ANDROGEN DEPRIVATION THERAPY DOES NOT INCREASE CARDIOVASCULAR RISK

Contrary to some earlier reports, men who have androgen deprivation therapy (ADT) for prostate cancer don’t have higher cardiovascular mortality, according to a report in the 15 August 2011 online Journal of Clinical Oncology.

“It is reassuring to me that most of the studies finding elevated cardiac risk have been retrospective, whereas secondary analyses of clinical trials randomizing patients to ADT or not tend to find no increase in cardiac mortality,” Dr. Matthew R. Cooperberg from University of California, San Francisco, told Reuters Health by email.

Dr. Cooperberg and colleagues assessed mortality outcomes for 7,248 men in the CaPSURE registry in an effort to clarify the association between treatment selection and cause of death.

Treatments were divided into local only (5170 men, 71.3%), primary androgen deprivation therapy (1087 men, 15%), local treatment plus ADT (485 men, 6.7%), and watchful waiting/active surveillance (WW/AS; 506 men, 7.0%).

Overall, 103 men died as a result of prostate cancer, 195 men died as a result of cardiovascular disease, and 678 men died as a result of other causes.

In competing-risk analyses, there was a

(Continued on page 4)

FIVE GENES LINKED TO AGGRESSIVE PROSTATE CANCER

Researchers in Seattle and Sweden have identified five inherited genetic markers that could help spot men with the most aggressive and deadly forms of prostate cancer. They say the discovery may lead to a simple blood test to help distinguish between prostate cancers that need aggressive treatment and those that don’t.

The study was published online 16 August 2011 in Cancer Epidemiology, Biomarkers and Prevention.

Genetic markers that can distinguish between patients with aggressive and non-aggressive prostate cancers are urgently needed, stated Janet L. Stanford, PhD, of the Fred Hutchinson Cancer Center. She adds that her research team has identified markers that represent the first evidence that gene variants known as single-nucleotide polymorphisms (SNPs) play a role in prostate cancer progression. SNPs are single-letter variations in the four-letter DNA alphabet. They are known to have an important role in disease progression.

“Ultimately, these markers could be used in the clinic, along with other known predictors that are used to assess tumor aggressiveness, such as a high Gleason score, to identify men with a high-risk profile,” Stanford stated.

In the newly published study, Stanford and colleagues analyzed DNA samples

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VA ADDS TO LIST OF AGENT ORANGE-EXPOSED SHIPS

The Veterans Affairs Department has expanded its list of Navy and Coast Guard ships whose crews may be eligible for disability compensation as a result of exposure to the toxic defoliant Agent Orange.

It is an updated inventory of “Blue Water” platforms that operated along Vietnam’s coastline from 1962 to 1975. The designated vessels either entered the country’s inland waterways, docked in Vietnam, or their sailors went ashore, possibly exposing them to the widely used herbicide.

Many of the new ships are landing vessels or destroyers that operated near shore. The large escort carrier Kula Gulf also was added because it served as a helicopter and troop transport in Cam Ranh Bay for 3 days in November 1965.

“Posting of the ships list is an important recognition of the sacrifices U.S. Navy and Coast Guard veterans made for this nation,” VA Secretary Eric Shinseki said in a Friday release.

VA pays disability compensation to veterans or survivors for 14 medical conditions associated with exposure to Agent Orange. Department officials couldn’t say how many veterans might meet the criteria for exposure from the named ships.

(Continued on page 3)
TWO CUSTIRSEN STUDIES RELEASED

OncoGenex Pharmaceuticals, Inc. announced that data from two studies, a Phase 2 clinical study and a pre-clinical study, evaluating the investigational compound custirsen (OGX-011/TV-1011), were published in the September issues of the journals Clinical Cancer Research and Cancer Research.

Custirsen inhibits the production of clusterin, a protein commonly over-produced in cancer cells and a cause of treatment resistance. Two Phase 3 studies evaluating custirsen in men with castrate-resistant prostate cancer (CRPC) are ongoing: the SYNERGY clinical trial and the Prostate Cancer SATURN Trial. Both studies are currently enrolling CRPC patients.

Data from a Phase 2 clinical study of custirsen in combination with docetaxel retreatment or mitoxantrone as second-line chemotherapy in patients with metastatic CRPC (mCRPC) was published in Clinical Cancer Research.

In the clinical study, custirsen combined with docetaxel retreatment resulted in overall survival of 15.8 months. When custirsen was combined with mitoxantrone, overall survival was 11.5 months. The Phase 2 study also evaluated pain responses in patients with mCRPC. Overall, the pain response was durable (greater than or equal to three months) in 88 percent of patients who had pain or were on opioids for pain at study entry.

“These are encouraging results because we observed durable pain responses in many patients who had disease progression while on or shortly after first-line docetaxel treatment,” said Dr. Fred Saad, Professor of Surgery/Urology at the University of Montreal and lead investigator on the study. “These data suggest that custirsen may restore docetaxel sensitivity and potentially provide improvements in pain control for this difficult-to-treat patient population.”

Results showed feasibility, safety and pain relief, and associated low serum clusterin levels with longer survival. The authors believe this warrants further testing of custirsen combined with second-line chemotherapy in mCRPC.

Drug Discovery & Development
12 September 2011

SURVEY FINDS GOOD LONG-TERM QOL AFTER PROSTATE CANCER BRACHYTHERAPY

Long-term toxicity is low and quality of life good or acceptable after low-dose rate brachytherapy for prostate cancer, UK researchers say.

Lead investigator Dr. Amr M. Emara from Royal Surrey County Hospital and colleagues sent questionnaires to 226 men whose cancer was successfully treated with low-dose brachytherapy (alone or with external beam radiotherapy and/or hormonal treatment) at least five years previously.

They received responses from 174 men (77%), according to a report 19 August 2011 in BJU International.

Just over a quarter (27.6%) had received brachytherapy alone; 49.4% had been treated with hormones and brachytherapy; 20.7% had received hormones, brachytherapy, and external beam radiotherapy; and the remaining 2.3% received brachytherapy and external beam radiotherapy.

Most of those who presented with mild or moderate urinary symptoms still had them at follow-up. Just under a third of men who started out with mild symptoms (31.2%) developed moderate symptoms, and 10.9% of men with moderate symptoms at baseline transitioned to severe symptoms.

More than a quarter (28.1%) of men with moderate baseline symptoms had only mild symptoms at follow-up, however. Quality of life related to urinary symptoms was rated as good by 77%, acceptable by 21%, and poor by 2% of the survey respondents.

Of the 62 men who were potent before brachytherapy, 62.9% were still potent at follow-up, although the mean IIEF-5 score (a measure of erectile function) had worsened from 13.1 at baseline to 8.0.

“The finding is more favorable than the potency outcomes reported in other studies,” the researchers note. They attribute the improvement to lower doses of brachytherapy to the penile bulb.

At follow-up, 51.7% of patients reported normal bowel function and 45.4% reported mild bowel symptoms. Only

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The VA ship list is not static; officials said vessels will be added based on documentation such as deck logs, ship histories and cruise books as well as records kept in the National Archives. The day before the VA published the expanded ship list, it disclosed it has paid $2.2 billion in benefits to 89,000 Vietnam veterans or survivors who qualify for compensation in the past year since three conditions were added to the list of health conditions presumed to be related to Agent Orange exposure.

The VA faces a backlog of claims from applicants that served in that era, as well as new claims filed by troops returning from Iraq and Afghanistan.

Military Times, 2 September 2011

Dendreon Unlikely to Develop Diagnostic Despite Potential to Allay Reimbursement Fears

Dendreon’s prostate cancer vaccine Provenge® will continue to see overwhelming uptake due to the lack of a predictive test, oncologists told BioPharm Insight. There is a low likelihood that researchers in the field will focus their efforts on developing an assay, due to the entrance of newer prostate cancer drugs on the market.

Provenge has no measurable markers of efficacy such as changes in tumor size as visible through X-rays or pain improvement, said Dr. Thomas Hutson, a medical oncologist at Texas Oncology. However, the pivotal Phase III IMPACT study met the primary endpoint of improving overall survival, he added. It’s also not clear which patients benefit from Provenge, stated Dr. Martin Sanda, director of the Prostate Care Center at Beth Israel Deaconess Medical Center. It is unlikely that all these men will benefit and there is no information to determine who will and will not he said.

Dr. Celestia Higano, professor, Medicine and Urology at the University of Washington noted that Dendreon has interesting data showing that longer survival with Provenge may relate to the patients’ immune response during and after therapy. Early data was presented

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CARDIOVASCULAR MORTALITY

(Continued from page 1)

94% increased risk of cardiovascular mortality among men treated with primary ADT compared with local therapy alone, but there was no increased risk for men treated with a combination of local therapy and ADT.

Men in the WW/AS group had a 2.46-fold higher risk of cardiovascular mortality compared with men treated with local therapy alone. In contrast, when patients were matched by likelihood of receiving ADT in a propensity-adjusted multivariate analysis, ADT exposure was associated with a 25% increase in all-cause mortality, but prostate cancer-specific mortality or cardiovascular mortality were not significantly different.

“We were unable to identify an association between ADT use and cardiovascular mortality,” researchers conclude, “which suggests previous studies that found an association may have been confounded by unmeasured variables affecting both treatment selection and various non-prostate cancer-specific outcomes, including cardiovascular mortality.”

“We already know a great deal about cancer-specific and all-cause mortality following various treatments for prostate cancer, and we know the situations where ADT is clearly helpful (e.g., given early after surgery for N+ disease, given together with radiation for high-risk disease) and where it is not (e.g., given as monotherapy for low-risk localized disease, given before surgery),” Dr. Cooperberg said. “Growing recognition of potential complications such as adverse skeletal and metabolic effects, does not change the indications for treatment, but does offer an opportunity to ameliorate these effects.”

“Bone loss can be mitigated with medication and exercise,” Dr. Cooperberg explained. “Cardiac risk can be ameliorated with diet and exercise, and medication as appropriate. Remember that the most common cause of death for men with prostate cancer in the U.S. is cardiac disease, not prostate cancer—so men with prostate cancer should be counseled universally regarding cardiac risk reduction, whether or not ADT is part of their treatment regimen.”

New Provenge Plant Opens in California

PROVENGE®, the first FDA approved cellular immunotherapy for the treatment of advanced prostate cancer, is now more broadly available on the West Coast and across the country with the opening of Dendreon’s second plant, a new 184,000 square foot facility in the coastal town of Seal Beach, California. On August 15, former Us TOO International Prostate Cancer Education & Support Network board member, Tom Hiatt, current board member, Howard Kaczmarek, HotSheet co-editor Jonathan McDermed and several other patient advocates had an opportunity to examine the workings of Dendreon’s newest manufacturing facility.

Members of the group of advocates provided the company with valuable insight into prostate cancer from an individual patient’s point of view. Also during the visit, a team of experts gave the group an overview of how PROVENGE works and explained the intricate process for preparing each individual dose as well as the complex logistics necessary to get each dose to the patient.

The plant, which started production in July of this year, has 36 additional workstations to manufacture PROVENGE and is pristine in every way. The actual processing is done in a clean room environment that would rival any high tech electronics plant around the world. This includes extensive air handling and filtration systems that take up a significant portion of the plant and ensure the cleanest possible environment during production.

PROVENGE is approved by the FDA for the treatment of men with asymptomatic or minimally symptomatic metastatic, hormone refractory prostate cancer. PROVENGE is made from a patient’s own immune cells which are taken at designated centers and sent in a timely manner to a Dendreon manufacturing facility. There the cells are carefully introduced to a protein which functions as a prostate cancer antigen. The resultant processed cells are then quickly returned for infusion back into the patient. A complete course of treatment is three infusions, typically administered about two weeks apart. The therapy is designed to stimulate an immune response against prostate cancer.

In addition to the facility tour, the group also received an overview of patient resources available, including an online tool <www.Provenge.com> that helps find local physicians offering this therapy as well as Dendreon’s patient assistance programs for those who are underinsured, uninsured or need travel assistance for PROVENGE treatment.

More information is available by calling 1-877-336-3736.
2.9% had moderate symptoms, and none reported severe symptoms.

“The interpretation of data of bowel symptoms at follow-up is limited by the fact that we did not have baseline data available with which to make any comparison,” the investigators say.

“Overall, the results obtained in the present study confirm that brachytherapy has a favorable side effect profile over the long-term with regard to potency, urinary, and bowel toxicity,” the authors conclude.

“Improvements in brachytherapy techniques should allow even better outcomes for patients treated with brachytherapy in the future,” they add.

Reuters Health, 8 September 2011

Elastography Beats Ultrasound in Prostate Cancer Detection

Compared with conventional grey-scale ultrasonography (GSU), transrectal real-time elastography (RTE) improves prostate cancer detection – but it’s not ready for prime time, German researchers say.

GSU is a frequently used, cost-effective imaging technique, but lesions can appear hypo-, iso- or hyperechoic, Dr. Brock and colleagues at Ruhr-Universitat Bochum, Herne noted 5 August 2011 online in BJU International.

They say ultrasonically-based RTE can detect the lower elasticity caused by higher cell density in malignant tissue, and its sensitivity reportedly ranges from 57% to 100%, but until now it hasn't been compared to conventional GSU.

In their new study, the authors used both methods to screen for cancer-suspicious areas in the prostate and for extracapsular extension (ECE) in 229 men with biopsy proven prostate cancer. Biopsies were positive in 894 evaluated sectors. RTE correctly detected 594 (66%), and GSU found 215 (24%). Sensitivity was 51% with RTE and 18% with GSU. Specificity was 72% and 90% with RTE and GSU, respectively.

Forty-seven patients had ECE. RTE was 38% sensitive and 96% specific; GSU was 15% sensitive and 97% specific. Overall, higher Gleason grade lesions were more likely to be identified on RTE. But the researchers note that because of its low sensitivity and specificity, RTE is not recommended in the European guidelines for local staging of prostate cancers or ECE.

They conclude that adding RTE to GSU is better, but “improvement is still needed to achieve a clinically meaningful sensitivity.”

Reuters Health, 22 August 2011

Good Long-Term QOL after Prostate Cancer Brachytherapy

(Continued from page 2)
My Dad has prostate cancer with recurrent lung metastasis. He received radiation initially when diagnosed with stage III disease and is currently on Lupron for a year. His last PSA was 1.74. What do you suggest? Does diet, supplements, or Ayurvedic treatments play any role?

This is a great question that allows me to discuss the problem of lung metastases. Prostate cancer often leaves the prostate through the veins draining the gland. These cancer cells are carried to the right side of the heart and then pumped into the lungs. After passing through the lungs, blood and cancer cells are pumped by the left side of the heart out into the arteries. Arterial blood feeds to other organs in the body, including muscle, skin, kidneys, bone marrow, and brain.

This sequence of events has profound implications. In newly diagnosed prostate cancer patients, it is common to find circulating cancer cells in the blood. To get there, the cells had to pass through the lungs and then to the site where blood was drawn. This means that cancer has already spread to the lungs in most newly diagnosed patients! We also see this in autopsy studies in men who die of prostate cancer: lungs are nearly always involved. However, in all my years of caring for prostate cancer, I have only seen four patients where lung metastases caused a clinical problem. How is this possible? I think that the consensus is that prostate cancer does not grow very well in lung tissue, so it gets there and just sits. The bottom line:

(Continued on page 8)

**Bottom Line:** Preliminary research suggests that the plant/herb Sage and/or the sage dietary supplement may reduce hot flashes in some individuals.¹

The search is on! And, I am not talking about some rescue mission or the search for better and less irritating toilet paper! The search is on for an effective safe and science-based over the counter nutritional item or supplement that may reduce hot flashes in women and men. Soy, fish oil and flaxseed are heart healthy and may help a little, and black cohosh (the dietary supplement) may also provide a benefit, but none of these products are completely effective so what else are you supposed to do now? There are always effective prescription medications, for example estrogen, progesterone and a class of medications known as “SSRIs” or “SNRIs” (drugs such as venlafaxine). However, these drugs are not for everyone because they come with their own list of side effects and some of these medications can be quite costly, but for the more moderate to severe hot flashes they are very effective. What about for more mild but annoying hot flashes right now if none of the other over the counter products are working? Well, here is where giving you SAGE advice may help some individuals a little. A recent clinical study of a fresh sage extract preparation (280 mg per day) not only demonstrated a reduction in hot flashes, but an improved quality of life in women. And, almost everything that has been found to be effective for hot flashes in women has been effective against hot flashes for men on androgen deprivation treatment (ADT). Sage appeared to work within the first week, and by weeks 4 and 8 the average number of hot flashes was reduced by 50% and 59%.

Sage is a plant/herb that contains several plant estrogen-like compounds in them that may be doing the trick, or it is a placebo that is working really well. Only 2 out of 71 participants experienced gastrointestinal issues during the study attributed to the sage preparation. Thus, sage (the herb) can be purchased at the local grocery or health store and added to food. It can be used as a seasoning for tomato sauce, add to morning eggs or omelets, on a piece of pizza, in salads, and with chicken or fish when cooking so the food will absorb the herbs nice flavor. You can even take Sage dietary supplements because they are cheap, and 250 mg to 400 mg capsules are commonly for sale but no more than 2 per day can be used (in my opinion) because of the lack of research on higher doses. The other problem with fully recommending higher doses of the supplement right now is that there is not much prescription drug interaction data on sage as of yet. Regardless, I believe this plant and/or supplement may be worth a try if your doctor gives you the 2 thumbs up! Sage advice from a sage dude (that would be me-I am a legend in my own mind)!

**Reference:**
1. Bommer S, Klein P, Suter A. First time proof of sage's tolerability and efficacy in menopausal women with hot flashes.
ERG IS UNRELATED TO PSA RECURRENT IN RADICALLY OPERATED PROSTATE CANCER IN THE ABSENCE OF ANTI-HORMONAL THERAPY

Minner S, Enodien M, Sirma H, et al
Clin Cancer Res, 26 July 2011; Epub

Purpose: About 50% of prostate cancers have TMPRSS2-ERG fusions with concurrent ERG overexpression. The aim of this study was to determine whether clinical differences exist between ERG-positive and ERG-negative cancers in surgically treated patients not exposed to anti-hormonal therapy. A secondary aim was to search for differences between these tumor classes.

Experimental design: A tissue microarray containing samples from more than 2,800 prostate cancers with clinical data was analyzed for ERG alterations by immunohistochemistry and fluorescence in-situ hybridization (FISH). Results were compared with tumor phenotype, biochemical recurrence, and molecular features considered important for prostate cancer. The effect of ERG on androgen receptor (AR)-dependent transcription was analyzed in cell lines.

Results: ERG expression was found in 52.4% of 2805 cancers with a 95% concordance between ERG expression and AR gene rearrangement detected by FISH. ERG expression was unrelated to clinical outcome and tumor phenotype. Differences in AMACR, annexin A3, Bcl2, CD10, ALCAM, chromogranin A, EGFR, HER2, mTOR, p53 and synaptophysin status were significant but minimal in absolute numbers. The most striking difference was found for AR expression, which was markedly higher in ERG-positive cancers. In vitro studies demonstrated ERG-dependent impairment of AR-mediated transcriptional activity.

Conclusions: The striking similarities between these two types of prostate cancers rules out a major impact of ERG on tumor aggressiveness in early, not hormonally treated cancer. The marked difference in AR levels between ERG-positive and -negative cancers supports a systematic difference in potential response to hormonal therapy as previously observed in clinical trials.

Doctor Chodak’s Bottom Line (Ref Key: article #, page #, column #)

Author: Winning The Battle Against Prostate Cancer, 2011

a1p1c1 Does androgen deprivation therapy increase deaths from heart disease? This question continues to be debated every time another article is published. A new study from UCSF by Cooperberg and coworkers attempts to answer this question using data from a self selected, uncontrolled group of patients known as the CaPSURE database.

In this case, use of ADT did not cause an increased risk of dying of cardiovascular disease. If we had no additional studies, the question still would remain open because other uncontrolled studies show the opposite effect. But, at least four prospective studies have been done in men receiving radiation therapy. Fortunately, none showed an increased risk of cardiovascular deaths. Since those studies were not intended to test the effect of ADT on the heart, a final conclusion is not possible.

THE BOTTOM LINE: Based on the best studies available to date, ADT does not appear to increase the risk of heart related problems. Nevertheless, a cardiac evaluation in men with pre-existing heart disease may be warranted when this treatment is starting.

a2p1c2 Most doctors believe that a great advance would be to find other ways to predict which tumors are dangerous and which ones do not need treatment. One recent report identified 5 genes that seemed to put men at greater risk for dying from prostate cancer. Unfortunately, the overall impact is difficult to assess at this time because too much information is missing. For now the problem is that the test will not identify all men needing treatment and a significant portion will be told they need treatment incorrectly.

THE BOTTOM LINE: This type of research may lead to other more reliable ways to identify which men really need treatment but more work is needed.

a4p2c2 Custirsen is another drug working its way through the testing process for men with advanced disease. As reported here, combining this drug with docetaxel gave a longer survival compared to custirsen and mitoxantrone. Based on this study, additional testing is likely to occur which we hope leads to further benefit.

THE BOTTOM LINE: Custirsen is still showing promise for a possible role in helping men with advanced disease.

a5p2c3 In order for men to make more informed decisions about treatment, they need a better understanding of the impact on their quality of life. A recent study of low dose rate brachytherapy from the UK provides some additional information about this treatment.

Readers should understand that there are two parts to understanding the side effects; how often they occur and how men feel it is affecting them. Nearly one third of men lost the ability to have erections and many of those still functioning were doing worse compared to prior to treatment. Interestingly, about three fourths of the group thought their urinary symptoms were acceptable.

The problem with this study is it was retrospective and it really is not possible to compare these results to other treatments. Reasons include varying age, health, sexual, urinary and bowel function, incomplete or missing surveys and variable follow-up time. Still, these results can be of help in trying to understand the disadvantages of this treatment.

THE BOTTOM LINE: Every patient facing a treatment decision should make every effort to find out the odds of getting side effects and their impact on quality of life that are specific for the doctor who will deliver that treatment.

Thank you Military and Federal Employees for your CFC contributions!

Us TOO International Providing education & support services to prostate cancer patients & their families

Us TOO CFC# 11614
Five Genes Linked
(Continued from page 1)

from 1,309 prostate cancer patients, looking for gene variants suspected of being involved in tumor progression. Of 156 candidate genes, 22 SNPs were linked to prostate cancer-specific death.

In a separate analysis, researchers examined these variants in stored DNA samples from close to 2,900 prostate cancer patients in Sweden followed for an average of six and a half years. Five of the 22 SNPs emerged as being significantly associated with death from prostate cancer in this larger group of patients.

The variants included LEPR, a leptin receptor gene, RNASEL, Interleukin 4, Cytochrome 1, and ARVCF, a gene previously linked to cancer progression.

Patients who carried four or all five of the SNPs had a 50% higher risk of dying from their cancer than patients who had two or fewer of the SNP variants.

Confirmation of these findings is needed in different patients groups to determine if these five SNPs or any of the others identified are useful for predicting death from prostate cancer, Stanford says.

WebMD Health 16 August 2011

Diagnostic for Provenge?
(Continued from page 3)

at the Society for Immunotherapy of Cancer meeting in September 2010. If an effort exists to develop such an assay by Dendreon or the National Institutes of Health, it is not known, Sanda added.

Dr. Philip Kantoff, chief of the Division of Solid Tumor Oncology and director of the Lank Center for Genitourinary Oncology at Dana Farber, said that the determination in advance of which patient will respond to therapy is a critical issue in oncology in general and is not unique to this therapy. Determining which individuals stand to benefit is a work in progress that could take several years, he added. Scientists and clinicians are also studying how to best combine the drug with other recently approved therapies.

While a predictive assay for Provenge and how the drug may fit among other treatments is valid scientific issues, these are secondary to reimbursement, said Kantoff. There is demand for Provenge and it is easy to administer, he added, but Dendreon must financially de-risk it for individual practitioners to take it on without guaranteed reimbursement.

Adapted from Financial Times, 29 August 2011

Ask Doctor Snuffy Myers
(Continued from page 6)

is that the lung lesions are not likely to present a problem going forward.

After one year, I am worried about his PSA close to 2 ng/ml. We normally expect the PSA to be below 0.1 and often below 0.01 ng/ml. This suggests that his cancer may be resistant to treatment. If his PSA is increasing, resistance is a sure thing. We would do very careful staging to find where his resistant disease is. We would then move to second line hormonal therapy as discussed in past issues of the HotSheet. If fewer than five sites showed cancer progression, we would then discuss whether radiation might be useful to treat these sites of progression.

Hormonal therapy dramatically increases the risk of hypertension, heart disease, and diabetes. We advise men to start a Mediterranean heart healthy diet as multiple randomized trials support this advice. We would keep the serum 25-hydroxyvitamin D in the 60-80 ng/mL range. We would place him on pomegranate extract but use curcumin and resveratrol depending on his situation, especially if he were on drugs likely to interact with either of these two agents.