Research Article

A Randomized, Double-Blind, Placebo-Controlled Phase II Clinical Trial of Lovastatin for Various Endpoints of Melanoma Pathobiology

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Abstract
On the basis of large cardiovascular clinical trials of lipid-lowering agents that showed a considerable decrease in the incidence of primary melanomas in the active agent arm, we have carried out a randomized, double-blind clinical trial examining the impact of lovastatin on various biomarkers of melanoma pathogenesis. Subjects with at least two clinically atypical nevi were randomized to receive oral lovastatin or placebo for a 6-month period. Clinical, histopathologic, and molecular biomarkers were evaluated for change in the two groups. Eighty subjects were randomized, evaluable, and included in the analyses. Lovastatin showed no benefit in comparison with placebo in the primary endpoint of decreasing the level of histopathologic atypia, nor in any of the secondary endpoints of decreasing clinical atypia, impact on nevus number, nor in showing significant changes in any of the molecular biomarkers. There were no significant differences in adverse event profiles for lovastatin compared with placebo. The lovastatin arm did show a significant and considerable decrease in total serum cholesterol and serum low-density lipoprotein (LDL) levels compared with placebo, an expected result. This finding bolsters confidence in subject compliance. Given the results of this trial, it is concluded that if lovastatin were to lower the incidence of melanoma, it would appear not to be doing so by reversing atypia of precursor atypical nevi over the 6-month time frame studied. Further research into the pathogenesis of melanoma and in other potential chemopreventive agents is needed. Cancer Prev Res; 7(5); 496–504. ©2014 AACR.

Introduction
Although recent advances in treatment of stage IV melanoma are exciting and encouraging, the long-term prognosis for melanoma once it has disseminated remains dismal. Given this, it is imperative that research be carried out not only on therapeutics for melanoma but also on other aspects, including prevention and detection. Chemoprevention of melanoma is a little explored area (1) that deserves more attention, especially given the failures in therapeutics for advanced melanoma.

Two large cardiovascular clinical trials showed a significant reduction in the incidence of melanoma in the lipid-lowering agent arm versus the control arm (2, 3). However, clinical trial evidence is not uniformly in support of an effect of lipid-lowering agents on melanoma incidence, with a recently published prospective analysis of association between use of statins and melanoma risk in the Women’s Health Initiative showing no difference in risk between those using statins and those not using statins (4). In addition, 2 meta-analyses showed no decreased risk with statin use (5, 6). However, an epidemiologic study in the Netherlands found that though statins did not seem to influence the incidence of melanoma, their use was associated with a reduced Breslow thickness in melanomas upon diagnosis, possibly suggesting a beneficial effect of statins on melanoma progression (7). Additionally, a recent large case–control study of 300,000 subjects conducted in the Netherlands showed an overall reduction in cancer incidence among statin users, but not in melanoma incidence (8). In addition to clinical trial data, various in vitro, animal model, and theoretical work has lent support to the concept of statins as potential chemoprevention or chemotherapy agents (9–11). There are several theoretical mechanisms whereby statins...
could influence melanoma development. They might function through their action on HMG Co-A reductase to change the geranylation or farnesylation patterns of key cell-cycle regulatory proteins such as those in the RAS pathway (9, 11). Also, statins may be acting by immunomodulation through possible effects on steroids known to be generated in the skin, including melanoma cells (12, 13).

Because atypical (dysplastic) nevi can be precursors to melanoma and can be considered precancerous lesions (14, 15), reduction of atypia clinically and histopathologically by a chemopreventive agent should lead to a reduction in risk of these lesions developing melanoma and would provide strong evidence of a chemopreventive effect. To address this, we conducted a randomized, placebo-controlled phase II trial testing the effects of lovastatin on atypical nevi. Two groups of patients were randomized to treatment with lovastatin or placebo. Each patient in the first group had 2 nevi matching in size and clinical degree of atypia; each patient in the second group had one large clinically atypical nevus at least 8-mm diameter, with a second atypical nevus that could be followed photographically. The goals of the trial were to analyze clinical, microscopic, and molecular endpoint biomarkers in atypical nevi pre- and posttreatment, to quantify potential chemopreventive effects of lovastatin, and to obtain data needed for subsequent trials.

Materials and Methods

Protocol design

The study was a randomized, double-blind, placebo-controlled phase II clinical trial of lovastatin in patients with atypical nevi. The trial involved four clinical sites in the United States with subjects on trial from December 2007 through April 2011. Human subjects committees at each site approved the study protocol. The study was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from all subjects. The trial has been registered at ClinicalTrials.Gov, registration number NCT00462280.

Recruitment and study population

Patients older than 18 years of age were eligible for study entry if they had 2 atypical nevi with the following characteristics: Group 1: two nevi matching in size and clinical degree of atypia or group 2: one large clinically atypical nevus ≥8-mm diameter, with a second atypical nevus that could be followed photographically. This design with these 2 different groups was chosen to enable comparison of these 2 different groups with respect to evaluation of study endpoints and reproducibility. It may be argued that biopsies of different nevi (group 1), despite being clinically matched, may yield such variability in the biomarkers as to be less desirable. Conversely, biopsy of a portion of a large nevus both pre- and posttreatment (group 2) may lead to errors due to variability within different portions of the nevus, or, more importantly, the inflammatory and healing process from the initial biopsy may lead to exposure to cytokines, and effects from the inflammatory and healing process might alter the endpoint biomarkers independent of the agent being tested.

All target lesions were clinically atypical nevi (16), but must not have had a level of clinical atypia that required a biopsy to rule out melanoma. Subjects were ineligible if they were currently on lipid-lowering agents, had been on lipid-lowering agents of any type within the last 3 months, or had a history of coronary artery disease or stroke. Females were ineligible if they were pregnant, breast feeding, or of child-bearing age and were not using a reliable method of contraception, as use of lovastatin is contraindicated in pregnancy.

Randomization, assignment, and dose regimen

Eligible subjects were randomized to receive either lovastatin or placebo in a 1:1 ratio. Stratified randomization was used to balance the treatment arms with respect to clinical center because clinical site variability is the largest source of variation in multicenter clinical trials (17). Subjects were stratified into groups: group 1, two matched atypical nevi; group 2, one large, >8-mm atypical nevus + another atypical nevus. The groups were placed in blocks of fours alternating with blocks of twos. A random number generator was used to determine the randomization assignments. A randomization table was established for each site. The statistician created the random allocation sequences. The allocations were presented as a sequence of numbers specific for each site, for example, 1011001, 1011002, 1011003, 1011004, 1021005, and 1021006. Site study teams enrolled the subjects and contacted staff at the Central Site, UC Irvine, to obtain the appropriate randomization number. In this way, the staff could verify whether enrollment criteria had been met.

Study treatments were dispensed to trial participants as encapsulated tablets in labeled bottles. Initially, participants were given a 40-mg capsule of lovastatin or placebo orally on a daily basis. If the 40-mg dose was tolerated and laboratory results were acceptable, at 6 weeks the dose was increased to 80 mg (two 40-mg capsules) given orally on a daily basis. The monitoring and dosage adjustment guidelines followed in this study were within the normal range for clinical use of this drug. The duration of study participation and study drug was 6 months.

Masking

The study was conducted in an entirely double-blinded manner. The study statistician generated the random allocation sequence. Investigators at each of the 4 sites enrolled subjects and obtained allocations from the study pharmacist in a blinded fashion. All subjects were given identical overencapsulated pills and were completely blinded to their treatment arm for the duration of the study. Similarly, all evaluations were carried out in a blinded fashion by evaluators completely blinded as to which arm the study subjects were on.

Participant flow and follow-up

Adherence and compliance. Participant compliance was monitored at the 2-week after randomization visit and at
each subsequent visit (1, 3, and 6 months), and telephone monitoring was performed 6, 8, and 16 weeks after randomization.

**Clinical assessments.** During the randomization visit, the target atypical nevi were identified, mapped, and photographed; the randomly designated nevus of the matched pair of nevi or a portion of the ≥8-mm nevus was biopsied. Each participant then received study medication and was started on the study. Follow-up visits with laboratory assays were performed at intervals of a few weeks during the time the subject was on study. For the 50 subjects with 2 matched atypical nevi, the nevi were designated nevus A and nevus B, respectively.

**Final visits and off-study monitoring.** Participants returned to the clinic 24 weeks (±2 weeks) after randomization for off-study monitoring that included complete skin examination for atypical nevi; photographs of the remaining intact target nevus; photographs of the entire back from shoulders to natal cleft; biopsy of the matched remaining atypical nevus or a section of the ≥8-mm designated study nevus; monitoring of any adverse events, and received a laboratory order for a complete blood count (CBC), Chem 20, creatine phosphokinase (CPK), fasting lipid panel, C-reactive protein, and, for females of childbearing potential, a urine pregnancy test. The “dosing calendar” was reviewed and collected with returned medication containers for pill counts. Study subjects were seen 2 weeks later for suture removal and to follow-up on laboratory tests.

**Trial endpoints and analysis**

**Histopathologic analysis of biopsied atypical nevi.** The primary endpoint was histopathologic regression of atypical nevi in response to treatment. Standard histopathologic evaluation of all or portions of atypical nevi was done pre- and posttreatment by 2 dermatopathologists nationally recognized in pigmented lesion/melanoma evaluation (R.J. Barr and A.J. Cochran). Atypia in nevomelanocytic lesions is characterized by cytologic atypia, architectural atypia or disorder, and host response. Cytologic atypia consists of one or more of an increase in the nuclear/cytoplasmic ratio, prominent nucleoli, an irregular chromatin pattern, variations in the thickness of the nuclear membrane, or finely distributed melanin pigment in the cytoplasm. Architectural atypia consists of one or more of asymmetry, bridging of theques between rete ridges, nevus cells at the shoulders of rete ridges, a lentigenous distribution of nevus cells at the dermoepidermal junction, or nevus cells present above the basal layer of the epidermis. Host response is characterized by a lymphocytic infiltrate, fibroplasia, capillary/endothelial hyperplasia, and/or incontinence of pigment. All of these factors are considered together while evaluating sufficient multiple microscopic fields and sections of the histopathologic specimen to arrive at a diagnosis with a corresponding assigned level of atypia (Supplementary Fig. S1; see ref. 18 for details on the description and grading of levels of atypia). The level of atypia was graded in a standard fashion on a discrete scale of seven levels of atypia, with 0 for no atypia and 6 for melanoma. The grading system was as follows: 0, no atypia/normal nevus; 1, mild atypia; 2, mild-to-moderate atypia; 3, moderate atypia; 4, moderate-to-severe atypia; 5, severe atypia; and 6, melanoma. For each patient, the change from baseline in the level of atypia was calculated.

**Clinical analysis of photography of target nevi.** Secondary endpoints included clinical regression of atypical nevi and change in the number of nevi on the back. Pre- and posttreatment macroscopic photographs were taken of target atypical nevi and evaluated by a panel of 3 physicians who are clinically active in the pigmented lesion clinics at their respective institutions. The physicians, blinded to treatment arm and pre- or posttreatment status, assigned a grade to each pair of photographs (Supplementary Fig. S2). The grading system was as follows: 1, the left photograph shows a complete resolution of atypia relative to the right photograph; 2, the left photograph shows a strong lessening of atypia relative to the right photograph; 3, the left photograph shows a mild lessening of atypia relative to the right photograph; 4, the left and right photographs show the same degree of atypia; 5, the right photograph shows a mild lessening of atypia relative to the left photograph; 6, the right photograph shows a strong lessening of atypia relative to the left photograph; and 7, the right photograph shows a complete resolution of atypia relative to the left photograph. After unblinding of pre- or posttreatment status for photographs, an ordinal variable was created representing clinical regression of atypical grade.

To determine change in the number of nevi on the back, photographs of the subjects’ backs, superiorly from the horizontal line formed by the shoulders and inferiorly to the top of the natal cleft, were obtained both pre- and posttherapy, identifiers were removed, and photographs were assessed in the similar blinded fashion by study clinicians (Supplementary Fig. S3). The grading system was as follows: 1, moles apparent in the left photograph that are not present in the right photograph; 2, both photographs, left and right, show the same nevi; and 3, moles apparent in the right photograph that are not present in the left photograph. An ordinal categorical variable was generated after the pre- or posttreatment status was unblinded. The back is the anatomic region with the highest number of atypical nevi on average and is the anatomic region with the highest incidence of melanoma.

**Molecular biomarkers.** Molecular biomarkers selected for evaluation were candidates along the nevomelanocytic carcinogenesis pathway and could be measured on standard formalin-fixed, paraffin-embedded sections. Biomarkers were measured pre- and post-study and included measures of angiogenesis, proliferation, p21 (WAF1/CIP1) protein, RelA, and expression of c-cadherin and n-cadherin. Please see the Supplementary Materials for details on the immunohistochemical staining and analysis. Angiogenesis is closely linked with carcinogenesis. As a biomarker associated with angiogenesis, VEGF expression was measured because it has been shown to correlate with level of atypia (19), and a reduction in VEGF
expression may indicate change toward a more benign phenotype. In addition, modulation of angiogenesis has been associated with statins (20). We also analyzed the expression of HIF-1α, an important regulatory protein in angiogenesis.

Increased proliferation is a hallmark of carcinogenesis progression. Several studies have shown that Ki-67 expression correlates with the level of atypia in the nevomelanocytic system (21–25). However, the main increases are seen in the transition from atypical nevus to melanoma, with further increases occurring with invasive and metastatic potential within melanomas.

Another protein involved in proliferation inhibition, p21 (WAF1/CIP1), was measured because there is evidence that p21 may be affected by HMG-CoA reductase inhibitors (9, 26).

RelA was measured because we and colleagues have identified RelA as a biomarker that varies with the level of atypia of nevomelanocytic lesions (27).

Expression of e-cadherin and n-cadherin was measured because differences in expression patterns of these proteins have been demonstrated between benign nevomelanocytic cells and melanoma (28).

Serum components. An objective was to evaluate the correlation between serum markers known to be affected by lovastatin and the tissue endpoints. To this end, blood was collected both pre- and post-study. A standard lipid panel was performed and C-reactive protein was measured. C-reactive protein is involved in immune and inflammatory process modulation and could possibly affect carcinogenesis in targets such as nevomelanocytic precursors. If melanoma incidence is indeed decreased by oral statins, a key question, which we have not seen asked, is whether this is due to a direct effect of the statins intracellularly on the molecular machinery of the nevomelanocytic cells, or is the effect a secondary one brought about by changes in the extracellular milieu that then affect the nevomelanocytic cells, or some combination of these 2 pathways. It is conceivable that chemoprevention of melanoma by statins could be due to effects of statins on serum components or on the stroma, rather than the statins directly acting on the nevomelanocytic cells themselves.

Statistical considerations
The study was designed with adequate power to detect a significant reduction in atypia in the lovastatin arm, should such a reduction occur. Power calculations for a Wilcoxon rank-sum test were performed using nQuery Advisor 5.0 (Statistical Solutions, Ltd., 2002). Let \( u_1 \) be the mean change in histopathologic grade from baseline for the placebo group, and let \( u_2 \) be the mean change for patients treated with lovastatin. Assuming a common SD, \( \sigma \), the effect size is \( \delta = (u_1 - u_2)/\sigma \). Because statistical comparisons were to be made for each of the 2 study groups, the Bonferroni multiple comparisons procedure was applied to achieve an overall significance level of 0.05. With 25 subjects in each treatment arm and a 0.025 significance level, the two-sided Wilcoxon rank-sum test would have 80% power to detect an effect size of \(-0.972\) (29). The accrual goal was 120 subjects, with at least 2 current atypical nevi in locations that could be easily biopsied, to ensure 100 evaluable patients, one group of 50 subjects with 2 matched atypical nevi and a second group of 50 patients with one large \( \geq 8\)-mm atypical nevus and another atypical nevus.

The Wilcoxon rank-sum test was applied to compare treatment arms with regard to change from baseline in histopathologic score after treatment. Values were determined by subtracting the histopathologic score after treatment from that obtained before treatment. A categorical variable was created representing regression, no change, or increase in the level of atypia after treatment; the \( \chi^2 \) test was applied to assess the association between change in histopathologic score and treatment group.

For analysis of the secondary endpoint, clinical regression of atypical nevi, the Wilcoxon rank-sum test was applied to compare the change in clinical grade between treatment groups. A categorical variable was created to indicate no change, decrease, or increase in the number of nevi after treatment; the Fisher exact test was applied to assess the association between change in the number of nevi on the back and treatment group. Analyses of clinical secondary endpoints were exploratory and intended for hypothesis generation. No adjustment for multiple comparisons was made.

Seven biomarkers were analyzed in terms of the changes in the percentage of staining intensity from baseline and the mean change from baseline on immunostained histology slides. The estimated mean changes and 95% confidence intervals for the means were reported by treatment group and pathologist. Independent 2-sample \( t \) tests were applied to compare mean changes from baseline between treatment arms, adjusted for multiple comparisons (30). Similarly, independent sample \( t \) tests were used to compare mean changes from baseline in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides and in 16 additional laboratory tests, adjusted for multiple comparisons.

Data were combined for the group with 2 matching nevi and the group with one large clinically atypical nevus. The Fisher exact test was applied to test for an association between treatment arm and occurrence of at least one adverse event.

Results
Accrual
Eighty subjects total were randomized. All were at least partially evaluable and were included in one or more of the analyses. Sixty-six subjects with 2 matched nevi were randomized to treatment with lovastatin (\( n = 34 \)) or placebo (\( n = 32 \)). Ten subjects in the lovastatin arm and 7 in the placebo arm discontinued the trial early. Thus, there were 49 evaluable subjects in group 1, 24 in the lovastatin arm and 25 in the placebo arm (Fig. 1). Accrual for group 2 with one large atypical nevus, partially biopsied pre- and poststudy, was slow and was halted after accrual of 14 subjects (Supplementary Fig. 54). Subjects in this group were not...
included in the analysis of primary endpoints or biomarkers. However, for this group, the results of photographic secondary endpoints, adverse events, and serum lipid measurements are included.

**Demographics of participants**

Baseline variables were similar across the two treatment groups (Table 1).

**Primary endpoint**

Figure 2 displays the change from baseline in the level of histopathologic atypia for the treatment groups as determined by 2 pathologists. On the basis of atypia grades determined by pathologist 1, the lovastatin group showed a mean increase in the grade of atypia of 0.50 compared with a mean decrease of 0.12 for the group treated with placebo (Wilcoxon rank-sum test: \( P = 0.048 \)). On the basis of grades determined by pathologist 2, the lovastatin and placebo groups showed a mean increase in the grade of atypia of 0.17 and 0.04, respectively; these means did not differ significantly (\( P = 0.919 \)).

As determined by pathologist 1, 12.5% of 24 patients who took lovastatin showed regression of atypia, 29.2% showed no change, and 58.3% showed an increase in the level of atypia after treatment. In comparison, for 25 patients taking placebo, these percentages were 40.0%, 28.0%, and 32.0%, respectively. The association between change in histopathologic score and treatment group was marginal (\( \chi^2 \) test: \( P = 0.068 \)).

As determined by pathologist 2, 37.5% of 24 patients who took lovastatin showed a regression of atypia, 25.0% showed no change, and 37.5% showed an increase in the level of atypia after treatment, compared with 36.0%, 20.0%, and 44.0%, respectively, for 25 patients who took placebo. There was no significant association between change in histopathologic score and treatment group (\( \chi^2 \) test: \( P = 0.873 \)). Concordance between the two pathologists' evaluations was analyzed (see Supplementary Fig. S5).

**Secondary endpoints**

**Nevi grade.** Clinical analysis of target nevi was performed by a panel of 3 physicians' expert in the evaluation of pigmented lesions, who examined pre- and posttreatment photographs of nevi (Supplementary Fig. S2). For each participant, the mean of changes recorded by 3 reviewers was computed. The mean difference between treatment arms was 0.06 (\([-0.11 \text{ to } 0.23]\)). No significant difference in the clinical regression of atypical grades was found between treatment arms (\( P = 0.61 \); Supplementary Fig. S6).

**Number of nevi.** From photographs taken pre- and posttreatment, the 3 physicians determined the number of nevi on the backs of 23 patients who took lovastatin and 26 patients who took placebo (Supplementary Fig. S3). Data from the 3 physicians were combined. Six percent of photographs from the lovastatin group were found to have fewer nevi after the treatment, 93% with the same number of nevi, and 1% with more nevi after the treatment compared with 4%, 87%, and 9%, respectively, in the placebo group. No significant association was found between treatment arm and change category overall (Fisher exact test: \( P = 0.13 \)) or for any of the 3 evaluators (Fisher exact test: \( P = 1.00 \) for evaluator 1, \( P = 0.51 \) for evaluator 2, and \( P = 0.49 \) for evaluator 3).

**Molecular biomarkers**

As a secondary endpoint, changes in molecular biomarkers based on immunostaining intensity on
Histopathologic slides were evaluated by 2 pathologists in a blinded fashion (Fig. 3). Molecular biomarkers examined included HIF-1α, e-cadherin, n-cadherin, VEGF, RelA, p21, and Ki-67. On the basis of assessments by pathologists 3 and 4, none of the molecular biomarkers showed a significant difference between treatment arms with regard to mean change from baseline (2-sample t test).

Concordance analyses for the 2 pathologists were performed (see Supplementary Table S1 and Supplementary Figs. S7 and S8).

Serum components and adverse events

The lovastatin arm showed a statistically significant decrease in total cholesterol and LDL cholesterol post-study compared with the placebo arm (Fig. 4; Supplementary Table S2). This confirms expectations that lovastatin would lower cholesterol levels, including LDL, and is a reassuring check on subject compliance with taking the study medication. Evaluation of 16 additional laboratory tests, including liver enzymes and CPK (U/L), showed no significant difference between the lovastatin and placebo arms at the end of the study, corrected for multiple comparisons (Supplementary Table S2).

Safety and adverse events

In considering safety and adverse events, 34% of 41 participants taking lovastatin reported at least one study-related adverse event during the study compared with...
28% of 39 participants taking placebo. These observed differences were not significant (Fisher exact test: \( P = 0.48 \)).

Discussion

This study showed no beneficial changes in the primary endpoint, which was change in histopathologic atypia of the...
target atypical nevi for lovastatin compared with placebo, nor any of the secondary endpoints, including clinical atypia, nevi numbers, or biomarkers for lovastatin compared with placebo. Only the expected beneficial changes in lipids in the lovastatin arm were seen. It is concluded that if lovastatin were to lower the incidence of melanoma, it would appear not to be doing so by reversing atypia of atypical nevi as a group over the 6-month time frame studied.

It can always be argued that the length of time subjects were on the trial was insufficient to manifest an effect, and a positive result with subjects on study medication for a longer period of time cannot be ruled out. The length of time on medication is always a compromise of resources and effort devoted to the trial, and study subjects’ willingness to participate (recruitment and compliance) affecting choice of trial length. Length of time on study medication for future trials will be dependent on understanding the proposed mechanism of action, along with any further information that is developed for the progression of precancorous changes in the formation of melanoma.

It may also be the case that if lovastatin were to lower the incidence of melanoma, it may act through a mechanism other than reversing atypia in precursor atypical nevi. Although around 25% of cutaneous melanomas arise from a pre-existing nevus, 75% are thought to arise de novo from isolated skin melanocytes. Perhaps if statins did have an effect, they could be acting on reducing melanomas arising in this latter group. Also, perhaps they could be acting at a later stage, after the formation of the melanoma, but through slowing its progression, as previously discussed (7). This study highlights the difficulty in designing a chemoprevention trial for melanoma: If the primary endpoint of the trial is the reduction in the incidence of new melanomas, the trial must encompass many thousands of subjects followed over several years. This would be a costly and resource intensive endeavor that would require a considerable degree of pre-study evidence that the huge effort would be worthwhile. On the other hand, atypical nevi, known precursors to melanoma, if used as a surrogate endpoint biomarker, are difficult to evaluate in a reproducible fashion, particularly in regard to quantitation of the level of atypia. In addition, there are currently no well-characterized biomarkers for progression of atypical nevi to melanoma.

This makes the study of putative chemoprevention agents for melanoma problematic at this time.

Despite these difficulties, the pursuit of chemoprevention agents for melanoma is a desirable goal, given the high degree of morbidity and mortality currently associated with this disease. Further preclinical work on understanding the developmental pathways of melanoma and in characterizing potential biomarkers is needed for future clinical trials testing potential chemopreventive agents.

Disclosure of Potential Conflicts of Interest
S.A. Leachman has received honoraria from the speakers’ bureau and is a consultant/advisory board member of Myriad Genetics Laboratory. P.M. Carpenter has received commercial research grant and honoraria from the speakers’ bureau of Ventana Medical Systems Inc. No potential conflicts of interest were disclosed by the other authors.

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