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# 研究患者

Patients  
Eligible patients had documented stage IIIB/IV or recurrent non-squamous NSCLC following radiation therapy or surgical resection, and disease recurrence or progression during or after one prior platinum-based regimen.

# 样本量

From November, 2012 to December, 2013, 792 patients were enrolled and 582 randomized to either nivolumab 3 mg per kilogram every 2 weeks (n = 292), or docetaxel 75 mg per square meter every 3 weeks (n = 290), both intravenously (Fig.

# 基线特征

Of randomized patients, 287 were treated with nivolumab and 268 were treated with docetaxel. Median age was 62 years. Most patients were ECOG performance status 1, stage IV, and current/former smokers (Table 1 and S1). Baseline characteristics were balanced between treatment groups, with slight imbalances for male sex and age 65 or younger.

# 试验设计

1. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum- containing chemotherapy regimens.

# 研究背景

Abstract  
Background— Options for patients with non-squamous non-small cell lung cancer (NSCLC) whose disease progresses after first-line chemotherapy are limited. This randomized, open-label, international phase 3 study evaluated efficacy and safety of nivolumab versus docetaxel in this patient population after failure of platinum doublet chemotherapy.

# 研究结果

Results— Nivolumab improved overall survival versus docetaxel. Median overall survival was 12.2 months (95% CI, 9.7 to 15.0) for nivolumab (n=292) and 9.4 months (95% CI, 8.1 to 10.7) for docetaxel (n=290) (hazard ratio, 0.73; 96% CI, 0.59 to 0.89; P=0.002).

# 研究结论

Conclusions— Compared to docetaxel, nivolumab demonstrated superior overall survival, with PD-L1 expression conferring enhanced efficacy in patients with advanced non-squamous NSCLC after failure of platinum-based chemotherapy.

# 表格相关

Of randomized patients, 287 were treated with nivolumab and 268 were treated with docetaxel. Median age was 62 years. Most patients were ECOG performance status 1, stage IV, and current/former smokers (Table 1 and S1)

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At the time of interim analysis, 15% of nivolumab and no docetaxel patients were continuing treatment (Table S2)

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. Subsequent systemic therapy was received by 42% of nivolumab and 50% of docetaxel patients. Of nivolumab patients, 23% received subsequent docetaxel; 2% of docetaxel patients received subsequent immunotherapy (Table S3)

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Confirmed objective response rate was significantly higher for nivolumab versus docetaxel (Table 2 and Fig. S4)

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; 19% (95% CI, 15 to 24) versus 12% (95% CI, 9 to 17) (P=0.02). Median time to response was 2.1 months (range, 1.2–8.6) for nivolumab and 2.6 months (range, 1.4–6.3) for docetaxel (Table 2 and Fig. 1C)

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In total, 71 (25%) nivolumab patients continued treatment beyond initial progression, 16 (23%) of whom demonstrated a non-conventional pattern of benefit. Characteristics of patients treated beyond progression, including change in tumor burden over time, are provided (Fig. S6 and Table S4)

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Of randomized patients, 78% (455/582) had quantifiable PD-L1 expression. Rates of PD-L1 expression were balanced between groups (Table S5)

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. At the time of interim analysis, test for interaction suggested a strong predictive association between PD-L1 and clinical outcome at all expression levels for all efficacy endpoints (Table S6)

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. Nivolumab demonstrated improved overall survival, progression-free survival (Fig. S7) and objective response rates (Table S5)

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at prespecified ≥1%, ≥5% and ≥10% PD-L1 expression levels. Progression-free survival across all prespecified PD-L1 subgroups based on the interim analysis database lock is provided in Fig. S8A. Overall survival by PD-L1 expression level based on the July 2015 database lock is shown in Fig. S8B; the difference in overall survival between nivolumab and docetaxel among patients whose tumors express PD-L1 was still evident with additional follow-up. Median duration of response was longer with nivolumab versus docetaxel across all PD-L1 expression levels (Table S5)

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The frequencies of all-causality, any-grade adverse events were similar between arms, but fewer grade 3– 4 adverse events were reported with nivolumab than docetaxel (Table S7)

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. Treatment-related adverse events were low in severity with nivolumab and less frequent (any-grade: 69%; grade 3–4: 10%) than with docetaxel (any-grade: 88%; grade 3–4: 54%) (Table 3 and S8)

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. The most frequently reported any-grade treatment-related adverse events for nivolumab were fatigue (16%), nausea (12%), decreased appetite (10%), and asthenia (10%). The most frequently reported any-grade treatment-related adverse events for docetaxel were neutropenia (31%), fatigue (29%), nausea (26%), and alopecia (25%). Treatment-related serious adverse events were less frequent with nivolumab (any-grade: 7%; grade 3–4: 5%) than docetaxel (any-grade: 20%; grade 3–4: 18%) (Table S9)

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The most frequently-reported (≥2.5% of patients) any-grade treatment-related select adverse events (nivolumab versus docetaxel) were rash (9% versus 3%), pruritus (8% versus 1%), erythema (1% versus 4%), diarrhea (8% versus 23%), hypothyroidism (7% versus 0%), increased alanine aminotransferase (3% versus 1%), increased aspartate aminotransferase (3% versus 1%), infusion related reaction (3% versus 3%), and pneumonitis (3% versus <1%) (Table S10)

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. Across categories, median times to onset of any-grade treatment-related select adverse events for nivolumab ranged from 0.9 to 31.1 weeks (Table S11)

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. Of those who experienced treatment-related select adverse events across categories (Table S11)

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, 11% to 70% were treated with immune-modulating agents (generally glucocorticoids), per protocol guidelines. Across categories, 44% to 100% of treatment-related select adverse events resolved, with median times to resolution ranging from 0.1 to 12.1 weeks (Table S11)

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. Median time to resolution of treatment-related select endocrinopathies was not reached, as a proportion of these events are not expected to resolve. The frequencies of treatment-related adverse events, serious adverse events and adverse events leading to discontinuation were similar between patients with ≥1% PD-L1and <1% PD-L1 expression (Table S12)

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The current study, which included patients regardless of tumor PD-L1 expression level and comparison to a control arm, is the first to demonstrate a predictive association between PD- L1 expression and benefit from anti-PD-1 treatment. Analyzed tumor samples included archived tissue, suggesting applicability in a real world setting where fresh tissue may not be available or repeat biopsy not feasible. For each of the predefined expression levels examined, the descriptive treatment-biomarker interaction P value met the predefined threshold, suggesting a predictive association with clinical benefit. Although benefit of nivolumab was observed in the overall population, the magnitude of benefit across all efficacy endpoints was greater among those whose tumors express PD-L1 (Figs. S7 and S8 and Table S5)

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The safety profile of nivolumab observed in this study (Table 3)

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