Medical Oncology; HR, hazard ratio; JLCS, Japan Lung Cancer Society; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; TPS, tumor proportion score

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https://doi.org/10.1016/j.lungcan.2019.07.004
Received 6 May 2019; Received in revised form 3 July 2019; Accepted 6 July 2019

patients (overall, 68.5% vs 94.3%; grade ≥3, 24.2% vs 61.0%) versus chemotherapy. Immune-mediated AEs and infusion reactions were more common with pembrolizumab versus chemotherapy (overall, 24.8% vs 6.7%; grade 3–4: 9.4% vs 0%; no grade 5 events).

Conclusions: In this pooled analysis of elderly patients with advanced NSCLC with PD-L1–positive tumors, pembrolizumab improved OS versus chemotherapy, with a more favorable safety profile. Outcomes with pembrolizumab in patients ≥75 years were comparable to those in the overall populations in the individual studies.

1. Introduction

Lung cancer is the most common cancer worldwide and is responsible for more deaths than any other type of cancer [1]. More than half of lung cancer cases affect patients ≥65 years of age, and older patients have higher mortality compared with younger patients [2–4]. The high incidence of lung cancer among the elderly is reflective of the global rise in the aging population along with an age-associated increase in cancer incidence [1]. Despite this high incidence of lung cancer among the elderly, these patients are underrepresented in clinical trials for lung cancer drugs, with patients ≥75 years of age demonstrating the greatest disparity between cancer diagnosis (approximately 30% [in United States]) and clinical trial representation (approximately 10% [in United States]) [5–7]. While age itself is not an exclusion criterion, enrollment of elderly patients in clinical lung cancer trials may be limited because of their potentially reduced ability to withstand treatment, lower functional capacity (for example, in patients with Eastern Cooperative Oncology Group performance score [ECOG PS] ≥2 [8]), preexisting comorbidities, ongoing treatments that may be contraindicated, and potential differences in drug metabolism [9]. Additionally, there is a general perception that age-associated decline in the immune system, or immunosenescence, may alter the efficacy of immune-based therapies in older patients [10–12]. Thus, the limited enrollment of elderly patients in these trials and the lack of data specifically in this patient population restrict the development of evidence-based treatment recommendations in these patients.

Recently, immunotherapies have transformed the management of patients with non–small-cell lung cancer (NSCLC), which are generally associated with improved overall survival (OS), lower toxicity, and better quality of life compared with chemotherapy [13–16]. Current therapy recommendations for patients with advanced or metastatic NSCLC with ECOG PS 0–1 include treatment options with immune checkpoint inhibitors that target the programmed death 1 (PD-1) receptor or its ligands (PD-L1 and PD-L2), either as monotherapy or in combination with chemotherapy, with the specific regimen being determined by tumor histology, biomarker status, and other factors. However, there are limited evidence-based recommendations for the use of immunotherapies specifically in elderly patients (≥75 years of age) [13–17].

Pembrolizumab has shown efficacy as monotherapy in both patients with previously treated and treatment-naive advanced NSCLC. In the phase 2/3 randomized controlled KEYNOTE-010 study, patients with previously treated NSCLC with PD-L1–positive (PD-L1 tumor proportion score [TPS] ≥1%) tumors received pembrolizumab (2 mg/kg or 10 mg/kg) or docetaxel. OS was improved for all patients receiving pembrolizumab compared with docetaxel (pembrolizumab 2 mg/kg vs docetaxel: hazard ratio [HR], 0.71 [95% CI, 0.58–0.88], $P = 0.0008$; pembrolizumab 10 mg/kg vs docetaxel: HR, 0.61 [95% CI, 0.49–0.75], $P < 0.0001$). The OS benefit of pembrolizumab was also demonstrated among patients with PD–L1 TPS ≥50% (pembrolizumab 2 mg/kg vs docetaxel: HR, 0.54 [95% CI, 0.38–0.77], $P = 0.0002$; pembrolizumab 10 mg/kg vs docetaxel: HR, 0.50 [95% CI, 0.36–0.70], $P < 0.0001$) [18]. Pembrolizumab monotherapy as a first-line treatment option for patients with advanced NSCLC was established by the phase 3 KEYNOTE-024 study, which enrolled patients with previously untreated NSCLC with PD-L1 TPS ≥ 50% and without *EGFR/ALK* alterations [19]. OS was improved in patients who received pembrolizumab monotherapy compared with platinum-based chemotherapy (HR, 0.60 [95% CI, 0.41–0.89], $P = 0.005$). Pembrolizumab as first-line therapy for advanced NSCLC was further assessed in the phase 3 KEYNOTE-042 study, which was largely similar in design to KEYNOTE-024 but enrolled patients with PD-L1 TPS ≥1% [20]. Pembrolizumab improved OS in each of the prespecified PD-L1 TPS groups, ≥50%, ≥20%, and ≥1%, compared with platinum-based chemotherapy (HR [95% CI] by PD-L1 TPS cutoff: ≥50%, 0.69 [0.56–0.85], $P = 0.0003$; ≥20%, 0.77 [0.64–0.92], $P = 0.0020$; ≥1%, 0.81 [0.71–0.93], $P = 0.0018$). In all 3 studies (KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042), pembrolizumab monotherapy was associated with fewer treatment-related adverse events (AEs) compared with those who received chemotherapy (range, 63%–73% vs 81%–90%).

Here, we present a pooled analysis on the efficacy and safety of pembrolizumab monotherapy compared with chemotherapy in patients ≥75 years of age using data from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies.

2. Methods

To evaluate the efficacy and safety of pembrolizumab monotherapy in elderly patients (≥75 years), eligible patients were pooled from 3 large, open-label, randomized controlled trials (KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042), all of which enrolled patients ≥18 years of age with advanced, PD-L1–positive NSCLC. Eligible patients in all studies also had ECOG PS 0–1 and were without the following: unstable or untreated brain metastases or carcinomatous meningitis, active autoimmune disease requiring systemic steroids, interstitial lung disease, or history of pneumonitis requiring systemic steroids. Only KEYNOTE-010 allowed enrollment of patients with sensitizing *EGFR* mutations or *ALK* translocations whose disease progressed following treatment with a US FDA-approved tyrosine kinase inhibitor. In KEYNOTE-010, patients with previously treated advanced NSCLC with PD-L1 TPS ≥ 1% were randomized to receive pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks (Q3W) or docetaxel 75 mg/m^2 Q3W [18]. In KEYNOTE-024, patients with treatment-naive advanced NSCLC with PD-L1 TPS ≥ 50% were randomized to receive pembrolizumab 200 mg Q3W or investigator's choice of 1 of 5 platinum-chemotherapy regimens (carboplatin-pemetrexed, cisplatin-pemetrexed, carboplatin-gemcitabine, cisplatin-gemcitabine, or carboplatin-paclitaxel) [19]. In KEYNOTE-042, patients with treatment-naive locally advanced or metastatic NSCLC with PD-L1 TPS ≥ 1% were randomized to receive pembrolizumab 200 mg Q3W or investigator's choice of platinum-chemotherapy (carboplatin-paclitaxel or carboplatin-pemetrexed) [20]. In all 3 studies, treatment continued until 35 administrations of pembrolizumab, documented disease progression, intercurrent illness preventing administration, unacceptable toxicity, or study withdrawal. OS was a primary endpoint in KEYNOTE-010 and KEYNOTE-042 and was a secondary endpoint in KEYNOTE-024. Safety was a secondary endpoint in all 3 studies. AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Serious AEs included any event that resulted in death, was life-threatening, or resulted in significant disability/incapacity, prolonged inpatient hospitalization, or another important medical event (including a new cancer or an overdose). For each study,

PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) in formalin-fixed samples from a nonirradiated tumor, obtained at or after diagnosis of advanced or metastatic disease [18–20].

Data on patient demographics, efficacy, and safety were pooled by the following 2 age groups: ≥75 years or < 75 years. For the assessment of OS, HR was estimated using the Cox regression model with treatment as a covariate, and the Kaplan-Meier method was used to estimate the OS curves in a combined analysis for all 3 trials, and additionally in patients with PD-L1 TPS ≥ 50%. OS was also estimated for patients with PD-L1 TPS ≥ 50% who received pembrolizumab as first-line therapy in KEYNOTE-024 and KEYNOTE-042. Safety was assessed in a combined analysis of patients from all 3 trials who received ≥1 dose of the study drug; safety data were summarized for the pooled analysis. The data cutoff date was March 24, 2017 for KEYNOTE-010; May 9, 2016 for KEYNOTE-024; and February 26, 2018 for KEYNOTE-042.

3. Results

3.1. Patients

This pooled analysis included 264 elderly patients (≥75 years of age) with advanced NSCLC and PD-L1 TPS ≥ 1% from the intention-to-treat populations of KEYNOTE-010 (n = 90), KEYNOTE-024 (n = 45), and KEYNOTE-042 (n = 129), and 2348 patients of < 75 years of age (Table 1). Half of the patients in the elderly subgroup (50.0% [132/264]) had PD-L1 TPS ≥ 50%. The median age among elderly patients was 77.0 (range, 75–90) years, 173 (65.5%) were male, and 195 (73.9%) had ECOG PS of 1. The majority (65.2% [172/264]) had nonsquamous histology and 15 (5.7%) had stable brain metastases at baseline.

As of data cutoff, the median follow-up time was 11.7 (range, 0.3–36.0) months in the elderly population, and was 12.9 (range, 0.1–38.3) months in younger patients. Among elderly patients, median (range) treatment duration was 5.6 (0.03–34.8) months for pembrolizumab, and 3.5 (0.03–29.5) months for chemotherapy. Among younger patients, median (range) treatment duration was 4.3 (0.03–37.5) months for pembrolizumab and 3.5 (0.03–37.0) months for chemotherapy. Among 775 previously untreated patients whose disease progressed, 46.2% (18/39) of elderly patients in each treatment arm, and 60.9% (227/373) of younger patients in the pembrolizumab arm versus 54.6% (177/324) in the chemotherapy arm received subsequent therapy.

3.2. Efficacy assessments

In the pooled analysis of elderly patients with treatment-naive and previously treated NSCLC from all 3 studies, pembrolizumab improved OS for patients with PD-L1 TPS ≥ 1% (median OS [95% CI], months: pembrolizumab 15.7 [10.7–20.2], chemotherapy 11.7 [8.4–15.8]; HR, 0.76 [95% CI, 0.56–1.02]; Fig. 1A) and PD-L1 TPS ≥ 50% (median OS [95% CI], months: pembrolizumab 23.1 [11.9–not reached],

Table 1
Patient Demographics and Baseline Clinical Characteristics.

	Patients ≥75 Years of Age						Patients < 75 Years of Age					
	All		Pembrolizumab		Chemotherapy		All		Pembrolizumab		Chemotherapy	
	n = 264		n = 149		n = 115		n = 2348		n = 1332		n = 1016	
Age, years, median (range)	77.0	(75–90)	77.0	(75–90)	77.0	(75–90)	62.0	(20–74)	62.0	(20–74)	62.0	(31–74)
Sex												
Male	173	(65.5)	100	(67.1)	73	(63.5)	1550	(66.0)	867	(65.1)	683	(67.2)
Female	91	(34.5)	49	(32.9)	42	(36.5)	798	(34.0)	465	(34.9)	333	(32.8)
Race												
White	173	(65.5)	102	(68.5)	71	(61.7)	1635	(69.6)	917	(68.8)	718	(70.7)
Asian	61	(23.1)	30	(20.1)	31	(27.0)	578	(24.6)	329	(24.7)	249	(24.5)
Black or African American	12	(4.5)	7	(4.7)	5	(4.3)	43	(1.8)	26	(2.0)	17	(1.7)
Other	14	(5.3)	7	(4.7)	7	(6.1)	65	(2.8)	43	(3.2)	22	(2.2)
Missing	4	(1.5)	3	(2.0)	1	(0.9)	27	(1.1)	17	(1.3)	10	(1.0)
PD-L1 TPS												
≥1%	264	(100.0)	149	(100.0)	115	(100.0)	2348	(100.0)	1332	(100.0)	1016	(100.0)
≥50%	132	(50.0)	77	(51.7)	55	(47.8)	1214	(51.7)	666	(50.0)	548	(53.9)
ECOG performance score												
0	69	(26.1)	39	(26.2)	30	(26.1)	775	(33.0)	444	(33.3)	331	(32.6)
1	195	(73.9)	110	(73.8)	85	(73.9)	1565	(66.7)	883	(66.3)	682	(67.1)
Other	0		0		0		8	(0.3)	5	(0.4)	3	(0.3)
Histology												
Squamous	83	(31.4)	55	(36.9)	28	(24.3)	687	(29.3)	373	(28.0)	314	(30.9)
Nonsquamous	172	(65.2)	91	(61.1)	81	(70.4)	1585	(67.5)	914	(68.6)	671	(66.0)
Other	9	(3.4)	3	(2.0)	6	(5.2)	76	(3.2)	45	(3.4)	31	(3.1)
Smoking status												
Current	90	(34.1)	59	(39.6)	31	(27.0)	1080	(46.0)	665	(49.9)	415	(40.8)
Former	114	(43.2)	59	(39.6)	55	(47.8)	823	(35.1)	426	(32.0)	397	(39.1)
Never	59	(22.3)	31	(20.8)	28	(24.3)	437	(18.6)	239	(17.9)	198	(19.5)
Missing	1	(0.4)	0		1	(0.9)	8	(0.3)	2	(0.2)	6	(0.6)
Brain metastasis at baseline	15	(5.7)	8	(5.4)	7	(6.1)	235	(10.0)	149	(11.2)	86	(8.5)
Prior lines of therapy for advanced disease												
0	173	(65.5)	87	(58.4)	86	(74.8)	1403	(59.8)	702	(52.7)	701	(69.0)
1	69	(26.1)	47	(31.5)	22	(19.1)	665	(28.3)	447	(33.6)	218	(21.5)
2	19	(7.2)	13	(8.7)	6	(5.2)	193	(8.2)	124	(9.3)	69	(6.8)
≥3	3	(1.1)	2	(1.3)	1	(0.9)	87	(3.7)	59	(4.4)	28	(2.8)
Prior adjuvant therapy	7	(2.7)	6	(4.0)	1	(0.9)	96	(4.1)	64	(4.8)	32	(3.1)
Prior neoadjuvant therapy	3	(1.1)	3	(2.0)	0		26	(1.1)	14	(1.1)	12	(1.2)
Prior radiation therapy	45	(17.0)	36	(24.2)	9	(7.8)	576	(24.5)	344	(25.8)	232	(22.8)

Values are n (%) unless otherwise noted.
ECOG, Eastern Cooperative Oncology Group; TPS, tumor proportion score.

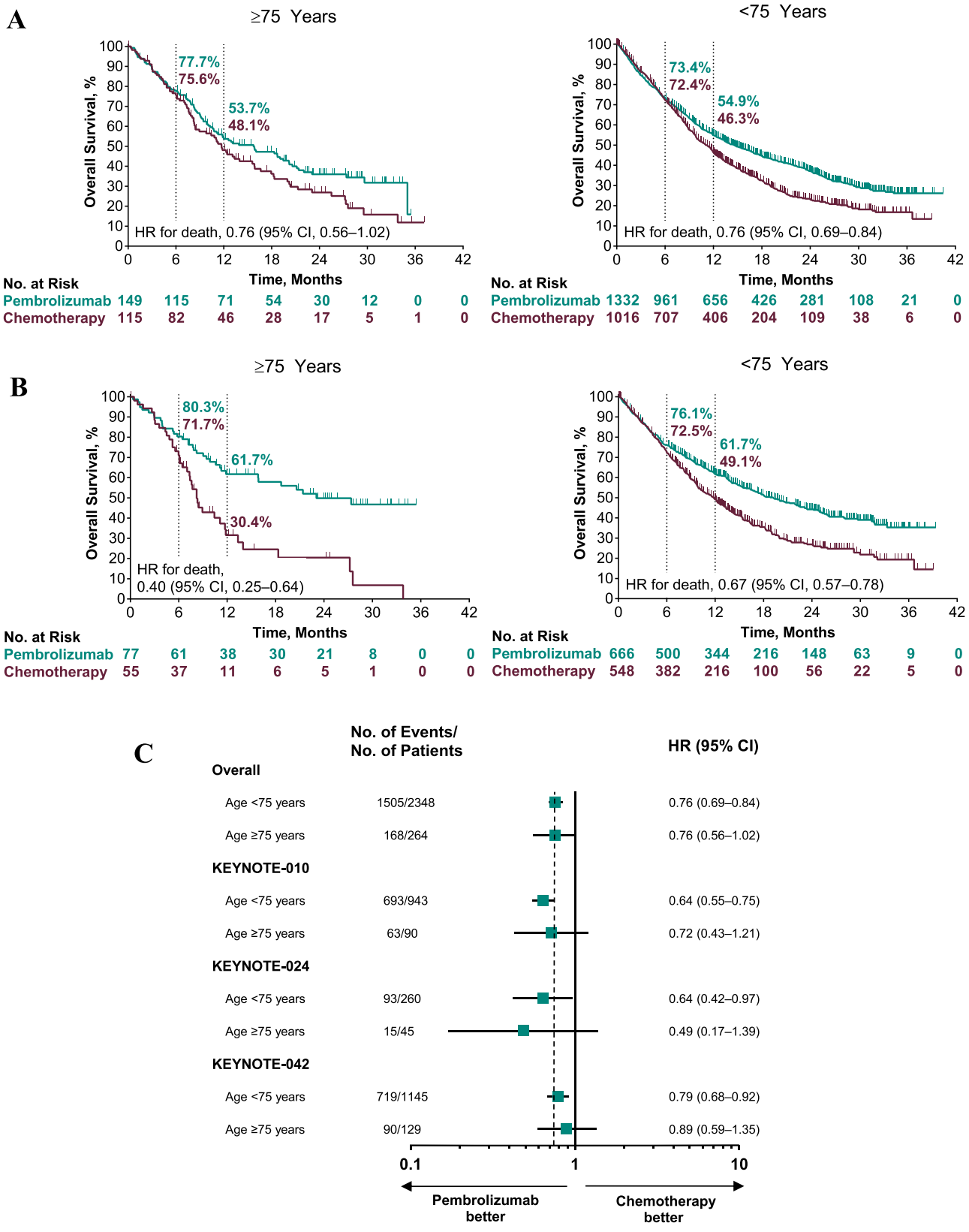

Fig. 1. Overall survival following treatment with pembrolizumab or chemotherapy by patient age (≥75 years or < 75 years) in the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 pooled analysis of patients with PD-L1 TPS ≥ 1% (A) or PD-L1 TPS ≥ 50% (B), and in an analysis of patients from each individual study (C). Patients in the intent-to-treat population of each study were included in these analyses. Vertical dotted lines represent 6- and 12-month survival rates in panels (A) and (B), and HR point estimates (0.76 for both elderly and younger patients) in the overall pooled population in panel (C). HR, hazard ratio; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

chemotherapy 8.3 [7.0–11.1]; HR, 0.40 [95% CI, 0.25–0.64]; Fig. 1B), compared with chemotherapy. OS was also improved for younger patients with PD-L1 TPS ≥ 1% (median OS [95% CI], months: pembrolizumab 14.6 (13.1–16.6), chemotherapy 11.1 (10.0–11.9); HR, 0.76 [95% CI, 0.69–0.84]) and PD-L1 TPS ≥ 50% (median OS [95% CI], months: pembrolizumab 19.2 (16.4–22.4), chemotherapy 11.9 (10.1–13.1); HR, 0.67 [95% CI, 0.57–0.78]) who received pembrolizumab monotherapy compared with chemotherapy (Fig. 1). In a further evaluation, the OS benefit of pembrolizumab versus chemotherapy was shown in both elderly and younger patients across each individual study, although confidence intervals were wide owing to smaller numbers of patients in some of the groups (Fig. 1C).

An additional pooled analysis of the 93 previously untreated elderly patients with a PD-L1 TPS ≥ 50% from KEYNOTE-024 (n = 45) and KEYNOTE-042 (n = 48) also showed improved OS with pembrolizumab compared with chemotherapy (median OS [95% CI], months: pembrolizumab 27.4 [10.6–not reached], chemotherapy 7.7 [6.1–11.1]; HR, 0.41 [95% CI, 0.23–0.73]; Fig. 2). Similar results were observed in younger patients with PD-L1 TPS ≥ 50% (median OS [95% CI], months: pembrolizumab 20.0 [16.7–25.1], chemotherapy 13.0 [11.3–15.4]; HR, 0.71, [95% CI, 0.59–0.87]; Fig. 2).

3.3. Safety assessments

The safety analyses for the pooled population of patients (PD-L1 TPS ≥ 1%) from all 3 studies included 254 elderly patients, of whom 149 received pembrolizumab and 105 received chemotherapy, and 2292 younger patients, of whom 1323 received pembrolizumab and 969 received chemotherapy (Table 2). Among elderly patients, the incidence of treatment-related AEs was lower in patients who received pembrolizumab (102 patients [68.5%]) compared with chemotherapy (99 patients [94.3%]). Fatigue was the most common treatment-related AE among elderly patients who received pembrolizumab (17.4%), followed by decreased appetite, and pruritus (12.8% each) (Table 2). Treatment with pembrolizumab compared with chemotherapy was also associated with fewer treatment-related AEs of grade ≥3 (24.2% vs 61.0%) and fewer serious treatment-related AEs (16.1% vs 26.7%). Treatment-related AEs that led to discontinuation occurred in 16 elderly patients in each treatment group (10.7% for pembrolizumab vs 15.2% for chemotherapy); most commonly due to pneumonitis (n = 6) and increased alanine aminotransferase (n = 2). Treatment-related AEs led to death in 2 elderly patients in each treatment group (1.3% for pembrolizumab vs 1.9% for chemotherapy). These trends were comparable for younger patients (Table 2).

Immune-mediated AEs and infusion reactions of special interest (regardless of attribution to study treatment or immune relatedness by the investigator) were more frequent with pembrolizumab than with chemotherapy but were reported with similar frequency among patients who received pembrolizumab, regardless of age (pembrolizumab: 24.8% in elderly patients, 25.0% in younger patients; chemotherapy: 6.7% in elderly patients, 5.9% in younger patients). The most common immune-mediated AEs and infusion reactions with pembrolizumab were hypothyroidism (elderly, 8.7% vs younger, 10.4%), pneumonitis (7.4% vs 6.8%), and hyperthyroidism (5.4% vs 5.7%; Table 2). Among these, grade 3 or 4 immune-mediated AEs and infusion reactions occurred in 14 elderly patients (9.4%) and 90 younger patients (6.8%), following treatment with pembrolizumab. There were no grade 5 immune-mediated AEs and infusion reactions in elderly patients following treatment with pembrolizumab or chemotherapy. In younger patients, 4 patients (0.3%) who received pembrolizumab died because of pneumonitis.

4. Discussion

In a pooled analysis of patients of ≥75 years of age with treatment-naive and previously treated advanced NSCLC with PD-L1–positive tumors from 3 randomized studies (KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042), pembrolizumab improved OS compared with chemotherapy. As observed in previous studies investigating pembrolizumab monotherapy in patients with advanced NSCLC [18,20,21], the magnitude of benefit with pembrolizumab increased with higher levels of PD-L1 expression. In particular, the HR for OS strongly favored pembrolizumab versus chemotherapy as first-line treatment for elderly patients with PD-L1 TPS ≥ 50% (HR, 0.41 [95% CI, 0.23–0.73]). This pooled analysis represents the largest dataset in elderly patients (≥75 years of age) with PD-L1–positive NSCLC who were able to meet the required study eligibility criteria to receive immunotherapy in a randomized study setting across many countries worldwide. Our data show that the improvements in OS in elderly patients with pembrolizumab compared with chemotherapy are consistent with the outcomes observed in the overall study populations [18–20].

Safety is an especially important consideration among elderly patients because of their potential drug tolerability concerns due to impaired renal function, cardiac or other comorbidities, declining organ function, and reduced cognitive function [22]. Prior reports have shown that the incidence of AEs such as leukopenia or fatigue, and the treatment discontinuation rate due to patient/physician choice or AEs is higher among patients with advanced NSCLC aged ≥70 years than in younger patients treated with platinum-based chemotherapy [23–25]. In our pooled analysis, pembrolizumab was associated with fewer treatment-related AEs compared with chemotherapy, including those of grade ≥3 severity. Additionally, comparatively fewer elderly patients

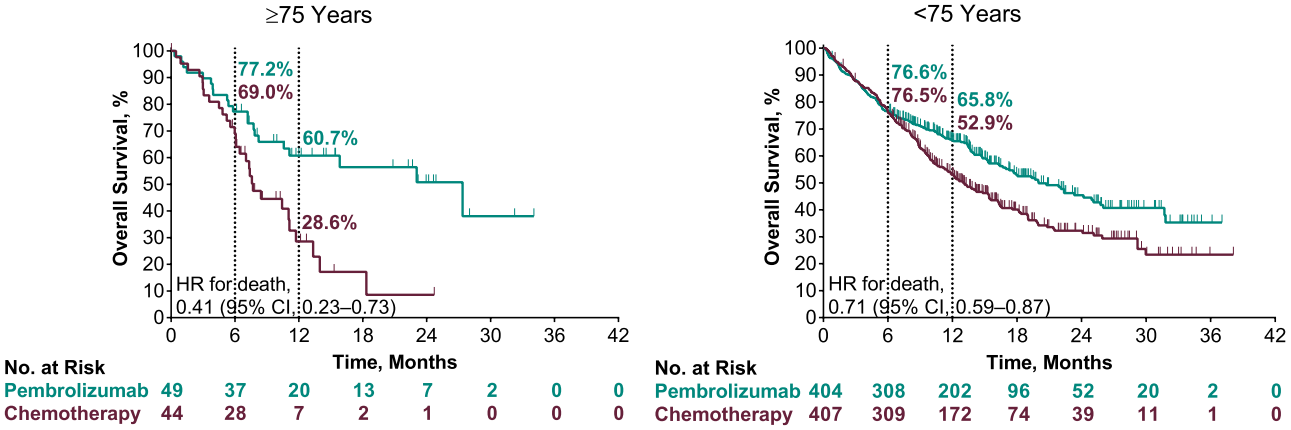

Fig. 2. Overall survival following first-line therapy with pembrolizumab or chemotherapy in the pooled analysis of patients with PD-L1 TPS ≥ 50% from the KEYNOTE-024 and KEYNOTE-042 studies (ITT population) by age (≥75 years or < 75 years). Vertical dotted lines represent 6- and 12-month survival rates. HR, hazard ratio; ITT, intent-to-treat; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

Table 2
Summary of AEs in a Pooled Analysis of Patients With PD-L1 TPS ≥ 1% Enrolled in the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 Studies by Age.

Patients With ≥1 Event, n (%)[a]	Pembrolizumab								Chemotherapy							
	Age ≥75 Years, n = 149				Age < 75 Years, n = 1323				Age ≥75 Years, n = 105				Age < 75 Years, n = 969			
	Any		Grade ≥3		Any		Grade ≥3		Any		Grade ≥3		Any		Grade ≥3	
Treatment-related AEs	**102**	**(68.5)**	**36**	**(24.2)**	**862**	**(65.2)**	**224**	**(16.9)**	**99**	**(94.3)**	**64**	**(61.0)**	**840**	**(86.7)**	**379**	**(39.1)**
Serious	24	(16.1)	20	(13.4)	170	(12.8)	137	(10.4)	28	(26.7)	25	(23.8)	136	(14.0)	130	(13.4)
Led to discontinuation	16	(10.7)	10	(6.7)	90	(6.8)	73	(5.5)	16	(15.2)	7	(6.7)	93	(9.6)	61	(6.3)
Led to death[b]	2	(1.3)	2	(1.3)	17	(1.3)	17	(1.3)	2	(1.9)	2	(1.9)	20	(2.1)	20	(2.1)
Occurring in > 10% of patients in any group																
Fatigue	26	(17.4)	3	(2.0)	140	(10.6)	13	(1.0)	34	(32.4)	4	(3.8)	187	(19.3)	20	(2.1)
Decreased appetite	19	(12.8)	1	(0.7)	119	(9.0)	9	(0.7)	33	(31.4)	0		165	(17.0)	16	(1.7)
Pruritus	19	(12.8)	1	(0.7)	106	(8.0)	3	(0.2)	3	(2.9)	0		21	(2.2)	1	(0.1)
Rash	18	(12.1)	2	(1.3)	119	(9.0)	4	(0.3)	5	(4.8)	0		39	(4.0)	0	
Nausea	14	(9.4)	1	(0.7)	103	(7.8)	2	(0.2)	31	(29.5)	0		263	(27.1)	11	(1.1)
Diarrhea	9	(6.0)	1	(0.7)	102	(7.7)	12	(0.9)	8	(7.6)	1	(1.0)	115	(11.9)	9	(0.9)
Anemia	7	(4.7)	1	(0.7)	62	(4.7)	11	(0.8)	48	(45.7)	17	(16.2)	290	(29.9)	98	(10.1)
Asthenia	4	(2.7)	1	(0.7)	73	(5.5)	6	(0.5)	14	(13.3)	1	(1.0)	92	(9.5)	17	(1.8)
Constipation	3	(2.0)	0		34	(2.6)	0		18	(17.1)	0		81	(8.4)	0	
Vomiting	3	(2.0)	0		43	(3.3)	2	(0.2)	14	(13.3)	0		137	(14.1)	5	(0.5)
Platelet count decreased	1	(0.7)	0		4	(0.3)	1	(0.1)	13	(12.4)	6	(5.7)	71	(7.3)	24	(2.5)
Thrombocytopenia	1	(0.7)	0		7	(0.5)	2	(0.2)	12	(11.4)	1	(1.0)	68	(7.0)	18	(1.9)
WBC count decreased	1	(0.7)	0		5	(0.4)	0		11	(10.5)	5	(4.8)	93	(9.6)	41	(4.2)
Alopecia	0		0		9	(0.7)	0		17	(16.2)	1	(1.0)	233	(24.0)	8	(0.8)
Neutropenia	0		0		8	(0.6)	1	(0.1)	21	(20.0)	12	(11.4)	145	(15.0)	92	(9.5)
Neutrophil count decreased	0		0		5	(0.4)	0		19	(18.1)	14	(13.3)	111	(11.5)	66	(6.8)
Immune-mediated AEs and infusion reactions	**37**	**(24.8)**	**14**	**(9.4)**	**331**	**(25.0)**	**94**	**(7.1)**	**7**	**(6.7)**	**0**		**57**	**(5.9)**	**13**	**(1.3)**
Hypothyroidism	13	(8.7)	0		138	(10.4)	1	(0.1)	3	(2.9)	0		10	(1.0)	0	
Pneumonitis	11	(7.4)	4	(2.7)	90	(6.8)	39	(2.9)	3	(2.9)	0		7	(0.7)	4	(0.4)
Hyperthyroidism	8	(5.4)	0		76	(5.7)	2	(0.2)	0		0		9	(0.9)	0	
Severe skin reactions	4	(2.7)	3	(2.0)	30	(2.3)	24	(1.8)	1	(1.0)	0		2	(0.2)	2	(0.2)
Hypophysitis	3	(2.0)	3	(2.0)	5	(0.4)	4	(0.3)	0		0		0		0	
Hepatitis	2	(1.3)	2	(1.3)	10	(0.8)	6	(0.5)	0		0		0		0	
Colitis	2	(1.3)	1	(0.7)	14	(1.1)	9	(0.7)	0		0		2	(0.2)	1	(0.1)
Adrenal insufficiency	2	(1.3)	1	(0.7)	8	(0.6)	2	(0.2)	0		0		1	(0.1)	0	
Myocarditis	1	(0.7)	1	(0.7)	0		0		0		0		0		0	
Infusion reactions	1	(0.7)	0		16	(1.2)	1	(0.1)	0		0		28	(2.9)	6	(0.6)
Thyroiditis	1	(0.7)	0		19	(1.4)	0		0		0		0		0	
Pancreatitis	1	(0.7)	0		6	(0.5)	4	(0.3)	0		0		0		0	
Myositis	0		0		6	(0.5)	0		0		0		1	(0.1)	0	
Nephritis	0		0		5	(0.4)	3	(0.2)	0		0		0		0	
Type 1 diabetes mellitus	0		0		4	(0.3)	4	(0.3)	0		0		0		0	

AE, adverse event; PD-L1, programmed death ligand 1; TPS, tumor proportion score; WBC, white blood cell.

[a] All patients as treated (those who received ≥1 dose of study drug).

[b] The treatment-related AEs leading to death among elderly patients were sepsis in 1 patient, and 1 death had an unspecified cause in the pembrolizumab group; and infection and pulmonary sepsis in 1 patient each in the chemotherapy group. Among younger patients, treatment-related AEs leading to death in the pembrolizumab group were pneumonitis in 4 patients, acute cardiac failure, myocardial infarction, ileus, *Klebsiella* infection, *Pneumocystis jirovecii* pneumonia, malignant neoplasm progression, encephalopathy, hemoptysis, pulmonary embolism, respiratory failure, and hypovolemic shock in 1 patient each; 2 of the deaths in this group had an unspecified cause. Treatment-related AEs leading to death in younger patients in the chemotherapy group were pneumonia in 4 patients, febrile neutropenia, pancytopenia, cardiac failure, acute cardiac failure, neutropenic sepsis, pulmonary sepsis, respiratory tract infection, septic shock, dehydration, ketoacidosis, dyspnea, interstitial lung disease, pulmonary alveolar hemorrhage, pulmonary embolism, and respiratory distress in 1 patient each; 1 death in this group had an unspecified cause.

discontinued pembrolizumab because of a treatment-related AE versus chemotherapy. As expected, given its mechanism of action, the incidence of immune-mediated AEs and infusion reactions was higher in patients who received pembrolizumab compared with chemotherapy; however, the incidence and types of AEs in elderly patients were similar to those observed in the overall study populations [18–20].

Since the data were analyzed post hoc, a potential limitation is that the analyses were retrospective and exploratory in nature. Our pooled analysis combined data from patients enrolled in 3 large randomized clinical trials, with some notable differences among these studies. For example, our pooled analysis included patients with treatment-naive and those with previously treated NSCLC, with PD-L1 TPS ≥ 1% or ≥50%. In an effort to account for these differences, we investigated outcomes in both TPS subgroups and conducted an additional analysis specifically in patients with PD-L1 TPS ≥ 50% who received pembrolizumab in the first-line setting to align the patient populations further. Importantly, the results from these analyses were similar to those observed for the overall pooled population and comparable with the individual study populations. The chemotherapy regimens also differed among the 3 studies, with KEYNOTE-010 investigating docetaxel 75 mg/m^2 Q3W in the comparator arm, KEYNOTE-024 investigating the inclusion of the investigator's choice of 1 of 5 platinum-based chemotherapies in the comparator arm, and KEYNOTE-042 investigating carboplatin plus paclitaxel or carboplatin plus pemetrexed in the comparator arm. However, OS was consistently longer and improved with pembrolizumab in each of these 3 studies irrespective of the comparator regimen, and the safety profiles were in line with expected AEs associated with individual drugs, with no new safety signals observed. Finally, randomization was not stratified by age in the individual studies that were included, and because of the generally low

rate of accrual of elderly patients in clinical trials, there was a large disparity in the total number of elderly patients in our pooled analysis compared with younger patients (≥75 years, n = 264; < 75 years, n = 2348). However, because this imbalance was prevalent across both the pembrolizumab and chemotherapy arms, we do not anticipate that this introduced a bias in our analyses. As discussed, the elderly patients included in this pooled analysis included those who met the inclusion criteria for each of the individual studies, which would have selected for a relatively fit elderly patient population. The results of this pooled analysis should therefore be considered in the context of patients ≥75 years of age with an ECOG PS 0–1 and without conditions or comorbidities that would have prevented study enrollment and should be confirmed in a real-world population of elderly patients.

While there is a general perception of immunosenescence in elderly patients [10,11], we found no evidence to support reduced efficacy in these patients since treatment with pembrolizumab was associated with improved OS compared with chemotherapy in all patients included in our analysis, regardless of age. Further, our pooled analyses of pembrolizumab monotherapy in elderly patients with advanced NSCLC is consistent with growing evidence that older patients can derive benefit from immunotherapy without additional toxicity compared with standard chemotherapy regimens [26–29]. A recent pooled analysis of anti–PD-(L)1 agents as second-line therapy for advanced or metastatic NSCLC showed that immune checkpoint inhibitors provided a survival benefit compared with docetaxel in patients across younger and older age groups (OS HR [95% CI]: all patients, 0.68 [0.63–0.76]; < 65 years, 0.71 [0.63–0.80]; > 65 years, 0.66 [0.57–0.76]; > 70 years, 0.67 [0.55–0.82]; and > 75 years, 0.81 [0.58–1.13]). Moreover, no additional toxicity was observed in older patients compared with younger patients. Interestingly, the incidence of treatment-related AEs was higher in the subgroup of patients aged < 65 years compared with those aged ≥75 years (grade 1–2, 88% vs 49%; grade 3–4, 47% vs 23%). The incidences of serious AEs, AEs leading to discontinuation, and the distribution of immune-mediated AEs were similar across the age groups [29]. In a separate retrospective study in 75 patients of ≥70 years of age with advanced NSCLC who received anti–PD-(L)1 agents, a lower ECOG PS (0–1 vs ≥2) was found to be the only covariate to predict OS and time to treatment failure of anti–PD-(L)1 therapy. Other covariates evaluated in the multivariate model were age (≥80 vs < 80), sex (male vs female), and line of therapy (first-line vs later) [30]. Consistent with our results, in a phase 3 study (OAK), atezolizumab (an anti–PD-L1 agent) was associated with longer OS in patients with previously treated NSCLC aged < 65 years (HR, 0.80 [95% CI, 0.64–1.00]) and those ≥65 years of age (HR, 0.66 [95% CI, 0.52–0.83]) compared with docetaxel [31].

5. Conclusion

In this pooled analysis of patients with PD-L1–positive advanced NSCLC enrolled in 3 large randomized controlled trials, pembrolizumab monotherapy improved OS compared with chemotherapy in patients of ≥75 years of age. Additionally, older age was not associated with increased toxicity with pembrolizumab therapy. Overall, the efficacy and safety outcomes observed in elderly patients were largely similar to the overall study populations in each of the 3 individual studies included in our pooled analysis. These findings should be confirmed in a real-world population with elderly patients.

Declaration of Competing Interest

K Nosaki: personal fees from AstraZeneca, Chugai Pharmaceutical, and Eli Lilly; grants and personal fees from MSD.

Y Hosomi: personal fees from AstraZeneca, Eli Lilly Japan, Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, and Bristol-Myers Squibb.

H Saka: Grants/research support from AstraZeneca, MSD, and Ono Pharmaceutical, and honoraria from AstraZeneca, MSD, Ono Pharmaceutical, Chugai Pharmaceutical, Boehringer Ingelheim, and KYORIN Pharmaceutical.

P Baas: grants from Bristol-Myers Squibb and MSD; consulting role for Bristol-Myers Squibb, MSD, Aldeyra Therapeutics, AstraZeneca, and Pfizer.

G. de Castro Jr: personal fees and/or honoraria for consulting, advisory boards, lectures, travel, and accommodation expenses from AstraZeneca, MSD, Bristol-Myers Squibb, Roche, and Pfizer.

M Reck: honoraria for lectures and consultancy from Amgen, Roche, Lilly, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, MSD, Merck, Novartis, Pfizer, and AbbVie.

Y-L Wu: grant to institute and speaker fees from AstraZeneca and Boehringer Ingelheim; speaker fees from Roche, Pfizer, MSD, Eli Lilly, and Bristol-Myers Squibb.

JR Brahmer: personal fees for advisory board participation from Merck during the conduct of this study; uncompensated advisory board participation for Bristol-Myers Squibb; personal fees for advisory board participation from AstraZeneca, and Genentech; advisory council participation for Amgen; consulting agreements with Celgene and Eli Lilly; and participated in advisory boards for Janssen and Syndax.

E Felip: personal fees for consulting, advisory role, and speakers bureau from Boehringer Ingelheim; personal fees for advisory role and speaker's bureau from AbbVie, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck KGaA, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda; personal fees for advisory role from Blueprint Medicines, Celgene, Guardant Health, Janssen, Medscape, and TouchTime.

Board independent member of Grifols.

T Sawada: employee of MSD K.K., Tokyo, Japan.

K Noguchi: employee of MSD K.K., Tokyo, Japan.

SR Han: employee of MSD K.K., Tokyo, Japan.

B Piperdi: employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and owns stock in the company.

D Kush: employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

G Lopes: research funding to the institution from Merck Sharp & Dohme, EMD Serono, AstraZeneca, Blueprint Medicines, Tesaro, Bavarian Nordic, Novartis, and G1 Therapeutics; honoraria from Merck, Bristol-Myers Squibb, and Boehringer Ingelheim; consulting or advisory role for Pfizer and AstraZeneca; travel, accommodations, and expenses from Boehringer Ingelheim, Pfizer, E.R. Squibb Sons, LLC, and Janssen; research grant/support from Merck, Bristol-Myers Squibb, and AstraZeneca.

Data sharing

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Acknowledgments

Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. We thank the patients and their families and caregivers for participating in the studies, along with all investigators and site personnel. Critical review of the final version of the manuscript was provided by Jonathan Cheng, MD, and additional statistical analysis support was provided by Yue Shentu, PhD, all of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD). Medical writing and editorial assistance was provided by Charlotte Majerczyk, PhD, of C4 MedSolutions, LLC (Yardley, PA, USA), a CHC Group company. This assistance was funded by MSD.

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