The results are applicable to patients similar to those eligible for the clinical trials included in the analysis; that is, patients with a good performance status and normal organ function can be considered for treatment with PD-1 blockade with nivolumab regardless of \( \text{BRAF} \) mutation status. However, clinicians should exercise caution in applying these results to patients who would not meet the trial eligibility criteria of the study population—for example, patients with a poor performance status, because response rates to nivolumab may not be similar in patients with and without \( \text{BRAF} \) mutations in a nontrial population. \( \text{BRAF} \)-directed therapy may offer a higher chance of response and clinical benefit in some patients with \( \text{BRAF} \)-mutant melanoma and should be considered in all patients with \( \text{BRAF} \)-mutant melanoma.

It is clear that patients both with and without \( \text{BRAF} \)-activating mutations gain benefit from PD-1 blockade, with durable responses observed in both subsets of patients, regardless of prior therapies. Ongoing studies will further define the role of sequencing of \( \text{BRAF} \)-targeted therapy and PD-1 or CTLA-4 blockade on clinical outcomes. Clinical trials that include PD-1 blockade as well as novel immune therapy combination studies or targeted therapy combination studies can be considered among the first line of therapy options for all patients with advanced melanoma.

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**ARTICLE INFORMATION**

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**Published Online:** May 21, 2015. doi:10.1001/jamaoncol.2015.1237.

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**Progress in Understanding What Is Being Statin(ed) in Prostate Cancer**

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**In this issue** of *JAMA Oncology*, Harshman et al\(^1\) report longer time to progression (TTP) while receiving androgen deprivation therapy (ADT) for patients with prostate cancer who are using statins compared with nonusers (median TTP, 27.5 vs 17.4 months, respectively). The authors\(^1\) propose a mechanism through statin-induced competitive inhibition of the androgen precursor, dehydroepiandrosterone-sulfate (DHEAS), uptake via an organic anionic transporting polypeptide (OATP) encoded by \( \text{SLCO2B1} \). Preclinical mechanistic data support DHEAS uptake dependence on \( \text{SLCO2B1} \) expression, and DHEAS uptake and cell proliferation are decreased at physiologic statin concentrations. As the authors\(^1\) point out, the main challenges to the clinical findings of this study are potential inherent confounders and bias associated with any retrospective analysis, of which all cannot be accounted for in a multivariate analysis. For example, patients prescribed statin therapy had generally better prognostic features and likely represent a group more apt to seek early medical care and health maintenance, such as prostate-specific antigen (PSA) screening. Nevertheless, we are provided with intriguing evidence for a mechanism of how statins may exert an antitumor effect in patients being treated for prostate cancer.

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**Conflict of Interest Disclosures:** None reported.
The strongest clinical evidence for a cancer “protective effect” from statins, across a wide range of malignant neoplasms, was generated from a Danish, population-based observational study. Overall, patients prescribed statins prior to cancer diagnosis had a 15% risk reduction in all-cause and cancer-specific mortality. The decrease in cancer-specific mortality was seen in 13 of 27 primary tumor sites, including the 4 most commonly diagnosed malignant neoplasms: lung, colon, breast, and prostate cancer. The authors hypothesized that statins may act through several possible mechanisms: (1) disruption of cellular processes, such as cell signaling, cell-cycle progression, protein synthesis, and membrane integrity; (2) induction of apoptosis; (3) reduced angiogenesis; and/or (4) reduced serum cholesterol levels. Other studies have shown comparable findings, most evaluating statins in cancer prevention. One of the most notable studies revealed a 50% relative risk reduction of colorectal cancer in patients prescribed statin therapy for at least 5 years. Despite these encouraging results, multiple negative observational studies and meta-analyses, coupled with a lack of strong mechanistic data, temper overall enthusiasm.

More convincing clinical data for the ability of statins to improve advanced disease outcomes, rather than prevention, may exist for prostate cancer. Although there have been mixed results in multiple observational studies of statin use on prostate cancer mortality, a meta-analysis showed a 20% reduced risk of developing advanced prostate cancer. More recently, Yu et al demonstrated a decreased prostate cancer-specific mortality rate in those patients treated with a statin, with the greatest mortality benefit in patients on a statin prior to the diagnosis of prostate cancer.

Statins may have activity in prostate cancer through direct or indirect inhibition of the androgen axis. In advanced prostate cancer, patients are typically treated with ADT, suppressing the availability of testosterone ligand for androgen receptor (AR) signaling. Interestingly, as castration-resistant prostate cancer (CRPC) develops, intratumoral androgen levels remain elevated, prompting considerations of intratumoral androgen synthesis. DHEAS, an adrenal androgen precursor, has been shown to play a role in castration resistance. Therefore, a clinical trial in the neoadjuvant setting that may offer pharmacodynamic information (NCT01821404, NCT01992042, NCT00572468). Another trial is evaluating the impact of astatin on the rate of biochemical recurrence in patients with a Gleason score of 8 or greater, positive surgical margin, or pT3-T4 disease who underwent radical prostatectomy (NCT01759836).

However, based on current clinical and biologic evidence, statins may be most effective in patients with more advanced disease, in which DHEAS and intratumoral androgen synthesis have been shown to play a role in castration resistance. Therefore, a potential clinical setting for further investigation of statins is in patients with nonmetastatic CRPC, for whom there is no current standard of care, and in whom PSA could be evaluated in early trials as a clinical marker of response. In all, Harshman et al have conducted an interesting analysis linking in vitro preclinical data with retrospective patient outcomes, providing a framework for future evaluation. Nonetheless, the current data are not sufficient to support incorporation of statin use into clinical oncology practice for patients with prostate cancer, and additional studies are required.

Conflict of Interest Disclosures: None reported.

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Delivering Patient-Centered Care in the Setting of Advanced Cancer
What Does a Clinical Risk-Prediction Model Have to Do With It?

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In 2013, the Institute of Medicine (IOM) released a consensus report entitled “Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis,” which provides a blueprint for improving the quality of cancer care in the United States. In particular, its central focus is the need for delivering patient-centered cancer care and ensuring that patients have an opportunity to receive effective, high-value, and safe treatments that are consistent with their individual needs, values, and preferences. The IOM report’s goals and recommendations are hierarchical and move from those perceived to be most achievable—those directly associated with the patient-clinician encounter—to those that are more difficult to accomplish, such as the elimination of disparities in care and comprehensive delivery-system reform, including new payment models. The first 2 recommended goals of the IOM report focus on the importance of engaged patients. Goal 1 emphasizes the critical role of the cancer care team in providing patients and their families with understandable information on cancer prognosis, treatment benefits and harms, palliative care, psychosocial support, and estimates of the total and out-of-pocket costs of cancer care. Goal 2 stresses the importance, in the setting of advanced cancer, of providing patients with end-of-life care consistent with their needs, values, and preferences.

In this issue of JAMA Oncology, Brooks et al describe the development of a clinical prediction model to assess the risk of chemotherapy-related hospitalization (CRH) in patients with advanced cancer initiating palliative chemotherapy. The model was developed using a retrospectively designed nested case-control study drawing on data from a single community hospital clinical registry. The authors make the case for the potential value of information regarding the risk for CRH in this patient population, noting that the ability of oncologists to predict CRH risk with standard indicators (eg, performance status) is poor. They propose that being able to identify the profile of patients most at risk for this clinically adverse event may “improve the chemotherapy informed-consent process, allow for modification of treatment regimens to reduce the risk of toxic effects, and identify patients who may benefit from aggressive supportive care around the time of chemotherapy initiation.” The authors acknowledge that there has been considerable research already focused on development of strategies to assess the risks associated with chemotherapy toxic effects; however, they posit that the risks and burdens associated with CRH make it a more meaningful end point than a laboratory value in the toxic range. That being said, whether a hospital admission was related to recent (within the past 30 days) administration of chemotherapy was determined by adjudication and consensus of a team of oncology care clinicians, including representatives from medical oncology, nursing, and pharmacy.

The clinical registry used in this study was developed for quality-improvement purposes, and the authors had to retrospectively collect demographic and medical data from the clinical records of case and control patients to develop their risk model. Important data that should have been provided in this report include the number of medical oncologists treating patients during the registry observation period and their distribution between cases and controls, the matching of the cases and controls in terms of year of treatment, and whether cases and controls received guideline-concordant support for white blood cell (WBC) growth factor during treatments. A large population-based study conducted during this same period showed both underuse and overuse of WBC growth-factor support in patients receiving chemotherapy for lung and colorectal cancer.