

VOL. 372 NO. 21

ESTABLISHED IN 1812

MAY 21, 2015

NEJM.ORG



1986 THIS WEEK AT NEJM.ORG

PERSPECTIVE

- 1977 Three Cheers for Logrolling — The Demise
of the SGR H.J. Aaron
- 1979 The Children's Cliff — Extending CHIP
J. Oberlander and D.K. Jones
- 1981 The CMS Innovation Center — A Five-Year
Self-Assessment R. Rajkumar, M.J. Press,
and P.H. Conway
- 1984 Symbol of Health System Transformation?
Assessing the CMS Innovation Center
L.P. Casalino and T.F. Bishop

ORIGINAL ARTICLES

- | | |
|------|--|
| 1987 | Allergen-Induced Asthmatic Responses Modified by a GATA3-Specific DNase
N. Krug and Others |
| 1996 | Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection
R.G. Sawyer and Others |
| 2006 | Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma
M.A. Postow and Others |
| 2018 | Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer
E.B. Garon and Others |

SPECIAL ARTICLE

- 2029 Trends in Mental Health Care among Children
and Adolescents
M. Olfson, B.G. Druss, and S.C. Marcus

REVIEW ARTICLE

- 2039 Pelvic Inflammatory Disease
R.C. Brunham, S.L. Gottlieb, and J. Paavonen

IMAGES IN CLINICAL MEDICINE

- 2049 Verrucous Tongue Lesion
Y. Hassona and C. Scully
- e27 Hemichoreoathetosis in Neurosarcoidosis
A. Ataya and E. Harman

CASE RECORDS OF THE MASSACHUSETTS
GENERAL HOSPITAL

- 2050 A Girl with Loss of Consciousness and Seizures
E. Wyllie, S.P. Rincon, and V.M. Pierce

EDITORIALS

- 2060 Out of the Orphanage and into the Clinic
— Therapeutic Targeting of GATA-3
B.S. Bochner and R.P. Schleimer

- 2062 Antibiotics for Abdominal Sepsis
-
- R.P. Wenzel and M.B. Edmond

MEDICINE AND SOCIETY

- 2064 Beyond Moral Outrage — Weighing the Trade-Offs
of COI Regulation
L. Rosenbaum

- 2069 **CORRESPONDENCE**
HIV-Positive-to-HIV-Positive Kidney Transplantation
Driving Pressure as a Key Ventilation Variable
Rapid Eradication of a Bulky Melanoma Mass
with One Dose of Immunotherapy

- 2074 CORRECTIONS

- 2075 CONTINUING MEDICAL EDUCATION



Owned & published by the MASSACHUSETTS MEDICAL SOCIETY
© 2015. All rights reserved. ISSN 0028-4793.

610.5

NE

v.372 no.21

May 21 15

Health Sci.

|||||
|||
*****FIRM
000713943/3 # 20160204 20150521
UNIT WASHINGTON
HLTH SCI LIB
SERIALS SECTION BOX 357155
SEATTLE WA 98195-7155

YOUR CUSTOMER NUMBER: 000713943

Amgen Exhibit 1031
Amgen v. BMS

The most
recent articles
are available
online now.

VIDEOS, IMAGES, AND MULTIMEDIA

IMAGES IN CLINICAL MEDICINE

Hemichorea/athetosis in Neurosarcoidosis



A 39-year-old man presented with progressively worsening involuntary movements of the left arm that had

been sudden in onset. A physical examination revealed chorea of the left upper arm and athetosis of the fingers of the left hand, shown in a video.

QUICK TAKE

Treating Intraabdominal Infection



In patients with complicated intra-abdominal infection, is a short, fixed-duration course of antibiotics as effective

as a course that continues through the resolution of fever and other abnormalities? New research findings are summarized in a short video.

PERSPECTIVE AUDIO INTERVIEW

Replacing the SGR

Henry Aaron discusses new legislation that abandons the sustainable growth rate formula and reforms physician reimbursement under Medicare.

INTERACTIVE MEDICAL CASE

A Man with Diarrhea and Back Pain



This interactive feature presents the case of a 43-year-old man with a 6-week history of constant and diffuse abdominal pain and diarrhea six to

seven times daily. Test your diagnostic and therapeutic skills at NEJM.org.

THIS WEEK IN THE JOURNAL

ORIGINAL ARTICLES

Allergen-Induced Asthma and a GATA3-Specific DNzyme

GATA3 is thought to be a critical checkpoint in the allergic diathesis. In this study, a synthetic DNzyme that catalyzes the inactivation of GATA3 when administered by inhalation attenuated the late asthmatic response in laboratory challenges.

EDITORIAL, COMMENTING, PPT SLIDES

Antimicrobial Therapy for Intraabdominal Infection

This randomized, controlled trial involving patients with complicated intraabdominal infections and proper source control showed similar outcomes after fixed-duration antimicrobial therapy (4 days) and after a longer course (approximately 8 days).

EDITORIAL, CME, QUICK TAKE, PPT SLIDES

Ipilimumab and Nivolumab in Metastatic Melanoma

The combination of a CTLA-4 blocker and a PD-1 blocker produced responses in more than 60% of previously untreated patients with *BRAF* wild-type advanced melanoma, including complete responses in more than 20% of these patients.

PPT SLIDES

Pembrolizumab in Lung Cancer

Pembrolizumab, an inhibitor of programmed cell death 1 (PD-1), produced responses in 24% of patients with non-small-cell lung cancer, with a median overall survival of 16.2 months. The response rate increased to 45% if more than 50% of tumor cells expressed the PD-1 ligand.

PPT SLIDES

SPECIAL ARTICLE

Trends in Mental Health Care among Youths

Use of outpatient mental health services by U.S. children and adolescents increased between 1996 and 2012. Youths with more severe impairment were more likely to receive services, but youths with less severe impairment accounted for most of the absolute increase.

PPT SLIDES

REVIEW ARTICLE

Pelvic Inflammatory Disease

Pelvic inflammatory disease can produce acute symptoms and result in infertility, ectopic pregnancy, and chronic pelvic pain. This review summarizes current approaches to diagnosis and treatment and the future prospects for better prevention strategies.

CME, PPT SLIDES

MEDICINE AND SOCIETY

Beyond Moral Outrage — Weighing the Trade-Offs of COI Regulation

By casting physician-industry interactions as a moral issue, the conflict-of-interest movement has subverted rational weighing of trade-offs. The resulting “gotcha quest” has paradoxically resulted in an erosion of public trust in medicine and science.

POLL, COMMENTING

RECENTLY PUBLISHED ONLINE FIRST

Persistence of Ebola Virus in Ocular Fluid during Convalescence

The Affordable Care Act at 5 Years

Progress and Hurdles for Follow-on Biologics

NEJM ARCHIVE

The complete archive of all *Journal* content includes

Comparison of Polymerized and Unpolymerized Antigen E for Immunotherapy of Ragweed Allergy

W. James Metzger, Roy Patterson, C. Raymond Zeiss, John S. Irons, Jacob J. Pruzansky, Irena M. Suszko, and Doris Levitz

November 18, 1976

NEJM.org/doi/full/10.1056/

NEJM197611182952103

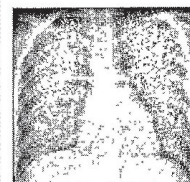
TOPICS



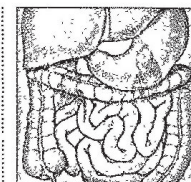
Medicine and Society

A focus on context, connections, and community, at NEJM.org/medicine-and-society

SPECIALTIES



Pulmonary/ Critical Care
Latest research reports online, at NEJM.org/pulmonary



Gastroenterology
Latest research reports online, at NEJM.org/gastroenterology



The *New England Journal of Medicine* is a publication of NEJM Group, a division of the Massachusetts Medical Society.

CUSTOMER SERVICE

NEJM Customer Service
P.O. Box 54803
Waltham, MA 02454-0803
Telephone: 800-THE-NEJM (800-843-6356)
Fax: 781-893-0413
Email: nejmcust@mms.org
Web: nejm.org/contact-nejm

BUSINESS OFFICE ADDRESS

The New England Journal of Medicine
860 Winter Street
Waltham, MA 02451-1413

ADVERTISING SALES

DISPLAY ADVERTISING
Telephone: 800-635-6991
Email: salessupport@nejm.org
Web: nejm.org/r/advertising

CLASSIFIED ADVERTISING
Telephone: 800-635-6991
Email: ads@nejmcareercenter.org
Web: recruiters.nejmcareercenter.org

INSTITUTIONAL SALES

Telephone: 781-434-7135
Email: institutionsales@nejm.org
Web: nejm.org/r/institutions

CORPORATE SALES

Telephone: 781-434-7041
Email: corporatesales@nejm.org
Web: nejm.org/r/institutions

PERMISSIONS

Email: permissions@nejm.org
Web: nejm.org/r/permissions

EDUCATIONAL CLASSROOM USE
Copyright Clearance Center (CCC)
222 Rosewood Drive, Danvers, MA 01923
Telephone: 978-750-8400
Fax: 978-750-4470
Web: copyright.com

ARTICLE REPRINTS

Telephone: 877-241-7159
Email: reprints@nejm.org
Web: nejm.org/r/reprints

MEDIA RELATIONS

Telephone: 781-434-7847
Email: mediasupport@nejm.org
Web: nejm.org/media

SUBSCRIPTIONS

Individual one-year NEJM subscriptions include weekly print issues, access to: NEJM.org (1990 to present), the NEJM iPad Edition, 20 free online CME exams, and 50 free 1812–1989 Archive views. Online-only subscriptions are also available.

USA RATES

Individual Print + Online + iPad
Physician: \$179
Resident: \$69
Student: \$65

Institutional Print-Only: \$1,150. Contact Institutional or Corporate Sales for online Site License rates.

SUBSCRIBE OR RENEW

Contact Customer Service or go to my.nejm.org/subscribe or my.nejm.org/renew.

ACTIVATE SUBSCRIPTION AT NEJM.ORG

Activate your individual subscription to get access to subscriber content at NEJM.org and the NEJM iPad Edition. Go to my.nejm.org/activate. You'll need your customer number, which is located on your address label, or inquire with Customer Service.

ADDRESS CHANGE

Advise Customer Service of changes to your delivery address four to six weeks in advance to ensure uninterrupted service. Provide current mailing label information (including customer number), new address, and effective date of change. If a postal office advises us that your issues are undeliverable, we will have no further obligation unless we receive a corrected address within one year.

REPLACING MISSING OR DAMAGED ISSUES

Please notify Customer Service within three months of the missed or damaged issue for replacement without charge. Provide issue date(s) and a copy of a mailing label.

SINGLE COPY AND VOLUME PURCHASE

Single copies of print issues may be purchased for \$6.00 and print unbound volumes (26 issues, Jan–June or July–Dec) are available for \$179. Prepayment is required; contact Customer Service to order. Copies are provided subject to their availability. Issues are only retained for three years.

DISPLAY ADVERTISING

All advertising material is expected to conform to ethical, medical, and business standards. Acceptance of display advertising does not imply endorsement by NEJM. Please contact Display Advertising Sales for more information about advertising policies.

PERMISSIONS

Requests to reproduce articles from NEJM for educational classroom use should be directed to the Copyright Clearance Center (CCC). For additional permissions information, please visit nejm.org/r/permissions.

LIST RENTAL

The NEJM subscriber mailing list is available to select approved third parties for rental on a controlled basis. Please contact Customer Service if you prefer to have your name withheld from such rentals and not to receive promotional material. We do not sell or rent your email address to any third parties. List rental requests should be directed to List Manager: Mike Rovello, Infogroup Targeting Solutions, Telephone: 402-836-5639, Email: Mike.Rovello@infogroup.org.

COPYRIGHT

Copyright ©2015 Massachusetts Medical Society. All rights reserved.

ORIGINAL ARTICLE

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

Michael A. Postow, M.D., Jason Chesney, M.D., Ph.D., Anna C. Pavlick, D.O., Caroline Robert, M.D., Ph.D., Kenneth Grossmann, M.D., Ph.D., David McDermott, M.D., Gerald P. Linette, M.D., Ph.D., Nicolas Meyer, M.D., Jeffrey K. Giguere, M.D., Sanjiv S. Agarwala, M.D., Montaser Shaheen, M.D., Marc S. Ernstoff, M.D., David Minor, M.D., April K. Salama, M.D., Matthew Taylor, M.D., Patrick A. Ott, M.D., Ph.D., Linda M. Rollin, Ph.D., Christine Horak, Ph.D., Paul Gagnier, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and F. Stephen Hodi, M.D.

ABSTRACT

BACKGROUND

In a phase 1 dose-escalation study, combined inhibition of T-cell checkpoint pathways by nivolumab and ipilimumab was associated with a high rate of objective response, including complete responses, among patients with advanced melanoma.

METHODS

In this double-blind study involving 142 patients with metastatic melanoma who had not previously received treatment, we randomly assigned patients in a 2:1 ratio to receive ipilimumab (3 mg per kilogram of body weight) combined with either nivolumab (1 mg per kilogram) or placebo once every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram) or placebo every 2 weeks until the occurrence of disease progression or unacceptable toxic effects. The primary end point was the rate of investigator-assessed, confirmed objective response among patients with BRAF V600 wild-type tumors.

RESULTS

Among patients with BRAF wild-type tumors, the rate of confirmed objective response was 61% (44 of 72 patients) in the group that received both ipilimumab and nivolumab (combination group) versus 11% (4 of 37 patients) in the group that received ipilimumab and placebo (ipilimumab-monotherapy group) ($P < 0.001$), with complete responses reported in 16 patients (22%) in the combination group and no patients in the ipilimumab-monotherapy group. The median duration of response was not reached in either group. The median progression-free survival was not reached with the combination therapy and was 4.4 months with ipilimumab monotherapy (hazard ratio associated with combination therapy as compared with ipilimumab monotherapy for disease progression or death, 0.40; 95% confidence interval, 0.23 to 0.68; $P < 0.001$). Similar results for response rate and progression-free survival were observed in 33 patients with BRAF mutation-positive tumors. Drug-related adverse events of grade 3 or 4 were reported in 54% of the patients who received the combination therapy as compared with 24% of the patients who received ipilimumab monotherapy. Select adverse events with potential immunologic causes were consistent with those in a phase 1 study, and most of these events resolved with immune-modulating medication.

CONCLUSIONS

The objective-response rate and the progression-free survival among patients with advanced melanoma who had not previously received treatment were significantly greater with nivolumab combined with ipilimumab than with ipilimumab monotherapy. Combination therapy had an acceptable safety profile. (Funded by Bristol-Myers Squibb; ClinicalTrials.gov number, NCT01927419.)

From Memorial Sloan Kettering Cancer Center (M.A.P., J.D.W.), Weill Cornell Medical College (M.A.P., J.D.W.), and New York University, Perlmutter Cancer Center (A.C.P.) — all in New York; J. Graham Brown Cancer Center, University of Louisville, Louisville, KY (J.C.); Institute Gustave Roussy, Villejuif (C.R.), Paris-Sud University, Orsay (C.R.), and Institut Universitaire du Cancer, Toulouse (N.M.) — all in France; Huntsman Cancer Institute, Salt Lake City (K.G.); Beth Israel Deaconess Medical Center (D. McDermott) and Dana-Farber Cancer Institute (P.A.O., F.S.H.) — both in Boston; Washington University in St. Louis, St. Louis (G.P.L.); Greenville Health System, Greenville, SC (J.K.G.); St. Luke's Cancer Center, Bethlehem, PA (S.S.A.); University of New Mexico, Albuquerque (M.S.); Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland (M.S.E.); California Pacific Center for Melanoma Research, San Francisco (D. Minor); Duke University, Durham, NC (A.K.S.); Oregon Health and Science University, Portland (M.T.); Bristol-Myers Squibb, Lawrenceville, NJ (C.H.); and Bristol-Myers Squibb, Wallingford, CT (L.M.R., P.G.). Address reprint requests to Dr. Hodi at the Dana-Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215, or at stephen_hodi@dfci.harvard.edu; or to Dr. Wolchok at the Ludwig Center at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065, or at wolchokj@mskcc.org.

Drs. Wolchok and Hodi contributed equally to this article.

This article was published on April 20, 2015, at NEJM.org.

N Engl J Med 2015;372:2006-17.

DOI: 10.1056/NEJMoa1414428

Copyright © 2015 Massachusetts Medical Society.

RECENT APPROACHES TO THE TREATMENT of metastatic melanoma enhance antitumor immunity by blocking immune checkpoints, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed death 1 (PD-1) receptor. Ipilimumab, an anti-CTLA-4 antibody, is approved by the Food and Drug Administration (FDA) on the basis of improvement in overall survival among patients with advanced melanoma, with objective responses in approximately 11% of the patients.^{1,2} Nivolumab, an anti-PD-1 monoclonal antibody, has recently been shown to improve overall survival, as compared with dacarbazine (objective response rate, 40% vs. 14%), among previously untreated patients with advanced BRAF wild-type melanoma.³ Nivolumab is approved by the FDA on the basis of an improvement in confirmed objective responses, as compared with chemotherapy (32% vs. 11%), among patients with metastatic melanoma who have disease progression after treatment with ipilimumab or a BRAF inhibitor.⁴

Targeted therapies, such as BRAF and MEK inhibitors that are approved for the treatment of patients with advanced melanoma who harbor BRAF V600 mutation-positive tumors, result in a high rate of initial tumor responses, with a significant survival advantage over dacarbazine; however, the median duration of response is less than 1 year.⁵⁻¹² Therefore, there is a need for new treatment options, particularly for the 50 to 60% of patients with BRAF wild-type melanoma.

CTLA-4 and PD-1 inhibit antitumor immunity through complementary and nonredundant mechanisms.¹³ Preclinical models have shown that dual blockade, as compared with blockade of either pathway alone, synergistically improves antitumor responses.^{14,15} High rates of objective response (including complete responses), a prolonged duration of response, and a favorable overall survival rate of 79% at 2 years were observed in a phase 1 dose-escalation study involving patients with advanced melanoma who received the combination regimen of nivolumab and ipilimumab.^{16,17} Here, we report the results of a randomized, double-blind trial comparing nivolumab in combination with ipilimumab with standard-of-care ipilimumab monotherapy as a first-line treatment in patients with advanced melanoma.

METHODS

PATIENTS

Eligible patients had histologically confirmed, unresectable, previously untreated stage III or IV melanoma with measurable disease. Other inclusion criteria included a known BRAF V600 mutation status, an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability), and the availability of tumor tissue from a metastatic or unresectable site for immunohistochemical assessment of PD-1 ligand (PD-L1) expression. Key exclusion criteria were active brain metastases, uveal melanoma, and serious autoimmune disease.

STUDY DESIGN AND TREATMENT

Patients were randomly assigned, in a 2:1 ratio and in a double-blinded manner, to receive both nivolumab and ipilimumab (combination group) or ipilimumab alone (ipilimumab-monotherapy group). Randomization was stratified according to BRAF mutation status (V600 wild-type vs. mutation-positive). In the combination group, nivolumab was administered intravenously at a dose of 1 mg per kilogram of body weight over a period of 60 minutes, once every 3 weeks for four doses. Thirty minutes after the completion of each nivolumab infusion, patients received 3 mg of ipilimumab per kilogram over a period of 90 minutes. After the fourth dose of both agents, ipilimumab was discontinued, and thereafter (maintenance phase), nivolumab was administered as a single agent at a dose of 3 mg per kilogram over a period of 60 minutes, once every 2 weeks.

In the ipilimumab-monotherapy group, the same dosing schedule was used, except that nivolumab was replaced with matched placebo during both the combination and maintenance portions of the trial. Treatment was continued as long as clinical benefit (as defined by the investigator) was observed or until unacceptable side effects occurred.

Patients who had investigator-assessed disease progression could be treated beyond progression (with blinding maintained) or have blinded study therapy discontinued (after which time the treatment assignment could be disclosed to the investigator and patient). After unblinding, patients in the ipilimumab-monotherapy group had the op-

tion of receiving nivolumab at a dose of 3 mg per kilogram every 2 weeks until further disease progression, and patients in the combination group were required to discontinue treatment (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The primary end point was the rate of investigator-assessed, confirmed objective response among patients with *BRAF* V600 wild-type tumors. The primary end point was restricted to this group of patients because at the time of study enrollment, approved treatment options were limited for these patients and only ipilimumab had shown an overall survival benefit in a randomized, controlled trial. Secondary end points included investigator-assessed progression-free survival in patients with *BRAF* wild-type tumors, the objective response rate and progression-free survival among patients with *BRAF* V600 mutation-positive tumors, and safety.

ASSESSMENTS

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1,¹⁸ at the following time points: 12 weeks after the first treatment, every 6 weeks thereafter for the first year, then every 12 weeks until disease progression or discontinuation of treatment. Safety evaluations were performed in patients who had received at least one dose of study treatment, and the severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.¹⁹ Guidelines for the management of adverse events were provided by the sponsor and are available in the Supplementary Appendix.

STUDY OVERSIGHT

The study protocol, available along with the most recent version of the statistical analysis plan at NEJM.org, was approved by the institutional review board at each participating center. The study was conducted in accordance with the provisions of the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. All the patients provided written informed consent. An independent radiology review committee was established to provide a sensitivity assessment of objective responses, and a data and safety monitoring committee provided general oversight. Data were collected

by the sponsor, Bristol-Myers Squibb, and were analyzed in collaboration with the authors. The authors vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol. The first draft of the manuscript was written by the first and last authors, with all the authors contributing to subsequent drafts. Medical-writing support, funded by the sponsor, was provided by StemScientific. All the authors made the decision to submit the manuscript for publication.

IMMUNOHISTOCHEMICAL ASSESSMENT OF PD-L1

The expression of PD-L1 on the surface of tumor cells was assessed in pretreatment tumor samples at a central laboratory with the use of an automated immunohistochemical assay (Bristol-Myers Squibb and Dako), as described previously.¹⁷ A tumor was considered to be PD-L1-positive if at least 5% of tumor cells showed cell-surface PD-L1 staining of any intensity in a section containing at least 100 tumor cells that could be evaluated.

STATISTICAL ANALYSIS

We planned to enroll approximately 100 patients with *BRAF* V600 wild-type tumors who would be randomly assigned in a 2:1 ratio to one of the two treatment groups (the intention-to-treat population). Patients with *BRAF* V600 mutation-positive tumors were eligible for the study, with approximately 50 planned to undergo randomization. Analyses in the population with *BRAF* V600 mutation-positive tumors were intended to be descriptive only and were not part of the sample-size consideration. Given a two-sided alpha level of 0.05, we calculated that the sample of 100 patients with *BRAF* wild-type tumors would give the study approximately 87% power to detect a significant difference in the objective response rate between the combination group and the ipilimumab-monotherapy group, assuming an objective response rate of 40% versus 10%. In order to preserve an experiment-wide type I error rate of 5%, a hierarchical testing approach was applied to key secondary end points after analysis of the primary end point of the objective response rate in all patients with *BRAF* wild-type tumors who underwent randomization. Of the key secondary end points, the objective response rate among all randomly assigned patients was tested first, followed by testing of progression-free survival among all patients with *BRAF* wild-type tumors who under-

went randomization; progression-free survival among all randomly assigned patients was tested last.

RESULTS

PATIENTS

Baseline characteristics were well balanced between the study groups (Table 1). At trial entry, the majority of patients (87%) had stage IV disease according to the American Joint Committee on Cancer staging system, and 46% of the patients had tumors characterized as M1c disease (metastases to visceral sites other than skin, subcutaneous, distant lymph nodes, or lung, or distant metastases to any site along with elevated serum lactate dehydrogenase level). Elevated lactate dehydrogenase levels were observed in 35 patients (25%), and 23% of the patients had BRAF V600 mutation-positive tumors. Of 118 patients whose PD-L1 expression could be evaluated, 35 (30%) had PD-L1-positive tumors.

From September 16, 2013, to February 6, 2014, a total of 179 patients were screened in the United States and France, and 142 patients (109 with BRAF wild-type tumors and 33 with BRAF V600 mutation-positive tumors) were randomly assigned to one of the two treatment groups (Table S1 in the Supplementary Appendix). Clinical database lock for the results reported here occurred on January 30, 2015, with a minimum follow-up period of 11 months after randomization.

EFFICACY

The rate of investigator-assessed, confirmed objective response among the patients with BRAF wild-type tumors was 61% (95% confidence interval [CI], 49 to 72) in the combination group, versus 11% (95% CI, 3 to 25) in the ipilimumab-monotherapy group (odds ratio, 12.96; 95% CI, 3.91 to 54.49; $P < 0.001$) (Table 2). A complete response was observed in 16 patients (22%) in the combination group and no patients in the ipilimumab-monotherapy group. Figure 1A shows the distribution of tumor-burden change from baseline among patients with BRAF wild-type tumors. The median change in investigator-assessed tumor volume was a 68.1% decrease in the combination group and a 5.5% increase in the ipilimumab-monotherapy group.

Among the patients with BRAF wild-type tumors who underwent randomization, the median

duration of response was not reached in either group, with an ongoing response observed in 36 of the 44 patients with a response (82%) in the combination group and in 3 of the 4 patients with a response (75%) in the ipilimumab-monotherapy group (Fig. 1B). The time to a response did not differ significantly between the groups, with the majority of all responses observed at the time the first scan was obtained (Fig. 1B).

Among patients with BRAF mutation-positive tumors, the objective response rate was 52% (12 of 23 patients) in the combination group, with the percentage of complete responses (22% [5 patients]) similar to that in patients with BRAF wild-type tumors (Table 2). In the population with BRAF wild-type tumors, the median progression-free survival was not reached with the combination therapy and was 4.4 months (95% CI, 2.8 to 5.7) with ipilimumab monotherapy (hazard ratio associated with combination therapy as compared with ipilimumab monotherapy for disease progression or death, 0.40; 95% CI, 0.23 to 0.68; $P < 0.001$) (Fig. 1C). Among patients with BRAF mutation-positive tumors, the median progression-free survival was 8.5 months (95% CI, 2.8 to not estimable) in the combination group and 2.7 months (95% CI, 1.0 to 5.4) in the ipilimumab-monotherapy group (hazard ratio associated with combination therapy as compared with ipilimumab monotherapy for disease progression or death, 0.38; 95% CI, 0.15 to 1.00) (Fig. S2 in the Supplementary Appendix). Among all randomly assigned patients who discontinued study treatment owing to toxic effects, the objective response rate was 68% (95% CI, 52 to 81) in the combination group (30 of 44 patients), as compared with 10% (95% CI, 0 to 45) in the ipilimumab-monotherapy group (1 of 10 patients).

In patients with BRAF wild-type tumors, the response benefit with the nivolumab-and-ipilimumab combination, as compared with ipilimumab alone, was observed across all prespecified patient subgroups, including patients with stage M1c disease and those with elevated lactate dehydrogenase levels (Fig. S3 in the Supplementary Appendix). In the combination group, the objective response rate was independent of tumor PD-L1 status: 58% (95% CI, 37 to 78) among patients with PD-L1-positive tumors and 55% (95% CI, 41 to 69) among patients with PD-L1-negative tumors (Table S2 in the Supplementary Appendix). In the ipilimumab-monotherapy group, a numerically higher objective re-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Patients with <i>BRAF</i> Wild-Type Tumors		All Randomly Assigned Patients		
	Nivolumab plus Ipilimumab (N=72)	Ipilimumab (N=37)	Nivolumab plus Ipilimumab (N=95)	Ipilimumab (N=47)	Total (N=142)
Age — yr					
Median	66	69	64	67	65
Range	27–87	46–80	27–87	31–80	27–87
Sex — no. (%)					
Male	48 (67)	23 (62)	63 (66)	32 (68)	95 (67)
Female	24 (33)	14 (38)	32 (34)	15 (32)	47 (33)
Disease stage at study entry — no. (%)†					
III	8 (11)	8 (22)	10 (11)	9 (19)	19 (13)
IV	64 (89)	29 (78)	85 (89)	38 (81)	123 (87)
ECOG performance-status score — no. (%)‡					
0	62 (86)	30 (81)	79 (83)	37 (79)	116 (82)
1	9 (12)	7 (19)	14 (15)	10 (21)	24 (17)
≥2	1 (1)	0	2 (2)	0	2 (1)
Metastasis stage at study entry — no. (%)§					
M0	6 (8)	5 (14)	8 (8)	5 (11)	13 (9)
M1a	9 (12)	7 (19)	15 (16)	8 (17)	23 (16)
M1b	22 (31)	8 (22)	27 (28)	12 (26)	39 (27)
M1c	34 (47)	16 (43)	44 (46)	21 (45)	65 (46)
Not reported	1 (1)	1 (3)	1 (1)	1 (2)	2 (1)
Lactate dehydrogenase — no. (%)¶					
≤ULN	57 (79)	30 (81)	70 (74)	36 (77)	106 (75)
>ULN	15 (21)	7 (19)	24 (25)	11 (23)	35 (25)
≤2× ULN	69 (96)	36 (97)	88 (93)	46 (98)	134 (94)
>2× ULN	3 (4)	1 (3)	6 (6)	1 (2)	7 (5)
History of brain metastases — no. (%)					
Yes	4 (6)	0	4 (4)	0	4 (3)
No	67 (93)	37 (100)	90 (95)	47 (100)	137 (96)
<i>BRAF</i> V600 mutation — no. (%)	0	0	23 (24)	10 (21)	33 (23)

* P values were not calculated, per the statistical analysis plan. ULN denotes upper limit of the normal range.

† The disease stage was defined according to the staging system for melanoma of the American Joint Committee on Cancer.

‡ An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 indicates no symptoms, 1 mild symptoms, and 2 moderate symptoms, with the patient being ambulatory and capable of all self-care but unable to carry out any work activities. Two patients randomly assigned to the nivolumab-plus-ipilimumab group were inadvertently enrolled in the study, despite having an ECOG performance-status score of 2.

§ The metastasis stage was defined according to the tumor-node-metastasis system of the American Joint Committee on Cancer and the Union for International Cancer Control.

¶ One patient randomly assigned to the nivolumab-plus-ipilimumab group inadvertently did not have a baseline lactate dehydrogenase level of ≤2× ULN.

|| For one additional patient with a *BRAF* wild-type tumor who was randomly assigned to the nivolumab-plus-ipilimumab group, the history of brain metastases was not recorded on the clinical report form.

Table 2. Response to Treatment.

Variable	Patients with <i>BRAF</i> Wild-Type Tumors		Patients with <i>BRAF</i> V600 Mutation–Positive Tumors	
	Nivolumab plus Ipilimumab (N=72)	Ipilimumab (N=37)	Nivolumab plus Ipilimumab (N=23)	Ipilimumab (N=10)
Best overall response — no. (%) [*]				
Complete response	16 (22)	0	5 (22)	0
Partial response	28 (39)	4 (11)	7 (30)	1 (10)
Stable disease	9 (12)	13 (35)	3 (13)	1 (10)
Progressive disease	10 (14)	15 (41)	5 (22)	7 (70)
Could not be determined	9 (12)	5 (14)	3 (13)	1 (10)
Patients with objective response — no. (%) [95% CI] [†]	44 (61 [49–72])	4 (11 [3–25])	12 (52 [31–73])	1 (10 [0–45])

* The best overall response was assessed by the investigator with the use of the Response Evaluation Criteria in Solid Tumors, version 1.1.

† Data include patients with a complete response and those with a partial response. The calculation of the confidence interval (CI) was based on the Clopper–Pearson method. The estimated odds ratio for nivolumab plus ipilimumab as compared with ipilimumab alone was 12.96 (95% CI, 3.91 to 54.49) among patients with *BRAF* wild-type tumors ($P<0.001$) and 9.82 (95% CI, 0.99 to 465.39) among patients with *BRAF* V600 mutation–positive tumors (P value was not calculated, per the statistical analysis plan).

sponse rate was observed among patients with PD-L1–positive tumors than among patients with PD-L1–negative tumors (18% [95% CI, 2 to 52] vs. 4% [95% CI, 0 to 19]).

SAFETY

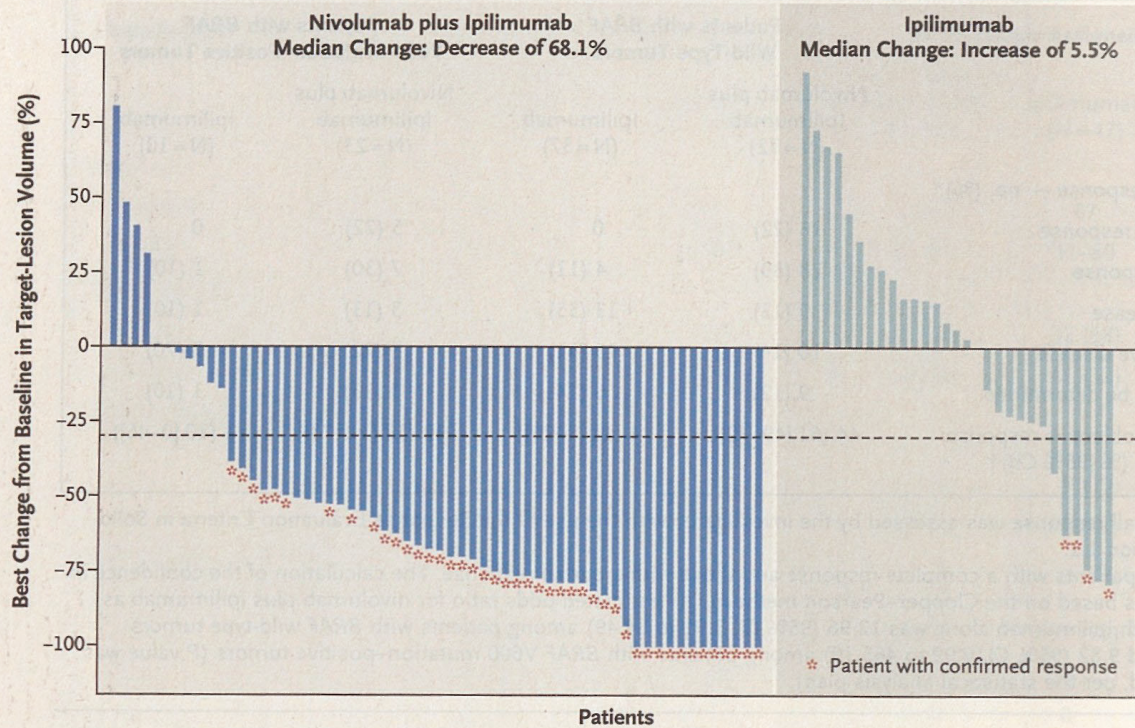
In the combination group, 59% and 57% of the patients received at least four doses of nivolumab and ipilimumab, respectively; in the ipilimumab monotherapy group, 70% of the patients received at least four doses of ipilimumab (Table S3 in the Supplementary Appendix). The rate of treatment-related adverse events, as assessed by the investigators, was 91% in the combination group and 93% in the ipilimumab-monotherapy group (Table 3). Drug-related adverse events of grade 3 or 4 were reported more frequently in the combination group than in the ipilimumab-monotherapy group (54% vs. 24%); in patients who received the combination regimen, the onset of most adverse events occurred during the combination phase rather than the maintenance (nivolumab-monotherapy) phase. The most common grade 3 or 4 adverse events associated with the combination therapy were colitis (17%), diarrhea (11%), and an elevated alanine aminotransferase level (11%). Diarrhea was the most frequently reported grade 3 or 4 adverse event associated with ipilimumab monotherapy (11%), followed by colitis (7%).

Select adverse events of potentially immune-

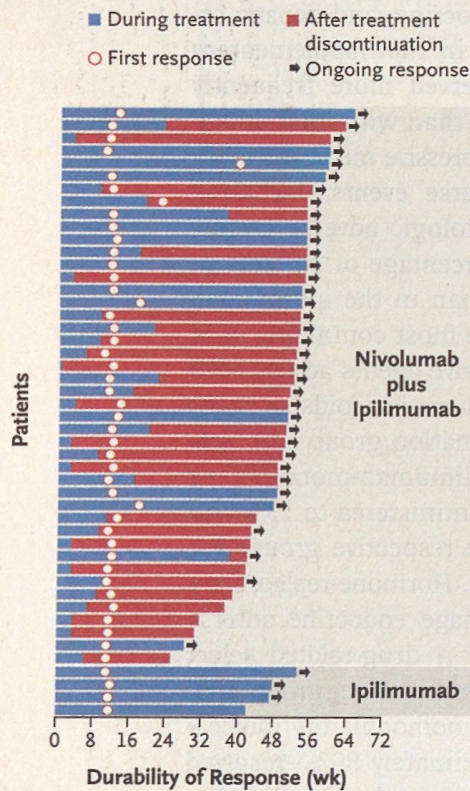
mediated cause occurred most frequently in the skin, gastrointestinal, endocrine, and hepatic organ categories (Table S4 in the Supplementary Appendix) and were observed more frequently with combination therapy than with ipilimumab monotherapy. Immunosuppressive medications for the management of adverse events, including topical agents for dermatologic adverse events, were used in a higher percentage of patients in the combination group than in the ipilimumab group (89% vs. 59%). The most commonly used systemic immunosuppressive agents across both treatment groups were glucocorticoids (82% of the patients in the combination group and 50% of the patients in the ipilimumab-monotherapy group). Infliximab was administered to 13% and 9% of the patients in the respective groups for adverse-event management. Hormone-replacement therapy was used to manage endocrine adverse events. Of 46 grade 3 or 4 drug-related select adverse events in the combination group that were managed with immunomodulatory medication, the majority (approximately 80%) resolved completely, or symptoms returned to baseline levels (Table 4). There was a similar resolution rate across organ categories in both treatment groups.

The most common reason for discontinuation of study treatment was drug-related adverse events in the combination group (45%) and disease progression in the ipilimumab-monothera-

A



B



C

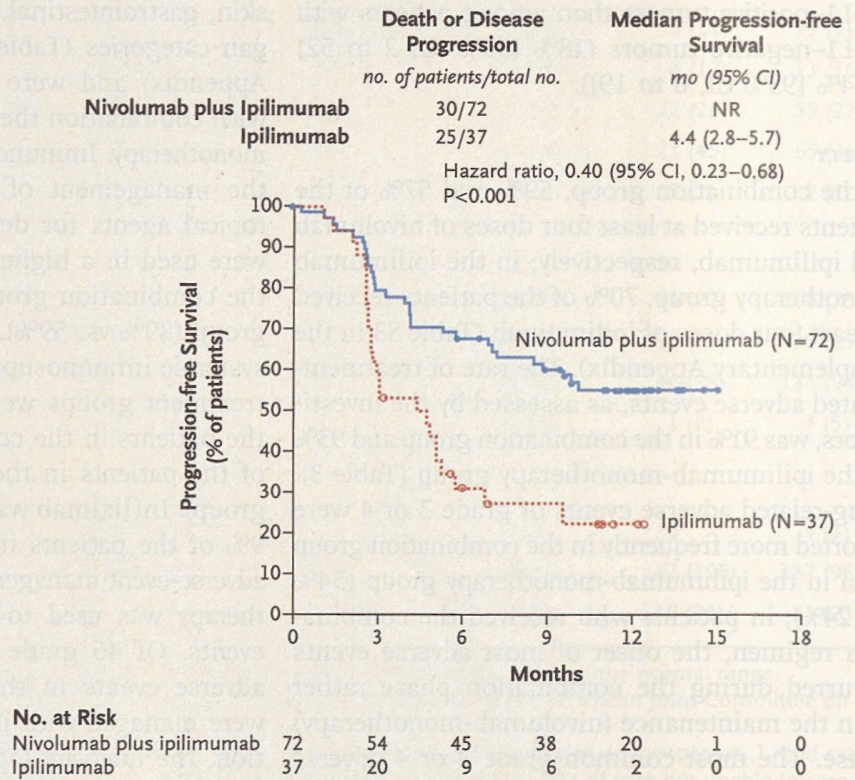


Figure 1 (facing page). Change in Tumor Burden, Durability of Tumor Regressions, and Progression-free Survival.

Panel A shows the best change from baseline in the sum of the reference diameters of the target lesion in patients receiving the combination of nivolumab and ipilimumab (left) and those receiving ipilimumab monotherapy (right). The dashed line indicates the 30% reduction in tumor burden that is consistent with a response to treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Panel B shows the durability of tumor regressions in patients with advanced melanoma with *BRAF* wild-type tumors who had objective responses to the combination regimen or ipilimumab monotherapy according to conventional RECIST guidelines. Open circles indicate the first evidence of objective response and arrows indicate an ongoing response at the time of the analysis. Panel C shows Kaplan–Meier curves for progression-free survival among patients with *BRAF* wild-type tumors treated with the combination regimen or ipilimumab alone. NR denotes not reached.

py group (37%) (Table S5 in the Supplementary Appendix). After the initial four doses, 40% of the patients in the combination group continued to receive nivolumab as monotherapy (Table S3 in the Supplementary Appendix).

The number of reported deaths among treated patients was 25 in the combination group (27%) and 17 in the ipilimumab-monotherapy group (37%); most deaths were due to progressive disease. Three deaths were related to the combination therapy according to investigator assessment — one patient with a history of cardiac disease died from ventricular arrhythmia 29 days after the last dose of study treatment; the second died suddenly 69 days after the last dose while clinically improving from pneumonitis and having an iatrogenic pneumothorax. The third patient died suddenly 86 days after the last dose of study treatment (3 days after the resolution of grade 3 pneumonia and grade 4 hypercalcemia). None of the deaths in the ipilimumab-monotherapy group were deemed to be related to the study drug.

DISCUSSION

In this double-blind, randomized study, the combination of nivolumab and ipilimumab resulted

in a significantly higher objective response rate, more frequent complete responses, and significantly longer progression-free survival than ipilimumab alone among previously untreated patients with advanced melanoma. The confirmed response rate associated with the combination therapy in this trial (61%) is numerically higher than the 40% response rate that was recently reported with nivolumab monotherapy as first-line therapy in patients with advanced melanoma who have *BRAF* wild-type tumors and also higher than the rate observed in trials of monotherapy with pembrolizumab, another anti-PD-1 agent.²⁰ However, it is inherently difficult to compare the efficacy of the combination therapy with that of anti-PD-1 monotherapy, because the demographic characteristics of the patients differed among the trials.

On the basis of the high degree of tumor reduction in the current study, with a high rate of complete responses (22% among the patients with *BRAF* wild-type tumors who were assigned to the combination therapy), a favorable clinical benefit can be anticipated with longer follow-up. Overall, the characteristics of response observed with nivolumab plus ipilimumab in the current study are consistent with results reported previously,^{16,17} with most responses occurring by the time of the first tumor assessment and, in many patients, responses continuing despite discontinuation of therapy. The response rate associated with the combination regimen in this current phase 2 study was even higher than response rates reported previously, which may be explained by the fact that the patient population in this study was previously untreated. A prior phase 1 trial of the combination regimen at varying doses showed high rates of overall survival at 1 year (85%) and 2 years (79%).^{16,17}

The primary end point of this study specifically addressed patients with *BRAF* wild-type melanoma because at the time of study enrollment, ipilimumab was the only approved therapy for this group of patients that had shown an overall survival benefit in a randomized phase 3 trial. Although *BRAF* inhibitors as single agents and *BRAF* inhibitor–MEK inhibitor combinations can result in high response rates among patients with *BRAF*-mutant melanoma,^{14,15,21} no

Table 3. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=94)		Ipilimumab (N=46)	
	Any Grade	Grade 3 or 4 <i>number of patients (percent)</i>	Any Grade	Grade 3 or 4
Any treatment-related adverse event	86 (91)	51 (54)	43 (93)	11 (24)
Most common treatment-related adverse events†				
Diarrhea‡	42 (45)	10 (11)	17 (37)	5 (11)
Rash	39 (41)	5 (5)	12 (26)	0
Fatigue	37 (39)	5 (5)	20 (43)	0
Pruritus	33 (35)	1 (1)	13 (28)	0
Colitis‡	22 (23)	16 (17)	6 (13)	3 (7)
Nausea	21 (22)	1 (1)	11 (24)	1 (2)
Elevated alanine aminotransferase	21 (22)	10 (11)	2 (4)	0
Elevated aspartate aminotransferase	20 (21)	7 (7)	2 (4)	0
Pyrexia	19 (20)	3 (3)	7 (15)	0
Maculopapular rash	15 (16)	3 (3)	8 (17)	0
Hypothyroidism	15 (16)	0	7 (15)	0
Decreased appetite	14 (15)	0	4 (9)	0
Headache	13 (14)	2 (2)	5 (11)	0
Vomiting	13 (14)	1 (1)	5 (11)	0
Increased lipase	12 (13)	8 (9)	2 (4)	1 (2)
Hypophysitis	11 (12)	2 (2)	3 (7)	2 (4)
Pneumonitis§	10 (11)	2 (2)	2 (4)	1 (2)
Arthralgia	10 (11)	0	4 (9)	0
Chills	10 (11)	0	3 (7)	0
Vitiligo	10 (11)	0	4 (9)	0
Abdominal pain	10 (11)	0	4 (9)	1 (2)
Constipation	10 (11)	1 (1)	4 (9)	0
Myalgia	9 (10)	0	6 (13)	0
Dyspnea	9 (10)	3 (3)	5 (11)	0
Asthenia	8 (9)	0	5 (11)	0
Pruritic rash	3 (3)	0	5 (11)	0
Treatment-related adverse event leading to discontinuation of treatment	44 (47)	36 (38)	8 (17)	6 (13)

* The table includes events reported after the first dose of study treatment and within 100 days after the last dose of study treatment.

† Shown are events that were reported in at least 10% of the patients in either study group.

‡ Diarrhea was defined as a disorder characterized by frequent and watery bowel movements; colitis was defined as a disorder characterized by inflammation of the colon. Grade 3 or 4 drug-related adverse events were reported more frequently in the combination group than in the ipilimumab-monotherapy group; in patients who received the combination regimen, most adverse events had first onset during the combination phase rather than the maintenance (nivolumab-monotherapy) phase.

§ One additional patient in the ipilimumab-monotherapy group had progressive disease on April 28, 2014, and data were unblinded before the patient started nivolumab monotherapy a day later. This patient received 10 cycles of nivolumab monotherapy before the onset of pneumonitis after the last dose on September 25, 2014.

single agent or combination of agents has similarly been shown to result in a high response rate among patients with BRAF wild-type melanoma. Nevertheless, among patients with BRAF-mutant melanoma, the overall response rate and progression-free survival associated with the combination regimen were also substantially higher than those with ipilimumab alone. These results are consistent with the results of a previous phase 1 trial and suggest that the presence of the BRAF V600 mutation does not influence the efficacy of checkpoint blockade.^{16,17,22}

In general, the spectrum of select adverse events that we observed was consistent with previous experience with the combination therapy.¹⁶ Three deaths related to the combination

regimen were reported in this study; these deaths could be linked to preexisting conditions that were related to the cause of death or that required medical procedures that might have contributed to the death. The proportion of patients who had a grade 3 or 4 treatment-related adverse event was higher with the nivolumab-and-ipilimumab combination than with ipilimumab monotherapy (54% vs. 24%). Select grade 3 or 4 adverse events generally occurred within the first 15 weeks of treatment with the combination regimen and typically required less than 9 weeks to resolve, depending on the specific adverse event. Aside from patients with endocrinopathies, which typically require continued hormone-replacement therapy, the majority of patients

Table 4. Select Adverse Events and Their Management with Immunomodulatory Medication (IMM), According to Organ Category.

Organ Category	Nivolumab plus Ipilimumab (N=94)				Ipilimumab (N=46)			
	Reported Adverse Event	Treatment with IMM	Resolution of Event after Treatment with IMM	Median Time to Resolution	Reported Adverse Event	Treatment with IMM	Resolution of Event after Treatment with IMM	Median Time to Resolution
	no. of patients	no. of patients/total no. (%)	no. of patients/total no. (%)	wk (95% CI)	no. of patients	no. of patients/total no. (%)	no. of patients/total no. (%)	wk (95% CI)
Skin								
Any grade	67	41/67 (61)	24/35 (69)	18.6 (9.3–35.1)	26	13/26 (50)	11/13 (85)	8.6 (3.3–22.0)
Grade 3 or 4	9	9/9 (100)	8/9 (89)	6.1 (0.9–24.1)	0	0	0	NE
Gastrointestinal								
Any grade	48	31/48 (65)	26/28 (93)	4.7 (3.0–6.7)	17	11/17 (65)	7/9 (78)	5.0 (1.4–12.1)
Grade 3 or 4	20	17/20 (85)	15/17 (88)	4.3 (1.4–10.7)	5	5/5 (100)	4/5 (80)	3.6 (0.7–5.0)
Endocrine†								
Any grade	32	14/32 (44)	2/14 (14)	NE (NE–NE)	8	3/8 (38)	1/3 (33)	NE (0.9–NE)
Grade 3 or 4	5	4/5 (80)	1/4 (25)	NE (5.6–NE)	2	2/2 (100)	1/2 (50)	NE (0.9–NE)
Hepatic								
Any grade	26	13/26 (50)	11/13 (85)	14.1 (3.1–19.6)	2	0/2	0	NE
Grade 3 or 4	14	12/14 (86)	10/12 (83)	8.3 (2.1–14.1)	0	0	0	NE
Pulmonary								
Any grade	11	8/11 (73)	6/8 (75)	6.1 (0.3–9.0)	2	2/2 (100)	2/2 (100)	3.2 (2.9–3.6)
Grade 3 or 4	3	3/3 (100)	2/3 (67)	9.0 (0.3–9.0)	1	1/1 (100)	1/1 (100)	3.6 (NE–NE)
Renal								
Any grade	3	2/3 (67)	2/2 (100)	0.4 (0.3–0.6)	1	0/1	0	NE
Grade 3 or 4	1	1/1 (100)	1/1 (100)	0.6 (NE–NE)	0	0	0	NE

* The table includes events reported after the first dose and within 100 days after the last dose of study treatment. Resolution of an event was restricted to patients who received IMM during their longest clustered event and was defined as complete resolution or improvement to the baseline level for all clustered events in a given category that occurred in the patient. NE denotes not estimable.

† Endocrine events were managed with hormone-replacement therapy. Patients requiring long-term hormone-replacement therapy were not counted as having resolution of an event.

eventually had complete resolution of grade 3 or 4 adverse events. It is noteworthy that of the patients who discontinued combination treatment owing to toxic effects, 68% had an objective response and most continue to have a response.

Positive expression of PD-L1, one of the ligands of PD-1, has been associated with increased response rates among patients treated with nivolumab as a single agent.^{23,24} Among patients treated with the combination regimen in our study, however, there was no significant difference in response rates between patients whose pretreatment tumors were defined as PD-L1-positive and those whose tumors were PD-L1-negative. These data suggest that PD-L1 should not be used to select patients to receive combination treatment. The mechanism for response independent of baseline PD-L1 status remains unclear. It is possible that ipilimumab drives T cells into the tumor and that this T-cell infiltration during treatment leads to a more favorable microenvironment for anti-PD-1 efficacy.^{25,26} It is also possible that assessment of PD-L1 status with the incorporation of PD-L1-expressing tumor-infiltrating macrophages or T cells (rather than tumor cells, as in our study) may be most relevant, but this possibility requires additional investigation.

In summary, the combination of ipilimumab plus nivolumab resulted in durable responses and

a substantially higher objective response rate, longer progression-free survival, and higher rates of complete response than ipilimumab monotherapy among patients with BRAF wild-type advanced melanoma and those with BRAF-mutant advanced melanoma. The incidence of grade 3 or 4 adverse events was higher with combination therapy, but adverse events were generally manageable when established safety guidelines were used. The risk-benefit profile of combined PD-1 and CTLA-4 blockade, as compared with monotherapy, will be further clarified by data from ongoing phase 3 double-blind, randomized trials, such as the CheckMate 067 study (ClinicalTrials.gov number, NCT01844505).

Supported by Bristol-Myers Squibb.

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

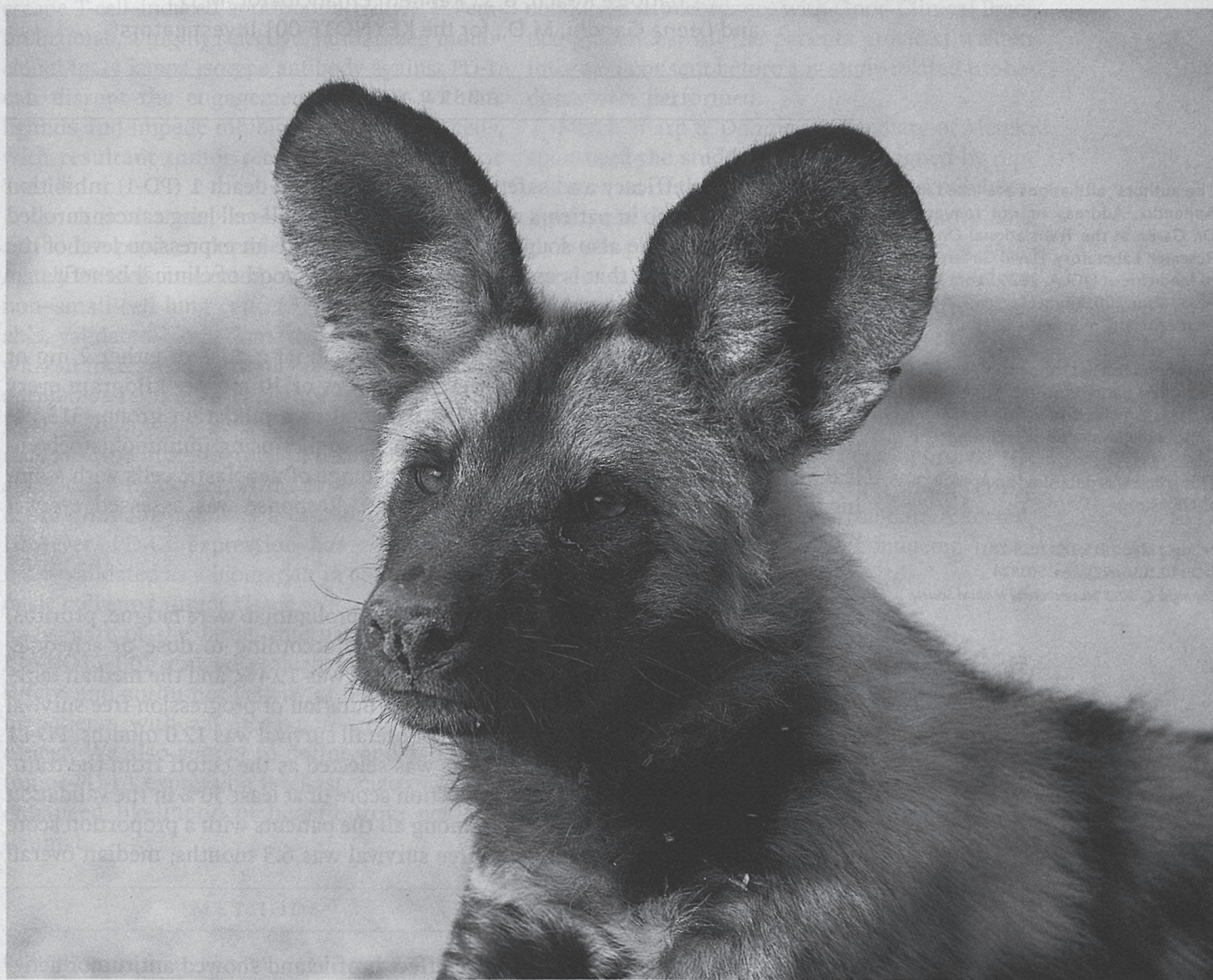
We thank the patients who participated in this study; clinical faculty and personnel, including Elizabeth Buchbinder, formerly of Beth Israel Deaconess Medical Center and currently of the Dana-Farber Cancer Institute; Ryan Sullivan of Massachusetts General Hospital; Jason Luke, formerly of the Dana-Farber Cancer Institute and currently of the University of Chicago; Marta Colgan, Jenessa Holder, Yelena Shames, Vanessa Reed, and Alyona Weinstein of Memorial Sloan Kettering Cancer Center; Rajni Kannan, Kathleen Madden, Ethel Yepes, Crystal Escano, Caroline Muren, Claire Stein, and Martina Romain of New York University Medical Center; and Miriam Faruqi and Jaclyn Neely of Bristol-Myers Squibb; and Wayne Peng and Karin McGlynn of StemScientific for editorial and writing assistance with an earlier version of the manuscript.

REFERENCES

- Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711-23. [Erratum, *N Engl J Med* 2010;363:1290.]
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011;364:2517-26.
- Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320-30.
- Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 2015 March 17 (Epub ahead of print).
- Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014;371:1867-76.
- Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med* 2014;371:1877-88.
- Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015;372:30-9.
- Johnson DB, Flaherty KT, Weber JS, et al. Combined BRAF (dabrafenib) and MEK inhibition (trametinib) in patients with BRAFV600-mutant melanoma experiencing progression with single-agent BRAF inhibitor. *J Clin Oncol* 2014;32:3697-704.
- Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012;367:1694-703.
- Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011;364:2507-16.
- McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol* 2014;15:323-32.
- Ascierto PA, Schadendorf D, Berking C, et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. *Lancet Oncol* 2013;14:249-56.
- Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. *Nat Immunol* 2013;14:1212-8.
- Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci U S A* 2010;107:4275-80.
- Selby M, Englehardt J, Lu L-S, et al. Antitumor activity of concurrent blockade of immune checkpoint molecules CTLA-4 and PD-1 in preclinical models. *J Clin Oncol* 2013;31:Suppl:3061. abstract.
- Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 2013; 369:122-33.
- Sznol M, Kluger HM, Callahan MK, et al. Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO), anti-PD-1, BMS-936558, ONO-

- 4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). *J Clin Oncol* 2014;32:Suppl:9003. abstract.
18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47.
19. NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 (<http://levs.nci.nih.gov/ftp1/CTCAE/About.html>).
20. Hamid O, Robert C, Daud A. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 2013;369:134-44.
21. Shahabi V, Whitney G, Hamid O, et al. Assessment of association between BRAF-V600E mutation status in melanomas and clinical response to ipilimumab. *Cancer Immunol Immunother* 2012;61:733-7.
22. Kluger H, Sznol M, Callahan M, et al. Survival, response duration, and activity by BRAF mutation (MT) status in a phase 1 trial of nivolumab (anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). *Ann Oncol* 2014;25:Suppl 4:iv-374-iv-393.
23. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443-54.
24. Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res* 2014;20:5064-74.
25. Hamid O, Schmidt H, Nissan A, et al. A prospective phase II trial exploring the association between tumor microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. *J Transl Med* 2011;9:204.
26. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 2014;515:568-71.

Copyright © 2015 Massachusetts Medical Society.



Wild Dog, Botswana

Anil Sain, M.D.