



original reports

# Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results From the EORTC 1325-MG/KEYNOTE-054 Trial

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abstract

**PURPOSE** We conducted the phase III double-blind European Organisation for Research and Treatment of Cancer (EORTC) 1325/KEYNOTE-054 trial to evaluate pembrolizumab versus placebo in patients with resected high-risk stage III melanoma. On the basis of 351 recurrence-free survival (RFS) events at a 1.25-year median follow-up, pembrolizumab prolonged RFS (hazard ratio [HR], 0.57;  $P < .0001$ ) compared with placebo. This led to the approval of pembrolizumab adjuvant treatment by the European Medicines Agency and US Food and Drug Administration. Here, we report an updated RFS analysis at the 3.05-year median follow-up.

**PATIENTS AND METHODS** A total of 1,019 patients with complete lymph node dissection of American Joint Committee on Cancer Staging Manual (seventh edition; AJCC-7), stage IIIA (at least one lymph node metastasis > 1 mm), IIIB, or IIIC (without in-transit metastasis) cutaneous melanoma were randomly assigned to receive pembrolizumab at a flat dose of 200 mg ( $n = 514$ ) or placebo ( $n = 505$ ) every 3 weeks for 1 year or until disease recurrence or unacceptable toxicity. The two coprimary end points were RFS in the overall population and in those with programmed death-ligand 1 (PD-L1)-positive tumors.

**RESULTS** Pembrolizumab (190 RFS events) compared with placebo (283 RFS events) resulted in prolonged RFS in the overall population (3-year RFS rate, 63.7% v 44.1% for pembrolizumab v placebo, respectively; HR, 0.56; 95% CI, 0.47 to 0.68) and in the PD-L1-positive tumor subgroup (HR, 0.57; 99% CI, 0.43 to 0.74). The impact of pembrolizumab on RFS was similar in subgroups, in particular according to AJCC-7 and AJCC-8 staging, and *BRAF* mutation status (HR, 0.51 [99% CI, 0.36 to 0.73] v 0.66 [99% CI, 0.46 to 0.95] for V600<sup>EK</sup> v wild type).

**CONCLUSION** In resected high-risk stage III melanoma, pembrolizumab adjuvant therapy provided a sustained and clinically meaningful improvement in RFS at 3-year median follow-up. This improvement was consistent across subgroups.

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## INTRODUCTION

In concordance with results obtained with immune checkpoint inhibitors and *BRAF* plus *MEK* inhibitors in advanced melanoma,<sup>1,2</sup> adjuvant therapies with ipilimumab,<sup>3-5</sup> nivolumab,<sup>6</sup> and pembrolizumab<sup>7</sup> in patients with melanoma at high risk for relapse regardless of *BRAF* mutation status and with dabrafenib plus trametinib<sup>8,9</sup> in patients with *BRAF* mutation demonstrated significant benefits that resulted in US Food and Drug Administration (FDA) approvals for all

of these drugs. The ipilimumab,<sup>3-5</sup> pembrolizumab,<sup>7</sup> and dabrafenib plus trametinib<sup>8,9</sup> trials were conducted in patients with stage III disease with the restriction that patients with American Joint Committee on Cancer (AJCC) stage IIIA disease had to be at higher risk of recurrence on the basis of tumor load in the sentinel node (diameter > 1 mm, according to the Rotterdam criteria).<sup>10-12</sup> The CheckMate-238 (ClinicalTrials.gov identifier: [NCT02388906](https://clinicaltrials.gov/ct2/show/study/NCT02388906)) nivolumab trial was conducted in patients with stage IIIB-C and completely resected stage IV melanoma.<sup>6</sup>

## ASSOCIATED CONTENT

### Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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The authors have declared that no competing interests exist.

## CONTEXT

### Key Objective

Does pembrolizumab treatment administration for 1 year lead to a sustained improvement of recurrence-free survival (RFS) in resected high-risk stage III melanoma?

### Knowledge Generated

Pembrolizumab as adjuvant therapy for patients with resected high-risk stage III melanoma provided a statistically significant and clinically relevant 20% improvement of the RFS rate at 3 years compared with placebo and had a safety profile consistent with the toxicity spectrum that already had been defined. Such RFS improvement was consistent across subgroups, in particular according to programmed cell death-ligand 1 status, American Joint Committee on Cancer Cancer Staging Manual (seventh edition; AJCC-7) and (eighth edition; AJCC-8), and *BRAF* mutation status.

### Relevance

More than 1 year ago, pembrolizumab was already approved by the US Food and Drug Administration and European Medicines Agency. These results confirm the clinical utility of pembrolizumab in the adjuvant setting in resected high-risk stage III melanoma. We expect that these RFS improvements will also translate in terms of distant metastasis-free survival and overall survival when long-term follow-up results are available.

We conducted the phase III, randomized, double-blind European Organisation for Research and Treatment of Cancer (EORTC) 1325/KEYNOTE-054 trial (ClinicalTrials.gov identifier: [NCT02362594](https://clinicaltrials.gov/ct2/show/study/NCT02362594)) to evaluate pembrolizumab versus placebo in patients with resected high-risk stage III melanoma. At the 1.25-year median follow-up, pembrolizumab adjuvant treatment prolonged RFS (hazard ratio [HR], 0.57,  $P < .0001$ ) compared with placebo.<sup>7</sup> This led to the approval of pembrolizumab adjuvant treatment by the European Medicines Agency (EMA) and FDA.

We report an updated analysis at 3-year median follow-up with regard to RFS outcome of the EORTC 1325/KEYNOTE-054 trial to investigate whether the benefit is sustained and whether patient characteristics, particularly programmed cell death-ligand 1 (PD-L1) status; baseline stage according to AJCC Cancer Staging Manual (seventh edition; AJCC-7), and AJCC-8 classifications<sup>13,14</sup>; and *BRAF*-V600<sup>E/K</sup> mutation status are of predictive importance for the treatment difference. Such analyses are important to confirm the initial findings with a shorter follow-up<sup>7,15</sup> and to compare them with those provided by the COMBI-AD trial (ClinicalTrials.gov identifier: [NCT01682083](https://clinicaltrials.gov/ct2/show/study/NCT01682083)) in *BRAF*-V600<sup>E/K</sup>-mutated melanoma at 44 months median follow-up.<sup>9</sup>

## PATIENTS AND METHODS

### Patients

Patients (age  $\geq 18$  years) with histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes were eligible to enter the study provided that a complete regional lymphadenectomy could be performed within 13 weeks before the start of treatment. Patients had either stage IIIA melanoma (patients with N1a or N2a had to have at least one micrometastasis measuring  $> 1$  mm in greatest diameter) or stage IIIB or IIIC disease with no in-

transit metastases according to the AJCC-7 classification.<sup>13</sup> Exclusion criteria included Eastern Cooperative Oncology Group performance status 2-4, presence of autoimmune disease, uncontrolled infections, use of systemic corticosteroids, and prior systemic therapy for melanoma. A tumor sample from melanoma-positive lymph nodes was required to be sent for central pathology evaluation of PD-L1 expression. Membranous PD-L1 expression in tumor and tumor-associated immune cells was assessed by an immunohistochemistry assay and scored on a scale of 0-5; a score  $\geq 2$  (staining on  $> 1\%$  of cells) was considered PD-L1 positive.<sup>16</sup>

### Study Design and Treatment

Registration was done centrally at the EORTC headquarters. The randomization, using a minimization technique, was stratified by AJCC-7 staging (stage IIIA v stage IIIB v stage IIIC with one to three positive nodes v stage IIIC with more than three positive nodes) and region. Only the local pharmacists were aware of trial group assignments.

Patients were randomly assigned (1:1) to receive either an intravenous infusion of pembrolizumab 200 mg or placebo every 3 weeks for a total of 18 doses for approximately 1 year or until disease recurrence, unacceptable toxicity, major protocol violation, or withdrawal of consent (Data Supplement, online only). The primary end point was RFS, as reported by the local investigators, in the overall population and in the subgroup of patients with PD-L1-positive tumors.

### Assessments

Computed tomography (CT) scans and magnetic resonance imaging (MRI; full chest, abdomen, and pelvis CT and/or MRI, neck CT and/or MRI for head and neck

primaries, CT and/or MRI for other localizations [eg, brain, deep soft tissue], only if clinically indicated) were performed every 12 weeks for the first 2 years and every 6 months through year 5. Recurrence or metastatic lesions had to be histologically confirmed whenever possible. The first date when recurrence was observed was taken into account.

RFS was defined as the time from random assignment until the date of first recurrence (local, regional, or distant metastasis) or death as a result of any cause. For patients without any event, the follow-up was censored at the latest disease evaluation performed according to the protocol.

### Statistical Analysis

Details with regard to sample size computations, implementation of an interim analysis in an amended protocol, and dissemination of the treatment outcome results were provided in the original publication.<sup>7</sup> The interim analysis, which became the final one, was based on 351 RFS events as reported on the clinical cutoff date of October 2, 2017. The clinical cutoff date for the current analysis was September 30, 2019. This updated analysis, with a longer follow-up, was performed to assess whether the initial findings still hold true.

RFS distribution was estimated using the Kaplan-Meier method, and the 95% CIs were estimated through the Greenwood variance formula. For treatment comparison, the log-rank test stratified by stage provided at randomization was used. The Cox model stratified by stage provided at randomization was used to estimate the HRs and the CIs, 95% for the overall population and 99% for different subgroups.

We investigated the possible predictive importance of several factors (eg, AJCC-7 and AJCC-8 staging classifications, *BRAF*-V600<sup>E/K</sup> mutation status) on the treatment differences with regard to RFS. Forest plots for the HRs were produced, and results of the test of interaction between each factor and the treatment group in an unstratified Cox model were indicated. The treatment HRs for each subgroup estimated using the model with the interaction term were plotted along with their 99% CIs.

The cumulative incidence of the appearance of a distant metastasis as the first RFS event was estimated by the Aalen-Johansen method, and the treatment comparison was performed using the Fine and Gray model stratified by stage at random assignment. The primary analysis of RFS included all the patients who underwent random assignment, according to the intention-to-treat (ITT) principle. Sensitivity analysis was based on the per-protocol treatment (PPT) population: Eligible patients who started the treatment were allocated by random assignment. The safety profile was assessed in patients who started treatment allocated by random assignment. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

### Trial Oversight

The protocol was approved by the EORTC protocol review committee and independent ethics committees. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent.

## RESULTS

### Patients and Trial Regimen

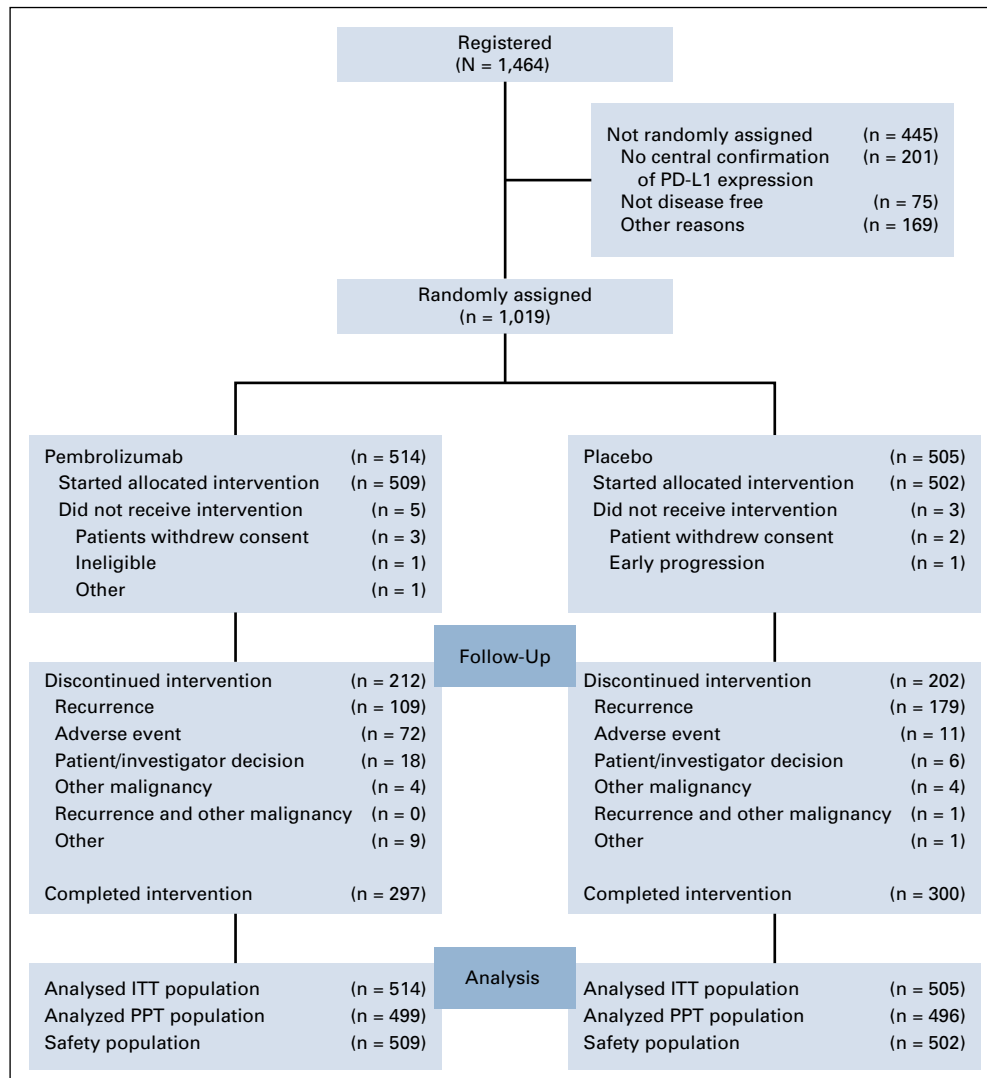
From August 2015 through November 2016, 1,019 patients were randomly assigned at 123 centers in 23 countries: 514 patients were assigned to the pembrolizumab group and 505 to the placebo group. The characteristics at baseline were similar between the two groups (Data Supplement).

Eight patients did not start the treatment allocated by random assignment (Fig 1). Of 509 patients who started pembrolizumab, 72 (14.1%) discontinued treatment because of an adverse event (AE). Among 502 patients who received placebo, 11 (2.2%) discontinued treatment because of an AE. A total of 109 (21.4%) patients in the pembrolizumab group discontinued treatment because of disease recurrence compared with 179 (35.7%) in the placebo group. A total of 297 (58.3%) patients in the pembrolizumab group and 300 (59.8%) patients in the placebo group completed 1 year of treatment (Fig 1). The median follow-up was 36.6 months (interquartile range [IQR], 35.0-40.2 months) overall, 36.6 months (IQR, 34.9-39.8 months) in the pembrolizumab group, and 36.5 months (IQR, 35.0-40.5 months) in the placebo group.

### Updated RFS

In the ITT overall population, the 3-year RFS rate was 63.7% (95% CI, 59.2% to 67.7%) in the pembrolizumab group and 44.1% (95% CI, 39.6% to 48.4%) in the placebo group (Fig 2A). RFS remained significantly longer in the pembrolizumab group than in the placebo group (HR stratified by stage, 0.56; 95% CI, 0.47 to 0.68;  $P < .001$ ).

During the additional follow-up period from the final analysis,<sup>7</sup> 122 new RFS events were reported—55 in the pembrolizumab group versus 67 in the placebo group. A total of 473 patients had a recurrence or died—190 (37.0%) in the pembrolizumab group and 283 (56.0%) in the placebo group (Data Supplement). Among them, 68 patients (13.2%) in the pembrolizumab group had a locoregional recurrence only versus 92 (18.2%) in the placebo group, and 117 (22.8%) patients developed distant metastases as their first recurrence (alone or combined with locoregional recurrences in the pembrolizumab group) versus 190 (37.6%) in the placebo group. The 3-year cumulative incidence rate of distant metastasis being the first site of recurrence was 22.3% (95% CI, 18.8% to 26.1%) in the pembrolizumab group and 37.3% (95% CI,



**FIG 1.** CONSORT diagram. Safety population indicates patients who started the allocated treatment. ITT, intention to treat; PD-L1, programmed cell death-ligand 1; PPT, per-protocol treatment.

33.0% to 41.6%) in the placebo group (HR, 0.55; 95% CI, 0.44 to 0.69; Data Supplement). There were four (0.8%) deaths without recurrence (one as a result of myositis and three unrelated to treatment) in the pembrolizumab group and one (0.2%) in the placebo group. Sensitivity analysis for RFS, on the basis of the PPT population, provided similar results (HR, 0.56; 95% CI, 0.47 to 0.68).

### Subgroup Analysis of RFS

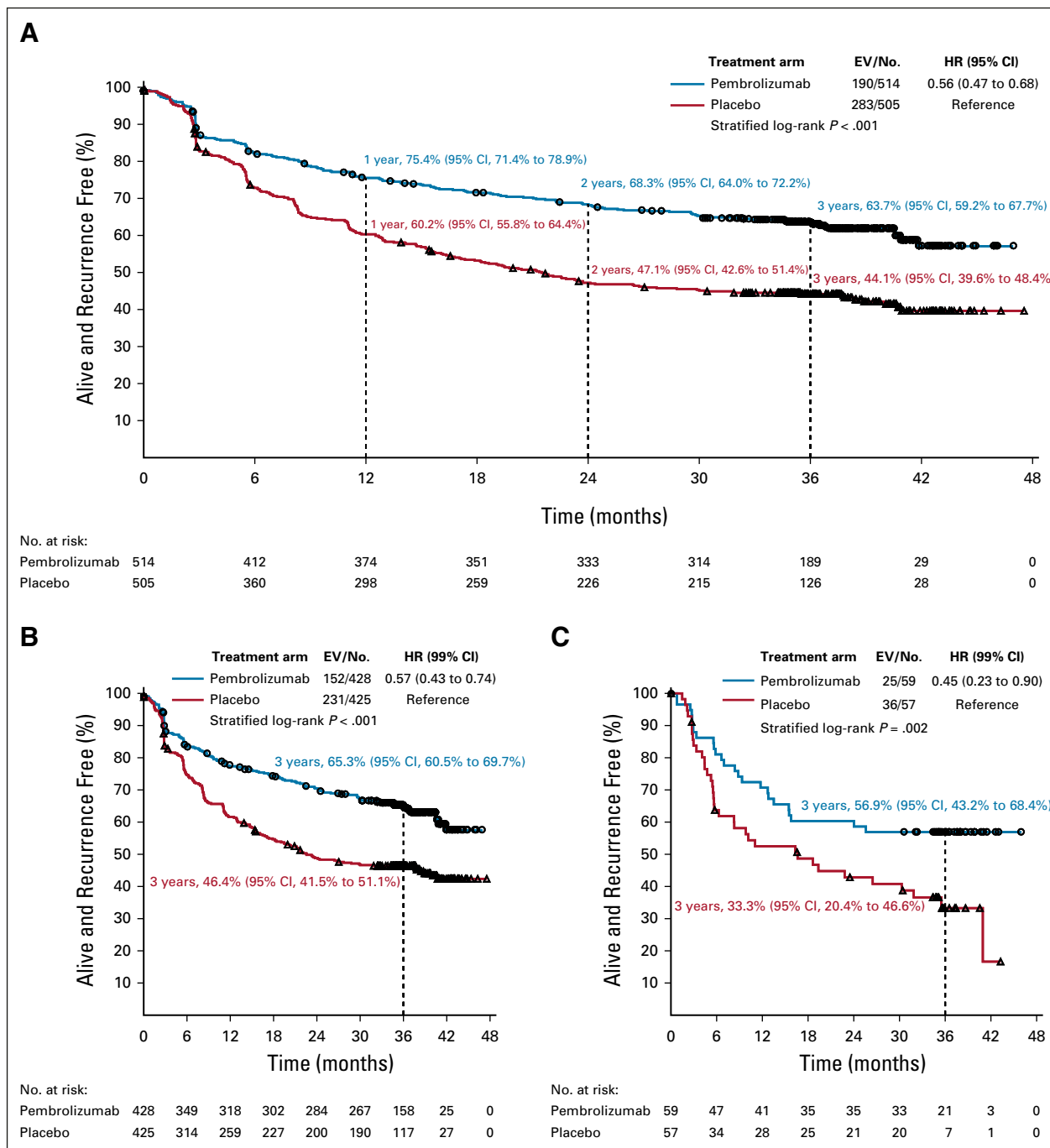
The treatment difference with regard to RFS was consistently observed across subgroups determined by all baseline characteristics (Fig 3; Data Supplement).

**RFS according to tumor PD-L1 expression.** In the 853 patients with PD-L1–positive tumors, the 3-year RFS rate was 65.3% (95% CI, 60.5% to 69.7%) in the pembrolizumab group and 46.4% (95% CI, 41.5% to 51.1%) in the placebo group (HR stratified by stage, 0.57; 99% CI, 0.43 to 0.74;  $P < .001$ ; Fig 2B). Pembrolizumab was also consistently effective in the 116 patients with PD-L1–negative tumors, with the 3-year RFS rate being 56.9% (95% CI, 43.2% to

68.4%) in the pembrolizumab group and 33.3% (95% CI, 20.4% to 46.6%) in the placebo group (HR stratified by stage, 0.45; 99% CI, 0.23 to 0.90; Fig 2C), and in those with an undetermined tumor PD-L1 expression (Fig 3).

**RFS according to AJCC-7 and AJCC-8.** The benefit of pembrolizumab was similar ( $P = .99$ ) in the three AJCC-7 subgroups (Fig 3). The HRs stratified by stage as indicated at random assignment were 0.50 (99% CI, 0.22 to 1.16), 0.56 (99% CI, 0.39 to 0.81), and 0.57 (99% CI, 0.40 to 0.81) in patients with stage IIIA, IIIB, and IIIC disease, respectively (Fig 4). The 3-year RFS rates in the pembrolizumab and placebo groups were 81.2% and 66.3% in the patients with stage IIIA, 65.7% and 47.0% in those with stage IIIB, and 54.3% and 32.3% in those with stage IIIC disease, respectively. The 99% CIs of these estimates are shown in Figures 4A-4C.

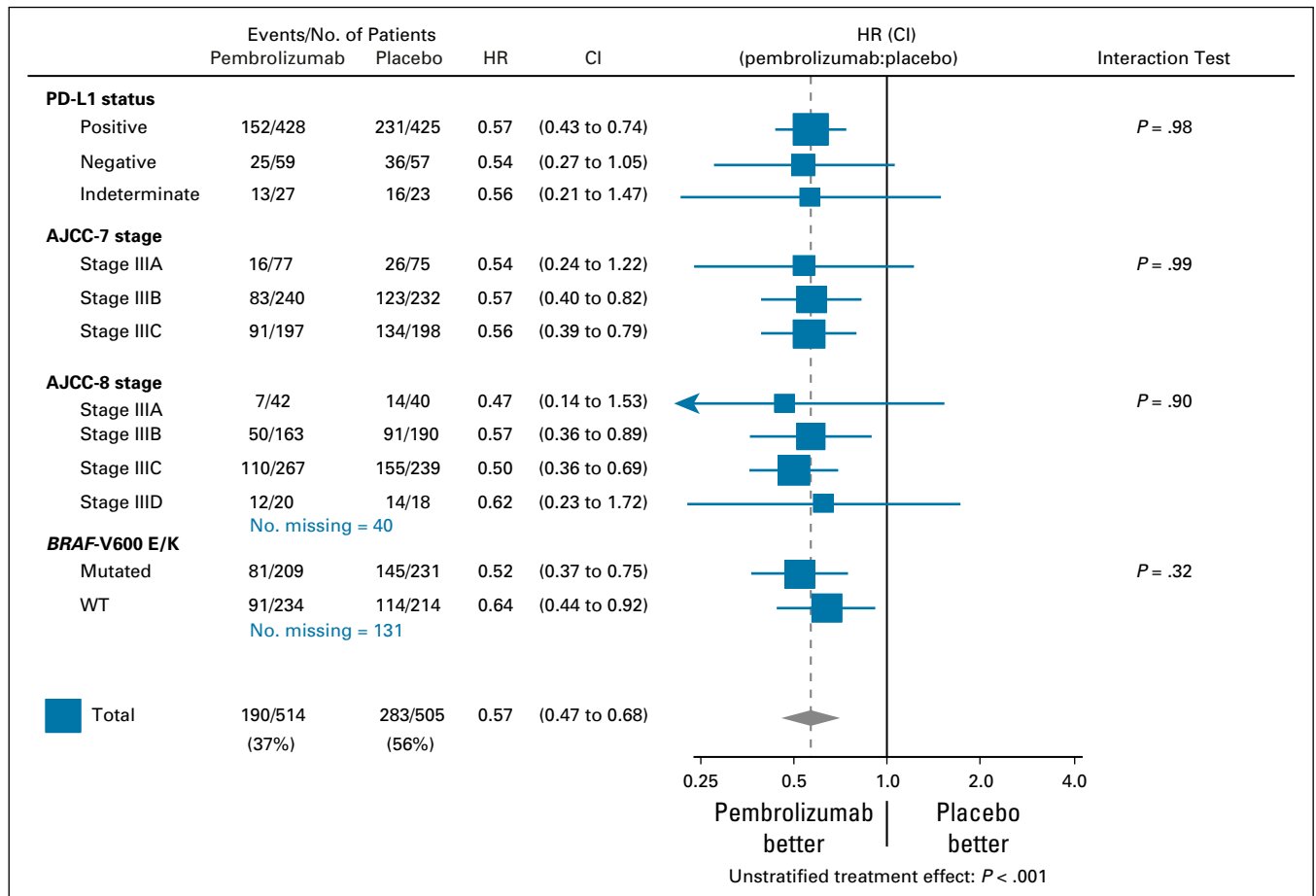
The benefit of pembrolizumab was similar ( $P = .90$ ) in the four AJCC-8 subgroups (Fig 3). The HRs stratified by stage provided at random assignment were 0.43 (99% CI, 0.13 to



**FIG 2.** Recurrence-free survival (RFS) by treatment group. (A) In the overall population and according to programmed cell death-ligand 1 (PD-L1) tumor status. (B) PD-L1 positive. (C) PD-L1 negative. EV/No., events/number of patients; HR, hazard ratio.

1.43), 0.57 (99% CI, 0.36 to 0.90), 0.51 (99% CI, 0.37 to 0.70), and 0.68 (99% CI, 0.24 to 1.91) in patients with stage IIIA, IIIB, IIIC, and IIID disease, respectively (Fig 5). The 3-year RFS rates in the pembrolizumab and placebo groups were 82.6% and 67.4% in the patients with stage IIIA, 70.4% and 51.7% in those with stage IIIB, 59.6% and 35.2% in those with stage IIIC, and 45.0% and 22.2% in those with stage IIID disease, respectively. The 99% CIs of these estimates are shown in Figures 5A-5D.

**RFS according to BRAF-V600<sup>EQ</sup> mutation status.** The benefit of pembrolizumab was consistent ( $P = .32$ ) according to BRAF status (Fig 3). In patients with BRAF-V600<sup>EQ</sup>-mutated melanoma the HR stratified by stage was 0.51 (99% CI, 0.36 to 0.73) and the 3-year RFS rates were 62.0% (95% CI, 54.9% to 68.3%) and 37.1% (95% CI, 30.8% to 43.4%) in pembrolizumab and placebo groups, respectively (Fig 6A). The approximate 1-, 2-, and 3-year RFS rate improvements were 15% (72.2% v 57.6%),



**FIG 3.** Forest plot of recurrence-free survival. AJCC, American Joint Committee on Cancer (seventh edition; AJCC-7; AJCC (eighth edition; AJCC-8), HR, hazard ratio; PD-L1, programmed cell death-ligand 1; WT, wild type.

25% (65.6% v 40.2%), and 25% (62.0% v 37.1%), respectively. In patients with *BRAF* wild-type melanoma the HR stratified by stage was 0.66 (99% CI, 0.46 to 0.95) and the estimated 3-year RFS rates in the pembrolizumab and placebo groups were 61.8% (95% CI, 55.1% to 67.8%) and 46.5% (95% CI, 39.6% to 53.2%), respectively (Fig 6B).

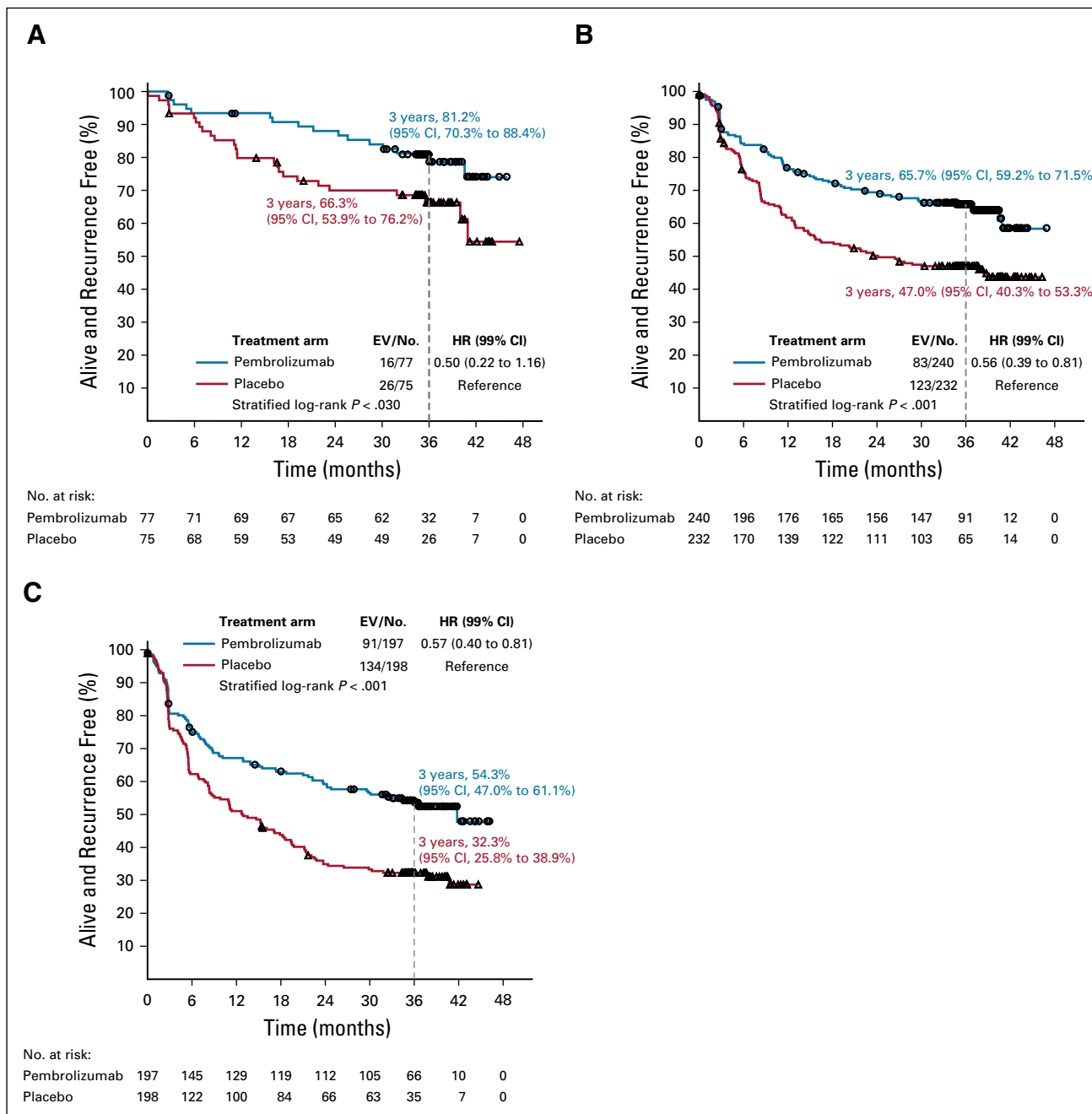
**RFS according to other variables.** The pembrolizumab benefit was also similar in patients with microscopic and macroscopic nodal involvement (test for interaction,  $P = .80$ ) and in patients with and without ulcerated melanomas (test for interaction,  $P = .38$ ). Age, sex, and baseline body mass index did not significantly influence the treatment difference (Data Supplement).

### Safety

At the time of the previous analysis, there were only 25 patients still receiving protocol treatment. Therefore, the incidence of the AEs already reported in the previous publication<sup>7</sup> remained almost unchanged in the current one. For instance, the treatment-related AEs of any grade occurred in 398 (78.8%) of 509 patients (two additional

patients) in the pembrolizumab group and in 333 (66.3%) of 502 patients (one additional patient) in the placebo group. Treatment-related grade 3-5 AEs were observed in 74 (14.5%) patients in the pembrolizumab group and 17 (3.4%) in the placebo group. There was one pembrolizumab-related death as a result of myositis.

Compared with the previous report, immune-related AEs (irAEs) of any grade occurred in two additional patients (ie, in 192 patients; 37.7%) in the pembrolizumab group and remained unchanged (9.0%) in the placebo group (Data Supplement). As in the previous report, an increased incidence of endocrine disorders was observed in the pembrolizumab group compared with the placebo group (23.4% v 5.0%); the most common endocrine disorders were hypothyroidism (14.5% v 2.6%) and hyperthyroidism (10.0% v 1.0%), and all were grade 1 or 2. The incidence of sarcoidosis was low (1.2% v 0%), and all occurrences were grade 1-2. The incidence of grade 3-4 irAEs remained low (7.7% v 0.6%), including colitis (2.2% v 0.2%), hypophysitis/hypopituitarism (0.6% v 0%), and type 1 diabetes mellitus (1.0% v 0%).



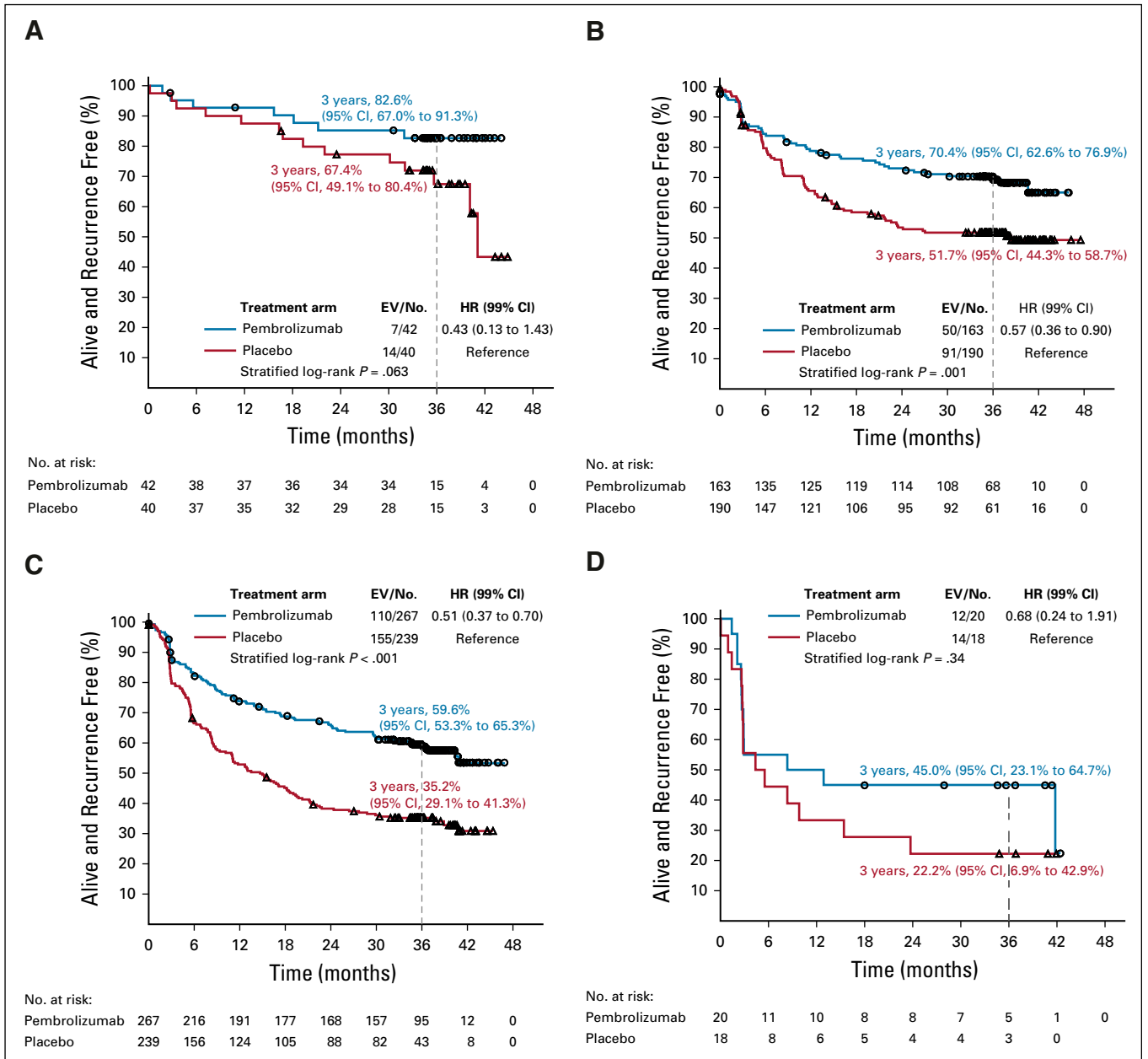
**FIG 4.** Recurrence-free survival by treatment group according to the American Joint Committee on Cancer Cancer Staging Manual (seventh edition; AJCC-7). (A) Stage IIIA. (B) Stage IIIB. (C) Stage IIIC. EV/No., events/number of patients; HR, hazard ratio.

## DISCUSSION

The analysis at 3-year median follow-up of the EORTC 1325/KEYNOTE-054 trial comparing adjuvant therapy with pembrolizumab with placebo in patients with resected high-risk stage III melanoma demonstrates a sustained RFS benefit. The updated HR estimate was 0.56, which is in line with the previous estimate of 0.57 as assessed at the 1.25-year median follow-up.<sup>7</sup> With regard to safety and irAEs, there were only a small number of additional cases compared with the initial report in 2018.<sup>7</sup> Therefore, we did not

re-analyze the positive association between irAEs and outcome in pembrolizumab-treated patients.<sup>17</sup>

The absolute difference in RFS rates between the pembrolizumab group and the placebo group increased from approximately 15% at 1 year to approximately 20% at 2 and 3 years. The benefit is consistent across all subgroups, in particular according to PD-L1 status, AJCC-7 and -8 staging, and *BRAF*-V600<sup>E/K</sup> status as illustrated in the forest plot (Fig 3). Predictive importance of ulceration status was weak; the HR observed in patients with ulcerated



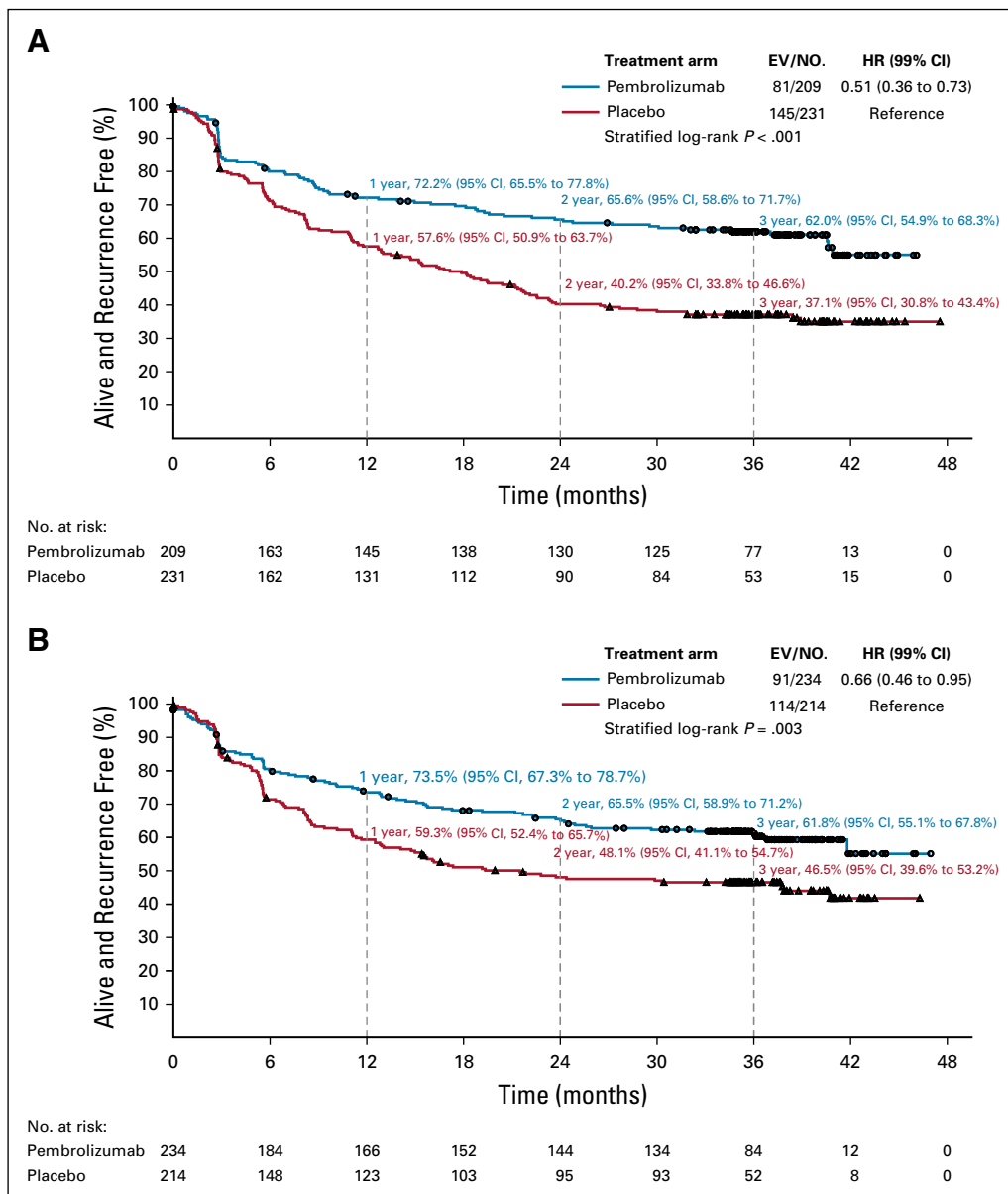
**FIG 5.** Recurrence-free survival by treatment group according to American Joint Committee on Cancer Cancer Staging Manual (eighth edition; AJCC-8). (A) Stage IIIA. (B) Stage IIIB. (C) Stage IIIC. (D) Stage IIID. EV/No., events/number of patients; HR, hazard ratio.

melanoma (0.54) was similar to the one in those with nonulcerated melanoma (0.64). This contrasts with adjuvant therapy with interferons (IFNs), where IFN sensitivity is probably limited to ulcerated melanoma as observed in retrospective studies.<sup>18-20</sup> This was recently substantiated by the results of the randomized adjuvant PEG-IFN EORTC 18081 trial in ulcerated stage II melanoma.<sup>21</sup> With regard to subgroup staging, it is interesting to observe that the estimated HR observed in the AJCC-7 stage IIIA subgroup (0.50) was lower than in the stage IIIB or IIIC subgroups and that among the four AJCC-8 subgroups, the lowest HR was reported in the best prognostic AJCC-8 IIIA subgroup

(0.43). This observation of a clear benefit is important because the indication of adjuvant therapy with anti-programmed death 1 in these best prognostic AJCC subgroups is debated because of the risk of chronic irAEs.<sup>22</sup>

Of note, in our EORTC 1325/KEYNOTE-054 trial, the estimated improvement of RFS as a result of pembrolizumab was larger in patients with *BRAF*-V600<sup>EK</sup> mutant melanoma (HR, 0.51) than in *BRAF* wild-type melanoma (HR, 0.66), with an increased difference in 3-year RFS rate of approximately 25% (62.0% v 37.1%) versus 15% (61.8% v 46.5%), respectively, versus placebo. It also indicates a lack of prognostic importance of *BRAF*-V600 mutation





**FIG 6.** Recurrence-free survival by treatment group. (A) *BRAF*-V600<sup>EK</sup> mutated melanoma. (B) *BRAF* wild-type melanoma. EV/No., events/number of patients; HR, hazard ratio.

status in the pembrolizumab group. In the advanced melanoma setting, Larkin et al<sup>23</sup> also showed that the nivolumab group had a 5-year overall survival (OS) rate of 46% and 43% in patients with *BRAF*-V600 mutant and wild-type melanoma, respectively, whereas in the nivolumab plus ipilimumab group, it was 60% and 48%, respectively. Of note, in patients with *BRAF*-V600 melanoma recruited in the COMBI-v trial (ClinicalTrials.gov identifier: [NCT01597908](https://clinicaltrials.gov/ct2/show/study/NCT01597908)), dabrafenib and trametinib combination yielded a lower 5-year OS rate (34%).<sup>24</sup> In addition, in patients with *BRAF*-V600 mutation in the pembrolizumab group of our EORTC 1325/KEYNOTE-054 trial, the 3-year RFS rate of 62% was practically identical to the 59% observed in the adjuvant dabrafenib plus trametinib combination arm of the COMBI-AD trial,<sup>8</sup> whereas the 3-year RFS

rates were practically identical in the respective placebo groups as well (37% v 40%). However, in each trial, the absolute RFS rate improvement changed over time: In the COMBI-AD trial,<sup>8</sup> the estimated RFS benefit of the *BRAF* and *MEK* inhibitor combination versus placebo was larger than in our trial at 1 year (32% v 15%) but was approximately the same at 2 years (23% v 25%) and inferior at 3 years (19% v 25%). This retrospective, indirect comparison would suggest a crossing of the RFS curve of dabrafenib plus trametinib combination with the one of pembrolizumab at approximately 30 months from the start of treatment, which would be similar to the crossing of the progression-free survival and OS curves at approximately 16 months in advanced melanoma in pooled analyses.<sup>2,25</sup>

Long-term RFS results are required to ascertain these preliminary findings.

Whether the association of RFS benefit and OS benefit in adjuvant trials in melanoma as established with IFNs and ipilimumab<sup>26</sup> will be upheld in the adjuvant trials with the more active drugs nivolumab, pembrolizumab, and the combination of dabrafenib and trametinib seems likely but has not been formally demonstrated at this point in time because of a lack of mature OS follow-up and a sufficient number of events. The EORTC 1325/KEYNOTE-054 trial is the only trial in which patients from the placebo arm could cross over at the time of recurrence and receive experimental treatment as part of the study protocol and, thus, will play an important role in addressing this question. Currently, CheckMate-915 is assessing the value of adjuvant combination therapy with nivolumab and ipilimumab

versus nivolumab in resected stage IIIB/CIV melanoma. A press release communicated that at interim analysis, the primary end point of RFS in the PD-L1–negative patient population was not met.<sup>27</sup> In resected stage IV melanoma, the combination nivolumab plus ipilimumab therapy seemed superior to nivolumab monotherapy in a randomized phase II trial, and both therapies were better than placebo.<sup>28</sup> Moreover, the current developments with neo-adjuvant immunotherapy create new opportunities in a constantly changing landscape of (neo)adjuvant therapy in melanoma.<sup>29-34</sup>

In conclusion, pembrolizumab adjuvant therapy in resected high-risk stage III melanoma provided at the 3-year median follow-up a sustained and clinically meaningful improvement in RFS. This finding was consistent across subgroups.

## AFFILIATIONS

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results From the EORTC 1325-MG/KEYNOTE-054 Trial**

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