original reports

Adjuvant Therapy of Nivolumab Combined With Ipilimumab Versus Nivolumab Alone in Patients With Resected Stage IIIB-D or Stage IV Melanoma (CheckMate 915)

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abstract

PURPOSE Ipilimumab and nivolumab have each shown treatment benefit for high-risk resected melanoma. The phase III CheckMate 915 trial evaluated adjuvant nivolumab plus ipilimumab versus nivolumab alone in patients with resected stage IIIB-D or IV melanoma.

PATIENTS AND METHODS In this randomized, double-blind, phase III trial, 1,833 patients received nivolumab 240 mg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks (916 patients) or nivolumab 480 mg once every 4 weeks (917 patients) for ≤ 1 year. After random assignment, patients were stratified by tumor programmed death ligand 1 (PD-L1) expression and stage. Dual primary end points were recurrence-free survival (RFS) in randomly assigned patients and in the tumor PD-L1 expression-level < 1% subgroup.

RESULTS At a minimum follow-up of approximately 23.7 months, there was no significant difference between treatment groups for RFS in the all-randomly assigned patient population (hazard ratio, 0.92; 95% CI, 0.77 to 1.09; $P = .269$) or in patients with PD-L1 expression < 1% (hazard ratio, 0.91; 95% CI, 0.73 to 1.14). In all patients, 24-month RFS rates were 64.6% (combination) and 63.2% (nivolumab). Treatment-related grade 3 or 4 adverse events were reported in 32.6% of patients in the combination group and 12.8% in the nivolumab group. Treatment-related deaths were reported in 0.4% of patients in the combination group and in no nivolumab-treated patients.

CONCLUSION Nivolumab 240 mg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks did not improve RFS versus nivolumab 480 mg once every 4 weeks in patients with stage IIIB-D or stage IV melanoma. Nivolumab showed efficacy consistent with previous adjuvant studies in a population resembling current practice using American Joint Committee on Cancer eighth edition, reaffirming nivolumab as a standard of care for melanoma adjuvant treatment.

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ASSOCIATED CONTENT

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

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INTRODUCTION

Adjuvant therapy in melanoma, including the immune checkpoint inhibitors ipilimumab,[1] nivolumab,[2] and pembrolizumab,[3] as well as the BRAF plus MEK inhibitor combination of dabrafenib plus trametinib,[4] has improved outcomes for patients with resected stage III melanoma. Adjuvant ipilimumab 10 mg/kg once every 3 weeks for four doses and then once every 3 months for ≤ 3 years significantly improved recurrence-free survival (RFS) and overall survival (OS) versus placebo in the phase III EORTC 18071 trial.[1] In the phase III CheckMate 238 study, adjuvant nivolumab 3 mg/kg once every 2 weeks for ≤ 1 year was associated with significant RFS benefit and reduced toxicity versus ipilimumab 10 mg/kg once every 3 weeks for four doses then every 12 weeks for ≤ 1 year in patients with resected stage IIIB-C or IV melanoma[2,5]; OS was nearly 80% in both groups at 4 years.[2,6] Population pharmacokinetic analyses showed that flat-dose nivolumab 240 mg once every 2 weeks and 480 mg once every 4 weeks were comparable with nivolumab 3 mg/kg once every 2 weeks.[7,8]

In CheckMate 067, response, progression-free survival, and OS were numerically improved with nivolumab

CONTEXT

Key Objective

Previous studies demonstrated that adjuvant nivolumab and ipilimumab each provide clinical benefit in patients with resected stage III or IV melanoma. CheckMate 915, a randomized, double-blind, phase III trial, evaluated the efficacy, safety, and health-related quality-of-life impact of adjuvant nivolumab 240 mg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks versus nivolumab 480 mg once every 4 weeks in patients with resected stage IIIB-D or IV melanoma.

Knowledge Generated

Adjuvant nivolumab plus ipilimumab did not improve recurrence-free survival versus nivolumab monotherapy in patients with stage IIIB-D or IV melanoma. Safety and health-related quality of life with both treatment regimens were consistent with previous studies.

Relevance *(G.K. Schwartz)*

These results reaffirm nivolumab as a standard of care for melanoma adjuvant treatment and do not support nivolumab plus ipilimumab use at the studied dosages.*

*Relevance section written by *JCO* Associate Editor Gary K. Schwartz, MD, FASCO.

1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks for four doses, followed by nivolumab 3 mg/kg once every 2 weeks versus nivolumab monotherapy 3 mg/kg once every 2 weeks in treatment-naive patients with stage III or IV melanoma.[9,10] The combination was also associated with more toxicity than nivolumab alone, but health-related quality of life (HRQoL) remained stable and comparable.[10] In a pilot phase II adjuvant study in patients with resected stage IIIC or IV melanoma, toxicity with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg led to a second cohort treated with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg once every 3 weeks.[11] These trials, along with ipilimumab 1 mg/kg once every 6 weeks safety results from CheckMate 012 in non–small-cell lung cancer[12] helped inform the phase III CheckMate 915 trial, which compared nivolumab 240 mg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks with nivolumab monotherapy 480 mg once every 4 weeks as adjuvant treatment for ≤ 1 year in patients with completely resected stage IIIB-D or IV disease. This dosing was designed to optimize adjuvant treatment benefit and risk profiles. CheckMate 915 dual primary end points were RFS in the all-randomized population and in patients with tumor programmed death ligand 1 (PD-L1) expression < 1%. Here, we present efficacy and safety overall, and outcomes in clinically relevant subgroups.

PATIENTS AND METHODS

Patients

Eligible patients were age 12 years or older, were diagnosed with resected stage IIIB-D or IV melanoma (per American Joint Committee on Cancer eighth edition [AJCC-8][13]), and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Complete resection with no evidence of residual disease was required within 12 weeks before random assignment. Complete lymph node dissection (CLND) was not required. Additional methods are detailed in the Data Supplement (online only).

The institutional review board or ethics committee at each study center approved the trial protocol and amendments. The trial was conducted in accordance with Good Clinical Practice guidelines, as specified by the International Conference on Harmonisation. Before enrollment, all patients provided written informed consent.

Study Design and Treatment

This randomized, double-blind, phase III study enrolled patients at 123 centers in 19 countries (Data Supplement). Patients were randomly assigned 1:1 to receive nivolumab 240 mg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks (combination group) or nivolumab 480 mg once every 4 weeks monotherapy (nivolumab group), along with appropriate placebo doses. Random assignment was stratified by tumor PD-L1 expression (< 1% or indeterminate *v* 1% to < 5% *v* ≥ 5%) and disease stage (AJCC-8 IIIB *v* IIIC-D *v* IV). Treatment continued for ≤ 1 year or until disease recurrence, unacceptable toxicity, or withdrawal of consent. Dose modifications were not permitted and both study drugs had to be discontinued simultaneously. The details regarding a 10 mg/kg ipilimumab group that was discontinued are provided (Data Supplement).

Assessments

Dual primary end points were RFS in all randomly assigned patients and in patients with tumor PD-L1 expression < 1%. Per a 2019 data monitoring committee review, results from the dual primary end point in patients with PD-L1 expression < 1% remained blinded because that end point (which occurred first) was not met; descriptive results in this population are presented here on the basis of the original all-randomized population database lock (September 8, 2020).

RFS was defined as the time from random assignment to the date of the first recurrence (local, regional, or distant), development of new primary melanoma (including in situ), or death from any cause, whichever occurred first. Secondary end points were OS and association of RFS and PD-L1 expression. OS was defined as the time between random assignment and the date of death from any cause. Exploratory end points included DMFS, safety and tolerability, and HRQoL. DMFS was assessed in all patients with baseline stage III disease and defined as the time from the random assignment date to the date of first distant metastasis or death from any cause, whichever occurred first.

All patients were evaluated for disease recurrence every 12 weeks for the first 3 years after random assignment and every 6 months thereafter for ≤ 5 years using contrast-enhanced computed tomography or magnetic resonance imaging scans. Baseline tumor PD-L1 membrane expression was assessed centrally with the PD-L1 IHC 28-8 pharmDx Kit (Dako, an Agilent Technologies company, Santa Clara, CA) to determine expression levels for stratification.

Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events, version 4.0; those reported occurred between the first study dose and 30 days after the last dose. Treatment-related adverse events (TRAEs) were investigator-assessed.

HRQoL was assessed at baseline and every 4 weeks until week 49 using the European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality-of-Life Questionnaire (QLQ-C30)[14,15] and the European Quality-of-Life–5 Dimensions (EQ-5D) summary index and visual analogue scale.[16,17]

Further study assessment details are provided in the Data Supplement.

Statistical Analysis

Efficacy analyses included all intention-to-treat randomly assigned patients. The details relating to the primary end point in patients with PD-L1 expression < 1%, and sample size calculations, are provided (Data Supplement).

RFS distributions were compared between the treatment groups using a two-sided log-rank test stratified by PD-L1 status and AJCC stage at screening. Hazard ratios (HRs) and CIs of the combination versus the nivolumab group were estimated using a Cox proportional hazards model with treatment group as a single covariate, stratified by the above factors. RFS was estimated using the Kaplan-Meier product-limit method. Median RFS and rates (with corresponding two-sided 95% CIs) were computed using the log-log transformation. DMFS and OS were similarly analyzed. OS data were not analyzed at the original all-randomized database lock because of low events. OS data are presented here from the final database lock (April 20, 2021), although the events were still well below those required for statistical significance with ≥ 80% power (243 of the 630 deaths required overall). All analyses were performed using SAS software (version 9.2; Cary, NC). The safety population included patients who received at least one study treatment dose.

RESULTS

Patients

From April 2017 to June 2018, 920 patients were randomly assigned to the combination group and 924 to the nivolumab group; 916 and 917 patients, respectively, received treatment (Fig 1). Baseline characteristics were similar between treatment groups (Table 1). The minimum follow-up (September 8, 2020 database lock) was 23.7 months for all patients (median, 28.0 months, combination; 28.1 months, nivolumab). Among all patients, 364 of 916 (39.7%) treated with nivolumab plus ipilimumab and 561 of 917 (61.2%) treated with nivolumab completed the 1-year treatment period; 317 of 916 (34.6%) and 104 of 917 (11.3%), respectively, discontinued treatment because of study drug toxicity. Patients treated with the combination had a shorter median duration of therapy (7.6 months) versus nivolumab alone (11.1 months), resulting in a lower median cumulative nivolumab dose (3,840 *v* 6,240 mg; Data Supplement). Subsequent therapy (including radiotherapy, surgery, and systemic therapy) was received by 296 (32.2%) patients in the combination group and 337 (36.5%) patients in the nivolumab group; subsequent systemic therapy was received by 187 (20.3%) and 215 (23.3%) patients, respectively (Data Supplement).

Efficacy

In the all-randomized population, 327 of 920 (35.5%) recurrence events occurred with nivolumab plus ipilimumab and 347 of 924 (37.6%) with nivolumab. Median RFS was not reached (NR) in either treatment group, with 24-month rates of 64.6% and 63.2% in the combination and nivolumab groups, respectively (HR, 0.92; 97.295% CI, 0.77 to 1.09; $P = .269$; Fig 2A). The nature of recurrence was similar between treatment groups, with distant metastases being most common (161 of 327 [49.2%] patients in the combination group and 157 of 347 [45.2%] patients for nivolumab; Data Supplement).

In the PD-L1 expression < 1% population, recurrence events occurred in 159 of 349 (45.6%) patients in the combination group and 166 of 351 (47.3%) patients in the nivolumab group. The median RFS was 33.2 months (95% CI, 22.2 to NR) in the combination group and 25.3 months (95% CI, 19.8 to NR) in the nivolumab group (HR, 0.91; 95% CI, 0.73 to 1.14), with 24-month RFS rates of 53.6% and 52.4%, respectively (Fig 2B).

Most prespecified subgroups had similar RFS HR to the all-randomized population (Fig 3). In patients with stage III and IV disease and across stage IIIB-D disease, RFS per

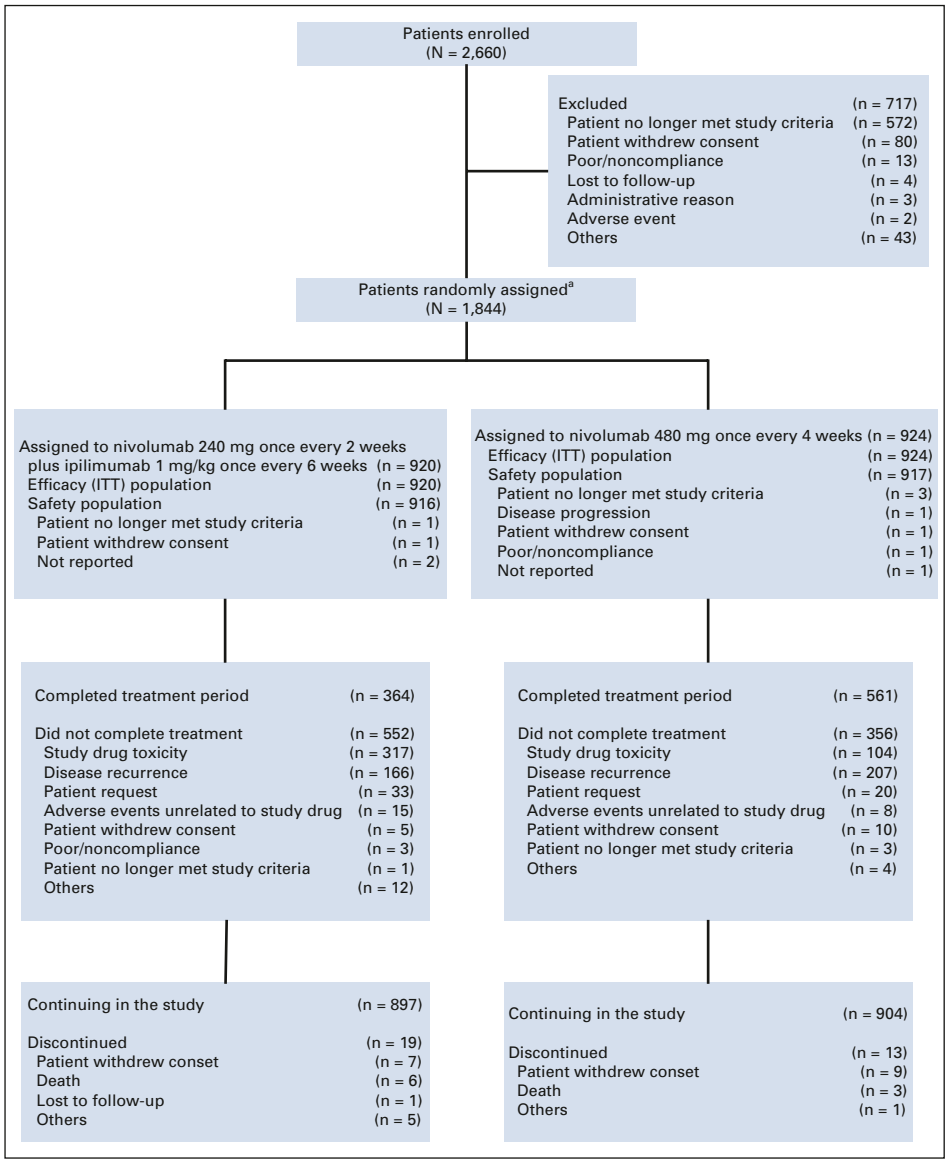

FIG 1. CONSORT diagram. [a]In addition, a further 99 patients were randomly assigned to an ipilimumab monotherapy cohort that was subsequently terminated following the results of CheckMate 238. The patients were unblinded and offered open-label treatment in one of the two other treatment groups. ITT, intention-to-treat.

treatment group was similar to the all-randomized population (Data Supplement). Twenty-four–month RFS rates were 54.0% and 62.3% for the combination and nivolumab groups, respectively, in patients with *BRAF*-mutated tumors and 69.3% and 62.2% in patients with wild-type tumors (Data Supplement). Of patients with *BRAF*V600E/K-mutated tumors, 504 of 567 (88.9%) had a V600E mutation and 63 of 567 (11.1%) had V600K. For combination therapy and nivolumab monotherapy, respectively, 24-month RFS rates were 66.0% and 66.6% in patients without in-transit metastases and 61.8% and 56.1% in patients with in-transit metastases (Data Supplement). In a landmark analysis of patients who were recurrence-free at 6 months, 24-month RFS was 74.9% in patients who had discontinued treatment because of study drug toxicity $\leq$ 6 months after starting treatment and 79.6% in those who had not (Data Supplement).

The median OS and DMFS were both NR in the treatment groups in the all-randomized (HR, 1.09; 95% CI, 0.80 to 1.32; and HR, 1.01; 95% CI, 0.83 to 1.23) and PD-L1 expression $<$ 1% populations (HR, 1.22; 95% CI, 0.85 to 1.73; and HR, 0.94; 95% CI, 0.70 to 1.25). Twenty-four–month rates in the combination versus the nivolumab group were 89.8% versus 91.8% (OS) and 75.4% versus 77.4% (DMFS) for all randomly assigned patients and 85.3% versus 89.6% (OS) and 67.9% versus 68.4% (DMFS) for the PD-L1 expression $<$ 1% population (Data Supplement).

TABLE 1. Demographic and Clinical Characteristics of the Patients at Baseline[a]

Characteristic	Nivolumab Plus Ipilimumab (n = 920)	Nivolumab (n = 924)
Sex, No. (%)		
Male	515 (56.0)	537 (58.1)
Female	405 (44.0)	387 (41.9)
Age, years		
Median (range)	55 (16-89)	55 (15-88)
Disease stage, No. (%)		
IIIB	282 (30.7)	287 (31.1)
IIIC	489 (53.2)	481 (52.1)
IIID	26 (2.8)	30 (3.2)
IV	121 (13.2)	124 (13.4)
Not reported	2 (0.2)	2 (0.2)
Type of lymph node involvement in stage III patients, No. (%)		
Clinically occult only	271 (29.5)	257 (27.8)
Clinically detected only	323 (35.1)	353 (38.2)
Clinically detected and clinically occult	117 (12.7)	97 (10.5)
No tumor-involved nodes	81 (8.8)	88 (9.5)
Not reported	5 (0.5)	3 (0.3)
Tumor ulceration by lymph node involvement in stage III patients, No. (%)		
Present and clinically occult only	160 (17.4)	149 (16.1)
Present and clinically detected only	104 (11.3)	108 (11.7)
Present and clinically detected and clinically occult	34 (3.7)	28 (3.0)
Absent and clinically occult only	81 (8.8)	91 (9.8)
Absent and clinically detected only	119 (12.9)	146 (15.8)
Absent and clinically detected and clinically occult	54 (5.9)	51 (5.5)
Unknown or no tumor-involved nodes	240 (26.1)	221 (23.9)
Not reported	5 (0.5)	4 (0.4)
M status in stage IV patients, No. (%)		
M1a	55 (6.0)	66 (7.1)
M1b	39 (4.2)	29 (3.1)
M1c	25 (2.7)	21 (2.3)
M1d	2 (0.2)	8 (0.9)
Melanoma subtype, No. (%)		
Mucosal	7 (0.8)	13 (1.4)
Cutaneous	802 (87.2)	814 (88.1)
Acral	30 (3.3)	24 (2.6)
Others[b]	78 (8.5)	71 (7.7)
Not reported	3 (0.3)	2 (0.2)
In-transit satellite and/or microsatellite metastases in stage III patients, No. (%)		
Present with no tumor-involved nodes	77 (8.4)	86 (9.3)
Present with tumor-involved nodes	163 (17.7)	149 (16.1)
Matted nodes	11 (1.2)	13 (1.4)
Not applicable	546 (59.3)	550 (59.5)

(continued on following page)

TABLE 1. Demographic and Clinical Characteristics of the Patients at Baseline[a] (continued)

Characteristic	Nivolumab Plus Ipilimumab (n = 920)	Nivolumab (n = 924)
Lactate dehydrogenase, No. (%)		
≤ ULN	824 (89.6)	817 (88.4)
> ULN	84 (9.1)	89 (9.6)
≤ 2 × ULN	907 (98.6)	905 (97.9)
> 2 × ULN	1 (0.1)	1 (0.1)
Not reported	12 (1.3)	18 (1.9)
PD-L1 expression, No. (%)		
< 1%	350 (38.0)	350 (37.9)
≥ 1%	527 (57.3)	534 (57.8)
< 5%	577 (62.7)	581 (62.9)
≥ 5%	300 (32.6)	303 (32.8)
Could not be determined or not reported	43 (4.7)	40 (4.3)
BRAF status,[c] No. (%)		
Mutation	281 (30.5)	286 (31.0)
No mutation	425 (46.2)	395 (42.7)
Not reported	214 (23.3)	243 (26.3)

Abbreviations: M, metastasis; PD-L1, programmed death ligand 1; ULN, upper limit of normal.
[a]Percentages may not total 100 because of rounding.
[b]Multiple melanoma subtype categories as per the electronic clinical report form.
[c]*BRAF* mutational analysis (V600E/K) was performed centrally via whole-exome sequencing.

Safety

Any-grade (or grade 3 or 4) TRAEs were reported in 94.2% (32.6%) of patients in the combination group and 85.9% (12.8%) in the nivolumab group (Table 2). Overall, 31.6% of combination group patients and 10.4% of nivolumab group had any-grade TRAEs leading to discontinuation; these events were grade 3 or 4 in 18.9% and 5.9% of patients, respectively (Data Supplement). Investigators attributed four (0.4%) deaths to study drug toxicity, all in the combination group as follows: one ≤ 30 days of last dose (respiratory distress syndrome), two between 30 and 100 days (myasthenia gravis [n = 1] and pneumonitis [n = 1]), and one > 100 days from last dose (liver failure). Select (ie, predefined immunologic) grade 3 or 4 gastrointestinal (6.9% *v* 1.4%), hepatic (7.9% *v* 1.4%), and endocrine (4.4% *v* 1.5%) TRAEs were more common in patients treated with the combination versus nivolumab monotherapy, respectively (Data Supplement). Additionally, immune-mediated AEs were more common in patients treated with the combination than with nivolumab monotherapy, except categories of nephritis and renal dysfunction (8 [0.9%] *v* 11 [1.2%] patients; Data Supplement).

HRQoL in both treatment groups remained within the cutoff for the clinically defined minimally important difference (MID) for the EORTC QLQ-C30 Global Health Status score (< 10 points), indicating no clinically meaningful deterioration over the 1-year treatment period and follow-up assessments (Data Supplement).[15] Similarly, no clinically meaningful deterioration per EQ-5D utility index (MID, 0.8) or visual analogue scale (MID, 7) scores were observed in either treatment group.[17]

DISCUSSION

Adjuvant nivolumab 240 mg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks did not improve RFS compared with nivolumab 480 mg once every 4 weeks in patients with resected stage IIIB-D or IV melanoma in the all-randomized or PD-L1 expression < 1% populations. The safety and tolerability of both treatments were consistent with their known safety profiles. HRQoL was comparable in both arms, with no clinically meaningful changes from baseline.

Despite descriptive analyses supporting the efficacy benefit with nivolumab plus ipilimumab over nivolumab alone for metastatic melanoma in CheckMate 067,[10] no such improvement in RFS was observed in CheckMate 915, with this lower, less frequently administered ipilimumab dosage. Absent a definitive explanation for the lack of improved efficacy here with the combination, possible hypotheses are drug exposure or dosing schedules differences. In Checkmate 915, duration of therapy was shorter, with a lower cumulative nivolumab dose in the combination than the nivolumab group. However, 6-month landmark RFS rates in patients treated with the combination were similar between those who did/did not discontinue combination treatment because of toxicity in the first 6 months.

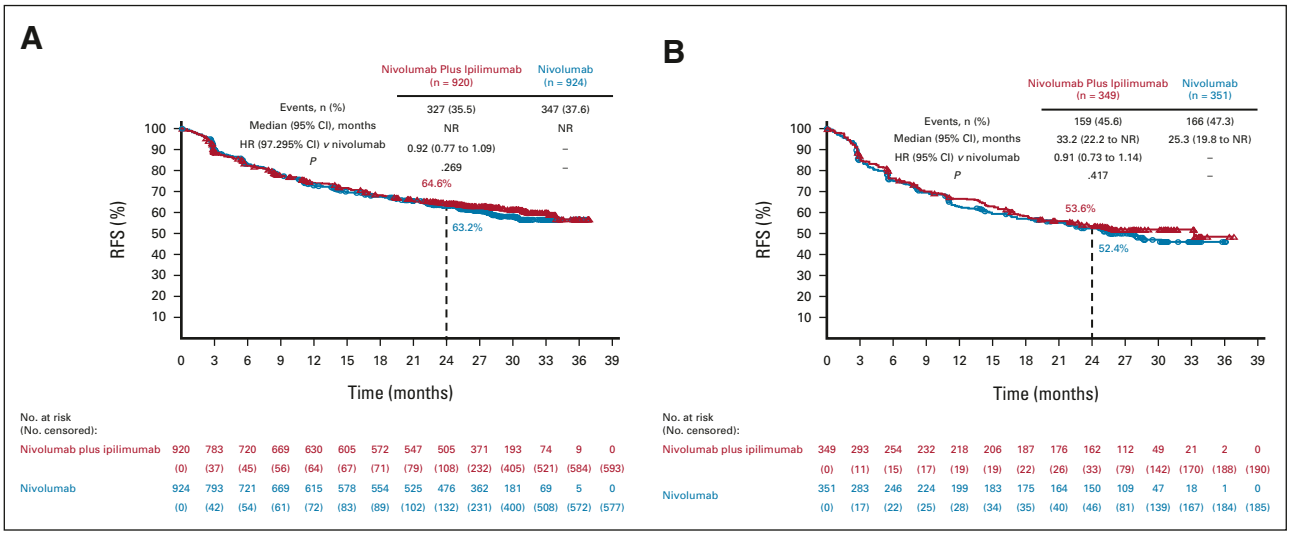

FIG 2. RFS in the all-randomized patient population and population with tumor PD-L1 expression < 1% represented as Kaplan-Meier estimates of RFS in the all-randomized (A) patient population and (B) in patients with PD-L1 tumor expression < 1%. Patients were followed for a minimum of 24 months (dashed line). HR, hazard ratio; NR, not reached; PD-L1, programmed death ligand 1; RFS, recurrence-free survival.

Therefore, early treatment discontinuations because of toxicity did not solely drive the lack of RFS benefit here.

After CheckMate 915 initiation, multiple studies investigating use of the combination for adjuvant treatment of melanoma reported initial efficacy data. A pilot phase II study of 20 patients with resected stage IIIC or IV melanoma per arm showed similar 2-year RFS for nivolumab 3 mg/kg plus ipilimumab 1 mg/kg and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (75% *v* 80%); both combinations were administered for ≤ 2 years with four induction doses once

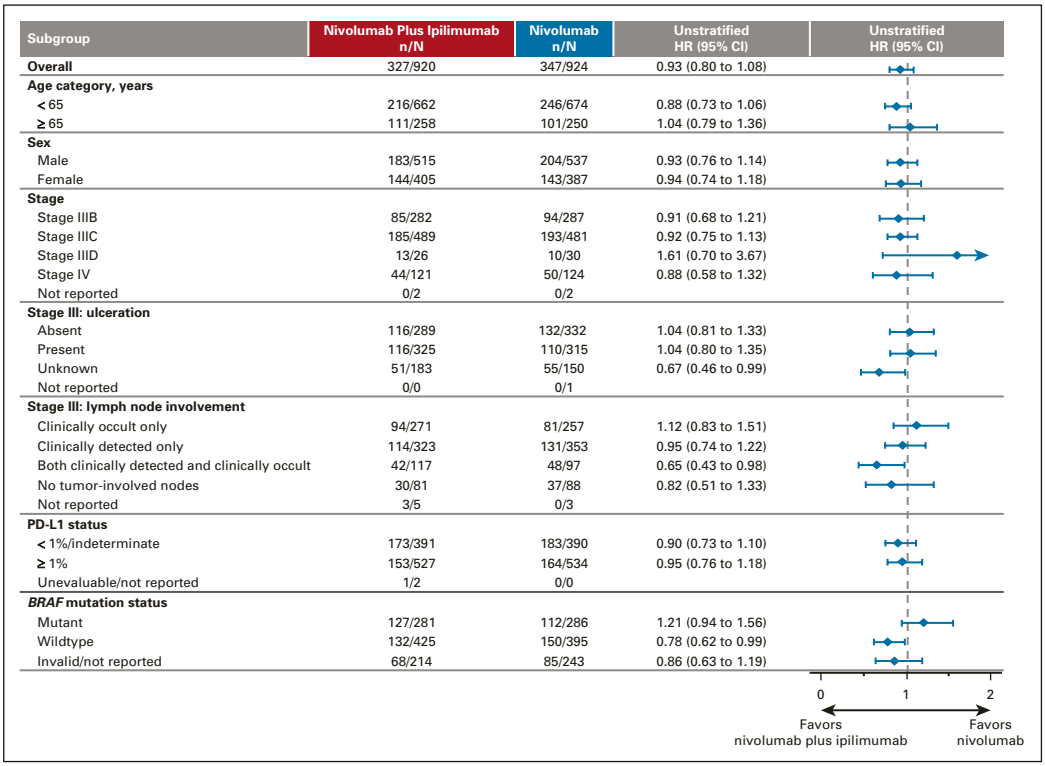

FIG 3. RFS in patient subgroups at 24 months with results expressed as unstratified HRs (with 95% CIs) for the risk of recurrence or death in the combination group compared with the nivolumab monotherapy group. HR, hazard ratio; PD-L1, programmed death ligand 1; RFS, recurrence-free survival.

TABLE 2. Treatment-Related Adverse Events[a]

Event	Nivolumab Plus Ipilimumab (n = 916), No. (%)		Nivolumab (n = 917), No. (%)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any	863 (94.2)	299 (32.6)	788 (85.9)	117 (12.8)
Pruritus	303 (33.1)	2 (0.2)	194 (21.2)	0
Fatigue	279 (30.5)	10 (1.1)	276 (30.1)	2 (0.2)
Diarrhea	248 (27.1)	22 (2.4)	187 (20.4)	5 (0.5)
Rash	222 (24.2)	5 (0.5)	192 (20.9)	6 (0.7)
Hypothyroidism	202 (22.1)	2 (0.2)	133 (14.5)	1 (0.1)
Hyperthyroidism	178 (19.4)	4 (0.4)	93 (10.1)	0
Asthenia	134 (14.6)	3 (0.3)	122 (13.3)	1 (0.1)
Nausea	130 (14.2)	2 (0.2)	100 (10.9)	0
Headache	124 (13.5)	1 (0.1)	81 (8.8)	0
Increase in ALT level	121 (13.2)	30 (3.3)	72 (7.9)	4 (0.4)
Increase in lipase level	105 (11.5)	48 (5.2)	47 (5.1)	17 (1.9)
Arthralgia	105 (11.5)	7 (0.8)	120 (13.1)	3 (0.3)
Increase in AST level	99 (10.8)	15 (1.6)	59 (6.4)	1 (0.1)
Hypophysitis	96 (10.5)	19 (2.1)	15 (1.6)	4 (0.4)

[a]The safety population included all patients who had received at least one dose of trial drug. The investigators determined whether adverse events were related to a trial drug. The events listed here were any grade reported in at least 10% of the patients in either treatment group and occurred between the first dose and 30 days after the last dose. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

every 3 weeks, followed by maintenance nivolumab.[18] Both nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks for four doses followed by nivolumab 3 mg/kg once every 2 weeks and nivolumab 3 mg/kg once every 2 weeks alone significantly improved RFS versus placebo in patients with resected stage IV melanoma enrolled in the phase II IMMUNED trial, with HRs of 0.23 (97.5% CI, 0.12 to 0.45) and 0.56 (97.5% CI, 0.33 to 0.94), respectively.[19] Improvement was also observed with the combination over the nivolumab group as an exploratory end point.[19] A pilot study of 21 patients with stage II-IV resected melanoma treated with nivolumab 3 mg/kg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks for 24 weeks showed 24-month RFS and OS rates of 85.7% and 90.5%, respectively.[20] Moreover, in the randomized phase II OpACIN-neo trial in patients with resectable stage III melanoma, neoadjuvant ipilimumab 1 mg/kg plus nivolumab 3 mg/kg once every 3 weeks was the best tolerated schedule and induced a high rate of pathological response.[21] In the current trial, there was a lack of RFS benefit between combination and nivolumab monotherapy with an apparent lack of OS benefit, albeit with immature data. In other recent trials evaluating adjuvant PD-1 antibodies (eg, CheckMate 238, SWOG S1404, and KEYNOTE-054), the lack of OS benefit despite RFS benefit raises questions of whether waiting for recurrence and receiving treatment for metastatic disease would be acceptable to patients.[5,22-24] This is complicated by the active control arms in the two trials (CheckMate 238 and SWOG S1404) that have reported OS data thus far and the relative immaturity of those OS data.[5,22] Longer follow-up is needed for these trials to ascertain any long-term benefits with adjuvant PD-1 blockade.

The CheckMate 915 ipilimumab dosing regimen was selected to balance efficacy and toxicity of adjuvant treatment in patients with melanoma on the basis of data in other tumor types.[12,25] Encouraging efficacy and improved safety with low-dose ipilimumab was observed in the phase IIIb/IV CheckMate 511 trial evaluating nivolumab 3 mg/kg plus ipilimumab 1 mg/kg versus nivolumab 1 mg/kg plus ipilimumab 3 mg/kg in patients with unresectable stage III/IV melanoma treated once every 3 weeks,[26,27] and the phase Ib KEYNOTE-029 study in patients with advanced melanoma who received pembrolizumab 2 mg/kg plus ipilimumab 1 mg/kg once every 3 weeks for four doses, followed by maintenance pembrolizumab.[28] Compared with melanoma studies that demonstrated clinical benefit with ipilimumab-containing treatment regimens, such as EORTC 18071, CheckMate 067, and IMMUNED, the ipilimumab dosage in CheckMate 915 was both lower and less frequent (95%, 83%, and 83% lower exposure, respectively, over a 6-week period),[1,9,19] suggesting that the lack of significant efficacy benefit with combination therapy in CheckMate 915 may be explained, in part, by the dose-dependent and induction exposure nature of ipilimumab activity.[6,29] The results observed here, combined with previous data on ipilimumab in melanoma, suggest that the dose and schedule of nivolumab plus ipilimumab in an adjuvant melanoma setting require further refinement for optimal balance of efficacy and toxicity.

During recruitment for CheckMate 915, clinical practice changed because of the results of the Multicenter Selective Lymphadenectomy Trial II,[30] and CLND was no longer standard therapy in patients with micrometastatic stage III melanoma (compared with CheckMate 238 recruitment period). The large CheckMate 915 patient population is representative of current practice: enrolled patients were staged per AJCC-8 criteria, received flat-dose nivolumab 480 mg once every 4 weeks, and were not required to have CLND. The 24-month RFS rate of 63.2% was consistent with that observed in CheckMate 238 with nivolumab 3 mg/kg once every 2 weeks (63%), with a similar toxicity profile.[31] Median monotherapy doses were comparable,[2] and flat-dose nivolumab is equivalent to the weight-based dose used in CheckMate 238.[2,7] The consistent results with nivolumab monotherapy in this study and CheckMate 238 suggest that including patients without CLND did not affect RFS.

Similar RFS was observed across most subgroups evaluated in CheckMate 915, regardless of PD-L1 expression and including poor prognostic patients with in-transit metastases.

In metastatic melanoma, nivolumab plus ipilimumab treatment increased efficacy in patients with *BRAF*-mutant versus *BRAF*–wild-type tumors,[10] but that trend was not observed here with adjuvant treatment.

In conclusion, the Checkmate 915 study of combination nivolumab 240 mg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks versus nivolumab 480 mg once every 4 weeks in patients with resected stage IIIB-D or IV melanoma did not demonstrate improved RFS in the all-randomized or PD-L1 expression $< 1\%$ populations. RFS with nivolumab 480 mg once every 4 weeks was consistent with previous adjuvant nivolumab results using weight-based dosing every 2 weeks. Nivolumab plus ipilimumab and nivolumab monotherapy safety and HRQoL were consistent with previous studies. The results of CheckMate 915 showed that nivolumab 240 mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks does not improve upon the consistent results obtained with standard-of-care nivolumab 480 mg once every 4 weeks in high-risk melanoma adjuvant treatment. Combination dosing in the adjuvant setting requires further refinement and investigation to determine the optimal balance between benefit and toxicity.

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BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html. Data are generally available 2 years after completion of the study and will be made available to qualified researchers who submit an in-scope proposal approved by the Independent Review Committee, with available information dependent upon the individual request. The de-identified and anonymized data sets may be accessed within a secured portal if the proposal is approved and upon execution of the agreement.

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Consulting or Advisory Role: Bristol Myers Squibb (Inst), Merck Sharp & Dohme (Inst), Novartis (Inst), Cartherics (Inst)
Research Funding: Bristol Myers Squibb (Inst), Merck Sharp & Dohme (Inst), Pharmaust (Inst), Zucero Therapeutics (Inst), CStone Pharmaceuticals (Inst)

Piotr Rutkowski
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Consulting or Advisory Role: Novartis, Blueprint Medicines, Bristol Myers Squibb, Pierre Fabre, MSD, Amgen
Speakers' Bureau: Pfizer, Novartis, Pierre Fabre
Research Funding: Novartis (Inst), Roche (Inst), Bristol Myers Squibb (Inst)
Travel, Accommodations, Expenses: Orphan Europe, Pierre Fabre

Andrew Haydon
Honoraria: Novartis, Merck, Novartis
Consulting or Advisory Role: Novartis, Merck Sharp & Dohme, Bristol Myers Squibb
Speakers' Bureau: Novartis, Derek, Bristol Myers Squibb
Expert Testimony: BUS

Jean-Jacques Grob
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Speakers' Bureau: Novartis
Travel, Accommodations, Expenses: BMS, USD Oncology, Novartis, Pierre Fabre

Jacob Schachter
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Consulting or Advisory Role: MSD, Bristol Myers Squibb
Travel, Accommodations, Expenses: Bristol Myers Squibb

Paola Queirolo
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Travel, Accommodations, Expenses: MSD Oncology, Sanofi/Regeneron

Luis de la Cruz-Merino
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Research Funding: Roche (Inst), Celgene (Inst)
Travel, Accommodations, Expenses: Roche

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Consulting or Advisory Role: MSD Oncology, Novartis
Research Funding: Merck Serono
Travel, Accommodations, Expenses: Bristol Myers Squibb, Roche/Genentech, Novartis

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Sandra Re
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Stock and Other Ownership Interests: Merck Sharp & Dohme, Bristol Myers Squibb (I)
Consulting or Advisory Role: Healthcare Advisors (I)
Travel, Accommodations, Expenses: Merck Sharp & Dohme, Fiore Healthcare Advisors (I)

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Stock and Other Ownership Interests: Bristol Myers Squibb

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Stock and Other Ownership Interests: Bristol Myers Squibb
Travel, Accommodations, Expenses: Bristol Myers Squibb

Daniel J. Tenney
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Stock and Other Ownership Interests: Bristol Myers Squibb Foundation
Travel, Accommodations, Expenses: Bristol Myers Squibb/Celgene

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Georgina V. Long
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