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# 研究患者

NSCLC and an Eastern Cooperat ive Oncolog y Group (ECOG) performance-status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicat- ing greater disability)18 who had received no previ- ous systemic anticancer therapy as primary ther- apy for advanced or metastat ic disease were eligible.

# 样本量

No Match

# 基线特征

Table 1. Baseline Characteristics of Patients with a High Tumor Mutational Burden.

# 试验设计

t re, phase 2 t r ia l. Lancet 2016; 387: 1909- 20. 10. Powles T, Loriot Y, Ravaud A, et a l. Atezolizumab vs chemotherapy in plat i- num-treated locally advanced or metastat ic urothel ia l carcinoma: immune biomark- ers, tumor mutat ional burden and clinical outcomes from the phase III IMvigor211 study.

# 研究背景

BACKGROUND  
Nivolumab plus ipilimumab showed promising eff icacy for the treatment of non– small-cell lung cancer (NSCLC) in a phase 1 trial, and tumor mutational burden has emerged as a potential biomarker of benef it. In this part of an open-label, multipart, phase 3 trial, we examined progression-free survival with nivolumab plus ipilimumab versus chemotherapy among patients with a high tumor mutational burden (≥10 muta- tions per megabase).

# 研究结果

RESULTS  
Progression-free survival among patients with a high tumor mutational burden was signif icantly longer with nivolumab plus ipilimumab than with chemotherapy. The 1-year progression-free survival rate was 42.6% with nivolumab plus ipilimumab versus 13.2% with chemotherapy, and the median progression-free survival was 7.2 months (95% conf idence interval [CI], 5.5 to 13.2) versus 5.5 months (95% CI, 4.4 to 5.8) (hazard ratio for disease progression or death, 0.58; 97.5% CI, 0.41 to 0.81; P<0.001).

# 研究结论

CONCLUSIONS  
Progression-free survival was signif icantly longer with f irst-line nivolumab plus ipilimu- mab than with chemotherapy among patients with NSCLC and a high tumor muta- tional burden, irrespective of PD-L1 expression level.

# 表格相关

populat ion selected on the basis of tumor muta- t iona l burden. On the basis of previous f ind- ings,17 a prespecif ied cutof f for tumor muta- t iona l burden of at least 10 mutat ions per megabase was selected for preplanned analysis of the coprimar y end point. The other coprimar y end point was overa ll sur viva l with nivolumab plus ipilimumab versus chemotherapy in a patient populat ion selected on the basis of the PD-L1 expression level. Secondar y end points in pat ient populat ions selected on the basis of tumor mutational burden included progression-free survival with nivolumab versus chemotherapy among pat ients with a tu- mor mutat ional burden of at least 13 mutat ions per megabase and a PD-L1 expression level of at least 1% and overa ll sur viva l with nivolumab plus ipilimumab versus platinum doublet chemo- therapy among pat ients with a tumor mutat ional burden of at least 10 mutat ions per megabase (Table S1 in the Supplementary Appendix)

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sided 97.5% conf idence inter vals were computed for primar y and secondar y comparisons speci- f ied in the hierarchica l hypothesis test ing in- volving pat ients selected on the basis of tumor mutat ional burden (Table S1 in the Supplemen- tary Appendix)

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Of 2877 pat ients enrolled in part 1 of the trial from August 2015 through November 2016, 1739 underwent randomizat ion. Of the 1138 pat ients who did not undergo randomizat ion, 909 no longer met the trial criteria (common reasons included the ident if icat ion of EGFR or ALK muta- t ions, a decline in performance status, untreated brain metastases, and missing data on PD-L1 expression level), 88 withdrew consent, 40 died, 33 had adverse events (unrelated to a trial drug), 6 were lost to follow-up, and 62 were excluded for other reasons (Fig. S1 in the Supplementar y Appendix). Of the 1739 randomly assigned pat ients, 1649 (94.8%) had tumor samples available to attempt assessment of tumor mutat ional burden, and 1004 (57.7%) had valid data for tumor muta- t ional burden–based ef f icacy analyses (Table S2 in the Supplementar y Appendix)

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. Baseline char- acterist ics of all randomly assigned pat ients and pat ients whose tumor mutat ional burden could be evaluated were similar and balanced between treatment groups (Table S3 in the Supplemen- tar y Appendix)

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. Of the 1004 pat ients whose tumor mutat ional burden could be evaluated across all treatment groups, 444 (44.2%) had at least 10 mutat ions per megabase, including 139 pat ients assigned to nivolumab plus ipilimumab and 160 pat ients assigned to chemotherapy. Baseline character- ist ics were well ba lanced between the two t reatment groups, including the dist ribut ion of PD-L1 expression levels (Table 1)

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therapy cont inued to receive treatment (Table S4 in the Supplementar y Appendix)

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Among pat ients with a high tumor mutat iona l burden (≥10 mutat ions per megabase), 24.4% t reated with nivolumab plus ipilimumab and 3.1% treated with chemotherapy were continuing treatment at the t ime of database lock; the most common reasons for discont inuing t reatment were disease progression (37.8% and 47.2%, re- spect ively), adverse ef fects of trial drugs (25.9% and 8.8%, respect ively), and complet ion of re- quired t reatment among pat ients in the chemo- therapy group (26.4%) (Table S4 in the Supple- mentar y Appendix)

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. Of pat ients assigned to chemotherapy, 30.0% received subsequent im- munotherapy (Table S5 in the Supplementar y Appendix)

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Analysis of the coprimar y end point in pat ients with a high tumor mutational burden (≥10 muta- t ions per megabase) showed signif icant ly longer progression-free sur viva l with nivolumab plus ipilimumab than with chemotherapy; the 1-year progression-free sur vival rate was 42.6% versus 13.2%, and the median progression-free sur vival was 7.2 months (95% CI, 5.5 to 13.2) versus 5.5 months (95% CI, 4.4 to 5.8) (hazard rat io for disease progression or death, 0.58; 97.5% CI, 0.41 to 0.81; P<0.001) (Fig. 2A). In a prespecif ied mult ivariate analysis of progression-free sur vival among pat ients with a high tumor mutat iona l burden, the t reatment ef fect of nivolumab plus ipilimumab versus chemotherapy with adjustment for baseline PD-L1 expression level (≥1% vs. <1%), sex, tumor histologic t ype (squamous vs. non- squamous), and ECOG performance-status score (0 vs. ≥1) was consistent with that in the pri- mar y progression-free sur vival analysis (hazard rat io for disease progression or death, 0.57; 97.5% CI, 0.40 to 0.80; P<0.001 by mult ivariate Cox model). The response rate was 45.3% with nivolumab plus ipilimumab and 26.9% with che- motherapy (Table 2)

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among pat ients with a tumor mutat ional burden of at least 10 mutat ions per megabase than among a ll t reated pat ients (Table S10 in the Supplementar y Appendix)

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