

The NEW ENGLAND JOURNAL of MEDICINE

VOL. 372 NO. 4

ESTABLISHED IN 1812

JANUARY 22, 2015

NEJM.ORG



310 THIS WEEK AT NEJM.ORG

PERSPECTIVE

- 301 Treating Millions for HIV — The Adherence Clubs of Khayelitsha E.W. Campion
- 303 Demedicalizing AIDS Prevention and Treatment in Africa T. Ellman
- 306 Foreseeable Risks? Informed Consent for Studies within the Standard of Care C.A. Sacks and C.E. Warren
- 308 Bridging the Hospitalist–Primary Care Divide through Collaborative Care A.H. Goroll and D.P. Hunt

ORIGINAL ARTICLES

- 311 PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma S.M. Ansell and Others
- 320 Nivolumab in Previously Untreated Melanoma without BRAF Mutation C. Robert and Others
- 331 Causes and Timing of Death in Extremely Premature Infants from 2000 through 2011 R.M. Patel and Others
- 341 TBX6 Null Variants and a Common Hypomorphic Allele in Congenital Scoliosis N. Wu and Others

REVIEW ARTICLE

- 351 Origins of Cystic Fibrosis Lung Disease D.A. Stoltz, D.K. Meyerholz, and M.J. Welsh

IMAGES IN CLINICAL MEDICINE

- 363 Bilateral Lower Palpebral MALT Lymphoma I. Lalya and H. Mansouri
- e5 Acute Colonic Pseudo-Obstruction F. Alahdab and S. Saligram

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

- 364 A Woman with Abdominal Pain, Dyspnea, and Diplopia W.S. David and Others

EDITORIAL

- 374 Release the Hounds! Activating the T-Cell Response to Cancer M. Sznol and D.L. Longo

HEALTH POLICY REPORT

- 376 Institute of Medicine Report on GME — A Call for Reform J.K. Iglehart

CLINICAL IMPLICATIONS OF BASIC RESEARCH

- 382 A Biologic Velcro Patch J. Tolar and J.E. Wagner

CORRESPONDENCE

- 385 Rituximab or Azathioprine Maintenance in ANCA-Associated Vasculitis
- Cost-Effectiveness of CT Screening in the National Lung Screening Trial
- Integration of Acid–Base and Electrolyte Disorders
- Hidden Formaldehyde in E-Cigarette Aerosols

CORRECTION

- 394 Genome & Co. v. Univ. of Chicago PGR2019-00002 UNIV. CHICAGO EX. 2064



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

610.5

NE

v.372 no.4

SEATTLE WA 98195-7155

PO BOX 357155

HEALTH SCIENCES LIBRARY

UNIVERSITY OF WASHINGTON

ANN GLEASON

#10091574575 #20141225-201450122 01

**DOCKET
ALARM**

Find authenticated court documents



The NEW ENGLAND JOURNAL of MEDICINE

Subscription and Business Information

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 in Previously Untreated Melanoma without BRAF Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalciou, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.

ABSTRACT

BACKGROUND

Nivolumab was associated with higher rates of objective response than chemotherapy in a phase 3 study involving patients with ipilimumab-refractory metastatic melanoma. The use of nivolumab in previously untreated patients with advanced melanoma has not been tested in a phase 3 controlled study.

METHODS

We randomly assigned 418 previously untreated patients who had metastatic melanoma without a BRAF mutation to receive nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks and dacarbazine-matched placebo every 3 weeks) or dacarbazine (at a dose of 1000 mg per square meter of body-surface area every 3 weeks and nivolumab-matched placebo every 2 weeks). The primary end point was overall survival.

RESULTS

At 1 year, the overall rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (hazard ratio for death, 0.42; 99.79% CI, 0.25 to 0.73; $P < 0.001$). The median progression-free survival was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group (hazard ratio for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; $P < 0.001$). The objective response rate was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; $P < 0.001$). The survival benefit with nivolumab versus dacarbazine was observed across prespecified subgroups, including subgroups defined by status regarding the programmed death ligand 1 (PD-L1). Common adverse events associated with nivolumab included fatigue, pruritus, and nausea. Drug-related adverse events of grade 3 or 4 occurred in 11.7% of the patients treated with nivolumab and 17.6% of those treated with dacarbazine.

CONCLUSIONS

Nivolumab was associated with significant improvements in overall survival and progression-free survival, as compared with dacarbazine, among previously untreated patients who had metastatic melanoma without a BRAF mutation. (Funded by Bristol-Myers Squibb; CheckMate 066 ClinicalTrials.gov number, NCT01721772.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Robert at Dermatology Service, INSERM Unité 981, Gustave Roussy, Villejuif-Paris Sud, France, or at caroline.robert@gustaveroussy.fr.

Drs. Atkinson and Ascierto contributed equally to this article.

This article was published on November 16, 2014, at NEJM.org.

N Engl J Med 2015;372:320-30.
DOI: 10.1056/NEJMoa1412082

Copyright © 2014 Massachusetts Medical Society.

THE GLOBAL INCIDENCE OF MELANOMA continues to rise, and the mortality associated with unresectable or metastatic melanoma remains high.¹ Globally, 132,000 new cases of melanoma are diagnosed and an estimated 48,000 persons die from advanced melanoma each year.^{2,3} Ipilimumab has been shown to improve the rate of survival at 2 years, as compared with a vaccine control, among previously treated patients with metastatic melanoma as well as among previously untreated patients who also received dacarbazine.^{4,5} BRAF and MEK inhibitors are approved agents that, as monotherapy, have been associated with a survival advantage as compared with chemotherapy, with a median overall survival of 13 to 20 months.⁶⁻⁸ Although the objective response rate is high with these agents (45 to 53%), the median duration of response is less than 1 year.⁶⁻¹⁰

Recently, a combination of anti-BRAF and anti-MEK agents has been associated with a higher response rate and longer duration of response, as compared with anti-BRAF monotherapies.^{11,12} However, the use of these targeted agents, as monotherapy or in combination, is limited to the approximately 40% of patients who have melanoma with a BRAF V600 mutation. Dacarbazine is associated with a median overall survival of 5.6 to 7.8 months and remained until recently a commonly used therapy in patients with previously untreated melanoma without a BRAF mutation.^{5,13} Despite new treatment options, there remains a substantial unmet need for treatments that extend survival and provide a better quality of life.

Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint-inhibitor antibody that selectively blocks the interaction of the PD-1 receptor with its two known programmed death ligands, PD-L1 and PD-L2, disrupting the negative signal that regulates T-cell activation and proliferation.¹⁴ In a phase 1 study, nivolumab was associated with promising antitumor activity and a favorable safety profile in patients with solid tumors, including advanced melanoma.^{15,16} In an open-label, randomized, phase 3 study involving patients with ipilimumab-refractory melanoma, nivolumab was associated with a higher rate of objective response than chemotherapy (32% vs. 11%).¹⁷ Recently, another anti-PD-1 antibody, pembrolizumab, has shown robust clinical activity and

has been approved in the United States on the basis of an objective response rate of 24% among patients with advanced melanoma that progressed after ipilimumab, as well as treatment with a BRAF inhibitor if the patient had a BRAF V600 mutation.¹⁸ Here, we report the results of a phase 3, randomized, double-blind study conducted to determine whether nivolumab, as compared with dacarbazine, improves overall survival among previously untreated patients who have advanced melanoma without a BRAF mutation.

METHODS

PATIENTS

Eligible patients had confirmed, unresectable, previously untreated stage III or IV melanoma without a BRAF mutation. Other eligibility criteria included an age of 18 years or more, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms and 1 indicating mild symptoms), and the availability of tumor tissue from a metastatic or unresectable site for PD-L1 biomarker analysis. Key exclusion criteria were active brain metastases, uveal melanoma, and a history of serious autoimmune disease. Patients who had received adjuvant therapy previously were not excluded.

STUDY DESIGN AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive by means of intravenous infusion either 3 mg of nivolumab per kilogram of body weight every 2 weeks, plus a dacarbazine-matched placebo every 3 weeks, or 1000 mg of dacarbazine per square meter of body-surface area every 3 weeks, plus a nivolumab-matched placebo every 2 weeks. Randomization was stratified according to tumor PD-L1 status (positive vs. negative or indeterminate) and metastasis stage (M0, M1a, or M1b vs. M1c, defined according to the tumor-node-metastasis system of the American Joint Committee on Cancer and the International Union against Cancer). Treatment continued until there was disease progression, as assessed by the investigator, or an unacceptable level of toxic effects. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse effects with the study drug, as determined by the investigator (Fig. S1 in the Supplementary

Appendix, available with the full text of this article at NEJM.org).

The primary end point was overall survival. Secondary end points included investigator-assessed progression-free survival, objective response rate, and PD-L1 expression in the tumor as a predictive biomarker of overall survival.

ASSESSMENT

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,¹⁹ at 9 weeks after randomization, every 6 weeks thereafter for the first year, and then every 12 weeks until disease progression or treatment discontinuation. Assessments for survival were performed every 3 months. Safety evaluations were performed for patients who received at least one dose of the study treatment, and the severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.²⁰

STUDY OVERSIGHT

The study protocol, available at NEJM.org with the most recent version of the statistical analysis plan, was approved by the institutional review board at each participating center. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All the patients provided written informed consent to participate in the study. Data were collected by the sponsor, Bristol-Myers Squibb, and analyzed in collaboration with the academic authors. All the authors vouch for the accuracy and completeness of the data and analyses reported and for 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.

A data and safety monitoring committee was established to provide oversight of safety and efficacy considerations. On June 10, 2014, the monitoring committee reviewed an expedited report after noting a potential difference in overall survival during an earlier safety review. Data from the abbreviated report, which was based on an unplanned interim database lock, showed a significant difference in overall survival in favor of nivolumab. As a result, the monitoring com-

mittee recommended that the study be unblinded and amended to allow patients enrolled in the dacarbazine group to receive nivolumab. Reported here are the results from the double-blind portion of the study before the amendment (clinical data cutoff on June 24, 2014).

PD-L1 ASSESSMENT

Before randomization, the expression of PD-L1 on the surface of the tumor cells was assessed in a central laboratory with the use of an automated immunohistochemical assay (collaboratively developed by Bristol-Myers Squibb and Dako), as described previously.²¹ PD-L1 positivity was defined as at least 5% of tumor cells showing cell-surface PD-L1 staining of any intensity in a section containing at least 100 tumor cells that could be evaluated. Indeterminate status was attributed to samples for which tumor cell-surface expression could not be discerned because of melanin content or strong cytoplasmic staining. PD-L1 status was prospectively determined, and the results were used to stratify randomization, which was performed by means of a fully automated interactive voice-response system. Statistical analyses were prespecified to assess the predictive value of PD-L1 expression.

STATISTICAL ANALYSIS

A sample of approximately 410 patients, randomly assigned in a 1:1 ratio to the two treatment groups, was planned. Overall survival and progression-free survival were compared between the two treatment groups with the use of a two-sided log-rank test stratified according to PD-L1 status (positive vs. negative or indeterminate) and metastasis stage (M0, M1a, or M1b vs. M1c). The hazard ratios for the nivolumab group, as compared with the dacarbazine group, and corresponding confidence intervals were estimated with the use of a stratified Cox proportional-hazards model. Survival curves for each treatment group were estimated with the use of the Kaplan-Meier product-limit method. Rates at fixed time points were derived from the Kaplan-Meier estimate, along with their corresponding log-log-transformed 95% confidence interval.

The objective response rate was compared between the two treatment groups with the use of a two-sided Cochran-Mantel-Haenszel test. The efficacy analyses were performed in the

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.