

LIBRARY OF CONGRESS



0 029 220 310 A

NEW ENGLAND JOURNAL OF MEDICINE 369 JULY 2013 1-4

R 11
.B7
Set 1

The NEW ENGLAND JOURNAL of MEDICINE

VOL. 369 NO. 2

ESTABLISHED IN 1812

JULY 11, 2013

NEJM.ORG



New England journal of medicine. Boston. 1828-
R11 .B7 v. 369, no. 2 (2013 July 11) uf30
2002-0456 *30030754* c-Ser

110 THIS WEEK AT NEJM.ORG

PERSPECTIVE

- 101 Guantanamo Bay: A Medical Ethics-free Zone?
G.J. Annas, S.S. Crosby, and L.H. Glantz
- 103 Force-Feeding, Autonomy, and the Public
Interest M.L. Gross
- 105 Failure to Launch? The Independent Payment
Advisory Board's Uncertain Prospects
J. Oberlander and M. Morrison
- 107 The Gross Domestic Product and Health Care
Spending V.R. Fuchs

ORIGINAL ARTICLES

- 111 Retinoic Acid and Arsenic Trioxide
for Acute Promyelocytic Leukemia
F. Lo-Coco and Others
- 122 Nivolumab plus Ipilimumab in Advanced Melanoma
J.D. Wolchok and Others
- 134 Safety and Tumor Responses with Lambrolizumab
(Anti-PD-1) in Melanoma
O. Hamid and Others
- 145 Cardiovascular Effects of Intensive Lifestyle
Intervention in Type 2 Diabetes
The Look AHEAD Research Group
- 155 U.S. Hospitalizations for Pneumonia
after a Decade of Pneumococcal Vaccination
M.R. Griffin and Others



Owned & published by the MASSACHUSETTS MEDICAL SOCIETY
© 2013. All rights reserved. ISSN 0028-4793.

- 164 Brief Report: Delayed Puberty and Estrogen Resistance
in a Woman with Estrogen Receptor α Variant
S.D. Quaynor and Others

IMAGES IN CLINICAL MEDICINE

- 172 Simultaneous Gangrene of Both Left Extremities
M. Fokou and A. Teyang
- e2 A Receding Hairline
A. Lencastre and A. Tosti

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

- 173 A Man with Metastatic Melanoma
R.J. Sullivan and Others

EDITORIALS

- 185 NEJM Group — More Offerings, Mission Unchanged
J.M. Drazen
- 186 Targeting Agents Alone to Cure Acute
Promyelocytic Leukemia
S.-J. Chen and Z. Chen
- 187 Combination Checkpoint Blockade — Taking
Melanoma Immunotherapy to the Next Level
J.L. Riley
- 189 Do Lifestyle Changes Reduce Serious Outcomes
in Diabetes?
H.C. Gerstein

CLINICAL IMPLICATIONS OF BASIC RESEARCH

- 191 Influenza — Time to Target the Host?
J.K. Baillie and P. Digard

194 CORRESPONDENCE

- Off-Pump or On-Pump Coronary-Artery Bypass
Grafting
- Progressive Multifocal Leukoencephalopathy
Associated with Ruxolitinib
- e3 The OHRP and SUPPORT — Another View

199 CONTINUING MEDICAL EDUCATION

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

ABSTRACT

BACKGROUND

In patients with melanoma, ipilimumab (an antibody against cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) prolongs overall survival, and nivolumab (an antibody against the programmed death 1 [PD-1] receptor) produced durable tumor regression in a phase 1 trial. On the basis of their distinct immunologic mechanisms of action and supportive preclinical data, we conducted a phase 1 trial of nivolumab combined with ipilimumab in patients with advanced melanoma.

METHODS

We administered intravenous doses of nivolumab and ipilimumab in patients every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen). The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses.

RESULTS

A total of 53 patients received concurrent therapy with nivolumab and ipilimumab, and 33 received sequenced treatment. The objective-response rate (according to modified World Health Organization criteria) for all patients in the concurrent-regimen group was 40%. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for ≥ 24 weeks) was observed in 65% of patients. At the maximum doses that were associated with an acceptable level of adverse events (nivolumab at a dose of 1 mg per kilogram of body weight and ipilimumab at a dose of 3 mg per kilogram), 53% of patients had an objective response, all with tumor reduction of 80% or more. Grade 3 or 4 adverse events related to therapy occurred in 53% of patients in the concurrent-regimen group but were qualitatively similar to previous experience with monotherapy and were generally reversible. Among patients in the sequenced-regimen group, 18% had grade 3 or 4 adverse events related to therapy and the objective-response rate was 20%.

CONCLUSIONS

Concurrent therapy with nivolumab and ipilimumab had a manageable safety profile and provided clinical activity that appears to be distinct from that in published data on monotherapy, with rapid and deep tumor regression in a substantial proportion of patients. (Funded by Bristol-Myers Squibb and Ono Pharmaceutical; ClinicalTrials.gov number, NCT01024231.)

From the Ludwig Center, Memorial Sloan-Kettering Cancer Center, New York (J.D.W., M.K.C., M.A.P., N.A.R., A.M.L., N.H.S., C.E.A., R.-A.G., S.A.K., B.U.A.); Yale University School of Medicine and Smilow Cancer Center, Yale-New Haven Hospital, New Haven, CT (H.K., K.R., M.M.B., A.C., M.S.); Dako North America, Carpinteria (X.Z.), and Bristol-Myers Squibb, Redwood City (A.J.K.) — both in California; and Bristol-Myers Squibb, Princeton, NJ (I.L., H.D.I., W.F., C.E.H., Q.H., J.M.W., A.G.). Address reprint requests to Dr. Wolchok at Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10065, or at wolchokj@mskcc.org.

This article was published on June 2, 2013, at NEJM.org.

N Engl J Med 2013;369:122-33.

DOI: 10.1056/NEJMoa1302369

Copyright © 2013 Massachusetts Medical Society.

ESCAPE FROM IMMUNE SURVEILLANCE IS a recognized feature of cancer; therefore, the development of therapies to enhance tumor immunity is a rational treatment strategy.^{1,2} Immune checkpoint blockade is one approach that has induced regressions in several types of cancer. Ipilimumab, a fully human, IgG1 monoclonal antibody blocking cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), improved overall survival in patients with advanced melanoma.^{3,4} Nivolumab, a fully human IgG4 antibody blocking the programmed death 1 (PD-1) receptor, produced durable objective responses in patients with melanoma, renal-cell cancer, and non–small-cell lung cancer.⁵

CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.^{6,7} On the basis of these observations, we conducted a phase 1 study to investigate the safety and efficacy of combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively) in patients with advanced melanoma. Data for 86 patients treated in this ongoing study are reported.

METHODS

PATIENTS

Eligible patients were at least 18 years of age; had received a diagnosis of measurable, unresectable, stage III or IV melanoma; had an Eastern Cooperative Oncology Group performance status of 0 (asymptomatic) or 1 (ambulatory but restricted in strenuous activity)⁸; had adequate organ function; and had a life expectancy of at least 4 months. Exclusion criteria were active, untreated central nervous system metastasis, a history of autoimmune disease, previous therapy with T-cell modulating antibodies (excluding ipilimumab for patients in the sequenced-regimen cohorts), human immunodeficiency virus infection, and hepatitis B or C infection.

In the sequenced-regimen cohorts, patients were required to have received at least three previous doses of ipilimumab, with the last dose administered 4 to 12 weeks before the administration of nivolumab. Patients with a complete response, progression with evidence of clinical deterioration,

or a history of high-grade adverse events related to ipilimumab were excluded.

STUDY DESIGN

In this phase 1 study we treated successive cohorts of patients with escalating doses of intravenous nivolumab and ipilimumab administered concurrently every 3 weeks for four doses, followed by nivolumab alone every 3 weeks for four doses (concurrent-regimen group) (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The combined treatment was subsequently continued every 12 weeks for up to eight doses. When the two drugs were administered together, nivolumab was administered first. Within a cohort, doses of nivolumab and ipilimumab were kept constant.

The protocol-specified dose levels in the cohorts were as follows. In the concurrent-regimen group, cohort 1 was designated to receive 0.3 mg of nivolumab per kilogram of body weight and 3 mg of ipilimumab per kilogram; cohort 2, 1 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram; cohort 2a, 3 mg of nivolumab per kilogram and 1 mg of ipilimumab per kilogram; cohort 3, 3 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram; cohort 4, 10 mg of nivolumab per kilogram and 3 mg of ipilimumab; and cohort 5, 10 mg of nivolumab per kilogram and 10 mg of ipilimumab per kilogram. In the sequenced-regimen group, patients in cohorts 6 and 7 were treated with nivolumab at doses of 1 mg per kilogram and 3 mg per kilogram, respectively, every 2 weeks for up to 48 doses (Fig. S1 in the Supplementary Appendix).

Patients could be followed for a total of 2.5 years after the initiation of therapy. Patients with a complete response, a partial response, or stable disease for at least 24 weeks and subsequent disease progression could be retreated with the original regimen. Disease assessment was performed per protocol, with the use of computed tomography or magnetic resonance imaging, as appropriate. For both regimen groups, tumor responses were adjudicated with the use of modified World Health Organization (WHO) criteria and immune-related criteria (see the Supplementary Appendix).⁹ In the concurrent-regimen group, tumor assessments were performed at weeks 12, 18, 24, 30, and 36 and then every 12 weeks thereafter. In the sequenced-regimen group, tumor assess-

ments were performed at week 8 and then every 8 weeks thereafter.

The safety evaluation was performed per protocol. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.¹⁰

STUDY OVERSIGHT

The study protocol was approved by the institutional review boards at the participating centers, and the study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. For additional safety oversight, an independent Early Development Advisory Committee was responsible for reviewing and adjudicating individual high-grade adverse events as potentially dose-limiting and for guiding the study team on decisions regarding dose escalation and cohort expansion. All participating patients provided written informed consent.

The study was designed by the senior academic authors and the sponsor, Bristol-Myers Squibb. Study medications were provided by the sponsor. Data were collected by the sponsor and analyzed and interpreted in collaboration with the academic authors. Manuscript drafts were prepared by the authors with editorial assistance from a professional medical writer paid by the sponsor. All the authors vouch for the accuracy and completeness of the data reported and the adherence of the study to the protocol, and all the authors made the decision to submit the manuscript for publication. The protocol, including the statistical analysis plan, is available at NEJM.org.

DOSE ESCALATION AND COHORT EXPANSION

The study was initially planned to evaluate the concurrent regimen with the use of a standard 3+3 design for the dose-escalation phase, followed by cohort expansion to a total of up to 16 patients at the maximum doses that were associated with an acceptable level of adverse events or the maximum administered dose. The period for evaluating dose-limiting toxicity for the purposes of dose escalation was 9 weeks. A modified definition of dose-limiting toxicity was incorporated in the protocol. No dose escalation was allowed in an individual patient, and patients who had dose-limiting adverse events discontinued therapy.

During the period for evaluating dose-limit-

ing toxicity, patients who withdrew from the study owing to reasons other than drug-related adverse events could be replaced. The protocol was amended to permit the expansion of any concurrent-regimen cohort during the dose-escalation phase to a maximum of 12 patients, with approval by the Early Development Advisory Committee. Two sequenced-regimen cohorts (6 to 16 patients each) were added later.

IMMUNOHISTOCHEMICAL ASSESSMENT FOR PD-L1

Expression of one of the ligands of PD-1, PD-L1, before treatment was measured by means of immunohistochemical testing in formalin-fixed, paraffin-embedded tumor specimens with the use of a rabbit monoclonal antihuman PD-L1 antibody (clone 28-8) and an automated assay developed by Dako. Antibody specificity was assessed by means of Western blotting against recombinant PD-L1 protein and lysates from PD-L1-expressing and PD-L1-nonexpressing cell lines. An immunohistochemical assay with and without the addition of antigen that competes with binding to the antibody was performed, with a comparative assessment of staining patterns in normal human tissues. Analytic sensitivity, specificity, repeatability, reproducibility, and robustness of the immunohistochemical assay were tested and met all prespecified acceptance criteria. Two pathologists, who were unaware of the clinical outcome, independently read and adjudicated scores for all clinical specimens. A sample was defined as PD-L1-positive if at least 5% of the tumor cells exhibited membrane PD-L1 staining of any intensity in a section containing at least 100 cells that could be evaluated.^{5,11}

STATISTICAL ANALYSIS

All 86 patients who had received treatment as of February 15, 2013, were included in the description of baseline characteristics and the analyses of safety and absolute lymphocyte count. Analysis of PD-L1 staining included tumor specimens available as of February 28, 2013. The efficacy population consisted of 82 patients who had a response that could be evaluated, defined as those patients who received at least one dose of study medication, had measurable disease at baseline, and had one of the following: at least one tumor evaluation during treatment, clinical progression of disease, or death before the first tumor evaluation during treatment.

Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 15.1. Selected adverse events with potential immunologic causes and those that require more frequent monitoring or intervention with immune suppression or hormone replacement were identified with the use of a predefined list of MedDRA terms. These are similar to events previously described as immune-related adverse events or adverse events of special interest.⁵

Best overall responses were derived programmatically from tumor measurements provided by the study-site radiologist and investigators according to the modified WHO criteria or immune-related response criteria.¹¹ Complete and partial responses were confirmed by means of at least one subsequent tumor assessment. The magnitude of the reduction in target lesions was assessed radiographically. A response was characterized as "deep" if a reduction of 80% or more from the baseline measurements was noted. Unconfirmed responses as of the date of this analysis were also included in an estimation of aggregate clinical activity.

RESULTS

BASELINE CHARACTERISTICS OF THE PATIENTS

A total of 86 patients were treated from December 2009 through February 2013; 53 patients received the concurrent regimen and 33 received the sequenced regimen. Baseline characteristics of the two regimen groups are shown in Table 1.

A total of 38% of patients in the concurrent-regimen group and 100% of patients in the sequenced-regimen group had received systemic therapy previously. The majority of patients had M1c disease (i.e., metastases to visceral sites other than skin, subcutaneous tissue, distant lymph nodes, or lung or distant metastases to any site combined with an elevated serum lactate dehydrogenase [LDH] level), and more than 30% of patients had an elevated level of LDH. Most patients (73%) enrolled in the sequenced-regimen cohorts had progression as assessed radiographically during prior treatment with ipilimumab.

SAFETY

Among the 53 patients in the concurrent-regimen group, adverse events of any grade, regardless of whether they were attributed to the therapy, were observed in 98% of patients (Table S1-A in the

Supplementary Appendix). Treatment-related adverse events were observed in 93% of patients, with the most common events being rash (in 55% of patients), pruritus (in 47%), fatigue (in 38%), and diarrhea (in 34%) (Table S1-B in the Supplementary Appendix). Grade 3 or 4 adverse events, regardless of attribution, were observed in 72% of patients, and grade 3 or 4 treatment-related events were noted in 53%, with the most common events being elevated levels of lipase (in 13% of patients), aspartate aminotransferase (in 13%), and alanine aminotransferase (in 11%). A total of 6 of 28 patients (21%) had grade 3 or 4 treatment-related events that were dose-limiting.

Serious adverse events related to the treatment were reported in 49% of patients in the concurrent-regimen group (Table S1-C in the Supplementary Appendix). Common grade 3 or 4 selected adverse events that were related to the therapy included hepatic events (in 15% of patients), gastrointestinal events (in 9%), and renal events (in 6%) (Table 2). Isolated cases of pneumonitis and uveitis were observed (Table S1-B in the Supplementary Appendix), a finding that is consistent with previous experience with monotherapy. A total of 11 patients (21%) discontinued therapy owing to treatment-related adverse events (Table S2 in the Supplementary Appendix).

The doses in cohort 3 (nivolumab at a dose of 3 mg per kilogram and ipilimumab at a dose of 3 mg per kilogram) exceeded the maximum doses that were associated with an acceptable level of adverse events (three of six patients had asymptomatic grade 3 or 4 elevated lipase levels that persisted for ≥ 3 weeks). The doses in cohort 2 (nivolumab at 1 mg per kilogram and ipilimumab at 3 mg per kilogram) were identified as the maximum doses that were associated with an acceptable level of adverse events (grade 3 uveitis in one patient and grade 3 elevated levels of aspartate aminotransferase and alanine aminotransferase in one).

Among the 33 patients in the sequenced-regimen group, adverse events of any grade, regardless of attribution, were observed in 29 patients (88%) (Table S1-A in the Supplementary Appendix). Treatment-related adverse events were observed in 24 patients (73%), with the most common events including pruritus (in 18% of patients) and elevated lipase levels (in 12%) (Table S1-B in the Supplementary Appendix). Grade 3 or 4 adverse events, regardless of whether they were attributed

Table 1. Baseline Characteristics of All Treated Patients.*

Characteristic	Concurrent Treatment (N=53)	Sequenced Treatment (N=33)
Age — yr		
Median	58	64
Range	22–79	23–89
Sex — no. (%)		
Male	32 (60)	18 (55)
Female	21 (40)	15 (45)
ECOG performance status — no. (%)†		
0	44 (83)	22 (67)
1	8 (15)	11 (33)
Unknown	1 (2)	0
Disease status — no. (%)‡		
M1a	8 (15)	5 (15)
M1b	11 (21)	5 (15)
M1c	30 (57)	18 (55)
Unknown	4 (8)	5 (15)
Lactate dehydrogenase — no. (%)		
≤Upper limit of the normal range	33 (62)	21 (64)
>Upper limit of the normal range	20 (38)	12 (36)
Prior therapy — no. (%)		
Surgery	51 (96)	31 (94)
Radiotherapy	11 (21)	17 (52)
Systemic therapy	20 (38)	33 (100)
Immunotherapy	9 (17)	33 (100)
Interleukin-2	8 (15)	1 (3)
BRAF inhibitor	3 (6)	2 (6)
No. of prior systemic therapies — no. (%)		
0	33 (62)	0
1	14 (26)	18 (55)
2	5 (9)	10 (30)
≥3	1 (2)	5 (15)
Lesions — no. (%)		
Bone	5 (9)	1 (3)
Central nervous system	0	1 (3)
Liver	16 (30)	13 (39)
Lung	25 (47)	16 (48)
Lymph node	26 (49)	8 (24)
Soft tissue or other organ	34 (64)	19 (58)

* Treatment groups were not formally compared in this phase 1 trial.

† An Eastern Cooperative Oncology Group (ECOG) performance status of 0 indicates that the patient is asymptomatic, and 1 indicates that the patient is ambulatory but restricted in strenuous activity.⁸

‡ M1a indicates metastases to the skin, subcutaneous tissue, or distant lymph nodes; M1b metastases to the lung; and M1c metastases to all other visceral sites or distant metastases to any site combined with an elevated serum lactate dehydrogenase level.

Table 2. Highest Grade of Selected Treatment-Related Adverse Events That Occurred in at Least One of the Patients Who Received the Concurrent Regimen.*

Event	Cohort 1 (N = 14)		Cohort 2 (N = 17)		Cohort 2a (N = 16)		Cohort 3 (N = 6)		All Patients in Concurrent-Regimen Group (N = 53)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Pneumonitis	1 (7)	0	2 (12)	1 (6)	0	0	0	0	3 (6)	1 (2)
Endocrinopathy	1 (7)	0	3 (18)	0	1 (6)	0	2 (33)	1 (17)	7 (13)	1 (2)
Hypothyroidism	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hypophysitis	0	0	1 (6)	0	0	0	1 (17)	1 (17)	2 (4)	1 (2)
Thyroiditis	0	0	1 (6)	0	1 (6)	0	1 (17)	0	3 (6)	0
Adrenal insufficiency	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hyperthyroidism	0	0	1 (6)	0	0	0	1 (17)†	0	2 (4)†	0
Thyroid-function results abnormal	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Hepatic disorder	4 (29)	3 (21)	5 (29)	3 (18)	2 (12)	1 (6)	1 (17)	1 (17)	12 (23)	8 (15)
Aspartate aminotransferase increased	4 (29)	3 (21)	4 (24)	2 (12)	2 (12)	1 (6)	1 (17)	1 (17)	11 (21)	7 (13)
Alanine aminotransferase increased	3 (21)	2 (14)	5 (29)	3 (18)	2 (12)	0	1 (17)	1 (17)	11 (21)	6 (11)
Gastrointestinal disorder	5 (36)	1 (7)	6 (35)	2 (12)	6 (38)	2 (13)	3 (50)	0	20 (38)	5 (9)
Diarrhea	5 (36)	0	5 (29)	1 (6)	5 (31)	2 (13)	3 (50)	0	18 (34)	3 (6)
Colitis	1 (7)	1 (7)	2 (12)	1 (6)	1 (6)	0	1 (17)	0	5 (9)	2 (4)
Renal disorder	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Blood creatinine increased	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Acute renal failure	0	0	1 (6)	1 (6)	1 (6)	1 (6)	0	0	2 (4)	2 (4)
Renal failure	0	0	1 (6)	1 (6)	0	0	0	0	1 (2)	1 (2)
Tubulointerstitial nephritis	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Skin disorder	10 (71)	1 (7)	14 (82)	0	10 (62)	1 (6)	3 (50)	0	37 (70)	2 (4)
Rash	8 (57)	1 (7)	11 (65)	0	7 (44)	1 (6)	3 (50)	0	29 (55)	2 (4)
Pruritus	6 (43)	0	11 (65)	0	7 (44)	0	1 (17)	0	25 (47)	0
Urticaria	0	0	0	0	1 (6)	0	0	0	1 (2)	0
Blister	0	0	1 (6)	0	0	0	0	0	1 (2)	0
Infusion-related reaction	0	0	1 (6)	0	0	0	0	0	1 (2)	0

* Only the highest grade of event was counted for each patient. Adverse events that require more frequent monitoring or intervention with immune suppression or hormone replacement are listed, according to a prespecified list of terms from the *Medical Dictionary for Regulatory Activities*, version 15.1. The dose levels in the cohorts were as follows: cohort 1 received 0.3 mg of nivolumab per kilogram of body weight and 3 mg of ipilimumab per kilogram, cohort 2 received 1 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram, cohort 2a received 3 mg of nivolumab per kilogram and 1 mg of ipilimumab per kilogram, and cohort 3 received 3 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram. The doses in cohort 3 exceeded the maximum doses that were associated with an acceptable level of adverse events, and the doses in cohort 2 were identified as the maximum doses that were associated with an acceptable level of adverse events. The numbers reported for the specific adverse events within an organ category may be greater than the total number reported for the organ category because patients who had more than one adverse event were counted for each event but were counted only once for the organ category.

† Data include one patient with an event of unknown grade.

to the therapy, were observed in 11 patients (33%), and grade 3 or 4 adverse events related to therapy were observed in 6 (18%), with an elevated lipase level as the most common event (in 6% of patients). Serious adverse events related to therapy were reported in 7 patients (21%) (Table S1-C in the Supplementary Appendix). Grade 3 or 4 endocrine events were noted as treatment-related selected adverse events in 2 patients (Table S1-D in the Supplementary Appendix). One patient had grade 2 pneumonitis. Three patients (9%) discontinued therapy owing to treatment-related adverse events (Table S2 in the Supplementary Appendix).

In both regimen groups, treatment-related adverse events were manageable and generally reversible with the use of immunosuppressants (or hormone-replacement therapy for endocrinopathies) according to previously established algorithms.¹² Among the 86 patients treated during the study, 28 of the 73 patients (38%) with drug-related adverse events were treated with systemic glucocorticoids. A total of 3 patients required additional immunosuppressive therapy with infliximab (2 patients) or mycophenolate mofetil (1 patient). No treatment-related deaths were reported.

CLINICAL ACTIVITY

Clinical activity was observed in both regimen groups (Table 3, and Table S4 in the Supplementary Appendix). In the concurrent-regimen cohorts, across all dose levels, confirmed objective responses according to modified WHO criteria were observed in 21 of 52 patients (40%; 95% confidence interval [CI], 27 to 55) who had a response that could be evaluated. In addition, 4 patients had an objective response according to immune-related response criteria and 2 had an unconfirmed partial response. These patients were not included in the calculation of objective-response rates.

After noting that several patients had major responses (approaching complete response), we performed a post hoc analysis of the number of patients with tumor reduction of 80% or more. This depth of response was uncommon in published studies of checkpoint blockade.^{3,5} A total of 16 patients had tumor reduction of 80% or more at 12 weeks, including 5 with a complete response (Table 3 and Fig. 1A and 2, and Fig. S2 and S3 in the Supplementary Appendix).

In the concurrent-regimen group, overall evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for ≥ 24 weeks) was observed in 65% of patients (95% CI, 51 to 78) (Table 3). The profound effect of the concurrent combination therapy is shown in the waterfall plot in Figure 1B. Responses were ongoing in 19 of 21 patients who had a response, with the duration ranging from 6.1 to 72.1 weeks at the time of data analysis (Table S3 in the Supplementary Appendix).

Among patients who received the maximum doses associated with an acceptable level of adverse events (cohort 2, with nivolumab at a dose of 1 mg per kilogram and ipilimumab at a dose of 3 mg per kilogram), objective responses occurred in 9 of 17 patients (53%; 95% CI, 28 to 77), including 3 with a complete response. All 9 patients who had a response had tumor reduction of 80% or more at their first scheduled assessment during treatment (Table 3 and Fig. 1A).

In the sequenced-regimen cohorts, 6 of 30 patients (20%; 95% CI, 8 to 39) had an objective response, including 1 with a complete response. A total of 4 patients (13%) had tumor reduction of 80% or more at 8 weeks (Table S4 and Fig. S4 in the Supplementary Appendix). An additional 6 patients had either an immune-related response (in 3 patients) or an unconfirmed response (in 3). When clinical activity was defined by objective, immune-related, or unconfirmed responses or stable disease for at least 24 weeks, 43% of patients (95% CI, 26 to 63) in the sequenced-regimen group had clinical activity. Some patients who had not had a response to previous treatment with ipilimumab did have a response to subsequent treatment with nivolumab (Fig. S4 in the Supplementary Appendix).

PD-L1 EXPRESSION AND ABSOLUTE LYMPHOCYTE COUNT

Tumor-cell expression of PD-L1 and alterations in the peripheral-blood absolute lymphocyte count have been explored as biomarkers for nivolumab monotherapy and ipilimumab monotherapy, respectively.^{5,13-16} We characterized tumor-cell expression of PD-L1 with the use of immunohistochemical staining and analyzed pharmacodynamic changes in the peripheral-blood absolute lymphocyte count. With PD-L1 positivity defined as expression in at least 5% of tumor cells, biopsy specimens from 21 of 56 patients (38%) were

Table 3. Clinical Activity in Patients Who Received the Concurrent Regimen.

Cohort No.	Dose	Patients with a Response*	Response			Immune-Related Disease for ≥ 24 Wk†	Stable Disease for ≥ 24 Wk	Immune-Related Disease for ≥ 24 Wk†	Objective-Response Rate (95% CI)‡	Aggregate Clinical-Activity Rate (95% CI)§	$\geq 80\%$ Tumor Reduction at 12 Wk
			Complete	Partial	Unconfirmed Partial¶						
	mg/kg					no.			%		no. (%)
1	Nivolumab, 0.3; ipilimumab, 3	14	1	2	0	2	2	0	21 (5–51)	50 (23–77)	4 (29)
2	Nivolumab, 1; ipilimumab, 3	17	3	6	0	0	0	2	53 (28–77)	65 (38–86)	7 (41)
2a	Nivolumab, 3; ipilimumab, 1	15	1	5	2	1	2	0	40 (16–68)	73 (45–92)	5 (33)
3	Nivolumab, 3; ipilimumab, 3	6	0	3	0	1	0	1	50 (12–88)	83 (36–100)	0
All	—	52	5	16	2	4	4	3	40 (27–55)	65 (51–78)	16 (31)

* Data are for patients who had a response that could be evaluated, defined as patients who received at least one dose of study therapy, had measurable disease at baseline, and had one of the following: at least one tumor evaluation during treatment, clinical progression of disease, or death before the first tumor evaluation during treatment.

† Data include patients who had a reduction in the target tumor lesion in the presence of new lesions, which was consistent with an immune-related partial response or stable disease.¹¹

‡ The objective-response rate was calculated as the number of patients with either a complete response or a partial response, divided by the number of patients with a response that could be evaluated, times 100. Unconfirmed or immune-related responses were not included in this calculation. Confidence intervals (CIs) were estimated by the Clopper–Pearson method.

§ The aggregate clinical-activity rate was calculated as the number of patients with a complete response, a partial response, an unconfirmed complete response, an unconfirmed partial response, an immune-related partial response, stable disease for at least 24 weeks, or immune-related stable disease for at least 24 weeks, divided by the number of patients with a response that could be evaluated, times 100.

¶ Data include patients who had a partial response after one tumor assessment but did not have sufficient follow-up time for confirmation of the initial partial response.

|| Two additional patients in cohort 2 had tumor reduction of 80% or more at their first scheduled assessment, which was conducted after week 12.

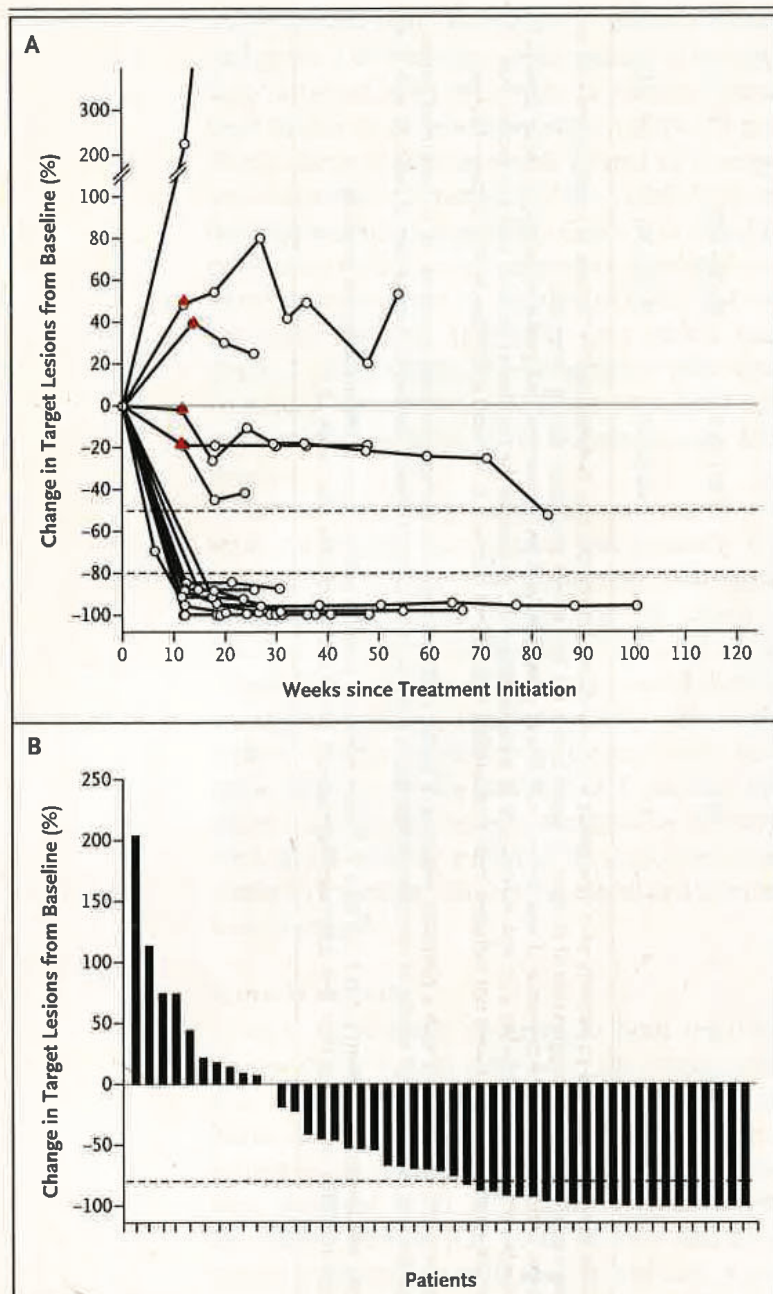


Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

Representative spider plots in Panel A show changes from baseline in the tumor burden, measured as the sum of the products of perpendicular diameters of all target lesions, in patients who received the concurrent regimen of nivolumab (at a dose of 1 mg per kilogram of body weight) and ipilimumab (3 mg per kilogram), the maximum doses that were associated with an acceptable level of adverse events. Red triangles indicate the first occurrence of a new lesion. Dashed lines indicate 50% and 80% improvement from baseline (gray line) in target lesions, as assessed by means of modified World Health Organization criteria. Panel B shows a representative waterfall plot of the maximum percentage change in target lesions, as compared with baseline measurements, in patients who received the concurrent regimen. A total of 47 patients had a response that could be evaluated in this analysis; 46 had a positive or negative change in target lesions from baseline, and 1 had no change. The dashed line denotes 80% tumor reduction in target lesions from baseline.

PD-L1-positive (Table S5 and Fig. S5 in the Supplementary Appendix).

Among patients treated with the concurrent regimen, objective responses were observed in patients with either PD-L1-positive tumor samples (6 of 13 patients) or PD-L1-negative tumor samples (9 of 22) ($P>0.99$ for a post hoc comparison by means of Fisher's exact test). In the sequenced-regimen cohorts, a higher number of overall responses was seen among patients with PD-L1-positive tumor samples (4 of 8 patients) than among patients with PD-L1-negative tumor samples (1 of 13), but the numbers were small.

In contrast to previous observations with ipilimumab monotherapy, an increase in the absolute lymphocyte count was not obvious among patients in either regimen group (Table S6 in the Supplementary Appendix), but changes may have been difficult to detect in this small cohort. In the concurrent-regimen group, the objective-response rate was similar among patients with a low absolute lymphocyte count (defined as <1000 cells per cubic millimeter)¹⁴ at weeks 5 to 7 and those with a normal or high absolute lymphocyte count at weeks 5 to 7 (43% and 40%, respectively) (Table S7 in the Supplementary Appendix). Likewise, in the sequenced-regimen group, 17% of patients with a low absolute lymphocyte count had an objective response and 23% of patients with a normal or high absolute lymphocyte count had an objective response.

DISCUSSION

The immune system is coordinately regulated to ensure the effective elimination of foreign pathogens, while minimizing damage to normal tissues. Until recently, cancer immunotherapy focused substantial effort on approaches that enhance antitumor immune responses by means of the adoptive transfer of activated effector cells, immunization against relevant antigens, or nonspecific immunostimulatory agents such as cytokines. In the past decade, agents that block inhibitory T-cell checkpoints, including antibodies blocking CTLA-4,^{3,4,17-19} PD-1,^{5,20,21} and PD-L1,²² have shown substantial clinical antitumor activity. Given that immunologic checkpoints are nonredundant and can inhibit T-cell activation, proliferation, and effector function within lymph nodes or the tumor microenvironment, we hypothesized that a combined blockade of CTLA-4 and PD-1 could produce greater antitumor activity than either single agent.²³

Although not formally compared in this study, concurrent treatment with nivolumab and ipilimumab was associated with rates of objective response that exceeded the previously reported results with either nivolumab or ipilimumab alone.^{3,5} Rapid and deep responses occurred in a substantial proportion of treated patients, with the majority of patients who had a response also having tumor regression of 80% or more at the time of the initial tumor assessment, including some patients who had had extensive and bulky tumors. Particularly striking was the observation that across the concurrent-regimen cohorts, 31% of the patients with a response that could be evaluated had tumor regression of 80% or more by week 12.

At the maximum doses for the concurrent regimen that were associated with an acceptable level of adverse events, all nine patients who had a response also had tumor regression of 80% or more, with three patients having a complete response. In contrast, on the basis of previous clinical experience with monotherapy for melanoma, less than 3% of patients who received nivolumab or ipilimumab at a dose of 3 mg per kilogram had a complete response.^{3,5} The overall activity of this immunotherapy combination compares favorably with that of other agents approved or being developed for advanced melanoma, including the targeted inhibitors of activated kinases,²⁴ although we recognize that these results must be interpreted with caution, given that this is a phase 1 trial that is subject to biases, including patient selection and small numbers of patients. The potential advantage of this combination is the durability of the response, as shown in previous trials of immunotherapy.^{25,26}

These initial data suggest that rapid responses of a greater magnitude may be achieved in patients treated with the combination of nivolumab and ipilimumab, as compared with the previous experience with either agent alone.^{3,5} Responses to combined therapy were generally durable and were observed even in patients whose treatment was terminated early because of adverse events. Patients who had a response included those with an elevated LDH level, M1c disease, and bulky, multifocal tumor burden.

As with previous studies of monotherapy with ipilimumab³ or nivolumab⁵ monotherapy, conventional objective-response rates may not fully capture the spectrum of clinical activity and potential benefit in patients treated with the con-

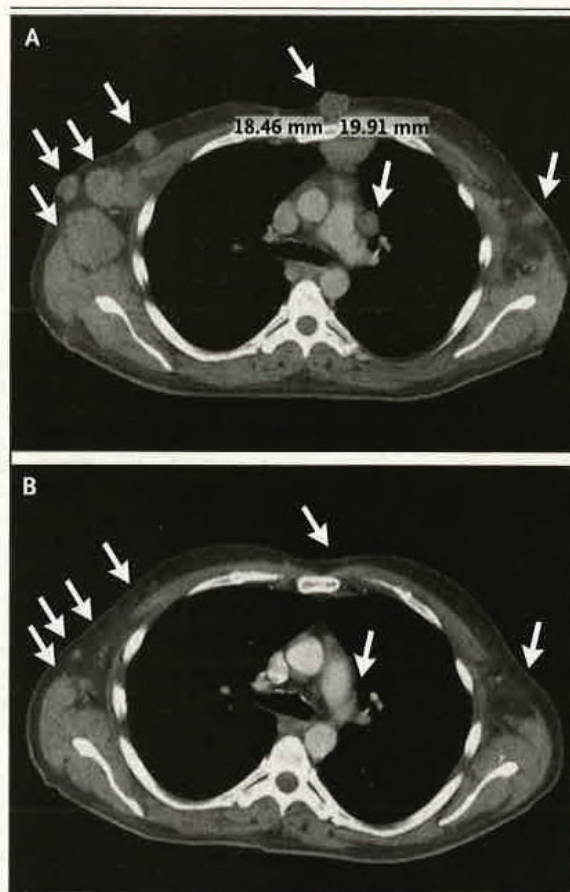


Figure 2. Computed Tomographic (CT) Scans of the Chest Showing Tumor Regression in a Patient Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

A 52-year-old patient was treated with the maximum doses that were associated with an acceptable level of adverse events (nivolumab at a dose of 1 mg per kilogram and ipilimumab at 3 mg per kilogram). The patient presented with extensive neck, mediastinal, axillary, abdominal, and pelvic lymphadenopathy; bilateral pulmonary nodules; small-bowel metastasis; and peritoneal implants; as well as diffuse subcutaneous nodules (shown in the CT scan in Panel A). The baseline level of lactate dehydrogenase (LDH) was 2.25 times the upper limit of the normal range, the hemoglobin level was 9.7 g per deciliter, and symptoms included nausea and vomiting. Within 4 weeks after the initiation of treatment, the LDH level normalized, symptoms improved (appetite increased and nausea decreased), and cutaneous lesions were regressing. The CT scan obtained at week 12 shows a marked reduction in all areas of disease (Panel B). Arrows indicate locations of metastatic disease.

current regimen of nivolumab and ipilimumab, given that a number of patients in our study had either long-term stable disease or unconventional immune-related patterns of response. Even among the seven patients in the concurrent-regimen group

who had stable disease for at least 24 weeks or immune-related stable disease for at least 24 weeks as the best response, six had meaningful tumor regression of at least 19%, and one had a declining tumor burden after prolonged stable disease. Prior experience with checkpoint-blockade monotherapy supports the observation that some patients may have stable disease for an extended period as the best objective response, lending credence to the hypothesis that reestablishment of the equilibrium phase of immune surveillance is a desirable outcome.¹

The observation that patients can have objective responses when treated with nivolumab after previous treatment with ipilimumab indicates that a lack of response to CTLA-4 blockade does not preclude a clinical benefit of PD-1 blockade and further supports the nonredundant nature of these coinhibitory pathways. Data from previous studies suggest a potential association between the occurrence of a response and tumor-cell expression of PD-L1 in patients receiving nivolumab⁵ and a correlation between overall survival and increases in the peripheral-blood absolute lymphocyte count in patients treated with ipilimumab.¹³⁻¹⁶

In this study of combination therapy, responses were observed in patients regardless of the absolute lymphocyte count or status with respect to tumor-cell expression of PD-L1 at baseline. PD-L1 expression was measured with the use of an immunohistochemical assay and antibody that are different from those used in previous studies,^{5,11,27} and variations in assay conditions and biopsy samples, as well as tumor heterogeneity, may have affected these results. However, the rate of PD-L1 positivity for the tumor specimens in this study (38%) is similar to the rates observed in previous studies of metastatic melanoma (40 to 43%).^{11,27} Thus, our results suggest that patients can have a response regardless of the PD-L1 status at baseline or the absolute lymphocyte count.

The spectrum of adverse events observed among patients treated with the concurrent regimen was qualitatively similar to previous experience with nivolumab or ipilimumab monotherapy, although the rate of adverse events was increased among patients treated with the combination therapy. We observed grade 3 or 4 treatment-related adverse events in 53% of patients treated with the concurrent regimen, as compared with previous rates of 20% among patients treated with ipilimumab monotherapy at a dose of 3 mg per kilogram

and 15% among those treated with nivolumab alone.^{3,5} In the sequenced-regimen cohorts, 18% of patients had grade 3 or 4 treatment-related adverse events. Adverse events in both regimen groups were manageable and were generally reversible with the use of existing treatment algorithms.¹²

Collectively, these results suggest that nivolumab and ipilimumab can be administered concurrently with a manageable safety profile. More rapid and deeper clinical tumor responses were observed in patients treated with the combination therapy, as compared with the previous experience with either agent alone, although comparative studies are needed to confirm this observation. Responses were durable, although longer follow-up is needed in some cohorts. The effect of the combination regimen on overall survival remains to be defined. The results of the current study support a randomized, phase 3 trial to compare the clinical efficacy of nivolumab alone, ipilimumab alone, and a concurrent regimen of nivolumab and ipilimumab in patients with advanced melanoma.

Supported by Bristol-Myers Squibb and Ono Pharmaceutical.

Dr. Wolchok reports receiving consulting fees from Bristol-Myers Squibb, Ziopharm Oncology, Polynoma, and Merck and grant support from Bristol-Myers Squibb, GlaxoSmithKline, and MedImmune on behalf of his institution. Dr. Postow reports receiving grant support from Bristol-Myers Squibb on behalf of his institution and serving as an unpaid consultant for and receiving reimbursement for travel expenses from Bristol-Myers Squibb. Dr. Lesokhin reports receiving consulting fees from Bristol-Myers Squibb and grant support from Bristol-Myers Squibb on behalf of his institution. Dr. Segal reports receiving grant support from Bristol-Myers Squibb on behalf of his institution. Dr. Ariyan reports receiving consulting fees from Bristol-Myers Squibb. Ms. Gordon reports receiving consulting fees from Bristol-Myers Squibb. Mr. Burke reports receiving lecture fees from Bristol-Myers Squibb. Dr. Lowy reports being a former employee of and holding stock in Bristol-Myers Squibb. U.S. patents on human monoclonal antibodies against *Bacillus anthracis* protective antigen and antibodies against *Clostridium difficile* toxins and a surrogate therapeutic end point for anti-CTLA-4-based immunotherapy of disease have been issued; Dr. Lowy is listed as an inventor on the patents, which are owned by Bristol-Myers Squibb. Dr. Inzunza reports being an employee of Bristol-Myers Squibb. Mr. Feely and Drs. Horak, Hong, Wigginton, and Gupta report being employees of and holding stock or stock options in Bristol-Myers Squibb. Dr. Korman reports being an employee of, holding stock or stock options in, and receiving reimbursement for travel expenses from Bristol-Myers Squibb. Dr. Sznol reports receiving consulting fees from Bristol-Myers Squibb, Genesis Biopharma, Nektar, Anaeropharma Science, Genzyme, BeiGene, Johnson & Johnson, and Prometheus Medical and lecture fees from the Institute for Medical Education and Research, TRM Oncology, DAVA Oncology, and the Center for Biomedical Continuing Education. No other potential conflict of interest relevant to this article was reported.

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 and the participating clinical faculty and personnel: Stephanie Terzulli, Ph.D., Valerie Russell, Nicholas Cimaglia, and Evelina Pogoriler, Memorial Sloan-Kettering Cancer Center; John

Gerks, Lifang Xie, and Konstantin Kogan, statistical programmers, and Christian Poehlein, medical director, Bristol-Myers Squibb; and Susan Leinbach, medical writer, Clinical Solutions Group.

REFERENCES

- Schreiber RD, Old LJ, Smyth MJ. Cancer immunoeediting: integrating immunity's roles in cancer suppression and promotion. *Science* 2011;331:1565-70.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646-74.
- 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.
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011;364:2517-26.
- 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.
- 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, Engelhardt 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. abstract.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.
- Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009;15:7412-20.
- Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Event v3.0 (CTCAE). Washington, DC: Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, August 9, 2006 (<http://ctep.cancer.gov/protocol> Development/electronic_applications/docs/ctcae3.pdf).
- Taube JM, Anders RA, Young GD, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med* 2012;4:127ra37.
- Yervoy. Princeton, NJ: Bristol-Myers Squibb, 2012 (package insert).
- Berman DM, Wolchok J, Weber J, et al. Association of peripheral blood absolute lymphocyte count (ALC) and clinical activity in patients (pts) with advanced melanoma treated with ipilimumab. *J Clin Oncol* 2009;27:Suppl.15s. abstract.
- Ku GY, Yuan J, Page DB, et al. Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. *Cancer* 2010;116:1767-75.
- Postow MA, Yuan J, Panageas K, et al. Evaluation of the absolute lymphocyte count as a biomarker for melanoma patients treated with the commercially available dose of ipilimumab (3mg/kg). *J Clin Oncol* 2012;30:Suppl. abstract.
- Delyon J, Mateus C, Lefeuvre D, et al. Experience in daily practice with ipilimumab for the treatment of patients with metastatic melanoma: an early increase in lymphocyte and eosinophil counts is associated with improved survival. *Ann Oncol* 2013 February 24 (Epub ahead of print).
- O'Day SJ, Hamid O, Urba WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. *Cancer* 2007;110:2614-27.
- Fong L, Small EJ. Anti-cytotoxic T-lymphocyte antigen-4 antibody: the first in an emerging class of immunomodulatory antibodies for cancer treatment. *J Clin Oncol* 2008;26:5275-83.
- Robert C, Ghiringhelli F. What is the role of cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma? *Oncologist* 2009;14:848-61.
- Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol* 2010;28:3167-75.
- Lipson EJ, Sharfman WH, Drake CG, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. *Clin Cancer Res* 2013;19:462-8.
- Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366:2455-65.
- Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol* 2005;25:9543-53.
- 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.
- Sznol M, Kluger HM, Hodi S, et al. Survival and long-term follow-up of safety and response in patients (pts) with advanced melanoma (MEL) in a phase 1 trial of nivolumab (anti-PD-1; BMS-936558; ONO-4538). *J Clin Oncol* 2013;31:Suppl. abstract.
- Wolchok JD, Weber JS, Maio M, et al. Four-year survival rates for patients with metastatic melanoma who received ipilimumab in phase II clinical trials. *Ann Oncol* 2013 May 10 (Epub ahead of print).
- Gordon MS, Hamid O, Powderly J, et al. A phase I study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors. Presented at the Annual Meeting of the American Association of Cancer Research, Washington, DC, April 6-10, 2013. abstract.

Copyright © 2013 Massachusetts Medical Society.

RECEIVE IMMEDIATE NOTIFICATION WHEN AN ARTICLE
IS PUBLISHED ONLINE FIRST

To be notified by e-mail when *Journal* articles
are published Online First, sign up at NEJM.org.

LC COPYRIGHT

0 032 589 719 3

AVAILABLE



LiptruzetTM

(ezetimibe and atorvastatin) tablets

10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg

**For additional information, we invite you to
contact a Merck representative at 1-866-410-0105.
We will be pleased to assist you Monday through Thursday
from 8 AM to 8 PM ET and Friday from 8 AM to 6 PM ET.^a**



^aHours subject to change.