APPENDIX

Supplementary Methods

Eligibility criteria

Eligibility criteria for both trials included age 18 years or older, a confirmed diagnosis of unresectable advanced or metastatic melanoma, measurable disease per immune-related response criteria in KEYNOTE-001 and Response Evaluation Criteria in Solid Tumors, version 1.1, in KEYNOTE-006, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function. In KEYNOTE-006, patients could have received up to 1 prior systemic therapy for advanced disease excluding anti–cytotoxic T-lymphocyte–associated protein 4, anti–programmed death 1 (PD-1), or anti–programmed death ligand 1 (PD-L1) agents. Patients with *BRAF*-mutant melanoma were required to have received prior BRAF inhibitor therapy unless they met specific criteria (normal lactate dehydrogenase level, no clinically significant tumor-related symptoms, and an absence of rapidly progressing disease). Patients with previously treated brain metastases who were stable for at least 4 weeks before the first dose of study drug and who had no evidence of new or enlarging brain metastases were eligible. Patients with an active infection requiring systemic therapy, a medical condition requiring chronic systemic steroids or immunosuppressive agents, previous treatment targeting the PD-1 pathway, or chemotherapy within 4 weeks of the first dose of study drug were excluded.

PD-L1 status

PD-L1 status was assessed in archival or newly obtained tumor samples by immunohistochemistry with the 22C3 antibody (Merck) at a central laboratory before

randomization. PD-L1 positivity was defined as membranous staining in at least 1% of tumor cells [1,2].

Baseline patient characteristics

Baseline characteristics evaluated in the current analysis included sex (male, female), tumor size (<2.5 cm, 2.5 to <5 cm, 5 to 10 cm, ≥10 cm), PD-L1 status (negative, positive), Eastern Cooperative Oncology Group performance status (0, 1), and metastatic stage (M0, M1a, M1b, M1c).

Procedures

In KEYNOTE-001, intravenous pembrolizumab at a dose of 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks, or 10 mg/kg every 3 weeks until disease progression, intolerable toxicity, or patient or physician's decision to withdraw from study. In KEYNOTE-006, patients were randomly assigned 1:1:1 to receive pembrolizumab 10 mg/kg every 2 weeks, 10 mg/kg every 3 weeks, or 4 doses of ipilimumab 3 mg/kg every 3 weeks; pembrolizumab treatment was continued for 24 months or until disease progression, intolerable toxicity, or patient or physician's decision to withdraw from study. Patients in both trials who stopped initial treatment after attaining stable disease (SD) or better were eligible for a second course of pembrolizumab if they experienced subsequent progression and met certain prespecified criteria.

Statistical analysis

The Kaplan-Meier method was used to estimate overall survival (OS). OS was calculated as time from week 12 and 24 assessment, respectively, to death due to any cause for those who died and date last known alive for those still alive.

References

[1] Daud AI, Wolchok JD, Robert C, Hwu WJ, Weber JS, Ribas A, et al. Programmed death-ligand 1 expression and response to the anti-programmed death 1 antibody pembrolizumab in melanoma. J Clin Oncol 2016;34(34):4102–9.

[2] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372(26):2521–32.