ORIGINAL ARTICLE

Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

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ABSTRACT

BACKGROUND

In phase 1–2 trials in patients with resectable, macroscopic stage III melanoma, neoadjuvant immunotherapy was more efficacious than adjuvant immunotherapy.

METHODS

In this phase 3 trial, we randomly assigned patients with resectable, macroscopic stage III melanoma to two cycles of neoadjuvant ipilimumab plus nivolumab followed by surgery or surgery followed by 12 cycles of adjuvant nivolumab. Only patients in the neoadjuvant group with a partial response or nonresponse received adjuvant treatment. The primary end point was event-free survival.

RESULTS

A total of 423 patients underwent randomization. At a median follow-up of 9.9 months, the estimated 12-month event-free survival was 83.7% (99.9% confidence interval [CI], 73.8 to 94.8) in the neoadjuvant group and 57.2% (99.9% CI, 45.1 to 72.7) in the adjuvant group. The difference in restricted mean survival time was 8.00 months (99.9% CI, 4.94 to 11.05; P<0.001; hazard ratio for progression, recurrence, or death, 0.32; 99.9% CI, 0.15 to 0.66). In the neoadjuvant group, 59.0% of patients had a major pathological response, 8.0% had a partial response, 26.4% had a nonresponse (>50% residual viable tumor), and 2.4% had progression; in 4.2%, surgery had not yet been performed or was omitted. The estimated 12-month recurrence-free survival was 95.1% in patients in the neoadjuvant group who had a major pathological response, 76.1% among those with a partial response, and 57.0% among those with a nonresponse. Adverse events of grade 3 or higher that were related to systemic treatment occurred in 29.7% of patients in the neoadjuvant group and in 14.7% in the adjuvant group.

CONCLUSIONS

Among patients with resectable, macroscopic stage III melanoma, neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy resulted in longer event-free survival than surgery followed by adjuvant nivolumab. (Funded by Bristol Myers Squibb and others; NADINA ClinicalTrials.gov number, NCT04949113.)

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The standard management of resectable, macroscopic stage III melanoma is currently surgery, which can be followed by adjuvant systemic therapy. The programmed death 1 (PD-1) inhibitors nivolumab and pembrolizumab both have been shown to prolong recurrence-free survival as compared with either the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor ipilimumab (52% with nivolumab and 41% with ipilimumab at 4 years) or placebo (55% with pembrolizumab and 38% with placebo at 5 years).[1,2] Among patients with melanoma with a *BRAF* V600E or V600K mutation, BRAF-targeted therapy with dabrafenib plus trametinib has shown a benefit as compared with placebo (recurrence-free survival, 54% with dabrafenib plus trametinib and 38% with placebo at 4 years).[3] Despite adjuvant systemic treatment, a substantial proportion of patients have disease recurrence within the first few years after surgery. In addition, none of the approved adjuvant immunotherapies have shown a significant overall survival benefit despite long-term follow-up,[2,4] a finding that emphasizes the need for new treatment approaches.

On the basis of preclinical and phase 1 data, neoadjuvant administration of immune checkpoint inhibitors is hypothesized to yield efficacy superior to that of adjuvant administration.[5,6] A recent randomized phase 2 trial (the Southwest Oncology Group Cancer Research Network S1801 trial [SWOG S1801]) showed that event-free survival was longer among patients who received three neoadjuvant cycles of pembrolizumab every 3 weeks (followed by 15 adjuvant cycles) than among patients who received 18 adjuvant cycles of pembrolizumab (estimated 2-year event-free survival, 72% vs. 49%; hazard ratio, 0.58; P=0.004).[7,8] Another phase 2 trial showed, in two independent cohorts, that a neoadjuvant combination regimen of two cycles of ipilimumab (at a dose of 1 mg per kilogram of body weight) plus nivolumab (at a dose of 3 mg per kilogram every 3 weeks) resulted in an event-free survival of 77 to 80% at 2 years, a finding that suggests an even higher efficacy than neoadjuvant anti–PD-1 monotherapy. Furthermore, this combination regimen was deemed to be safe, with grade 3 or 4 adverse events occurring in 27 to 30% of the patients and surgery being omitted in only 1% of the patients because of toxic effects.[9-11] Collectively, these data provided the rationale for testing this neoadjuvant regimen against the current standard care of adjuvant anti–PD-1 in the randomized phase 3 NADINA (Neoadjuvant Ipilimumab plus Nivolumab versus Standard Adjuvant Nivolumab in Macroscopic Stage III Melanoma) trial.

METHODS

A Quick Take is available at NEJM.org

PATIENTS

We enrolled patients who were at least 16 years of age and had resectable, macroscopic stage III cutaneous or acral melanoma or melanoma of unknown primary origin (according to the eighth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer) with at least one pathologically proven lymph-node metastasis and a maximum of three additional in-transit metastases. Patients with concurrent primary melanoma were eligible for inclusion. Macroscopic disease was defined as a pathologically proven lymph-node metastasis that was palpable, positive according to positron-emission tomography, or measurable on imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[12] Complete eligibility criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

TRIAL DESIGN AND TREATMENT

In this multicenter, international, phase 3 trial, patients were randomly assigned in a 1:1 ratio to receive either neoadjuvant or adjuvant immune checkpoint inhibition. Patients in the neoadjuvant group received two cycles of neoadjuvant ipilimumab (at a dose of 80 mg) plus nivolumab (at a dose of 240 mg) every 3 weeks,[9,11] followed by a therapeutic lymph-node dissection and, if applicable, resection of the in-transit metastases in week 6. Patients who had a locally assessed major pathological response (≤10% residual viable tumor) did not receive any adjuvant treatment, and patients who had a pathological partial response (11 to 50% residual viable tumor) or a pathological nonresponse (>50% residual viable tumor) received adjuvant dabrafenib (at a dose of 150 mg twice daily) plus trametinib (at a dose of 2 mg once daily) for 46 weeks if the melanoma had a *BRAF* V600E or V600K mutation or received an additional 11 cycles of adjuvant nivolumab (at a dose of 480 mg) every 4 weeks if the melanoma was *BRAF* wild type. Patients in

the adjuvant group underwent a therapeutic lymph-node dissection in week 0 followed by 12 cycles of adjuvant nivolumab every 4 weeks starting between week 6 and 12. Adjuvant radiotherapy was allowed in both groups, with the exception of patients who had a major pathological response after neoadjuvant treatment. Stratification factors included continent, the presence of a *BRAF* V600E or V600K mutation, and the presence of in-transit metastases (Fig. S1 in the Supplementary Appendix).

Treatment was discontinued if progression, death, unacceptable toxic effects, or withdrawal of consent occurred. Dose reductions of ipilimumab and nivolumab were not allowed. Additional details regarding dose delays, dose reductions of dabrafenib and trametinib, and the management of adverse events are provided in the protocol, available at NEJM.org.

END POINTS AND ASSESSMENTS

The primary end point was event-free survival, which was defined as the time from randomization to the occurrence of progression to unresectable melanoma before surgery, disease recurrence, or death due to melanoma or due to treatment. Data for patients who did not have an event were censored on the date of the last reported imaging. The key secondary end point was overall survival, and additional secondary end points included recurrence-free survival, distant metastasis–free survival, pathological response, safety measures, and measures of health-related quality of life. The assessment of pathological response was conducted according to the International Neoadjuvant Melanoma Consortium criteria, and retrospective central review was performed at the Netherlands Cancer Institute or the Melanoma Institute Australia.[13] Details regarding radiologic and pathological assessments are provided in the Supplementary Appendix. Adverse events were scored with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

TRIAL OVERSIGHT

The Netherlands Cancer Institute was responsible for oversight of the trial, and Melanoma Institute Australia was responsible for oversight of the participating centers in Australia. The protocol was written by investigators from both institutes and was approved by independent ethics committees or institutional review boards of the coordinating center of each participating country. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All the enrolled patients provided written informed consent. Data were collected and analyzed by the Netherlands Cancer Institute and Melanoma Institute Australia. The first two authors and the last author developed the first draft of the manuscript, and all coauthors contributed to the final version submitted for publication. No external writers were involved. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. An independent data and safety monitoring board was appointed to monitor the progress of the trial. On February 20, 2024, the data and safety monitoring board advised the investigators about the results of the first interim analysis and recommended that the results be reported. Data on overall survival remain blinded until the prespecified final analysis at 3 years after the last patient is enrolled.

STATISTICAL ANALYSIS

We planned to enroll 420 patients. It was estimated that 132 events would provide the trial with 90.5% power to show superiority of neoadjuvant treatment over adjuvant treatment, under the assumption of a 24-month event-free survival of 75% in the neoadjuvant group and 60% in the adjuvant group, with the use of a log-rank test with a two-sided alpha level of 5% for the final analysis. The prespecified interim analysis was conducted with the use of a two-sided alpha level of 0.1%, which conforms to the Haybittle–Peto stopping rule. Given the positive results, the first interim analysis became the final analysis for event-free survival. Details regarding a statistical amendment to the protocol are provided in the Supplementary Appendix.

The primary end point, event-free survival, was assessed in the intention-to-treat population, which included all the patients who had undergone randomization. Hazard ratios and corresponding 99.9% confidence intervals were estimated with the use of a multivariable Cox proportional-hazards model, with adjustment for the randomization stratification factors. The Kolmogorov-type supremum test was used to assess deviations from the proportional-hazards assumption.[14] For analyses in which this assumption was violated, we estimated the differ-

ence in restricted mean survival time between the treatment groups with adjustment for the stratification factors at randomization. The restriction time was determined on the basis of the shortest maximum follow-up in the two treatment groups. Event-free survival curves were estimated with the use of the Kaplan–Meier method, and 12-month event-free survival and 99.9% confidence intervals were calculated. Safety data were summarized for all the patients who started treatment; adverse events related to systemic treatment were assessed in all the patients who received at least one cycle of systemic treatment, and adverse events related to surgery were assessed in all the patients who underwent surgery. Pathological response was assessed in all the patients who were enrolled in the neoadjuvant group who received at least one cycle of neoadjuvant therapy.

The statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary end points or in subgroups, so the widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R software, version 4.2.1 (R Foundation for Statistical Computing).

RESULTS

PATIENTS AND TREATMENT

From July 2021 through December 2023, a total of 423 patients underwent randomization; 212 were assigned to the neoadjuvant group and 211 were assigned to the adjuvant group. The characteristics of the patients at baseline were balanced between the groups, and the trial population was considered to be representative of the overall population with stage III melanoma (Table 1 and Table S2). Three patients in the adjuvant group did not undergo surgery and thus did not start treatment according to the protocol (Fig. S2). In the neoadjuvant group, all the patients started systemic therapy; 199 of 212 patients (93.9%) received the prespecified two cycles of neoadjuvant ipilimumab plus nivolumab. Surgery was performed in 198 patients (93.4%) in the neoadjuvant group; these procedures were performed on time (within 1 week before or after the protocol-specified timing) in 162 patients (81.8%). The median time from the start of neoadjuvant treatment to surgery was 45.0 days (interquartile range, 42.0 to 49.0). A total of 197 patients underwent a therapeutic lymph-node dissection, and 1 patient had an index lymph-node procedure.[11] Surgery was not performed in patients in the neoadjuvant group because of toxic effects (in 3 patients), progression (in 5 patients), and an unknown reason (in 1 patient). Surgery was planned for after the data-cutoff date in 5 patients. In the adjuvant group, 207 therapeutic lymph-node dissections were performed, and 1 selective lymph-node dissection was performed. Of these procedures, 205 (98.6%) were performed on time. The median number of resected lymph nodes per region was 18 (interquartile range, 13 to 27) in the neoadjuvant group and 17 (interquartile range, 11 to 25) in the adjuvant group (Table S3). Of the 78 patients in the neoadjuvant group who were intended to receive adjuvant therapy because of the lack of major pathological response, 65 (83.3%) started systemic adjuvant treatment. In the adjuvant group, 170 of 208 patients (81.7%) started treatment with nivolumab (Fig. S3 and Table S4).

EFFICACY

Results in the Intention-to-Treat Population

At the time of data cutoff (January 12, 2024), the median duration of follow-up was 10.6 months (interquartile range, 5.2 to 16.8) in the neoadjuvant group and 9.9 months (interquartile range, 4.6 to 16.8) in the adjuvant group. A total of 100 events (progression, recurrence, or death from melanoma or treatment) had occurred in the intention-to-treat population, of which 28 were in the neoadjuvant group and 72 in the adjuvant group. Event-free survival was significantly longer in the neoadjuvant group than in the adjuvant group; the estimated event-free survival at 12 months was 83.7% (99.9% confidence interval [CI], 73.8 to 94.8) and 57.2% (99.9% CI, 45.1 to 72.7), respectively (Fig. 1 and Table S5).

The Kolmogorov-type supremum test indicated a violation of the proportional-hazards assumption ($P=0.04$), which was attributed to the wider separation of the curves in the first months after randomization. The adjusted difference in restricted mean survival time was 8.00 months (99.9% CI, 4.94 to 11.05; $P<0.001$), at a restriction time of 27.8 months. The results of sensitivity analyses incorporating piecewise hazard functions to address nonproportionality showed con-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Neoadjuvant Group (N=212)	Adjuvant Group (N=211)
Sex — no. (%)		
Female	71 (33.5)	76 (36.0)
Male	141 (66.5)	135 (64.0)
Median age (range) — yr	60 (22–84)	59 (19–87)
Continent — no. (%)		
Australia	71 (33.5)	71 (33.6)
Europe	141 (66.5)	139 (65.9)
North America	0	1 (0.5)
Median weight (range) — kg†	85.1 (52.0–144.0)	83.1 (49.0–151.0)
Median body-mass index (range)†	27.6 (19.1–52.3)	26.9 (19.1–42.0)
WHO performance-status score — no. (%)‡		
0	192 (90.6)	192 (91.0)
1	20 (9.4)	19 (9.0)
Tumor stage — no. (%)§		
T1	25 (11.8)	36 (17.1)
T2	41 (19.3)	39 (18.5)
T3	41 (19.3)	49 (23.2)
T4	52 (24.5)	46 (21.8)
Tx	7 (3.3)	6 (2.8)
Melanoma of unknown primary origin	46 (21.7)	35 (16.6)
Ulceration — no. (%)		
Yes	71 (33.5)	57 (27.0)
No	85 (40.1)	102 (48.3)
Melanoma of unknown primary origin	46 (21.7)	35 (16.6)
Unknown	10 (4.7)	17 (8.1)
In-transit metastases — no. (%)		
Yes	22 (10.4)	25 (11.8)
No	190 (89.6)	186 (88.2)
Short-axis diameter of largest lymph node — no. (%)¶		
<15 mm	67 (31.6)	74 (35.1)
15–30 mm	115 (54.2)	102 (48.3)
31–50 mm	24 (11.3)	29 (13.7)
>50 mm	4 (1.9)	4 (1.9)
No lymph node reported on CT scan	2 (0.9)	2 (0.9)
Median sum of diameters of lymph nodes (range) — mm^2	25 (15–74)	25 (15–82)
Location or locations of affected lymph nodes — no./total no. (%)‖		
Neck	55/211 (26.1)	57/211 (27.0)
Axilla	86/211 (40.8)	86/211 (40.8)
Groin	66/211 (31.3)	66/211 (31.3)

Table 1. (Continued.)

Characteristic	Neoadjuvant Group (N=212)	Adjuvant Group (N=211)
Axilla and neck	3/211 (1.4)	0
Other	1/211 (0.5)	2/211 (0.9)
No. of lymph nodes positive for disease on PET — no./total no. (%)**		
1	126/200 (63.0)	122/205 (59.5)
2 or 3	52/200 (26.0)	64/205 (31.2)
>3	17/200 (8.5)	12/205 (5.9)
0	5/200 (2.5)	7/205 (3.4)
BRAF mutation status — no. (%)		
V600E	95 (44.8)	87 (41.2)
V600K	17 (8.0)	25 (11.8)
Other *BRAF* mutation	5 (2.4)	4 (1.9)
Wild type	95 (44.8)	95 (45.0)
LDH level — no. (%)		
<ULN	196 (92.5)	192 (91.0)
1–1.5×ULN	16 (7.5)	19 (9.0)
Previous surgical treatment to nodal basin — no. (%)		
Sentinel-node procedure	75 (35.4)	78 (37.0)
Lymph-node dissection	1 (0.5)	1 (0.5)
Both procedures	0	3 (1.4)
None	136 (64.2)	129 (61.1)

* Data shown are for the intention-to-treat population, which included all the patients who had undergone randomization. Percentages may not total 100 because of rounding. LDH denotes lactate dehydrogenase, PET positron-emission tomography, and ULN upper limit of the normal range.
† The weight and body-mass index (the weight in kilograms divided by the square of the height in meters) are missing for 1 patient in the neoadjuvant group and 5 patients in the adjuvant group.
‡ World Health Organization (WHO) performance-status scores range from 0 to 5, with higher numbers indicating greater disability.
§ The stages are defined according to the eighth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.
¶ The sums of the diameters of the lymph nodes that were longer than 15 mm at the shortest axis were measured on the baseline computed tomographic (CT) scan, in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST). Data were missing for 68 patients in the neoadjuvant group and 76 patients in the adjuvant group.
‖ The locations of lymph nodes are based on the baseline CT scan. Data were missing for 3 patients in the neoadjuvant group and 5 patients in the adjuvant group and were thus determined on the basis of surgical information for 2 patients in the neoadjuvant group and 5 patients in the adjuvant group.
** Patients were eligible for inclusion in the trial if they had a pathologically proven lymph node that could be assessed with the use of RECIST, was positive for disease according to PET, or was palpable at baseline.

sistency with an overall adjusted hazard ratio of 0.32 (99.9% CI, 0.15 to 0.66). One death that was not related to melanoma or treatment (as determined by the local investigator) occurred before the occurrence of progression or disease recurrence. A sensitivity analysis accounting for competing risks yielded similar results to those of the primary analysis. The results of subgroup analyses that were performed according to baseline characteristics were consistent with those in the intention-to-treat population (Fig. S6).

Response in the Overall Neoadjuvant Group

In the neoadjuvant group, all 212 patients received at least one dose of neoadjuvant immunotherapy and could therefore be assessed for pathological response. As determined by central review, 47.2% of the patients had a pathological

Table 2. Pathological Responses in the Neoadjuvant Group.*

Type of Response	Local Assessment (N=212)	Central Review (N=212)
	number (percent)	
Major pathological response	120 (56.6)	125 (59.0)
Pathological complete response†	97 (45.8)	100 (47.2)
Pathological near-complete response	23 (10.8)	25 (11.8)
Pathological partial response	20 (9.4)	17 (8.0)
Pathological nonresponse	53 (25.0)	56 (26.4)
Progression before surgery	5 (2.4)	5 (2.4)
Not reported	5 (2.4)	0
Not available‡	9 (4.2)	9 (4.2)

* Patients in the neoadjuvant group who received at least one dose of neoadjuvant treatment were assessed for pathological response. The pathological response was determined according to the International Neoadjuvant Melanoma Consortium criteria. A pathological complete response was defined as 0% residual viable tumor in the surgical resection specimen, pathological near-complete response as 0 to 10% residual viable tumor, pathological partial response as 11 to 50% residual viable tumor, and pathological nonresponse as more than 50% residual viable tumor. Major pathological response included pathological complete response and pathological near-complete response.

† As confirmed by central review, the material from surgical resection in 9 of 100 patients who had a complete pathological response did not show any signs of viable or regressed tumor, nor were there clinical indications that the tumor was still in situ.

‡ At the time of the data cutoff, no material from surgical resection was available for 9 patients (5 patients underwent surgery after the data-cutoff date, 3 patients had not undergone surgery because of toxic effects, and 1 patient had not undergone surgery for an unknown reason).

complete response (0% residual viable tumor) and 11.8% had a pathological near-complete response (1 to 10% residual viable tumor), which yielded a major pathological response of 59.0%. Furthermore, 8.0% of the patients had a pathological partial response, 26.4% had a pathological nonresponse, and 2.4% had progression before surgery; in 4.2%, surgery had not yet been performed or was omitted (Table 2 and Fig. S7). Discordances between local and central assessment of pathological responses were infrequent and predominantly underestimated the depth of response; only 1 of 120 patients (0.8%) were classified as not having had a major pathological response according to central review instead of having had a major pathological response, and 4 of 74 patients (5.4%) were classified as having had a major pathological response instead of no major pathological response. Objective radiologic responses at week 6 occurred in 76 patients (35.8%) (Table S6).

Efficacy According to BRAF *Mutation Status*

The estimated event-free survival at 12 months among patients with melanoma with a *BRAF* V600E or V600K mutation was 83.5% (99.9% CI, 70.3 to 99.2) in the neoadjuvant group and 52.2% (99.9% CI, 35.9 to 75.8) in the adjuvant group (unadjusted hazard ratio for progression, recurrence, or death, 0.29; 99.9% CI, 0.11 to 0.79). Among patients with *BRAF* wild-type melanoma, the estimated event-free survival at 12 months was 83.9% (99.9% CI, 70.1 to 99.9) in the neoadjuvant group and 62.4% (99.9% CI, 46.0 to 84.7) in the adjuvant group (unadjusted hazard ratio for progression, recurrence, or death, 0.35; 99.9% CI, 0.12 to 1.03) (Fig. 2A and 2B). Among patients in the neoadjuvant group, 53.8% of those with *BRAF*-mutated melanoma and 65.3% of those with *BRAF* wild-type melanoma had a major pathological response.

Efficacy According to Pathological Response

Among the 212 patients in the neoadjuvant group, 198 patients (93.4%) had a major pathological response, a pathological partial response, or a pathological nonresponse and could be assessed for recurrence-free survival; the analysis was subdivided according to response category. The estimated recurrence-free survival at 12 months was

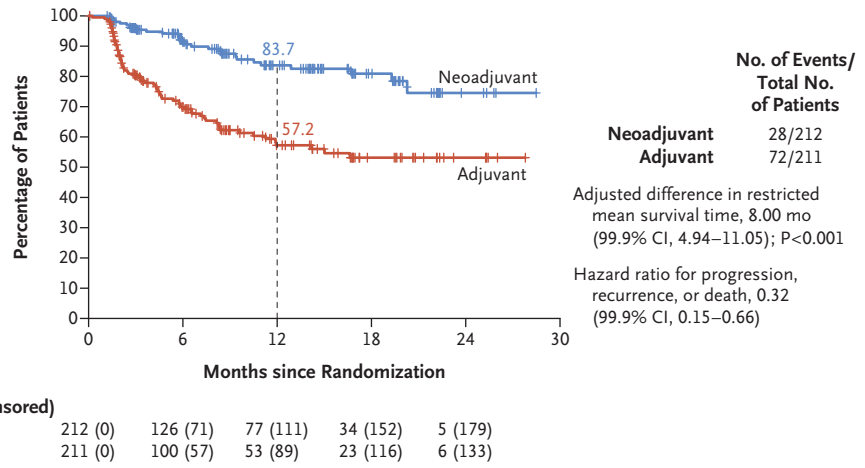


Figure 1. Event-free Survival in the Intention-to-Treat Population.

Shown are the Kaplan–Meier curves for event-free survival in the intention-to-treat population, which included all the patients who had undergone randomization. Event-free survival was significantly longer in the neoadjuvant group than in the adjuvant group. The estimated event-free survival at 12 months was 83.7% (99.9% confidence interval [CI], 73.8 to 94.8) in the neoadjuvant group and 57.2% (99.9% CI, 45.1 to 72.7) in the adjuvant group. The tick marks indicate censored data.

95.1% (99.9% CI, 87.4 to 99.9) among patients who had a major pathological response, 76.1% (99.9% CI, 44.4 to 99.9) among those who had a pathological partial response, and 57.0% (99.9% CI, 33.3 to 97.6) among those who had a pathological nonresponse (Fig. 2C). Among the patients who had a pathological complete response, the estimated recurrence-free survival was 95.4% (99.9% CI, 87.0 to 99.9); among those who had a pathological near-complete response, the estimated recurrence-free survival was 94.1% (99.9% CI, 77.1 to 99.9) (Fig. S8).

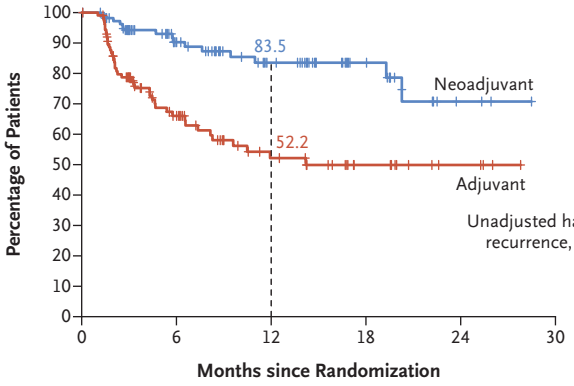
SAFETY

Adverse events of any cause of grade 3 or higher were reported in 47.2% of the patients in the neoadjuvant group and in 34.1% in the adjuvant group. Adverse events of grade 3 or higher that were related to systemic treatment occurred in 29.7% of the patients in the neoadjuvant group and in 14.7% of the patients in the adjuvant group, and surgery-related adverse events of grade 3 or higher occurred in 14.1% and 14.4% of the patients, respectively. In the neoadjuvant group, 23.1% of the patients had an adverse event of grade 3 or higher that was related to systemic treatment within the first 12 weeks and was therefore attributable solely to the neoadjuvant treatment. Endocrinopathies related to systemic treatment occurred in 30.7% of the patients in the neoadjuvant group and in 9.9% of those in the adjuvant group. At the time of the data cutoff, the events were ongoing in 25.0% of the patients in the neoadjuvant group and in 7.5% of the patients in the adjuvant group; the most frequent events were hypothyroidism (in 11.3% and 6.5%, respectively) and adrenal insufficiency (in 7.1% and 1.2%, respectively) (Table S10). No new adverse events related to nivolumab with or without ipilimumab or related to dabrafenib plus trametinib occurred. Serious adverse events were reported in 36.3% of the patients in the neoadjuvant group and in 24.0% of those in the adjuvant group. In the adjuvant group, one patient died from pneumonitis caused by nivolumab. In the neoadjuvant group, no treatment-related deaths occurred (Table 3 and Tables S7 through S11).

DISCUSSION

NADINA, a phase 3, investigator-initiated trial comparing neoadjuvant with adjuvant immunotherapy in resectable, macroscopic stage III melanoma, is distinctive in that it is evaluating a neoadjuvant regimen of immunotherapy alone.

A Event-free Survival among Patients with Melanoma with *BRAF* V600E or V600K Mutation



No. of Events/ Total No. of Patients

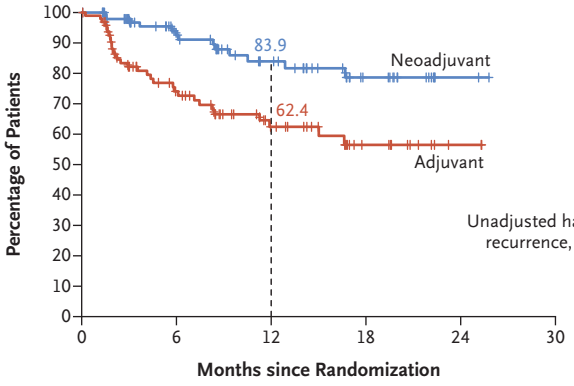
Neoadjuvant	15/112
Adjuvant	41/112

Unadjusted hazard ratio for progression, recurrence, or death, 0.29 (99.9% CI, 0.11–0.79)

No. at Risk (no. censored)

Neoadjuvant	112 (0)	63 (40)	38 (61)	18 (81)	3 (94)
Adjuvant	112 (0)	48 (32)	25 (47)	11 (60)	4 (67)

B Event-free Survival among Patients with *BRAF* Wild-Type Melanoma



No. of Events/ Total No. of Patients

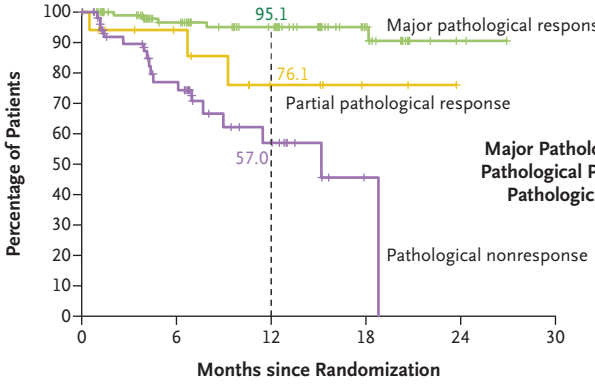
Neoadjuvant	13/100
Adjuvant	31/99

Unadjusted hazard ratio for progression, recurrence, or death, 0.35 (99.9% CI, 0.12–1.03)

No. at Risk (no. censored)

Neoadjuvant	100 (0)	63 (31)	39 (50)	16 (71)	2 (85)
Adjuvant	99 (0)	52 (25)	28 (42)	12 (56)	2 (66)

C Recurrence-free Survival According to Pathological Response



No. of Events/ Total No. of Patients

Major Pathological Response	5/125
Pathological Partial Response	3/17
Pathological Nonresponse	17/56

No. at Risk (no. censored)

Major pathological response	125 (0)	76 (46)	55 (66)	22 (99)	2 (118)
Pathological partial response	17 (0)	11 (5)	5 (9)	2 (12)	
Pathological nonresponse	56 (0)	29 (17)	11 (30)	1 (39)	

Figure 2 (facing page). Event-free Survival According to *BRAF* Mutation Status and Recurrence-free Survival.
Panel A shows the Kaplan–Meier curves for event-free survival among patients with melanoma with *BRAF* V600E or V600K mutation. The event-free survival at 12 months was 83.5% (99.9% CI, 70.3 to 99.2) in the neoadjuvant group and 52.2% (99.9% CI, 35.9 to 75.8) in the adjuvant group. Panel B shows the Kaplan–Meier curves for event-free survival among patients with *BRAF* wild-type melanoma. The event-free survival at 12 months was 83.9% (99.9% CI, 70.1 to 99.9) in the neoadjuvant group and 62.4% (99.9% CI, 46.0 to 84.7) in the adjuvant group. Panel C shows the Kaplan–Meier curves for recurrence-free survival according to pathological response category among patients in the neoadjuvant group. At 12 months, the recurrence-free survival was 95.1% (99.9% CI, 87.4 to 99.9) among patients who had a major pathological response (≤10% residual viable tumor), 76.1% (99.9% CI, 44.4 to 99.9) among patients who had a pathological partial response (11 to 50% residual viable tumor), and 57.0% (99.9% CI, 33.3 to 97.6) among patients who had a pathological nonresponse (>50% residual viable tumor). The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. The tick marks in all panels indicate censored data.

Here, we show that two cycles of ipilimumab plus nivolumab followed by a therapeutic lymph-node dissection and response-driven adjuvant treatment resulted in longer event-free survival than adjuvant treatment, with an absolute reduction of 27 percentage points in the risk of an event in the first 12 months as compared with the current standard care of up-front therapeutic lymph-node dissection followed by 12 cycles of adjuvant nivolumab.

The results in the neoadjuvant group (an estimated event-free survival at 12 months of 83.7% and a major pathological response in 59.0% of the patients) are in line with the efficacy found in the preceding phase 2 trials that evaluated neoadjuvant ipilimumab plus nivolumab (the Optimal Neo-adjuvant Combination Scheme of Ipilimumab and Nivolumab [OpACIN-neo] trial and the Personalized Response-Driven Adjuvant Therapy after OpACIN [PRADO] trial), in which the event-free survival at 12 months was 85 to 86%, and 60 to 61% of the patients had a major pathological response.[9-11] Updated data from the OpACIN-neo trial indicate that these outcomes are durable (recurrence-free survival at 3 years, 82%) and translate into a remarkable overall survival of 92% at 3 years.[15] The estimated event-free survival at 12 months in the adjuvant group (57.2%) in the current trial is lower than the recurrence-free survival at 12 months observed in the CheckMate 238 trial and the European Organization for Research and Treatment of Cancer (EORTC) 1325 trial (70.5% and 75.4% in the two trials, respectively), both of which evaluated adjuvant anti–PD-1 monotherapy.[16,17] This difference is most likely due to the inclusion of lower-risk patients with microscopic stage III melanoma, as well as the exclusion of patients with early recurrence before the start of adjuvant therapy, in the other two trials. Early disease recurrence before the start of adjuvant therapy is reflected in the reported 10 to 20% of patients in these trials who were excluded at screening because of recurrence, as well as in observations from the SWOG S1801 trial and retrospective reports.[7,18,19]

In this trial, we found a similar event-free survival in the neoadjuvant group regardless of *BRAF* mutational status. However, in the adjuvant group, event-free survival was shorter among the patients with *BRAF*-mutated melanoma than among those with *BRAF* wild-type melanoma. This finding indicates a benefit from the addition of ipilimumab, as previously observed for stage IV melanoma,[20] and potentially from the class switch for the patients with *BRAF*-mutated melanoma who had a partial response or no response. On the basis of the difference in major pathological response (53.8% of the patients with *BRAF*-mutated melanoma and 65.3% of the patients with *BRAF* wild-type melanoma) and the similarity in event-free survival, we estimate that this class switch may have accounted for an increase in 12-month event-free survival in the neoadjuvant group of approximately 5 percentage points.

Among the hypotheses proposed to explain the superior efficacy of neoadjuvant over adjuvant checkpoint inhibitor therapy is that stronger and more diverse T-cell responses are induced by neoadjuvant immunotherapy. This property is believed to be due to the presence of the entire tumor, and therefore the complete neoantigen repertoire, at the time the immunotherapy is initiated.[21,22] The addition of a CTLA-4 inhibitor to neoadjuvant PD-1 blockade improves the efficacy further, as shown in a phase 2 trial of neoadjuvant treatment, in pooled cross-trial comparisons, and in trials in stage IV melanoma.[20,23-25] Ipilimumab has been shown to broaden the tumor-specific T-cell rep-

Table 3. Adverse Events.*

Event	Neoadjuvant Group (N=212)	Adjuvant Group (N=208)
Any adverse event — no. (%)	204 (96.2)	194 (93.3)
Any grade ≥3 adverse event — no. (%)	100 (47.2)	71 (34.1)
Serious adverse event — no. (%)	77 (36.3)	49 (23.6)
Treatment-related adverse event — no. (%)	196 (92.5)	178 (85.6)
Treatment-related grade ≥3 adverse event — no. (%)	82 (38.7)	50 (24.0)
Surgery-related adverse event — no./total no. (%)	120/198 (60.6)	151/208 (72.6)
Surgery-related grade ≥3 adverse event — no./total no. (%)	28/198 (14.1)	30/208 (14.4)
Adverse event related to systemic treatment — no./total no. (%)	181/212 (85.4)	123/170 (72.4)
Grade ≥3 adverse event related to systemic treatment — no./total no. (%)	63/212 (29.7)	25/170 (14.7)
Discontinuation of treatment due to adverse event — no. (%)	19 (9.0)	30 (14.4)
Death due to treatment-related adverse event — no. (%)	0	1 (0.5)

* Included are adverse events that were reported between randomization and 100 days after the last trial treatment. The safety population included all the patients who started trial treatment. Surgery-related adverse events were assessed in all the patients who underwent surgery. Adverse events related to systemic treatment were assessed in all the patients who received at least one dose of systemic treatment. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

ertoire and might therefore benefit patients who did not have a preexisting antitumor immune response before the start of checkpoint inhibitor therapy.[26] In line with these biologic observations, the combination of ipilimumab plus nivolumab in the NADINA trial seems to result in a higher 12-month event-free survival than neoadjuvant pembrolizumab (84% vs. 72%).[7] However, this advantage comes with higher toxicity, which emphasizes the need to identify subgroups of patients who may benefit from one or the other scheme; the efficacy of these treatments in specific subgroups of patients should be investigated in head-to-head comparison trials. Alternative neoadjuvant regimens with anti–PD-1 backbones (including the combination with anti–LAG-3, which has shown promising results in a phase 2 trial) could be considered for comparison with neoadjuvant ipilimumab plus nivolumab.[27]

The results of our trial confirm previous findings that indicate that the pathological response correlates with recurrence-free survival, although prolonged follow-up is needed to draw conclusions about its association with long-term outcomes.[24] In addition, this trial incorporated a response-driven adaptive strategy, resulting in a favorable 1-year recurrence-free survival among patients with a major pathological response (95.1%), even without adjuvant therapy. Recent updates from phase 2 trials indicate that this strategy of omitting adjuvant therapy in patients with a major pathological response is safe and is associated with favorable long-term outcomes.[28] Because the majority of the patients in the neoadjuvant group in this trial had a major pathological response, allowing for de-escalation of adjuvant treatment, the effect on quality of life and health economics could be substantial. In the future, one could also envision de-escalation of surgery in patients who have a major pathological response, as in the PRADO trial.[11,29]

In the current trial, the recurrence-free survival was only 76.1% among patients with a pathological partial response, even though they received adjuvant treatment. Previous trials have shown either similar recurrence-free survival (73% in the PRADO trial) or better recurrence-free survival (100% in the OpACIN-neo trial) at 1 year without adjuvant treatment.[11,15] These data indicate that the subgroup of patients who had a pathological partial response might be too small and too heterogeneous in the individual trials, and therefore the role of adjuvant therapy in this subgroup remains poorly understood. Future (pooled) analyses are needed. With respect to patients who had a pathological nonresponse, the results of the current trial were consistent with those in the PRADO trial and the OpACIN-neo trial, which showed a reduction in the risk of recurrence with adjuvant therapy. However,

the estimated 1-year recurrence-free survival of 57.0% among the patients who had a pathological nonresponse indicates that new adjuvant therapies need to be explored in this subgroup.[30]

The success of such a response-driven adjuvant approach relies fundamentally on a robust response assessment by the local pathologist. The discrepancies between local and central pathological assessment were limited in our trial and were attributable to up-front education of the pathologists and adherence to the International Neoadjuvant Melanoma Consortium guidelines for pathological assessment.[13]

Despite the evident superiority of neoadjuvant treatment over adjuvant treatment, this first, preplanned interim analysis reflects a relatively short follow-up. Follow-up is ongoing for the assessment of long-term event-free and distant metastasis–free survival, health-related quality of life, and ultimately overall survival.

In this phase 3 trial, two cycles of neoadjuvant ipilimumab plus nivolumab was safe and resulted in longer event-free survival than adjuvant nivolumab among patients with resectable, macroscopic stage III melanoma.

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APPENDIX

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