ORIGINAL ARTICLE

Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

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ABSTRACT

BACKGROUND

Whether pembrolizumab given both before surgery (neoadjuvant therapy) and after surgery (adjuvant therapy), as compared with pembrolizumab given as adjuvant therapy alone, would increase event-free survival among patients with resectable stage III or IV melanoma is unknown.

METHODS

In a phase 2 trial, we randomly assigned patients with clinically detectable, measurable stage IIIB to IVC melanoma that was amenable to surgical resection to three doses of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab (neoadjuvant–adjuvant group) or to surgery followed by pembrolizumab (200 mg intravenously every 3 weeks for a total of 18 doses) for approximately 1 year or until disease recurred or unacceptable toxic effects developed (adjuvant-only group). The primary end point was event-free survival in the intention-to-treat population. Events were defined as disease progression or toxic effects that precluded surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause. Safety was also evaluated.

RESULTS

At a median follow-up of 14.7 months, the neoadjuvant–adjuvant group (154 patients) had significantly longer event-free survival than the adjuvant-only group (159 patients) ($P=0.004$ by the log-rank test). In a landmark analysis, event-free survival at 2 years was 72% (95% confidence interval [CI], 64 to 80) in the neoadjuvant–adjuvant group and 49% (95% CI, 41 to 59) in the adjuvant-only group. The percentage of patients with treatment-related adverse events of grades 3 or higher during therapy was 12% in the neoadjuvant–adjuvant group and 14% in the adjuvant-only group.

CONCLUSIONS

Among patients with resectable stage III or IV melanoma, event-free survival was significantly longer among those who received pembrolizumab both before and after surgery than among those who received adjuvant pembrolizumab alone. No new toxic effects were identified. (Funded by the National Cancer Institute and Merck Sharp and Dohme; S1801 ClinicalTrials.gov number, NCT03698019.)

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This article was updated on March 2, 2023, at NEJM.org.

N Engl J Med 2023;388:813-23.
DOI: 10.1056/NEJMoa2211437

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Patients with stage III or IV melanoma who have undergone surgical excision remain at high risk for relapse. Three randomized trials showed that these patients derived benefit from adjuvant therapy with a programmed death 1 (PD-1)–blocking antibody (nivolumab or pembrolizumab) as compared with no treatment or previous standard-care adjuvant therapies (interferon-α2b or ipilimumab).[1-3]

The clinical benefit of anti–PD-1 therapy in the adjuvant setting suggests that blocking the inhibitory PD-1 immune checkpoint causes a systemic antitumor response, resulting in the elimination of melanoma micrometastases by antitumor T cells. The mechanism of action of PD-1–blocking antibodies relies on the presence of preexisting antitumor T cells attempting to attack cancer cells, with the reactive expression of programmed death ligand 1 (PD-L1) by the cancer cells inhibiting the antitumor immune response.[4] Blocking the interaction between PD-L1 and PD-1 overcomes this immune checkpoint and allows the antitumor T cells to proliferate and mediate clinical responses (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[5,6]

On the basis of this mechanism of action, resection of the bulk of the tumor, along with the tumor-infiltrating lymphocytes contained in the surgical specimen, is likely to take away some or even most of the potential antitumor T cells that would proliferate after PD-1 blockade. The administration of anti–PD-1–blocking therapy before surgery, termed neoadjuvant therapy, was superior to the same therapy in the adjuvant setting alone in two murine breast cancer models.[7] Therefore, it has been hypothesized that neoadjuvant therapy may be able to activate more antitumor T cells and improve clinical outcomes than administration of the same amount of drug delivered postoperatively.[7,8] The presumed increase in exposure of T cells to tumor antigens may also play a role. Potential flaws in this reasoning include the possibility that tumor immune escape may be independent of the timing of treatment or even more likely when bulk tumor is present.

To test whether administration of anti–PD-1 therapy before and after surgery would result in better outcomes than administration of the same therapy entirely after surgery, we designed the Southwest Oncology Group (SWOG) Cancer Research Network S1801 trial involving patients with clinically detected, resectable stage III or stage IV melanoma. The primary end point of this phase 2, randomized clinical trial was event-free survival, with events including postsurgical recurrence events as well as disease progression and toxic effects before the initiation of adjuvant therapy.

METHODS

PATIENTS

From February 2019 to May 2022, we enrolled patients 18 years of age or older who had histologically confirmed cutaneous, acral, or mucosal melanoma; clinically detectable, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST)[9]; and stage IIIB to IIID melanoma or oligometastatic resectable stage IV (M1a, M1b, and M1c) melanoma (as defined in the eighth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer). "Clinically detectable" was defined as disease that is apparent and measurable on physical examination or on radiographic or magnetic resonance imaging. Resectable nodal metastases had to have a minimum short-axis diameter of 1.5 cm, whereas the minimum size for other metastases was 1 cm.

Patients were eligible at initial presentation or at the time of the first detected nodal (including recurrent disease in a previous lymphadenectomy basin), satellite, in-transit, or distant metastases. Patients were not eligible if they had local recurrences in the scar or surgical bed of the primary melanoma as the sole site of disease. The qualifying site of disease must have been confirmed histologically by means of nonexcisional biopsy. Patients with metastases in multiple regional nodal basins were eligible.

The type and extent of surgery were prespecified for all the patients, and surgery was expected to be carried out in patients who were randomly assigned to the neoadjuvant–adjuvant group, regardless of radiologic response to preoperative therapy. Patients may have received previous adjuvant therapy (other than immunotherapy) or previous radiotherapy. Imaging studies were performed within 42 days before randomization to document the patient's melanoma status at enrollment. Patients who were known to be positive for human immunodeficiency virus (HIV) were eligible if they had stable and adequate CD4 counts (≥350 cells per cubic milli-

meter) and a serum HIV viral load of less than 25,000 IU per milliliter, regardless of whether they were receiving antiviral therapy. The main exclusion criteria were the receipt of previous immunotherapy for melanoma, active autoimmune disease in patients who had received systemic treatment within 2 years before trial entry, uveal melanoma, and any history of brain metastasis. Full information on imaging requirements and eligibility criteria is included in the trial protocol, available at NEJM.org.

TRIAL DESIGN AND REGIMENS

In this open-label, phase 2 trial, patients were randomly assigned to receive either an intravenous infusion of 200 mg of pembrolizumab every 3 weeks for a total of three doses before surgery, followed by an additional 15 doses of pembrolizumab as adjuvant therapy (neoadjuvant–adjuvant group), or surgery followed by adjuvant intravenous infusion of 200 mg of pembrolizumab every 3 weeks for 18 doses (adjuvant-only group). The interval from the last dose of neoadjuvant pembrolizumab to surgery was expected to be no longer than 5 weeks. Postoperative radiotherapy was allowed at the discretion of the investigator before the initiation of adjuvant therapy; however, concomitant administration of radiotherapy and pembrolizumab was not allowed.

Randomization was performed centrally according to a dynamic balancing method for stratification with the use of the National Cancer Institute (NCI) Web-based Oncology Patient Enrollment Network platform. Stratification factors were stage (IIIB, IIIC, or IIID or IV) and lactate dehydrogenase level (at or below the institutional upper limit of the normal range or above the institutional upper limit of the normal range).

ASSESSMENTS

Investigator assessment of recurrence was based on imaging or physical examination, with biopsy confirmation wherever possible. Clinical assessment and whole-body imaging were to occur every 3 months for the first 2 years, then every 6 months. Brain imaging was to be performed annually. Beyond year 5, no trial-specific imaging was required, but status with respect to event-free and overall survival was to be monitored up to 10 years. Adverse events were scored with the use of the NCI Common Terminology Criteria for Adverse Events, version 5.0. In the neoadjuvant–adjuvant group, we used the RECIST, version 1.1,[9] to clinically assess the antitumor activity of three doses of neoadjuvant pembrolizumab.

TRIAL OVERSIGHT

The trial was funded by the NCI and Merck Sharp and Dohme and conducted by SWOG. The initial protocol and all amendments were reviewed and approved by SWOG, NCI, the NCI central institutional review board, and the institutional review board at each institution. The trial participants provided written informed consent, as approved by the institutional review board at each institution. The trial was conducted in compliance with ethical guidelines including Good Clinical Practice standards and the principles of the Declaration of Helsinki. Data were collected by staff members at each site and were monitored by SWOG and the SWOG data monitoring committee. The data were analyzed and interpreted by the authors, who wrote the article with no outside writing assistance. All the authors had access to the full data used in the manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

Event-free survival was measured from the date of randomization to the date of the first of the following events: disease progression or toxic effects of treatment that precluded surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause. Data on patients last known to be alive without an event were censored at the date of last contact. To account for differences in time to receipt of adjuvant therapy in the two groups, any events that occurred before adjuvant therapy were assigned the event time of day 84. Patients in the neoadjuvant–adjuvant group who declined surgery owing to complete radiographic response were not counted as having had an event and were followed for recurrence. Data on patients with surgery or adjuvant therapy that was canceled owing to coronavirus disease 2019 (Covid-19)–related trial limitations at the site were censored at the time of withdrawal without an event. Overall survival was measured from randomization to the date of death from any cause;

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Neoadjuvant–Adjuvant Group (N=154)	Adjuvant-Only Group (N=159)
Median age (range) — yr	64 (19–90)	62 (22–88)
Sex — no. (%)		
Female	62 (40)	48 (30)
Male	92 (60)	111 (70)
Zubrod's performance-status score — no. (%)†‡		
0	113 (73)	125 (79)
1	39 (25)	33 (21)
2	1 (<1)	0
LDH level — no. (%)		
Low or normal	132 (86)	138 (87)
High	22 (14)	21 (13)
Disease stage — no. (%)§		
IIIB	62 (40)	64 (40)
IIIC	69 (45)	74 (47)
IIID	9 (6)	10 (6)
IV	14 (9)	11 (7)
Primary melanoma subtype — no. (%)†		
Cutaneous or unknown	143 (93)	153 (96)
Acral	4 (3)	5 (3)
Mucosal	4 (3)	0
Ulceration — no. (%)†		
Yes	56 (36)	46 (29)
No	50 (32)	58 (36)
Unknown	46 (30)	55 (35)
BRAF mutation status — no. (%)		
Mutated	41 (27)	38 (24)
Wild-type	62 (40)	64 (40)
Unknown	51 (33)	57 (36)
Previous BRAF and MEK adjuvant therapy — no. (%)		
Yes	3 (2)	1 (1)
No	151 (98)	158 (99)
Previous radiotherapy — no. (%)		
Yes	2 (1)	1 (1)
No	152 (99)	158 (99)

* Percentages may not total 100 because of rounding. LDH denotes lactate dehydrogenase.
† Data were missing in less than 1% of the patients.
‡ Zubrod's performance-status scores range from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates that the patient is fully active, 1 that the patient is restricted in strenuous activity but is ambulatory, and 2 that the patient is unable to work but is ambulatory and capable of self-care and up and about more than 50% of waking hours.
§ Stages are defined according to the American Joint Committee on Cancer *Cancer Staging Manual*, 8th edition.

data on patients known to be alive were censored at the date of last contact.

The trial design called for the final analysis after 104 events had occurred. Under design assumptions prespecified in the protocol, we estimated that 104 events would provide the trial with 81% power to detect a hazard ratio of 0.64 (one-sided alpha level of 0.15) with the use of a

log-rank test for the comparison of the neoadjuvant–adjuvant group and the adjuvant-only group with respect to event-free survival. Patients were randomly assigned in a 1:1 ratio, and analyses included all the patients who had undergone randomization, according to the intention-to-treat principle. Safety was assessed in patients who had received at least one dose of the trial drug, according to the protocol. Two-sided P values and 95% confidence intervals are reported throughout. Confidence intervals were not corrected for multiplicity and so should not be used in place of hypothesis testing. All the analyses were performed with the use of R software, version 4.1.3.

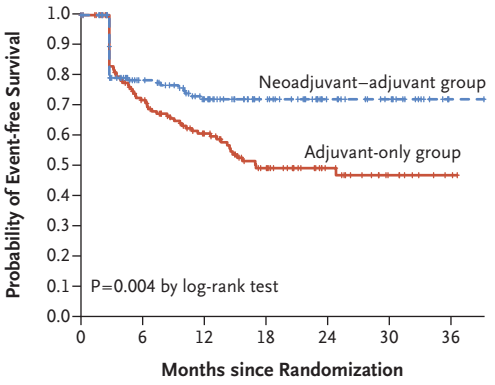
RESULTS

PATIENTS

A total of 313 eligible patients from 90 sites in the United States underwent randomization (154 patients to the neoadjuvant–adjuvant group and 159 to the adjuvant-only group) (Fig. S2). The characteristics of the patients at randomization were generally similar in the two groups; 40% of the patients in the neoadjuvant–adjuvant group and 30% of those in the adjuvant-only group were female (Table 1). The trial population was representative of the patients with melanoma in the United States with respect to race and ethnic group (Table S1). Among all eligible patients, 2 assigned to receive both neoadjuvant and adjuvant pembrolizumab and 7 assigned to receive adjuvant pembrolizumab alone did not receive any of the assigned treatment owing to withdrawal of consent.

EFFICACY

The median duration of follow-up was 14.7 months in both groups. A total of 105 events occurred (38 in the neoadjuvant–adjuvant group and 67 in the adjuvant-only group). Event-free survival was significantly longer in the neoadjuvant–adjuvant group than in the adjuvant-only group (P=0.004 by the log-rank test) (Fig. 1). In a landmark analysis, event-free survival at 2 years was 72% (95% confidence interval [CI], 64 to 80) in the neoadjuvant–adjuvant group and 49% (95% CI, 41 to 59) in the adjuvant-only group. At the time of data cutoff, 36 deaths (14 in the neoadjuvant–adjuvant group and 22 in the adjuvant-only group) had been reported; this small number of deaths precluded a definitive comparison of the groups with respect to overall survival (Fig. S3).



No. at Risk

Neoadjuvant–adjuvant group	154	96	69	46	25	17	1
Adjuvant-only group	159	98	67	40	22	10	2

Figure 1. Kaplan–Meier Estimates of Event-free Survival, as Assessed by the Local Investigators.

The log-rank test was stratified according to disease stage and lactate dehydrogenase level at randomization. In the intention-to-treat analysis of event-free survival, there were 105 events (38 in the neoadjuvant–adjuvant group and 67 in the adjuvant-only group). All events that occurred before the start of adjuvant therapy were assigned an event date of 84 days. Tick marks indicate censored data.

The between-group differences in event-free survival were consistently observed across subgroups according to baseline characteristics. The benefit of neoadjuvant pembrolizumab was seen across all subgroups of patients; sample sizes in some distinct subgroups were too small to draw conclusions (Fig. 2). Nine patients had acral melanoma (4 in the neoadjuvant–adjuvant group and 5 in the adjuvant-only group), and 4 patients had mucosal melanoma (all in the neoadjuvant–adjuvant group). All the patients with mucosal melanoma were alive at the last follow-up, and 2 of the 9 patients with acral melanoma had died, both in the adjuvant-only group (Fig. S4).

Among all the patients who underwent randomization, 10 were still receiving neoadjuvant pembrolizumab at the time of this analysis. Of the remaining patients, 127 of 144 (88%) in the neoadjuvant–adjuvant group and 151 of 159 (95%) in the adjuvant-only group had undergone definitive surgery. Reasons for not undergoing surgery in the neoadjuvant–adjuvant group were withdrawal of consent after randomization (2 patients), toxic effects (1 patient), disease progression (12 patients), and coexisting conditions (1 patient). In addition, 1 patient who had a clinical complete response declined surgery and continued in follow-up after 31.5 months without

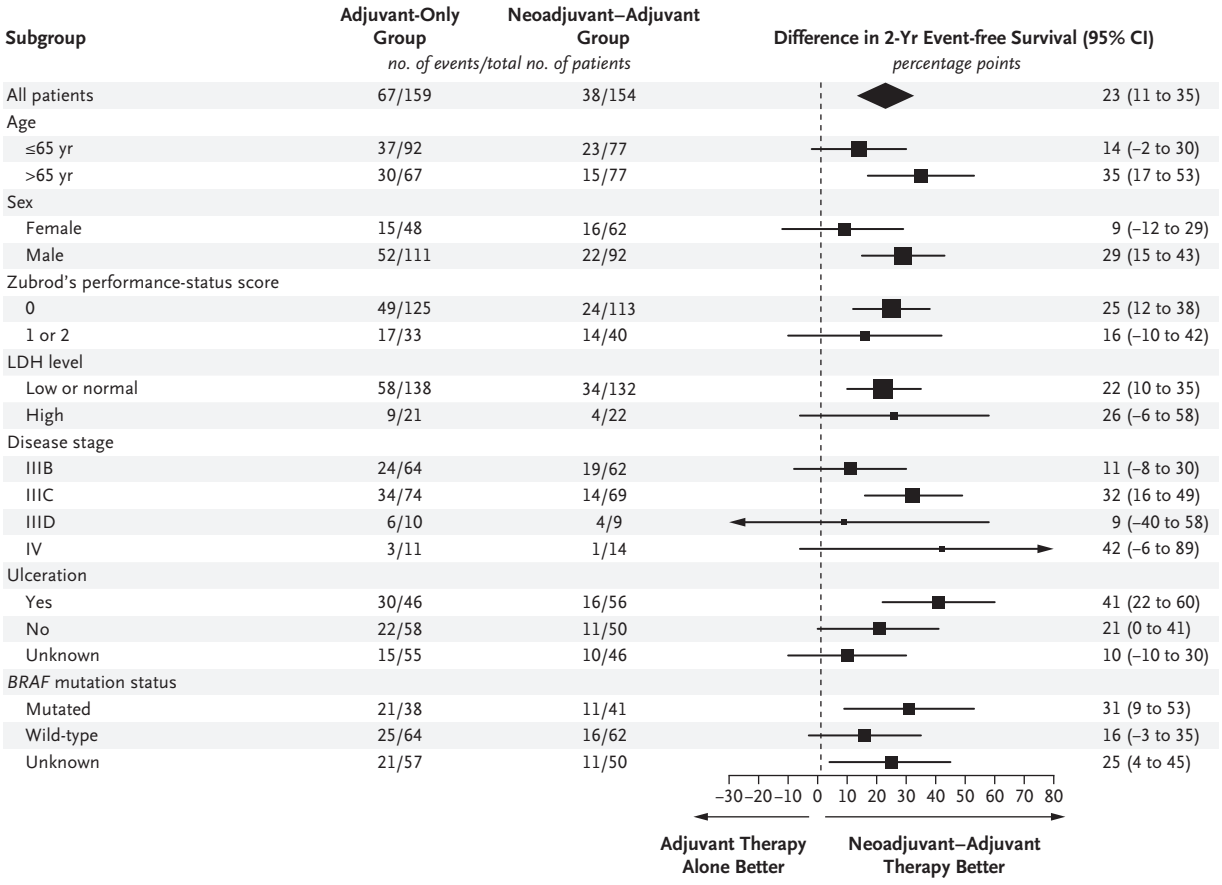


Figure 2. Forest Plot of Event-free Survival According to Subgroup.

Shown are Kaplan–Meier estimates of 2-year event-free survival in the neoadjuvant–adjuvant and adjuvant-only groups. The difference in 2-year event-free survival and 95% confidence intervals (horizontal lines) for the difference are reported. Zubrod's performance-status scores range from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates that the patient is fully active, 1 that the patient is restricted in strenuous activity but is ambulatory, and 2 that the patient is unable to work but is ambulatory and capable of self-care and up and about more than 50% of waking hours. Disease stages are defined according to the American Joint Committee on Cancer *Cancer Staging Manual*, 8th edition. The diamond represents the overall estimate, with the width of the diamond indicating the 95% confidence interval, and the horizontal lines also represent 95% confidence intervals. The sizes of the boxes are proportional to the numbers of events. LDH indicates lactate dehydrogenase.

evidence of disease. The patient who did not undergo surgery owing to toxic effects in the neoadjuvant–adjuvant group was alive without recurrence at a follow-up of 65 days. In the adjuvant-only group, 1 patient did not undergo surgery because of scheduling issues, and 7 withdrew consent.

In the neoadjuvant–adjuvant group, 14 of 127 patients (11%) who underwent surgery did not receive adjuvant therapy because of a defined event. One patient declined to receive adjuvant therapy. Other reasons were neoadjuvant toxic effects in 3 patients (colitis, pneumonitis, and polymyalgia rheumatica in 1 patient each), disease progression identified on imaging after surgery (9 patients), residual disease (1 patient), clinical trials closed because of Covid-19 (1 patient), concerns regarding exposure to Covid-19 (1 patient), and disease other than melanoma identified at surgery (2 patients). In the adjuvant-only group, 21 of 151 patients (14%) did not receive adjuvant therapy. Two patients declined to receive adjuvant therapy. Other reasons were disease progression identified on imaging after surgery (16 patients), residual disease (2 patients), and radiotherapy-related delays (1 patient) (Fig. S5). The use of adjuvant radiotherapy before adjuvant pembrolizumab was similar in the two

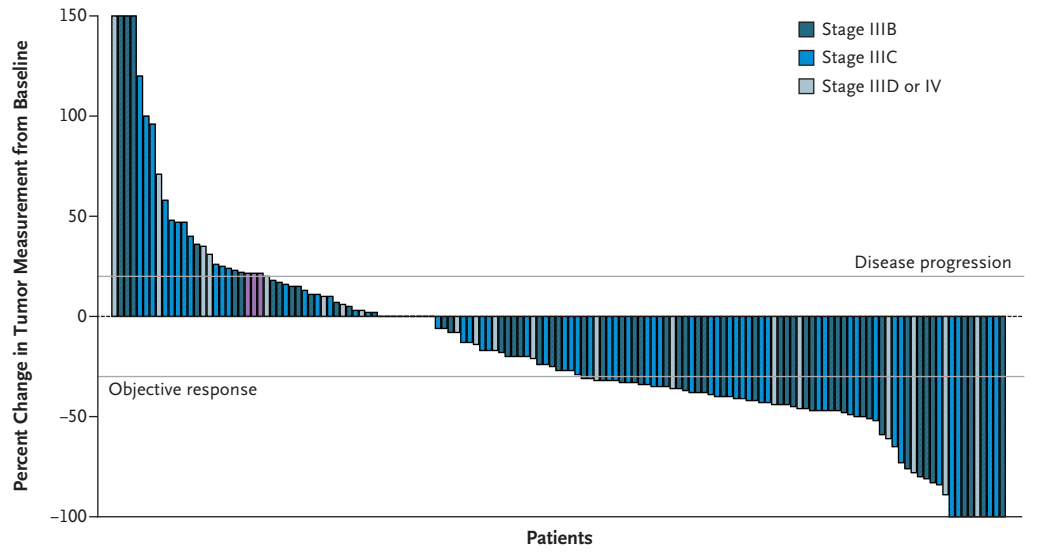


Figure 3. Overall Response in the Neoadjuvant–Adjuvant Group.

The waterfall plot shows the maximum percentage change in the size of target lesions from baseline in patients who were assigned to receive both neoadjuvant and adjuvant therapy. Each bar represents 1 patient, and the dark green, blue, and light green bars indicate the disease stage at the time of enrollment in patients who underwent imaging assessment after completing neoadjuvant therapy. The thresholds for objective response (≥30% decrease) and disease progression (>20% increase) according to Response Evaluation Criteria in Solid Tumors, version 1.1, are shown. The purple bars indicate 3 patients (1 in each disease-stage subgroup) who had clinical disease progression without a follow-up tumor imaging assessment (1 patient) or discontinued neoadjuvant therapy early because of toxic effects (2 patients; 1 underwent surgery without imaging and 1 did not undergo surgery). Data from 10 patients who were still receiving neoadjuvant therapy and 2 patients who withdrew consent immediately after randomization are excluded from this figure.

groups (2 patients in the neoadjuvant–adjuvant group and 1 patient in the adjuvant-only group). At the time of data cutoff, 9 patients in the neoadjuvant–adjuvant group and 41 of those in the adjuvant-only group had had disease recurrence during or after the adjuvant pembrolizumab portion of the trial (Table S2). In the neoadjuvant–adjuvant group, 50 patients had completed all adjuvant-therapy cycles, none of whom had subsequent disease recurrence; in the adjuvant-only group, 38 patients had completed all adjuvant cycles and 4 (11%) had subsequent disease recurrence.

Patients assigned to the neoadjuvant–adjuvant group underwent response assessment with imaging after completion of neoadjuvant therapy. Among evaluable patients, 9 of 142 patients (6%) had a complete imaging-based response and 58 (41%) had a partial response (Fig. 3). Review of the institutional pathology reports after neoadjuvant therapy revealed that 28 of 132 patients (21%) had a complete pathological response (no viable tumor). One patient who had a complete imaging-based response declined surgery and had not had a recurrence after 31 months of follow-up.

SAFETY

Among the 152 patients in the neoadjuvant–adjuvant group who had received at least one dose of pembrolizumab and for whom adverse-event data were available, 11 (7%) had at least one grade 3 or 4 adverse event that was deemed by the investigators to be related to pembrolizumab (Table 2). Among the 127 patients who completed protocol-specified surgery after neoadjuvant therapy and for whom adverse-event data were available, 9 (7%) had at least one grade 3 or 4 adverse event that was deemed by the investigators to be related to surgery. Among the 141 patients in the adjuvant-only group who underwent surgery and for whom adverse-event data were available, 5 (4%) had at least one grade 3 adverse event that was deemed by the investigators to be related to surgery; no grade 4 or higher surgery-related adverse events were noted. The incidence of adverse events of grade 3 or

Table 2. Highest Grade of Adverse Events Attributed by the Treating Physician to Pembrolizumab or to Surgery.

Event	Neoadjuvant–Adjuvant Group		Adjuvant-Only Group	
	Grade 3	Grade 4	Grade 3	Grade 4
	number of patients/total number			
Event attributed to neoadjuvant therapy				
Alanine aminotransferase level increased	2/152	1/152	NA	NA
Anemia	1/152	0	NA	NA
Aspartate aminotransferase level increased	2/152	0	NA	NA
Diarrhea	1/152	0	NA	NA
Fever	1/152	0	NA	NA
Hyperglycemia	1/152	1/152	NA	NA
Hypertension	1/152	0	NA	NA
Hypokalemia	1/152	0	NA	NA
Myocarditis	1/152	0	NA	NA
Neutrophil count decreased	0	1/152	NA	NA
Sepsis	0	1/152	NA	NA
Syncope	1/152	0	NA	NA
Urinary tract infection	1/152	0	NA	NA
White-cell count decreased	1/152	1/152	NA	NA
Event attributed to surgery				
Adrenal insufficiency	1/127	0	0	0
Alanine aminotransferase level increased	0	11/127	0	0
Aspartate aminotransferase level increased	1/127	0	0	0
Chest-wall pain	0	0	1/141	0
Fall	1/127	0	0	0
Infections or infestations — other	1/127	0	1/141	0
Maculopapular rash	1/127	0	0	0
Seroma	1/127	0	1/141	0
Skin infection	1/127	0	1/141	0
Surgical or medical procedures — other	1/127	0	0	0
Syncope	1/127	0	0	0
Thromboembolic event	0	0	1/141	0
Wound dehiscence	1/127	0	0	0
Wound infection	1/127	0	0	0
Event attributed to adjuvant therapy				
Alanine aminotransferase level increased	2/113	0	2/131	0
Alkaline phosphatase level increased	1/113	0	0	0
Arthritis	0	0	1/131	0
Aspartate aminotransferase level increased	2/113	0	2/131	0
Blood or lymph disorder — other	0	0	1/131	0
Cardiac disorder — other	0	1/113	1/131	0
Cognitive disturbance	0	0	1/131	0
Dehydration	1/113	0	0	0
Diarrhea	0	0	1/131	0
Fatigue	0	0	2/131	0

Table 2. (Continued.)

Event	Neoadjuvant–Adjuvant Group		Adjuvant-Only Group	
	Grade 3	Grade 4	Grade 3	Grade 4
	number of patients/total number			
Gallbladder infection	0	0	1/131	0
Headache	1/113	0	0	0
Hepatobiliary disorders — other	0	0	1/131	0
Hyperglycemia	0	0	2/131	0
Hypertension	0	0	1/131	0
Hypokalemia	1/113	0	0	0
Hyponatremia	1/113	0	0	0
Lung infection	0	1/113	0	0
Lymphocyte count decreased	1/113	0	2/131	0
Maculopapular rash	1/113	0	4/131	0
Metabolism or nutrition disorders — other	0	0	1/131	0
Nausea	2/113	0	0	0
Platelet count decreased	0	0	0	1/131
Pneumonitis	1/113	0	0	0
Pruritus	1/113	0	2/131	0
Skin or subcutaneous tissue disease — other	1/113	0	0	0
Soft-tissue infection	1/113	0	0	0
Stroke	1/113	0	0	0
Syncope	0	0	1/131	0
Urinary tract infection	1/113	0	1/131	0
Vomiting	1/113	0	3/131	1/131

higher during adjuvant therapy was similar in the two groups (12% in the neoadjuvant–adjuvant group and 14% in the adjuvant-only group). No new toxic effects of pembrolizumab were observed in either trial group, and no deaths attributed by the investigators to pembrolizumab occurred in either group.

DISCUSSION

In this phase 2, randomized trial involving patients with resectable stage III or IV melanoma, the percentage of patients with event-free survival at 2 years was 23 percentage points higher among those who received neoadjuvant pembrolizumab followed by adjuvant pembrolizumab than among those who received adjuvant pembrolizumab alone. In the neoadjuvant–adjuvant group, disease progression or toxic effects resulting in an inability to undergo surgery occurred in less than 10% of the patients, and the overall incidences of grade 3 or 4 toxic effects were lower than those reported in studies of neoadjuvant immune-checkpoint blockade combining anti–PD-1 and anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) therapies.[8,10]

Previous studies of neoadjuvant therapy with anti–PD-1 monotherapy in patients with resectable melanoma showed radiographic responses and an acceptable side-effect profile that were similar to what we report for this trial.[10,11] In our trial, the incidence of surgery-related adverse events did not appear to be higher with the use of neoadjuvant pembrolizumab than with surgery first in the adjuvant therapy group. The benefit of neoadjuvant pembrolizumab was seen across all subgroups, although sample sizes are too small to draw conclusions in some distinct subgroups. Because only nine patients had acral melanoma and four patients had mucosal melanoma, we are unable to conclude whether the value of neoadjuvant pembrolizumab would be different for these melanoma subtypes.

Our trial included an adjuvant-therapy period

for both treatment groups. However, some adaptively designed trials of neoadjuvant therapy for melanoma are investigating the de-escalation of surgery, the elimination of adjuvant therapy, or both in patients with a complete or near-complete pathological response (ClinicalTrials.gov numbers, NCT02977052, NCT04949113, and NCT04133948).[12,13]

In a phase 1b, randomized trial involving 20 patients with stage III melanoma, neoadjuvant administration of the anti–PD-1 antibody nivolumab and the anti–CTLA-4 antibody ipilimumab for two cycles before surgery resulted in a larger expansion of tumor-resident T-cell clones than administration of the same therapy postoperatively.[8] Several small studies involving patients with resectable melanoma have shown the feasibility and potential clinical benefit of administering neoadjuvant therapy with pembrolizumab,[11] the combination of nivolumab and ipilimumab,[10,12,13] or the combination of nivolumab and relatlimab.[14] Tumor response, as assessed by means of pathological analysis of a surgical specimen obtained after neoadjuvant therapy, is a promising marker of long-term therapeutic benefit. In a pooled analysis of previously reported results of trials of immune-checkpoint blockade as neoadjuvant therapy for melanoma, the combined incidence of pathological complete response was 33% (42% with the combination of anti–PD-1 antibody and anti–CTLA-4 antibody and 20% with anti–PD-1 monotherapy).[15] Balanced against the putative benefits of neoadjuvant therapy is the potential for tumor progression or treatment-related toxic effects to interfere with the patient's ability to undergo surgery in a timely fashion.[16]

Our trial shows that the timing of administration of an immune-checkpoint inhibitor relative to surgery can have a large effect on patient outcomes, even though the same systemic therapy was given to both trial groups. Our results, combined with our understanding of the mechanism of action of PD-1 blockade therapy, support the concept that neoadjuvant administration functionally inhibits the immune checkpoint before antitumor T cells are surgically resected. These data add to the body of knowledge supporting the use of neoadjuvant therapy in oncology. A recent trial showed that among patients with resectable non–small-cell lung cancer, those who received neoadjuvant immune-checkpoint blockade with the use of anti-PD1 therapy in combination with chemotherapy had longer event-free survival than those who received chemotherapy followed by surgery.[17] A meta-analysis showed that in patients with breast cancer, neoadjuvant chemotherapy resulted in tumor downsizing and increased use of breast-conserving surgical procedures but was associated with a higher frequency of local recurrence in the breast than the use of adjuvant chemotherapy.[18] In other trials involving patients with bladder cancer, the use of neoadjuvant chemotherapy led to tumor downstaging and improved long-term outcomes.[19,20]

Our trial showed that among patients with high-risk, resectable stage III and stage IV melanoma, those who received pembrolizumab as neoadjuvant therapy followed by adjuvant therapy had longer event-free survival than those who received standard-care adjuvant pembrolizumab alone.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supported by grants from the National Cancer Institute of the National Institutes of Health (U10CA180888, U10CA180819, U10CA180820, U10CA180821, U10CA180868, UG1CA233329, UG1CA233328, UG1CA233247, UG1CA233180, UG1CA189860, UG1CA233178, UG1CA233160, UG1CA189821, UG1CA233320, UG1CA233331, UG1CA189850, UG1CA233330, UG1CA233234, UG1CA233193, UG1CA189956, UG1CA239767, UG1CA189869, UG1CA180830, P30CA014089, UG1CA239758, P30CA016042, UG1CA189830, P30CA076292, P30CA033572, R35 CA197633, and P01 CA244118) and in part by Merck Sharp and Dohme, a subsidiary of Merck.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial participants, their families, and caregivers; Larry Flaherty, M.D., chair of the Southwest Oncology Group (SWOG) data monitoring committee for oversight of this trial; Danae Campos, M.B.A., and Catrina Mireles, B.S., for logistic and administrative support; Michael Tetzlaff, M.D., Ph.D., for pathological acumen; and Valerie Guild, M.B.A., M.S., (deceased) and Samantha Guild, J.D., patient advocates on the SWOG Melanoma Committee, for their invaluable contributions in support of this trial.

APPENDIX

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