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# 研究患者

Patients were eligible for enrollment if they were 18 years of age or older, had pathologically con- f irmed stage IV squamous NSCLC (as classif ied according to the seventh edition of the Cancer Stag- ing Manual of the American Joint Committee on Cancer12), had received no previous systemic therapy for metastatic disease, had an Eastern Co- operat ive Oncolog y Group (ECOG) performance- status score of 0 or 1 (on a 5-point scale, with higher scores indicat ing increasing disabilit y; a score of 0 indicates no symptoms, and 1 mild symptoms),13 had at least one measurable lesion according to version 1.

# 样本量

In this double-blind, phase 3 trial, we randomly assigned, in a 1:1 ratio, 559 patients with untreated metastat ic, squamous NSCLC to receive 200 mg of pembrolizumab or saline placebo for up to 35 cycles; all the pat ients also received carboplat in and either paclitaxel or nanoparticle albumin-bound [nab]–paclitaxel for the f irst 4 cy- cles.

# 基线特征

A total of 779 pat ients from 137 sites in 17 coun- tries were screened for randomizat ion (Fig. S2 in the Supplementary Appendix). Of the 561 patients who met all eligibilit y criteria, 2 were excluded from randomization because of a physician’s deci- sion. Between August 19, 2016, and December 28, 2017, the remaining 559 pat ients from 125 sites underwent randomizat ion; 278 pat ients were as- signed to the pembrolizumab-combination group and 281 to the placebo-combinat ion group. With respect to the stratif ication factors, a PD-L1 tumor proport ion score of 1% or greater was obser ved for 63.1% of patients, paclitaxel was the choice of taxane for 60.1% of pat ients, and East Asia was the region of enrollment for 19.0% of pat ients. Baseline demographic and disease characteristics were as expected for a trial involving patients with metastat ic, squamous NSCLC and were well bal- anced between groups (Table 1).

# 试验设计

pat ients with previously t reated non- sma ll-cell lung cancer (OAK): a phase 3, open-label, mult icent re randomised con- t rolled t ria l. Lancet 2017; 389: 255-65. 10. Lopes G, Wu Y-L, Kudaba I, et a l. Pem- brolizumab (pembro) versus plat inum- based chemotherapy (chemo) as f irst-line therapy for advanced/metastat ic NSCLC with a PD-L1 tumor proport ion score (TPS) ≥1%: open-label, phase 3 KEYNOTE-042 study. J Clin Oncol 2018; 36: Suppl: LBA4. abst ract. 11. Gandhi L, Rodríguez-Abreu D, Gadg- eel S, et a l. Pembrolizumab plus chemo- therapy in metastat ic non–sma ll-cell lung cancer. N Engl J Med 2018; 378: 2078-92. 12 . Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trot t i A, eds. AJCC cancer staging manua l. 7th ed. New York: Springer, 2010. 13. Oken MM, Creech RH, Tormey DC, et a l. Tox icit y and response criteria of the Eastern Cooperat ive Oncolog y Group. Am J Clin Oncol 1982; 5: 649-55. 14. Eisenhauer EA, Therasse P, Bogaerts J, et a l. New response eva luat ion criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47. 15. Roach C, Zhang N, Corigliano E, et a l. Development of a companion diagnost ic PD-L1 immunohistochemist r y assay for pembrolizumab therapy in non–small-cell lung cancer. Appl Immunohistochem Mol Morphol 2016; 24: 392-7. 16. Cut ica I, Vie GM, Pravet toni G. Per- sona lised medicine: the cognit ive side of pat ients. Eur J Intern Med 2014; 25: 685-8. 17. Carbone DP, Reck M, Paz-Ares L, et a l. First-line nivolumab in stage IV or recur- rent non-sma ll-cell lung cancer. N Engl J Med 2017; 376: 2415-26. 18. Govindan R, Szczesna A, Ahn MJ, et a l. Phase III t ria l of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-sma l l-cel l lung cancer.

# 研究背景

BACKGROUND  
Standard f irst-line therapy for metastat ic, squamous non–small-cell lung cancer (NSCLC) is platinum-based chemotherapy or pembrolizumab (for patients with pro- grammed death ligand 1 [PD-L1] expression on ≥50% of tumor cells). More recently, pembrolizumab plus chemotherapy was shown to signif icantly prolong overall sur- vival among pat ients with nonsquamous NSCLC.

# 研究结果

RESULTS  
After a median follow-up of 7.8 months, the median overall survival was 15.9 months (95% conf idence inter val [CI], 13.2 to not reached) in the pembrolizumab-combi- nat ion group and 11.3 months (95% CI, 9.5 to 14.8) in the placebo-combinat ion group (hazard ratio for death, 0.64; 95% CI, 0.49 to 0.85; P<0.001).

# 研究结论

CONCLUSIONS  
In patients with previously untreated metastatic, squamous NSCLC, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in signif icantly longer overall survival and progression-free survival than che- motherapy alone.

# 表格相关

of two interim analyses and a f inal analysis (Table S1 in the Supplementar y Appendix)

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. To improve the abilit y of the trial to ident if y long- term treatment effects, the protocol was amended to specify the performance of three interim analy- ses and a f inal analysis (Table S1 in the Supple- mentar y Appendix)

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A total of 779 pat ients from 137 sites in 17 coun- tries were screened for randomizat ion (Fig. S2 in the Supplementary Appendix). Of the 561 patients who met all eligibilit y criteria, 2 were excluded from randomization because of a physician’s deci- sion. Between August 19, 2016, and December 28, 2017, the remaining 559 pat ients from 125 sites underwent randomizat ion; 278 pat ients were as- signed to the pembrolizumab-combination group and 281 to the placebo-combinat ion group. With respect to the stratif ication factors, a PD-L1 tumor proport ion score of 1% or greater was obser ved for 63.1% of patients, paclitaxel was the choice of taxane for 60.1% of pat ients, and East Asia was the region of enrollment for 19.0% of pat ients. Baseline demographic and disease characteristics were as expected for a trial involving patients with metastat ic, squamous NSCLC and were well bal- anced between groups (Table 1)

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pembrolizumab-combination group and by 280 of 281 pat ients in the placebo-combinat ion group. The median duration of follow-up (def ined as the t ime from randomizat ion to death or the date of data cutof f for those who were alive) was 7.8 months (range, 0.1 to 19.1). The mean (±SD) dura- t ion of treatment was 6.3±4.1 months in the pembrolizumab-combinat ion group and 4.7±3.5 months in the placebo-combinat ion group. Four doses of carboplat in were received by 78.8% of the pat ients in the pembrolizumab-combinat ion group and by 73.2% of the patients in the placebo- combinat ion group (Table S2 in the Supplemen- tary Appendix)

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. Among the patients who received paclitaxel, 78.7% in the pembrolizumab-combi- nation group and 71.3% in the placebo-combina- t ion group received all 4 cycles; among the pa- tients who received nab-paclitaxel, 22.9% in the pembrolizumab-combinat ion group and 21.2% in the placebo-combinat ion group received all 12 doses (66.1% and 64.6%, respectively, received 5 to 11 doses) (Table S2 in the Supplementary Ap- pendix)

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ard ratio, 0.56; 95% CI, 0.39 to 0.80]; and among those with a score of ≥50%, 8.0 months vs. 4.2 months [hazard ratio, 0.37; 95% CI, 0.24 to 0.58]) (Fig. S5 in the Supplementar y Appendix). The response rate, as assessed by means of blinded, independent central radiologic review, was 57.9% (95% CI, 51.9 to 63.8) in the pembro- lizumab-combinat ion group and 38.4% (95% CI, 32.7 to 44.4) in the placebo-combinat ion group. The best overall response in each trial group is summarized in Table S3 in the Supplementary Appendix. The median t ime to response was 1.4 months in each group. The median durat ion of response was 7.7 months (range, 1.1+ to 14.7+ [the plus sign indicates ongoing response at the t ime of data cutof f ])

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combination group. Summaries of adverse events that occurred in the pat ients who received pacli- taxel and in those who received nab-paclitaxel are provided in Tables S5 and S6, respect ively, in the Supplementar y Appendix. The most common adverse events in both trial groups were anemia, alopecia, and neutropenia (Table 2)

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. Among the adverse events that were reported in at least 10% of pat ients, alopecia and pruritus occurred more frequently in the pembro- lizumab-combination group than in the placebo- combinat ion group, whereas back pain occurred more frequently in the placebo-combination group; after adjustment for exposure, rates of alopecia and pruritus were similar in the groups (Fig. S7A and Table S7 in the Supplementar y Appendix)

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. Adverse events of grade 3 or higher that occurred in at least 10% of pat ients were anemia and neu- tropenia (Table 2)

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. Adverse events of grade 3 or higher that occurred more frequently in the pem- brolizumab-combinat ion group than in the pla- cebo-combinat ion group were pneumonit is and autoimmune hepat it is (Fig. S7B in the Supple- mentary Appendix). Immune-mediated adverse events and infusion react ions occurred in 28.8% of pat ients in the pembrolizumab-combinat ion group and in 8.6% of pat ients in the placebo- combinat ion group (Table 3)

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Adverse events of any grade, regardless of attribu- tion to a trial regimen by an investigator, occurred in 98.2% of the pat ients in the pembrolizumab- combinat ion group and in 97.9% of the pat ients in the placebo-combination group (Table 2)

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