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# 研究患者

In this double-blind trial, patients were randomly assigned, in a 2:1 ratio, to receive either 200 mg of pembrolizumab or saline placebo, both adminis- tered intravenously every 3 weeks for up to 35 cy- cles. Randomizat ion was performed by means of an integrated interactive voice-response and Web- response system (i.e., treatment assignments could be provided by following a series of prompts on a touch-tone phone or by following the same prompts in a Web-based portal). Randomizat ion was strat if ied according to PD-L1 expression (tumor proport ion score, ≥1% vs. <1%), choice of plat inum-based drug (cisplat in vs. carboplat in), and smoking history (never vs. former or current). All the pat ients received four cycles of the invest igator’s choice of intravenously adminis- tered cisplat in (75 mg per square meter of body- surface area) or carboplatin (area under the con- centrat ion–t ime cur ve, 5 mg per milliliter per minute) plus pemetrexed (500 mg per square me- ter), all administered intravenously every 3 weeks, followed by pemetrexed (500 mg per square meter) every 3 weeks. All the patients received premedica- t ion with folic acid, vitamin B12, and glucocort i- coids administered according to local guidelines for pemetrexed use. Treatment was cont inued unt il radiographic progression, unacceptable toxic effects, investiga- tor decision, or pat ient withdrawal of consent. If toxicit y was clearly attributed to one agent, that drug alone could be discontinued. Patients in the placebo-combination group in whom disease pro- gression was verif ied by blinded, independent central radiologic review were eligible to cross over to receive pembrolizumab monotherapy.

# 样本量

In this double-blind, phase 3 trial, we randomly assigned (in a 2:1 ratio) 616 patients with metastatic nonsquamous NSCLC without sensitizing EGFR or ALK mutations who had received no previous treatment for metastat ic disease to receive pemetrexed and a plat inum-based drug plus either 200 mg of pembrolizumab or placebo ever y 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy.

# 基线特征

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.

# 试验设计

PD-L1 immunohistochemist r y assay for pembrolizumab therapy in non-sma ll-cell lung cancer. Appl Immunohistochem Mol Morphol 2016; 24: 392-7. 12 . Reck M, Rodríguez-Abreu D, Robin- son AG, et a l. Pembrolizumab versus che- motherapy for PD-L1–posit ive non–sma ll- cell lung cancer. N Engl J Med 2016; 375: 1823-33. 13. Brahmer JR, Rodr iguez-Abreu D, Robinson AG, et a l. Prog ression a f ter the nex t l ine of therapy (PFS2) and updated OS among pat ients w ith advanced NSCLC and PD-L1 TPS >=50% enrol led in KEYNOTE-024. J Clin Oncol 2017; 35: Suppl: 9000. abst ract. 14. Garon EB, Rizvi NA, Hui R, et a l. Pembrolizumab for the t reatment of non– sma l l-cel l lung cancer. N Eng l J Med 2015; 372: 2018-28. 15. Reck M, Socinsk i MA, Cappuzzo F, et a l. Primar y PFS and safet y ana lyses of a randomized phase III study of carboplat in + pacl it a xel +/− bevacizumab, w ith or w ithout atezol izumab in 1L non-squa- mous met ast at ic NSCLC (IMPower150).

# 研究背景

BACKGROUND  
First-line therapy for advanced non–sma ll-cell lung cancer (NSCLC) that lacks targetable mutations is platinum-based chemotherapy. Among patients with a tumor proportion score for programmed death ligand 1 (PD-L1) of 50% or greater, pembro- lizumab has replaced cytotoxic chemotherapy as the f irst-line treatment of choice.

# 研究结果

RESULTS  
After a median follow-up of 10.5 months, the est imated rate of overall sur vival at 12 months was 69.2% (95% conf idence inter val [CI], 64.1 to 73.8) in the pembro- lizumab-combinat ion group versus 49.4% (95% CI, 42.1 to 56.2) in the placebo- combinat ion group (hazard rat io for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001).

# 研究结论

CONCLUSIONS  
In pat ients with previously untreated metastat ic nonsquamous NSCLC without EGFR or ALK mutat ions, the addit ion of pembrolizumab to standard chemotherapy of pemetrexed and a plat inum-based drug resulted in signif icant ly longer overall survival and progression-free survival than chemotherapy alone.

# 表格相关

lizumab-combination group than in the placebo- combinat ion group (62.0% vs. 52.9%, P = 0.04) (Table 1)

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. A PD-L1 tumor proport ion score of 1% or greater was reported in 63.0% of the pat ients, carboplat in was the chosen plat inum-based drug in 72.2% of the patients, and 88.1% of the patients were current or former smokers. Of the 616 pat ients who were enrolled, 405 in the pembrolizumab-combination group and 202 in the placebo-combinat ion group received at least one dose of the assigned combinat ion therapy. With a median follow-up of 10.5 months (range, 0.2 to 20.4), the mean (±SD) duration of treatment was 7.4±4.7 months in the pembrolizumab-com- bination group and 5.4±4.3 months in the placebo- combinat ion group. All four planned doses of cisplat in or carboplat in were received by 82.5% of the pat ients in the pembrolizumab-combina- t ion group and by 74.3% of those in the placebo- combinat ion group; 76.5% and 66.8%, respec- t ively, received f ive or more doses of pemetrexed. (Table S1 in the Supplementar y Appendix shows the exposure to treatment in patients who received carboplatin and in those who received cisplatin.)

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The response rate as assessed by blinded, indepen- dent central radiologic review was 47.6% (95% CI, 42.6 to 52.5) in the pembrolizumab-combinat ion group and 18.9% (95% CI, 13.8 to 25.0) in the placebo-combination group (P<0.001). The results were similar when the response was assessed by investigator review (Table S3 in the Supplementary Appendix)

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Adverse events of any cause and regardless of at- tribution to treatment by the investigator occurred in 99.8% of the pat ients in the pembrolizumab- combinat ion group and in 99.0% of those in the placebo-combination group (Table 2)

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. These events were of grade 3 or higher in 67.2% and 65.8% of the pat ients, respect ively. Discont inuat ion of all trial drugs because of adverse events occurred in 13.8% of the pat ients in the pembrolizumab- combinat ion group and in 7.9% of those in the placebo-combination group; discontinuation rates of pembrolizumab and placebo were 20.2% and 10.4%, respectively (Table 2)

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. The rates of adverse events were similar in patients who received car- boplat in and cisplat in (Tables S4 and S5 in the Supplementar y Appendix). Adverse events led to death in 27 of 405 pat ients (6.7%) in the pem- brolizumab-combinat ion group and in 12 of 202 patients (5.9%) in the placebo-combination group. In the two groups, the most common adverse events were nausea, anemia, and fatigue (Table 2; exposure-adjusted rates are provided in Table S6 in the Supplementary Appendix)

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. The only adverse events that were reported in at least 10% of the pat ients that were more frequent in the pembro- lizumab-combinat ion group were diarrhea and rash (Fig. S6A in the Supplementar y Appendix). Adverse events of grade 3 or higher that were re- ported in at least 10% of the patients in the pem- brolizumab-combinat ion group or the placebo- combination group were anemia (16.3% and 15.3%) and neutropenia (15.8% and 11.9%) (Table 2)

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nat ion group and in 24 of 202 pat ients (11.9%) in the placebo-combination group (Table 3)

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