Pembrolizumab Plus Chemotherapy vs Chemotherapy in Asian Patients With PD-L1–Negative Advanced NSCLC: Pooled Analysis of KN021G, KN189, and KN407

Y. Cheng[1]; J.C.-H. Yang[2]; I. Okamoto[3]; L. Zhang[4]; J. Hu[5]; D. Wang[6]; C. Hu[7]; J. Zhou[8]; L. Wu[9]; L. Cao[10]; J. Liu[11]; H. Zhang[12]; H. Sun[13]; Z. Wang[14]; H. Gao[15]; Y. Yan[16]; S. Xiao[16]; J. Lin[17]; M.C. Pietanza[17]; T. Kurata[18]

[1]Department of Medical Oncology, Jilin Cancer Hospital, Chaoyang Borough, Changchun, China; [2]Department of Oncology, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Republic of China; [3]Kyushu University Hospital, Fukuoka, Japan; [4]Respiratory Medicine Department, Peking Union Medical College Hospital, Beijing, China; [5]Department of Pulmonary Medicine, Zhongshan Hospital Fudan University, Shanghai, China; [6]Department of Oncology, Chongqing Cancer Hospital, Chongqing, China; [7]Department of Respirology and Critical Care Medicine, Xiangya Hospital Central South University, Changsha, China; [8]Department of Respiratory Diseases, The First Affiliated Hospital of Zhejiang University, Hangzhou, China; [9]Department of Thoracic Medicine, Hunan Cancer Hospital, Changsha, China; [10]Department of Respiration, The First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital), Hefei, China; [11]Department of Oncology, The First Affiliated Hospital of Dalian Medical University, Dalian, China; [12]Department of Oncology, Tang Du Hospital, The Fourth Military Medical University, Xi'an, China; [13]Department of Oncology, The First Affiliated Hospital of Xi'An Jiaotong University, Xi'an, China; [14]Department of Thoracic Medical Oncology, Beijing Cancer Hospital, Beijing, China; [15]Department of Pulmonary Oncology, Affiliated Hospital of Academy of Military Medical Sciences, Beijing, China; [16]MSD China, Shanghai, China; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Department of Thoracic Oncology, Kansai Medical University Hospital, Osaka, Japan

Background

- Pembrolizumab plus platinum-based chemotherapy has shown improved overall survival (OS), progression-free survival (PFS), and ORR versus chemotherapy alone regardless of PD-L1 tumor proportion score (TPS) in patients with advanced non–small-cell lung cancer (NSCLC)[1-5]
- In an analysis of data pooled from 3 randomized studies, KEYNOTE-021 cohort G, KEYNOTE-189, and KEYNOTE-407, pembrolizumab plus chemotherapy improved OS (hazard ratio [HR], 0.63; 95% CI, 0.50–0.79), PFS (HR, 0.68; 95% CI, 0.56–0.83), PFS2 (HR, 0.57; 95% CI, 0.46–0.70), and ORR (50.0% vs 29.8%) versus chemotherapy alone in patients with PD-L1–negative (ie, TPS <1%) NSCLC[6]

Objectives

- Conduct an exploratory pooled analysis of pembrolizumab plus chemotherapy in East Asian patients with advanced or metastatic PD-L1–negative NSCLC enrolled in KEYNOTE-021 cohort G, KEYNOTE-189, KEYNOTE-189 Japan extension, KEYNOTE-407, and KEYNOTE-407 China extension
- Evaluate efficacy outcomes in East Asian patients with PD-L1–negative NSCLC in the pooled data set
- Evaluate safety outcomes in East Asian patients with PD-L1–negative NSCLC in the pooled data set

Methods

Study Design, Patients, and Treatment

Table 1. Study Designs for the Studies Included in the Pooled Data Set

Clinical Study	Study Design	Endpoints
KEYNOTE-021 cohort G[5] (NCT02039674) Phase 2	• Pembrolizumab 200 mg Q3W plus pemetrexed-carboplatin vs pemetrexed-carboplatin • 1:1 randomization • Previously untreated stage IIIB/IV nonsquamous NSCLC; no *EGFR/ALK* alteration	• Primary endpoint: ORR • Key secondary endpoint: PFS
KEYNOTE-189 (NCT02578680) and KEYNOTE-189 Japan extension (NCT03950674)[2,7] Phase 3	• Pembrolizumab 200 mg Q3W plus pemetrexed-platinum vs placebo plus pemetrexed-platinum • 2:1 randomization • Previously untreated stage IV nonsquamous NSCLC; no *EGFR/ALK* alteration	• Primary endpoints: OS and PFS • Key secondary endpoints: ORR, DOR, safety
KEYNOTE-407 (NCT02775435) and KEYNOTE-407 China Extension (NCT03875092)[1,8] Phase 3	• Pembrolizumab 200 mg Q3W plus carboplatin-paclitaxel/nab-paclitaxel vs placebo plus paclitaxel/nab-paclitaxel • 1:1 randomization • Previously untreated stage IV squamous NSCLC	• Primary endpoints: OS and PFS • Key secondary endpoints: ORR, DOR, safety

DOR, duration of response; Q3W, every 3 weeks.

Assessments

- PD-L1 expression was assessed centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA)
- Tumor response was assessed per RECIST version 1.1 by blinded independent central review
- Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (version 4.03 for KEYNOTE-407)

Analyses

- The current pooled analysis included patients from the studies of interest who enrolled in China, Japan, Korea, Thailand, and Taipei, Republic of China
- Efficacy was assessed in the pooled intention-to-treat population
- Safety was assessed in the pooled population of patients who received ≥1 dose of study treatment
- The Kaplan-Meier method was used to estimate OS, PFS, DOR, and PFS2
- HRs and 95% CIs for OS, PFS, and PFS2 were assessed using a stratified Cox regression model with the Efron's method of tie handling
- All analyses were descriptive only and not adjusted for multiplicity
- The database cutoff dates were August 19, 2019, for KEYNOTE-021G; August 28, 2020, for KEYNOTE-189 and KEYNOTE-189 Japan extension; and September 30, 2020, for KEYNOTE-407 and KEYNOTE-407 China extension

Results

Patients

- Median time from randomization to data cutoff for the pooled analysis was 33.4 (range, 25.3–49.2) months
- Of 1438 total patients enrolled in the 5 randomized studies, 107 (7.4%) were enrolled in East Asia, had PD-L1–negative NSCLC, and were included in this pooled analysis
- At data cutoff, 9 patients in the pembrolizumab plus chemotherapy group and 1 in the chemotherapy alone group had completed treatment
- 1 patient from each treatment group had ongoing treatment at data cutoff

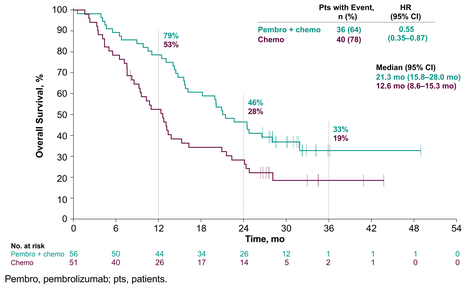
Table 2. Baseline Characteristics

Characteristic	Pembrolizumab + Chemotherapy n = 56	Chemotherapy Alone n = 51
Age, median (range), y	65.5 (31–87)	65.0 (43–82)
Men	47 (83.9)	47 (92.2)
ECOG PS 1	35 (62.5)	36 (70.6)
Current/former smoker	51 (91.1)	48 (94.1)
Squamous histology	40 (71.4)	44 (86.3)
Brain metastases	6 (10.7)	10 (19.6)

Values are presented as n (%) unless otherwise noted.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy

Figure 1. Overall Survival



Pembro, pembrolizumab; pts, patients.

Figure 2. Progression-Free Survival

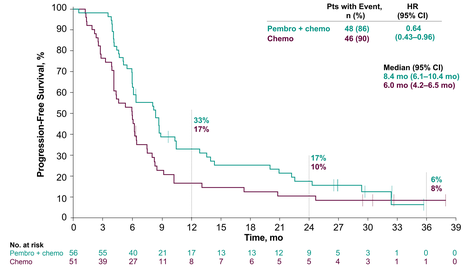
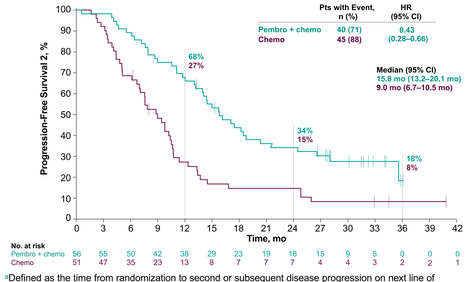


Figure 3. Progression-Free Survival 2 (PFS2)[a]



[a]Defined as the time from randomization to second or subsequent disease progression on next line of treatment or death from any cause.

Table 3. Tumor Response

	Pembrolizumab + Chemotherapy n = 56	Chemotherapy Alone n = 51
ORR (95% CI), %	71.4 (57.8–82.7)	43.1 (29.3–57.8)
Best overall response, n (%)		
CR	1 (1.8)	0
PR	39 (69.6)	22 (43.1)
SD	13 (23.2)	18 (35.3)
PD	0	8 (15.7)
NE[a]	3 (5.4)	2 (3.9)
NA[b]	0	1 (2.0)
DOR, median (range), mo	6.7 (2.1 to 34.5+)	4.9 (1.4+ to 36.6+)

CR, complete response; NE, not evaluable; NA, no assessment; PD, progressive disease; SD, stable disease. "+" indicates no PD by the time of last assessment.
[a]No postbaseline assessment available for response evaluation.
[b]Postbaseline assessment(s) available but NE (ie, all postbaseline assessment[s] NE or CR/PR/SD <6 weeks from randomization).

Safety

Table 4. Adverse Events

AEs, n (%)	Pembrolizumab + Chemotherapy n = 56	Chemotherapy Alone n = 51
All-cause AEs	56 (100.0)	51 (100.0)
Grade 3–5	45 (80.4)	42 (82.4)
Led to discontinuation	12 (21.4)	6 (11.8)
Led to death	3 (5.4)	2 (3.9)

Table 5. Immune-Mediated Adverse Events and Infusion Reactions

AE, n (%)	Pembrolizumab + Chemotherapy n = 56	Chemotherapy Alone n = 51
Any AE	22 (39.3)	4 (7.8)
Grade 3–5	6 (10.7)	2 (3.9)
Led to death	1 (1.8)[a]	0
Hyperthyroidism	6 (10.7)	0
Hypothyroidism	5 (8.9)	0
Infusion reactions	4 (7.1)	0
Pneumonitis	4 (7.1)	4 (7.8)
Adrenal insufficiency	2 (3.6)	0
Severe skin reactions	2 (3.6)	0
Thyroiditis	2 (3.6)	0
Colitis	1 (1.8)	0
Hepatitis	1 (1.8)	0
Hypophysitis	1 (1.8)	0
Type 1 diabetes mellitus	1 (1.8)	0

Events were included regardless of attribution to the study drug or immune relatedness by the investigator.
[a]Pneumonitis.

Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab

- Among 9 patients from the pembrolizumab plus chemotherapy group who completed 35 cycles of pembrolizumab:
  - All patients experienced PR and were alive at data cutoff
  - Median DOR was 31.1 (range, 9.1 to 34.5+) months

Outcomes in Patients Who Crossed Over to Pembrolizumab Monotherapy On-Study

- Among 18 patients who crossed over from the chemotherapy group to receive pembrolizumab monotherapy:
  - Median OS from the time of pembrolizumab initiation was 11.7 (95% CI, 6.0–18.9) months
  - Estimated 30-month OS rate was 25.0% (95% CI, 7.5%–47.6%)

Conclusions

- Pembrolizumab plus chemotherapy provided clinically meaningful benefit versus chemotherapy alone in this pooled analysis of East Asian patients with PD-L1–negative advanced or metastatic NSCLC
  - Pembrolizumab plus chemotherapy prolonged OS, PFS, and PFS2 versus chemotherapy alone
  - ORR was higher with pembrolizumab plus chemotherapy versus chemotherapy alone
- Pembrolizumab plus chemotherapy had manageable safety in these patients
- These results are consistent with the global phase 3 studies and support continued use of pembrolizumab plus chemotherapy as a standard of care therapy in patients with NSCLC without *EGFR/ALK* alterations, regardless of PD-L1 expression[1,2,6]

References

1. Paz-Ares L, et al. *N Engl J Med.* 2018;379(21):2040-2051.
2. Gandhi L, et al. *N Engl J Med.* 2018;378(22):2078-2092.
3. Borghaei H, et al. *J Thorac Oncol.* 2019;14(1):124-129.
4. Awad MM, et al. *J Thorac Oncol.* 2021;16(1):162-168.
5. Langer CJ, et al. *Lancet Oncol.* 2016;17(11):1497-1508.
6. Borghaei H, et al. *Cancer.* 2020;126(22):4867-4877.
7. Horinouchi H, et al. *Cancer Sci.* 2021;112(8):3255-3265.
8. Cheng Y, et al. *JTO Clin Res Rep.* 2021;2(10):100225.

Acknowledgments

The authors thank the patients and their families and all investigators and site personnel who participated in this study. This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing assistance was provided by Kathleen Estes, PhD, of ICON plc (North Wales, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Contact Information

Contact Ying Cheng at jl.cheng@163.com for questions or comments.

Slides https://bit.ly/3nTwRs6

Poster https://bit.ly/3mVFUw

Presented at the ESMO Immuno-Oncology Congress 2021; December 8–11, 2021; Geneva, Switzerland, and Virtually