

Association Between Immune-Related Adverse Events and Recurrence-Free Survival Among Patients With Stage III Melanoma Randomized to Receive Pembrolizumab or Placebo

A Secondary Analysis of a Randomized Clinical Trial

Alexander M. M. Eggermont, MD, PhD; Michal Kicinski, PhD; Christian U. Blank, MD, PhD; Mario Mandala, MD; Georgina V. Long, MD, PhD; Victoria Atkinson, MD; Stéphane Dalle, MD; Andrew Haydon, MD; Adnan Khattak, MD; Matteo S. Carlino, MD, PhD; Shahneen Sandhu, MD; James Larkin, MD; Susana Puig, MD, PhD; Paolo A. Ascierto, MD; Piotr Rutkowski, MD, PhD; Dirk Schadendorf, MD, PhD; Rutger Koornstra, MD; Leonel Hernandez-Aya, MD; Anna Maria Di Giacomo, MD; Alfonsus J. M. van den Eertwegh, MD; Jean-Jacques Grob, MD; Ralf Gutzmer, MD; Rahima Jamal, MD; Paul C. Lorigan, MD; Clemens Krepler, MD; Nageatte Ibrahim, MD; Sandrine Marreaud, MD; Alexander van Akkooi, MD, PhD; Caroline Robert, MD, PhD; Stefan Suci, PhD

+ Supplemental content

IMPORTANCE Whether immune-related adverse events (irAEs) indicate drug activity in patients treated with immune checkpoint inhibitors remains unknown.

OBJECTIVE To investigate the association between irAEs and recurrence-free survival (RFS) in the double-blind EORTC 1325/KEYNOTE-054 clinical trial comparing pembrolizumab therapy and placebo for the treatment of patients with high-risk stage III melanoma.

DESIGN, SETTING, AND PARTICIPANTS A total of 1019 adults with stage III melanoma were randomly assigned on a 1:1 ratio to receive treatment with pembrolizumab therapy or placebo. Eligible patients were adults 18 years and older with complete resection of cutaneous melanoma metastatic to lymph nodes, classified with stage IIIA (at least 1 micrometastasis measuring >1 mm in greatest diameter), IIIB, or IIIC (without in-transit metastasis) cancer. Patients were randomized from August 26, 2015, to November 14, 2016. The clinical cutoff for the data set was October 2, 2017. Analyses were then performed on the database, which was locked on November 28, 2017.

INTERVENTIONS Participants were scheduled to receive 200 mg of pembrolizumab or placebo every 3 weeks for a total of 18 doses for approximately 1 year or until disease recurrence, unacceptable toxic effects, major protocol violation, or withdrawal of consent.

MAIN OUTCOMES AND MEASURES The association between irAEs and RFS was estimated using a Cox model adjusted for sex, age, and AJCC-7 stage, with a time-varying covariate that had a value of 0 before irAE onset and 1 after irAE onset.

RESULTS Of 1011 patients who began treatment with pembrolizumab therapy or placebo, 622 (61.5%) were men and 389 (38.5%) were women; 386 patients (38.2%) were aged 50 to 64 years, 377 (37.3%) were younger than 50 years, and 248 (24.5%) were 65 years and older. Consistent with the reported main analysis in the intent-to-treat population, RFS was longer in the pembrolizumab arm compared with the placebo arm (hazard ratio [HR], 0.56; 98.4% CI, 0.43-0.74) among patients who started treatment. The incidence of irAEs was 190 (37.4%) in the pembrolizumab arm (n = 509) and 45 (9.0%) in the placebo arm (n = 502); in each treatment group, the incidence was similar for men and women. The occurrence of an irAE was associated with a longer RFS in the pembrolizumab arm (HR, 0.61; 95% CI, 0.39-0.95; $P = .03$) in both men and women. However, in the placebo arm, this association was not significant. Compared with the placebo arm, the reduction in the hazard of recurrence or death in the pembrolizumab arm was greater after the onset of an irAE than without or before an irAE (HR, 0.37; 95% CI, 0.24-0.57 vs HR, 0.61; 95% CI, 0.49-0.77, respectively; $P = .03$).

CONCLUSIONS AND RELEVANCE In this study, the occurrence of an irAE was associated with a longer RFS in the pembrolizumab arm.

TRIAL REGISTRATIONS ClinicalTrials.gov identifier: [NCT02362594](https://clinicaltrials.gov/ct2/show/study/NCT02362594); EudraCT identifier: [2014-004944-37](https://eudra.europa.eu/medres/eudra/identifier/index.jsp?identifier=EUCL18181)

JAMA Oncol. doi:[10.1001/jamaoncol.2019.5570](https://doi.org/10.1001/jamaoncol.2019.5570)
Published online January 2, 2020.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Stefan Suci, PhD, European Organisation for Research and Treatment of Cancer Headquarters, Avenue Mounier 83/11, 1200 Brussels, Belgium (stefan.suci@eortc.org).

Immune-related adverse events (irAEs) are commonly observed in patients treated with immunotherapies that include immune checkpoint inhibitors (ICIs), such as anti-CTLA-4 (anti-cytotoxic T-lymphocyte-associated protein 4) and anti-PD-L1 (anti-programmed cell death ligand 1).¹⁻⁴ Adverse events (AEs) related to autoimmunity have also been recognized in the context of treatments with other agents, such as interleukin-2^{5,6} and interferon.⁷⁻⁹

An association between irAEs and improved outcomes of patients treated with ICIs has been reported for both anti-CTLA-4 and anti-PD-1 (anti-programmed cell death 1), mostly in the context of melanoma¹⁰⁻¹³ and lung cancer.^{14,15} However, it remains uncertain whether these observations can be explained by the role of irAEs as an indicator of drug activity. These associations reported in advanced disease require validation in larger studies with prospectively collected data and a control group of patients who are not treated with ICIs. Furthermore, adequate statistical methods should be used, as a simple comparison of patients with and without irAEs is subject to bias and may produce spurious conclusions because patients who die or experience disease progression have a shorter follow-up period and less treatment exposure than those who do not.^{8,16} In addition, little is known regarding the impact of sex on the association between irAEs and outcomes of patients treated with ICIs; sex is a factor that has been reported to be associated with outcomes of patients treated with ICIs.¹⁷

The EORTC 1325/KEYNOTE-054 (EORTC 1325/KN-054) clinical trial demonstrated that treatment with adjuvant pembrolizumab therapy, compared with placebo, prolonged recurrence-free survival (RFS) in patients with stage III melanoma.¹⁸ In this study, we investigated the association between irAEs and RFS in the EORTC 1325/KN-054 clinical trial. We performed separate analyses by treatment and sex and investigated the influence of systemic steroid use on the outcome. The trial protocol is available in [Supplement 1](#).

Methods

Patients

Details of the inclusion criteria and study design have been previously reported.¹⁸ In brief, patients 18 years and older with completely resected histologically confirmed cutaneous melanoma metastatic to regional lymph nodes were eligible to participate in the EORTC 1325/KN-054 clinical trial. Patients had either stage IIIA (those with category N1a or N2a had to have at least 1 micrometastasis measuring >1 mm in greatest diameter), IIIB, or IIIC (excluding those with in-transit metastasis) disease according to the 2009 classification in *AJCC Cancer Staging Manual*, 7th edition (*AJCC-7*).^{14,19} Complete regional lymphadenectomy was required within 13 weeks before the start of treatment. Exclusion criteria included having an Eastern Cooperative Oncology Group performance-status score of more than 1, an autoimmune disease, uncontrolled infections, systemic corticosteroid use, and previous systemic therapy for melanoma.

Key Points

Question Are immune-related adverse events associated with recurrence-free survival in patients with high-risk stage III melanoma treated with pembrolizumab therapy compared with placebo?

Findings In this secondary analysis of a randomized clinical trial of 1019 adults with stage III melanoma, the occurrence of an immune-related adverse event was associated with longer recurrence-free survival among both men and women in the pembrolizumab arm. However, in the placebo arm, this association was not significant.

Meaning These findings suggest that the occurrence of an immune-related adverse event is an indicator of pembrolizumab activity in patients with high-risk stage III melanoma.

Study Design and Randomization

Patients were randomly assigned on a 1:1 ratio to receive either an intravenous infusion of 200 mg of pembrolizumab therapy or placebo every 3 weeks for a total of 18 doses (approximately 1 year) or until disease recurrence, unacceptable toxic effects, major protocol violation, or withdrawal of consent. Registration was conducted centrally at the European Organisation for Research and Treatment of Cancer (EORTC) headquarters. Randomization was stratified by the patient's cancer stage (stage IIIA, IIIB, or IIIC with 1-3 positive lymph nodes or stage IIIC with >3 positive lymph nodes) and geographic region (17 regions, each comprising 1-3 countries). Only the local pharmacists were aware of trial-group assignments, whereas the clinical investigators, patients, and individuals collecting or analyzing the data were not. The study was approved by independent ethics committees of all participating institutions (eTable 7 in [Supplement 2](#)) and conducted in accordance with the Declaration of Helsinki²⁰ and the *Guideline for Good Clinical Practice*.²¹ All patients provided written informed consent.

The primary end point of the clinical trial was RFS. Patients were randomized from August 26, 2015, to November 14, 2016. The clinical cutoff for the data set was October 2, 2017. Analyses were then performed on the database, which was locked on November 28, 2017.

Assessment

Computed tomography and/or magnetic resonance imaging was performed every 12 weeks for the first 2 years, every 6 months through year 5, and annually thereafter. Recurrence or metastatic lesions had to be histologically confirmed whenever possible. Recurrence-free survival was defined as the time from randomization until the date of first recurrence (local, regional, or distant metastasis) or death from any cause. For patients without any RFS event (recurrence or death), the follow-up was censored at the last disease evaluation.

The severity of AEs was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. The irAE terms were predefined in the study and were AEs that appeared to be associated with the mechanism of action of pembrolizumab. The following 3

groups of irAEs were considered: (1) any irAE (endocrine AE, pneumonitis/interstitial lung disease, sarcoidosis, vitiligo, severe skin reaction, colitis, pancreatitis, hepatitis, nephritis, uveitis, myositis, or myocarditis); (2) endocrine AE (hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, type 1 diabetes, or adrenal insufficiency); and (3) vitiligo. The irAEs were reported between the start of treatment and 30 days after the last dose of treatment for all AEs and 90 days after the last dose of treatment for serious AEs.

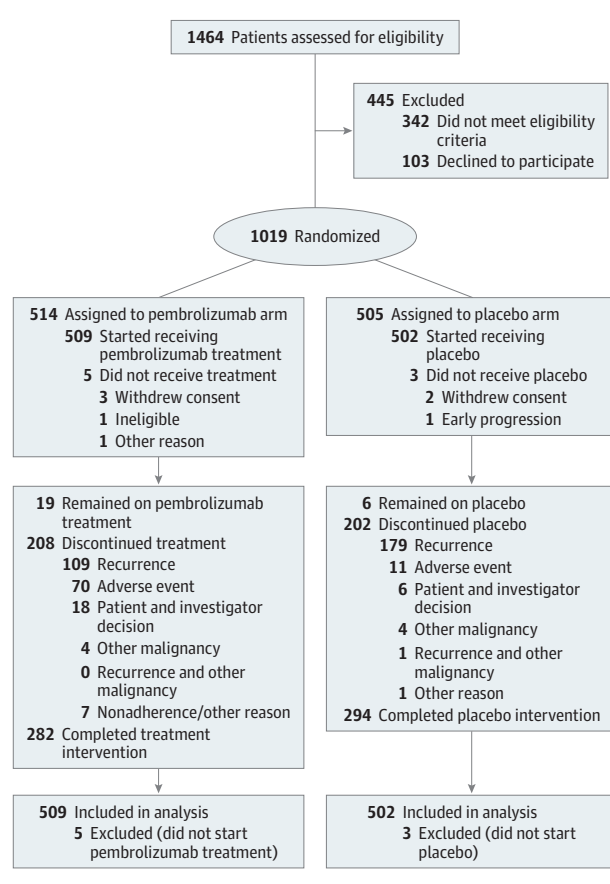
Statistical Methods

The standard Cox model, stratified by cancer stage as provided at the time of randomization, was used to compare placebo to pembrolizumab therapy among patients who started the treatment.²² Cox models, which included a time-varying covariate that had a value of 0 before the irAE onset and 1 after the irAE onset, were used to estimate the association between the occurrence of irAEs and RFS (for patients who did not experience any irAE, this covariate had a value of 0 during the entire follow-up period). Two models were fitted. Model 1 included the treatment indicator, the time-varying irAEs indicator, and the interaction term between these 2 variables. This model was used to estimate the hazard ratios (HRs) and 95% CIs for RFS associated with the occurrence of an irAE in the pembrolizumab and placebo arms. The difference in the association of irAEs and RFS between the 2 arms (ie, the difference between the 2 HRs) was investigated by testing whether the interaction term in the model was significantly different from 0. Model 2 included only the treatment indicator and the product of the treatment indicator and the time-varying irAEs indicator, and this model was used to estimate the HR for the randomized treatment in the presence and absence of irAEs. All models studying the effect of irAEs were adjusted for AJCC-7 stage provided at randomization (stage IIIA, IIIB, or IIIC with 1-3 positive lymph nodes and stage IIIC with >3 positive lymph nodes), sex, and age (<50, 50-64, and ≥65 years).

In addition, the influence of steroid use on the study conclusions was investigated by adding the product of the treatment indicator, the time-varying irAE indicator, and the time-varying steroid indicator to the model. Steroid use was modeled using a time-varying covariate that had a value of 1 after day 30 of systemic steroid use and a value of 0 by day 30 (and for patients who did not receive any systemic steroids). In the sensitivity analysis, we replaced the 30-day threshold with 14 days. No evidence of nonproportional hazards was found in any of the models.

The Aalen-Johansen estimator was used to estimate the cumulative incidence of an on-study irAE from the start of treatment.²³ The Fine and Gray model was used to investigate the effect of treatment on the incidence of irAEs.²³ A model that included the treatment arm, the covariate of interest, and the interaction term was used to test the difference in the effect of treatment on the incidence of irAEs between subgroups and to estimate the subdistribution HR within each subgroup. The earliest of the last date of treatment plus 91 days and the date of death was used as the date of a competing event.

Figure 1. CONSORT Diagram



All analyses were 2-sided with a significance threshold of $P = .05$ and were performed using SAS software, version 9.4 (SAS Institute).

Results

Among 1019 randomized patients, 1011 commenced treatment as allocated by randomization and were included in this analysis (Figure 1). Of those, 622 patients (61.5%) were men and 389 (38.5%) were women; 386 patients (38.2%) were aged 50 to 64 years, 377 (37.3%) were younger than 50 years, and 248 (24.5%) were 65 years and older. The characteristics of these 1011 patients were well balanced in the 2 treatment groups (Table 1). The median follow-up was 15 months (interquartile range, 13-17 months).

Incidence of irAEs

As previously reported,¹⁸ among patients who started the randomized treatment, the incidence of grade 1 or higher irAEs in the pembrolizumab arm ($n = 509$) was 19.4% (95% CI, 16.1%-23.0%) at 3 months and 37.4% (95% CI, 33.2%-41.6%) at 15 months and in the placebo arm ($n = 502$) was 4.0% (95% CI, 2.5%-6.0%) at 3 months and 9.0% (95% CI, 6.7%-11.7%) at 15 months (Table 2 and Figure 2A). The onset of the first irAE occurred within the first 6 months of treatment for most of the

Table 1. Characteristics of Patients Who Started Treatment

Characteristic	Treatment Arm, No. (%) ^a	
	Pembrolizumab (n = 509)	Placebo (n = 502)
Sex		
Male	320 (62.9)	302 (60.2)
Female	189 (37.1)	200 (39.8)
Age, y		
<50	192 (37.7)	185 (36.9)
50-64	193 (37.9)	193 (38.4)
≥65	124 (24.4)	124 (24.7)
BMI		
<25	154 (30.3)	182 (36.3)
25-29.9	222 (43.6)	194 (38.6)
≥30	121 (23.8)	123 (24.5)
Unknown	12 (2.4)	3 (0.6)
AJCC-7 stage at randomization		
III A	80 (15.7)	80 (15.9)
III B	233 (45.8)	228 (45.4)
III C (1-3 LN*)	95 (18.7)	92 (18.3)
III C (>3 LN*)	101 (19.8)	102 (20.3)
AJCC-7 stage at baseline		
III A	77 (15.1)	76 (15.1)
III B	236 (46.4)	230 (45.8)
III C (1-3 LN*)	87 (17.1)	94 (18.7)
III C (>3 LN*)	109 (21.4)	102 (20.3)
Type of LN involvement at baseline		
Microscopic	185 (36.3)	161 (32.1)
Macroscopic	324 (63.7)	341 (67.9)
No. of LNs involved at baseline		
1	224 (44.0)	236 (47.0)
2-3	176 (34.6)	164 (32.7)
>3	109 (21.4)	102 (20.3)
Ulceration of primary tumor at baseline		
No	228 (44.8)	250 (49.8)
Yes	207 (40.7)	196 (39.0)
Unknown	74 (14.5)	56 (11.2)
PD-L1		
Positive	423 (83.1)	423 (84.3)
Negative	59 (11.6)	57 (11.4)
Indeterminate	27 (5.3)	22 (4.4)

Abbreviations: AJCC-7, AJCC Cancer Staging Manual, 7th edition; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LN, lymph node; LN*, positive lymph node; PD-L1, programmed cell death ligand 1.

^a Totals may not equal 100% because of rounding.

patients who experienced an irAE. The most common irAEs included endocrine disorders (in particular, hypothyroidism and hyperthyroidism) and vitiligo. In both treatment arms, the incidence of irAEs was similar for men (36.6% [pembrolizumab arm]) and women (38.6% [pembrolizumab arm]; Table 2 and eTable 1 in Supplement 2), for younger and older patients (eTable 2 in Supplement 2), and across different disease stages (eTable 3 in Supplement 2). The exposure to pembrolizumab therapy compared with placebo resulted in similar increases

in the incidence of irAEs in all of these subgroups of patients (Figure 2B).

Among patients who experienced an irAE, 33 of 190 in the pembrolizumab arm and 6 of 45 in the placebo arm discontinued treatment owing to an irAE. Among patients with an endocrine irAE, 9 of 119 in the pembrolizumab arm and 1 of 25 in the placebo arm discontinued treatment owing to an irAE. Among patients with vitiligo, only 1 from the pembrolizumab arm discontinued treatment owing to an irAE (pneumonitis, not vitiligo). Among patients with grade 3 or higher irAEs, 19 of 36 from the pembrolizumab arm and 3 of 3 from the placebo arm discontinued treatment owing to an irAE.

Treatment, irAEs, and RFS

The EORTC 1325/KN-054 study previously reported that treatment with pembrolizumab therapy resulted in a longer RFS in the intent-to-treat population (HR, 0.57; 98.4% CI, 0.43-0.74).¹⁶ Consistent with these results, a prolonged RFS was observed in the pembrolizumab compared with the placebo arm in patients who started the treatment allocated at randomization (HR, 0.56; 98.4% CI, 0.43-0.74).

Based on model 1, the occurrence of an irAE was associated with a longer RFS in the pembrolizumab arm (HR, 0.61; 95% CI, 0.39-0.95; $P = .03$) but not in the placebo arm (HR, 1.37; 95% CI, 0.82-2.29; $P = .21$). The difference between the 2 HRs was unlikely due to chance ($P = .02$). Compared with the placebo arm, the reduction in the hazard of recurrence or death was greater ($P = .03$) after the onset of an irAE (HR, 0.37; 95% CI, 0.24-0.57) than without or before the onset of an irAE (HR, 0.62; 95% CI, 0.49-0.78) in patients who started pembrolizumab treatment (model 2 in Table 3). Similar results were obtained in each sex group. In men, the estimated HR was 0.36 (95% CI, 0.21-0.63) after the onset of an irAE and 0.59 (95% CI, 0.44-0.79) without or before the onset of an irAE compared with the entire group of patients in the placebo arm. In women, the 2 HR estimates were 0.42 (95% CI, 0.22-0.82) after the onset of an irAE and 0.71 (95% CI, 0.48-1.04) without or before the onset of an irAE.

Comparable results were obtained when only endocrine AEs were considered (Table 3). Patients treated with pembrolizumab therapy appeared to have a particularly low risk of recurrence or death after a vitiligo onset (HR, 0.13; 95% CI, 0.02-0.95). However, because only 24 patients from the pembrolizumab arm developed vitiligo, large uncertainty existed about this estimate, as reflected by the width of the CI. The occurrence of a severe irAE among patients treated with pembrolizumab therapy was not significantly associated with a prolonged RFS (Table 3).

Treatment, irAEs, Systemic Steroids, and RFS

Systemic steroids were used 30 days or longer from the start of the randomized treatment until 90 days from the last dose of treatment in 94 of 509 patients (18.5%) from the pembrolizumab arm and 25 of 502 patients (5.0%) from the placebo arm. Among patients with an irAE, systemic steroids were used 30 days or longer in 63 of 190 patients (33.2%) from the pembrolizumab arm and 5 of 45 patients (11.1%) from the placebo arm (eTable 4 in Supplement 2). Common irAEs among the 63 pa-

Table 2. Immune-Related Adverse Events in Each Treatment Arm by Sex

Adverse Event	Treatment Arm, No. (%)			
	Pembrolizumab		Placebo	
	Men (n = 320)	Women (n = 189)	Men (n = 302)	Women (n = 200)
Any immune-related event	117 (36.6)	73 (38.6)	22 (7.3)	23 (11.5)
Endocrine disorder	70 (21.9)	49 (25.9)	10 (3.3)	15 (7.5)
Hypothyroidism	41 (12.8)	32 (16.9)	4 (1.3)	10 (5.0)
Hyperthyroidism	30 (9.4)	22 (11.6)	2 (0.7)	4 (2.0)
Thyroiditis	11 (3.4)	5 (2.6)	1 (0.3)	0
Hypophysitis (including hypopituitarism)	4 (1.3)	7 (3.7)	1 (0.3)	0
Type 1 diabetes	3 (0.9)	2 (1.1)	0	0
Adrenal insufficiency	4 (1.3)	1 (0.5)	2 (0.7)	2 (1.0)
Respiratory/thoracic disorder	17 (5.3)	7 (3.7)	2 (0.7)	1 (0.5)
Pneumonitis or interstitial lung disease	12 (3.8)	5 (2.6)	2 (0.7)	1 (0.5)
Sarcoidosis	5 (1.6)	2 (1.1)	0	0
Skin disorder	20 (6.3)	7 (3.7)	3 (1.0)	5 (2.5)
Vitiligo	18 (5.6)	6 (3.2)	3 (1.0)	5 (2.5)
Severe skin reaction	2 (0.6)	1 (0.5)	0	0
Gastrointestinal disorder	11 (3.4)	9 (4.8)	4 (1.3)	0
Colitis	10 (3.1)	9 (4.8)	3 (1.0)	0
Pancreatitis	2 (0.6)	0 (0.0)	1 (0.3)	0
Hepatobiliary disorder	4 (1.3)	5 (2.6)	1 (0.3)	0
Hepatitis	4 (1.3)	5 (2.6)	1 (0.3)	0
Other disorder	9 (2.8)	6 (3.2)	3 (1.0)	2 (1.0)
Nephritis	1 (0.3)	1 (0.5)	0	1 (0.5)
Uveitis	1 (0.3)	1 (0.5)	0	0
Myositis	0	1 (0.5)	1 (0.3)	0
Myocarditis	1 (0.3)	0	0	0

tients in the pembrolizumab arm, for which systemic steroids were used, included 18 incidents (28.6%) of colitis, 13 (20.6%) of pneumonitis, 9 (14.3%) of hypophysitis, 4 (6.3%) of hepatitis, and 4 (6.3%) of hyperthyroidism. In the placebo arm, 2 patients received systemic steroids to treat pneumonitis, 1 to treat hepatitis, 1 to treat colitis, and 1 to treat adrenal insufficiency. Among those with grade 3 or higher irAEs, 26 of 36 patients from the pembrolizumab arm received systemic steroids for 30 days or longer. Compared with the placebo arm, the estimated HR was 0.50 (95% CI, 0.23-1.07) after an irAE onset and after day 30 of systemic steroid use and 0.34 (95% CI, 0.21-0.56) after an irAE onset and without systemic steroid use or by day 30 of steroid use (modified model 2 in eTable 5 in Supplement 2). In the sensitivity analysis, in which the 30-day threshold was replaced by 14 days, the 2 estimates were closer to each other (eTable 6 in Supplement 2).

Discussion

We evaluated the association between irAEs and patient outcomes in a double-blind randomized clinical trial comparing treatment with pembrolizumab therapy and placebo in patients with high-risk stage III melanoma. Compared with the placebo arm, the reduction in the hazard of recurrence or death in the pembrolizumab arm was substantially higher after the onset of an irAE (HR, 0.37; 95% CI, 0.24-0.57) than without

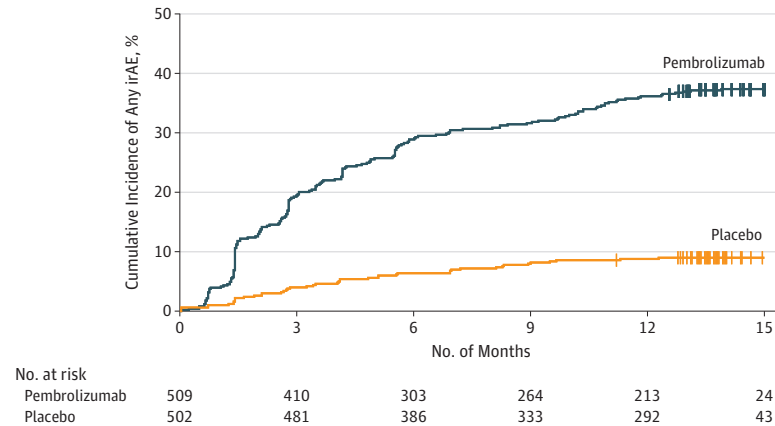
or before the onset of an irAE (HR, 0.61; 95% CI, 0.49-0.77). A similar pattern was observed for men and women. In the placebo arm, no association between irAEs and RFS was found.

Knowledge about the indicators of ICI activity in patients with adjuvant melanoma is of substantial importance. Treatment with ICIs has been previously associated with improved outcomes for patients with advanced melanoma,²⁴ has indicated efficacy in the adjuvant setting, and is becoming the standard of care among patients with high-risk stage III melanoma. In the EORTC 18071 study, which had a median follow-up period of 5.3 years, treatment with adjuvant ipilimumab therapy was associated with prolonged RFS (HR, 0.76; 95% CI, 0.64-0.89) and overall survival (HR, 0.72; 95% CI, 0.58-0.88) compared with placebo.²⁵ The EORTC 1325/KN-054 study reported an improvement in RFS (HR, 0.57; 98.4% CI, 0.43-0.74) among patients randomized to be treated with pembrolizumab therapy compared with placebo.¹⁸ The Checkmate 238 study reported an improvement in RFS (HR, 0.65; 97.56% CI, 0.51-0.83) in patients treated with nivolumab therapy compared with ipilimumab therapy.²⁶

Our observation of an association between irAEs and better outcomes among patients treated with ICIs is in line with previous studies of patients with advanced melanoma¹⁰⁻¹³ and lung cancer.^{14,15} An association between autoimmunity and patient outcomes has also been reported for other immunotherapies, including interleukin-2,⁶ interferon,^{7,27} and intralosomal talimogene laherparepvec injection.²⁸ Unfortunately,

Figure 2. Incidence of Immune-Related Adverse Events by Treatment Arm Among All Patients and Subgroups of Patients

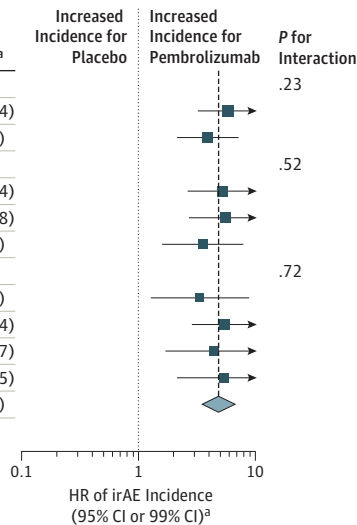
A Cumulative incidence of irAEs by treatment arm in all patients



B Hazard ratios of irAE incidence by subgroups

Source	Pembrolizumab Arm		Placebo Arm		HR (95% or 99% CI) ^a
	Events, No.	Patients, No.	Events, No.	Patients, No.	
Sex					
Male	117	320	22	302	5.96 (3.27-10.84)
Female	73	189	23	200	4.01 (2.17-7.40)
Age, y					
<50	76	192	17	185	5.33 (2.67-10.64)
50-64	72	193	15	193	5.71 (2.74-11.88)
≥65	42	124	13	124	3.62 (1.61-8.13)
Cancer stage at randomization					
III A	27	80	9	80	3.42 (1.27-9.18)
III B	87	233	18	228	5.63 (2.90-10.94)
III C (1-3 LN+)	35	95	9	92	4.53 (1.71-11.97)
III C (>3 LN+)	41	101	9	102	5.57 (2.16-14.35)
Total	190	509	45	502	4.95 (3.58-6.85)

Unadjusted treatment effect, $P < .001^b$



A, In the pembrolizumab arm (n = 509), 190 irAEs occurred, with a percentage incidence of 19.4% (95% CI, 16.1%-23.0%) at 3 months and 37.4% (95% CI, 33.2%-41.6%) at 15 months. In the placebo arm (n = 502), 45 irAEs occurred, with a percentage incidence of 4.0% (95% CI, 2.5%-6.0%) at 3 months and 9.0% (95% CI, 6.7%-11.7%) at 15 months. Vertical lines correspond to the time of censoring. B, The estimate of the subdistribution hazard ratio in the whole sample is based on an unstratified model with treatment as the only covariate. Blue boxes are centered on the estimated subdistribution hazard ratios. The green diamond is centered on the overall subdistribution hazard ratio (dashed line) and covers its 95% CI. HR indicates hazard ratio; irAE, immune-related adverse event; and LN+, positive lymph node.

^a For the whole sample estimate, a 95% CI is shown. For subgroups, 99% CIs are presented.

^b $P < .001$ corresponds only to the overall comparison, performed on all patients: HR, 4.95 (99% CI, 3.58-6.85).

many of these studies analyzed the data by comparing patients with and without irAEs using a log-rank test or a standard Cox model, which introduces a bias owing to the different follow-up times and treatment exposures between patients who did and did not develop irAEs. As previously reported, the size of that bias may be large enough to dramatically change the study conclusion.^{8,9,29} In this analysis, we dealt with this problem by using a time-dependent Cox model. Landmark analysis comparing the RFS after a landmark point in time from randomization (eg, 3 or 6 months) between patients with and without irAEs before that time would be a possible alternative approach. We did not use this method, as it excludes patients with an RFS event before the landmark time and misclassifies those who experience an irAE after the landmark time, leading to a substantially lower statistical power compared with the method using the time-dependent Cox model.

A recent meta-analysis of patients with advanced or metastatic melanoma reported a higher ICI efficacy regarding overall survival for men (HR, 0.66; 95% CI, 0.55-0.79) compared with women (HR, 0.79; 95% CI, 0.70-0.90).¹⁷ In our adjuvant study, the treatment HR regarding RFS was 0.53 (99% CI, 0.37-0.76) for men and 0.62 (99% CI, 0.39-1.00) for women.¹⁸ It has been suggested that the toxic effects profile for ICI may also be different for men than women.³⁰ In our study, the incidence of irAEs was similar for men (36.6%) and women (38.6%) in the pembrolizumab arm.

Patients with a history of pneumonitis or autoimmune disease in the past 2 years that required systemic treatment with steroids were not eligible to participate in our study. Because steroids are known to be immune-suppressive, treatment with pembrolizumab therapy was expected to be less effective in those patients. Consistent with that expectation, the esti-

mated treatment effect compared with placebo after an irAE onset and after day 30 of systemic steroid use (HR, 0.50; 95% CI, 0.23-1.07) appeared to be lower than the treatment effect after an irAE onset and without steroid use or by day 30 of systemic steroid use (HR, 0.34; 95% CI, 0.21-0.56). Previous studies reported an association between steroid use at the start of treatment with anti-PD-1 therapies because of disease conditions, such as brain metastasis and pulmonary disease, and poorer outcomes in lung cancer patients.^{31,32}

Strengths and Limitations

Our study has a number of strengths. First, the data were prospectively collected in the framework of a clinical trial with high-quality standards regarding assessment of disease and evaluation of AEs. Second, the study had a large sample that allowed a precise estimation of the association between irAEs and patient outcomes as well as subgroup analyses by sex. Third, we used adequate statistical methods to avoid bias that may have resulted from the differences in the duration of follow-up and the treatment exposure between patients who did and did not develop irAEs, and we adjusted the analyses for possible confounders, including cancer stage, age, and sex.

We were unable to explore the importance of some types of irAEs (eg, severe skin reactions) owing to the insufficient number of patients who experienced them. For the same reason, we could not investigate the effects of the characteristics (eg, type, dose, and duration of administration) of the systemic steroid treatments on the outcome.

Conclusions

Our study observed a strong association between irAEs and outcomes of patients with high-risk stage III melanoma who were treated with ICIs, which adds to the growing amount

Table 3. Treatment Effect in the Presence and Absence of Immune-Related Adverse Events

Immune-Related Adverse Event Status and Treatment Arm	Recurrence-Free Survival, HR (95% CI) ^a	P Value ^{a,b}
Any irAE		
Placebo	1	
Pembrolizumab without/before irAE	0.62 (0.49-0.78)	.03
Pembrolizumab after irAE onset	0.37 (0.24-0.57)	
Endocrine irAE		
Placebo	1	
Pembrolizumab without/before irAE	0.60 (0.48-0.75)	.03
Pembrolizumab after irAE onset	0.34 (0.20-0.57)	
Vitiligo		
Placebo	1	
Pembrolizumab without/before irAE	0.57 (0.46-0.70)	.15
Pembrolizumab after irAE onset	0.13 (0.02-0.95)	
Any severe (grade 3-4) irAE		
Placebo	1	
Pembrolizumab without/before irAE	0.55 (0.44-0.68)	.43
Pembrolizumab after irAE onset	0.78 (0.32-0.91)	

Abbreviations: HR, hazard ratio; irAE, immune-related adverse event.

^a A Cox model, which included a time-varying covariate for irAEs, the product of this covariate and the treatment indicator, and the patients' cancer stage, sex, and age, was used (model 2, see Statistical Methods).

^b P value was calculated for the test of a difference in the effect of the randomized treatment in the presence and absence of irAEs among the pembrolizumab-treated patients (ie, the difference between the 2 HRs).

of evidence that irAEs are indicators of greater ICI activity. However, in the absence of an irAE, patients in the pembrolizumab arm had a lower risk of recurrence or death compared with those in the placebo arm.

ARTICLE INFORMATION

Accepted for Publication: October 15, 2019.

Published Online: January 2, 2020.
doi:10.1001/jamaoncol.2019.5570

Open Access: This is an open access article distributed under the terms of the [CC-BY-NC-ND License](#). © 2020 Eggermont AMM et al. *JAMA Oncology*.

Author Affiliations: Gustave Roussy Cancer Campus Grand Paris, Université Paris-Saclay, Villejuif, France (Eggermont, Robert); European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium (Kicinski, Marreaud, Suci); Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands (Blank, van Akkooi); Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy (Mandala); Melanoma Institute Australia, University of Sydney and Mater and Royal North Shore Hospitals, Sydney, New South Wales, Australia (Long); Princess Alexandra Hospital, University of Queensland, Brisbane, Queensland, Australia (Atkinson); Hospices Civils de Lyon Cancer Institute, Lyon University, Lyon, France (Dalle); Alfred Hospital, Melbourne, Victoria, Australia (Haydon); Fiona Stanley Hospital, University of Western

Australia, Perth, Washington, Australia (Khattak); Westmead and Blacktown Hospitals, Melanoma Institute Australia and the University of Sydney, New South Wales, Australia (Carlino); Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia (Sandhu); Royal Marsden Hospital, London, United Kingdom (Larkin); Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain (Puig); Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy (Ascierto); Maria Skłodowska-Curie Institute Cancer Centre and Institute of Oncology, Warsaw, Poland (Rutkowski); University Hospital Essen, Essen, Germany (Schadendorf); Germany and German Cancer Consortium of Translational Cancer Research, Heidelberg, Germany (Schadendorf); Radboud University Medical Center Nijmegen, Nijmegen, Netherlands (Koonstra); Washington University School of Medicine, St Louis, Missouri (Hernandez-Aya); Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy (Di Giacomo); Vrije Universiteit Medical Center Amsterdam, Amsterdam, Netherlands (van den Eertwegh); Hospital de la Timone, Aix-Marseille University, Marseille, France (Grob); Skin Cancer Center, Hannover Medical School, Hannover, Germany (Gutzmer); Centre de Recherche, Centre

Hospitalier de l'Université de Montreal, Montreal, Quebec, Canada (Jamal); Christie NHS Foundation Trust, Manchester, United Kingdom (Lorigan); Merck & Co, Kenilworth, New Jersey (Krepler, Ibrahim).

Author Contributions: Drs Robert and Suci had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Eggermont, Kicinski, Long, Khattak, Lorigan, Marreaud, Robert, Suci.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Eggermont, Kicinski, Mandala, Khattak, Larkin, Hernandez-Aya, van Akkooi, Suci.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Eggermont, Kicinski.

Administrative, technical, or material support: Blank, Mandala, Carlino, Sandhu, Larkin, Rutkowski, Schadendorf, Koonstra, van den Eertwegh, Krepler, van Akkooi.

Supervision: Eggermont, Mandala, Atkinson, Haydon, Ascierto, Rutkowski, Koonstra, Lorigan, Ibrahim, Marreaud, van Akkooi, Suci.

Conflict of Interest Disclosures: Dr Eggermont reported being the study chair of the EORTC 18071 phase 3 clinical trial of ipilimumab therapy vs placebo in patients with stage III melanoma and receiving personal fees from Actelion, Agenus, Amgen, Bayer, Biogen, Bristol-Myers Squibb, Catalym, Celldex, Gilead Sciences, GlaxoSmithKline, HalioDx, Incyte, IO Biotech, ISA Pharmaceuticals, MedImmune, Merck Sharpe & Dohme, Nektar, Novartis, Pfizer, Polynoma, Regeneron Pharmaceuticals, Sanofi, and SkylineDx and owning equity in SkylineDx outside the submitted work. Dr Kicinski reported receiving grants from Merck during the conduct of the study. Dr Blank reported receiving grants from Bristol-Myers Squibb, NanoString Technologies, and Novartis and personal fees from AstraZeneca, Bristol-Myers Squibb, GenMab, GlaxoSmithKline, Lilly, Merck Sharpe & Dohme, NanoString Technologies, Novartis, Pfizer, Pierre Fabre, and Roche during the conduct of the study. Dr Mandala reported receiving grants from Genentech/Roche and Novartis and serving as an advisor for Bristol-Myers Squibb, Merck Sharpe & Dohme, Novartis, and Pierre Fabre outside the submitted work. Dr Long reported receiving personal fees from Amgen, Amgen, Array BioPharma, Bristol-Myers Squibb, Merck, Novartis, OncoSec, Pierre Fabre, and Roche outside the submitted work. Dr Atkinson reported receiving personal fees, speaking fees, and/or travel support from and/or serving on the advisory board of Bristol-Myers Squibb, Merck Serono, Merck Sharpe & Dohme, Novartis, OncoSec, Pierre Fabre, and Roche outside the submitted work. Dr Dalle reported receiving grants from Bristol-Myers Squibb and Merck Sharpe & Dohme outside the submitted work. Dr Haydon reported receiving personal fees from Merck outside the submitted work. Dr Carlino reported receiving personal fees from Amgen, Bristol-Myers Squibb, IDEAYA Biosciences, Merck Sharpe & Dohme, Novartis, and Roche outside the submitted work. Dr Sandhu reported receiving grants from Amgen, AstraZeneca, Bristol-Myers Squibb, Endocyte, and Merck Sharpe & Dohme outside the submitted work. Dr Larkin reported receiving grants from Achilles Therapeutics, AVEO Pharmaceuticals, Bristol-Myers Squibb, Covance, Genentech/Roche, Immunocore, Merck Sharpe & Dohme, Nektar, Novartis, Pharmacyclics, and Pfizer and personal fees from Achilles Therapeutics, AstraZeneca, Boston Biomedical, Bristol-Myers Squibb, Covance, Eisai, EUSA Pharma, Genentech/Roche, GlaxoSmithKline, Immunocore, Imugene, Incyte, iOnctura, Ipsen, Kymab, Merck Serono, Merck Sharpe & Dohme, Nektar, Novartis, Pfizer, Pierre Fabre, Secarna Pharmaceuticals, and Vitaccess during the conduct of the study. Dr Puig reported receiving patient fees for Merck Sharpe & Dohme during the conduct of the study and receiving grants from Almirall, Castle Biosciences, Leo Pharma, MelaGenix, and Novartis, personal fees and nonfinancial support from Almirall, Amgen, Bristol-Myers Squibb, ISDIN, La Roche-Posay, Leo Pharma, Lilly, Novartis, Pierre Fabre, Roche, and Sanofi, and patient fees for Biofrontera, Bristol-Myers Squibb, Philogen, and Regeneron Pharmaceuticals outside the submitted work. Dr Ascierto reported receiving grants and research funds from Array BioPharma, Bristol-Myers Squibb, and Genentech/Roche and receiving personal fees for serving as an advisor for 4SC, Array BioPharma, AstraZeneca, Bristol-Myers Squibb, Genentech/Roche Genmab, Idera

Pharmaceuticals, Immunocore, Incyte, MedImmune, Merck Serono, Merck Sharp & Dohme, NewLink Genetics, Novartis, Pierre Fabre, Sandoz, Sanofi, Sun Pharma, Syndax Pharmaceuticals, and Ultimovacs outside the submitted work. Dr Rutkowski reported receiving personal fees from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer, Pierre Fabre, and Roche outside the submitted work. Dr Schandendorf reported receiving personal fees and nonfinancial support from Merck Sharp & Dohme during the conduct of the study and receiving grants from Bristol-Myers Squibb and personal fees and nonfinancial support from 4SC, Array BioPharma, Boehringer Ingelheim, Bristol-Myers Squibb, Immunocore, InflaRx, NeraCare, Novartis, Philogen, Pierre Fabre, Regeneron Pharmaceuticals, Roche, Sandoz-Hexal, Sanofi, Sun Pharma, and Ultimovacs outside the submitted work. Dr Koonstra reported receiving grants from Bristol-Myers Squibb and Roche and personal fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Pierre Fabre outside the submitted work. Dr Hernandez-Aya reported receiving grants from Merck during the conduct of the study and receiving grants from Amgen, Bristol-Myers Squibb, Corvus Pharmaceuticals, Immunocore, MedImmune, Merck Serono, Merck Sharp & Dohme, Polynoma, Roche, and Takeda, personal fees from Bristol-Myers Squibb, and speaking fees and travel support from Regeneron Pharmaceuticals and Sanofi outside the submitted work. Dr Di Giacomo reported receiving personal fees from Merck Sharp & Dohme during the conduct of the study and receiving personal fees from Bristol-Myers Squibb, Incyte, and Pierre Fabre outside the submitted work. Dr van den Eertwegh reported receiving personal fees from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Roche outside the submitted work. Dr Grob reported receiving personal fees from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer, Pierre Fabre, and Roche outside the submitted work. Dr Gutzmer reported receiving grants from Johnson & Johnson and Pfizer and personal fees and nonfinancial support from 4SC, Almirall, Amgen, AstraZeneca, Bristol-Myers Squibb, Incyte, Merck Serono, Merck Sharpe & Dohme, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Sun Pharma, and Takeda outside the submitted work. Dr Jamal reported receiving grants and patient fees from Merck Sharpe & Dohme during the conduct of the study and receiving grants from Bristol-Myers Squibb, patient fees for Array BioPharma, Astellas, AstraZeneca, Bristol-Myers Squibb, the Canadian Cancer Trials Group, GlaxoSmithKline, Hoffman-La Roche, MedImmune, Merck Canada, Novartis Canada, Pfizer, and Genentech/Quintiles/Roche, and serving as an advisor for Amgen, Bristol-Myers Squibb, Merck Sharpe & Dohme, and Novartis outside the submitted work. Dr Lorigan reported receiving patient fees for the European Organisation for Research and Treatment of Cancer during the conduct of the study and receiving grants from Bristol-Myers Squibb and personal fees, speaking fees, and/or travel support from or serving as an advisor for Amgen, Bristol-Myers Squibb, Incyte, Merck, NeraCare, Novartis, and Pierre Fabre outside the submitted work. Dr Ibrahim reported owning financial shares in GlaxoSmithKline and Merck outside the submitted work. Dr van Akkooi reported receiving grants from 4SC, Amgen,

Bristol-Myers Squibb, Merck Sharpe & Dohme, Novartis, and Pfizer outside the submitted work. Dr Robert reported receiving personal fees from Merck Sharpe & Dohme during the conduct of the study and receiving personal fees from Amgen, Bristol-Myers Squibb, Novartis, Pierre Fabre, Roche, and Sanofi outside the submitted work. Dr Suci reported receiving grants from Merck during the conduct of the study. No other disclosures were reported.

Funding/Support: This study was supported by Merck & Co.

Role of the Funder/Sponsor: Merck & Co. participated in and supported the design and conduct of the study and the collection of the data. Merck & Co. also reviewed and approved the manuscript but had no role in the analysis and interpretation of the data or in the preparation of the manuscript. The decision to submit the manuscript for publication was made by the authors.

Meeting Presentation: The results were presented in part at the American Society of Clinical Oncology Annual Meeting, June 1, 2019; Chicago, Illinois.

Additional Contributions: The European Organisation for Research and Treatment of Cancer (EORTC) Headquarters 1325 study team members provided assistance with data and project management, statistical analysis, pharmacovigilance, and medical knowledge. The Merck Sharpe & Dohme KEYNOTE-054 study team members provided study oversight, protocol conception, and study design. In addition, Mikhail Lichinitser, MD (deceased), of the Russian Oncology Scientific Centre, Moscow, Russian Federation, made important contributions. We thank all of the additional investigators who participated in this clinical trial; a full list is provided in eTable 7 in Supplement 2.

REFERENCES

1. Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. *Lancet*. 2014;383(9919):816-827. doi:10.1016/S0140-6736(13)60802-8
2. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13(8):473-486. doi:10.1038/nrdclinonc.2016.58
3. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:190-209. doi:10.1016/j.ejca.2016.02.025
4. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:210-225. doi:10.1016/j.ejca.2016.02.024
5. Koon H, Atkins M. Autoimmunity and immunotherapy for cancer. *N Engl J Med*. 2006;354(7):758-760. doi:10.1056/NEJMe058307
6. Curti B, Daniels GA, McDermott DF, et al. Improved survival and tumor control with interleukin-2 is associated with the development of immune-related adverse events: data from the PROCLAIM registry. *J Immunother Cancer*. 2017;5(1):102. doi:10.1186/s40425-017-0307-5
7. Gogas H, Ioannovich J, Dafni U, et al. Prognostic significance of autoimmunity during treatment of

- melanoma with interferon. *N Engl J Med*. 2006;354(7):709-718. doi:10.1056/NEJMoa053007
8. Bouwhuis MG, Suci S, Collette S, et al; EORTC Melanoma Group and the Nordic Melanoma Group. Autoimmune antibodies and recurrence-free interval in melanoma patients treated with adjuvant interferon. *J Natl Cancer Inst*. 2009;101(12):869-877. doi:10.1093/jnci/djp132
 9. Bouwhuis MG, Suci S, Testori A, et al. Phase III trial comparing adjuvant treatment with pegylated interferon alfa-2b versus observation: prognostic significance of autoantibodies—EORTC 18991. *J Clin Oncol*. 2010;28(14):2460-2466. doi:10.1200/JCO.2009.24.6264
 10. Maher VE, Fernandes LL, Weinstock C, et al. Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody. *J Clin Oncol*. 2019;37(30):2730-2737. doi:10.1200/JCO.19.00318
 11. Attia P, Phan GQ, Maker AV, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. *J Clin Oncol*. 2005;23(25):6043-6053. doi:10.1200/JCO.2005.06.205
 12. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res*. 2016;22(4):886-894. doi:10.1158/1078-0432.CCR-15-1136
 13. Indini A, Di Guardo L, Cimminiello C, et al. Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma. *J Cancer Res Clin Oncol*. 2019;145(2):511-521. doi:10.1007/s00432-018-2819-x
 14. Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. *JAMA Oncol*. 2018;4(3):374-378. doi:10.1001/jamaoncol.2017.2925
 15. Ricciuti B, Genova C, De Giglio A, et al. Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis. *J Cancer Res Clin Oncol*. 2019;145(2):479-485. doi:10.1007/s00432-018-2805-3
 16. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. *J Clin Oncol*. 2008;26(24):3913-3915. doi:10.1200/JCO.2008.16.1000
 17. Conforti F, Pala L, Bagnardi V, et al. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. *Lancet Oncol*. 2018;19(6):737-746. doi:10.1016/S1470-2045(18)30261-4
 18. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018;378(19):1789-1801. doi:10.1056/NEJMoa1802357
 19. Edge SB, Byrd DR, Compton CC, et al, eds. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer-Verlag; 2009.
 20. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053
 21. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6 (R1). <https://apps.who.int/medicinedocs/documents/s22154en/s22154en.pdf>. Published June 10, 1996. Accessed November 14, 2019.
 22. Klein J, Moeschberger M. *Survival Analysis. Techniques for Censored and Truncated Data*. New York: Springer; 1997.
 23. Geskus RB. *Data Analysis With Competing Risks and Intermediate States*. New York: Chapman and Hall; 2015. doi:10.1201/b18695
 24. Ugurel S, Rohmel J, Ascierto PA, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies—update 2017. *Eur J Cancer*. 2017;83:247-257. doi:10.1016/j.ejca.2017.06.028
 25. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med*. 2016;375(19):1845-1855. doi:10.1056/NEJMoa1611299
 26. Weber J, Mandala M, Del Vecchio M, et al; CheckMate 238 Collaborators. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med*. 2017;377(19):1824-1835. doi:10.1056/NEJMoa1709030
 27. Satzger I, Meier A, Schenck F, Kapp A, Hauschild A, Gutzmer R. Autoimmunity as a prognostic factor in melanoma patients treated with adjuvant low-dose interferon alpha. *Int J Cancer*. 2007;121(11):2562-2566. doi:10.1002/ijc.22951
 28. Iglesias P, Ribero S, Barreiro A, et al. Induced vitiligo due to talimogene laherparepvec injection for metastatic melanoma associated with long-term complete response. *Acta Derm Venereol*. 2019;99(2):232-233. doi:10.2340/00015555-3061
 29. Bouwhuis MG, Ten Hagen TL, Suci S, Eggermont AM. Autoimmunity and treatment outcome in melanoma. *Curr Opin Oncol*. 2011;23(2):170-176. doi:10.1097/CCO.0b013e328341edff
 30. Özdemir BC, Coukos G, Wagner AD. Immune-related adverse events of immune checkpoint inhibitors and the impact of sex—what we know and what we need to learn. *Ann Oncol*. 2018;29(4):1067. doi:10.1093/annonc/mdx818
 31. Arbour KC, Mezquita L, Long N, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol*. 2018;36(28):2872-2878. doi:10.1200/JCO.2018.79.0006
 32. Scott SC, Pennell NA. Early use of systemic corticosteroids in patients with advanced NSCLC treated with nivolumab. *J Thorac Oncol*. 2018;13(11):1771-1775. doi:10.1016/j.jtho.2018.06.004