Single PSA Cut Point May Signal Progression

The best predictor of systemic progression after radical prostatectomy (RP) was a PSA cut point of 0.4 ng/mL or greater, a retrospective review of a large post-RP cohort showed.

Cut points of 0.2, 0.3, and 0.4 ng/mL were associated with systemic progression, and the percentage of men experiencing a continued PSA increase over five years was 61%, 67%, and 74%, respectively, R. Jeffrey Karnes, MD, of the Mayo Clinic, Rochester, MN, and colleagues reported online in The Journal of Urology.

“The PSA climb plateaued at a threshold of 0.4 to 0.49 ng/mL and this appeared to be the strongest predictor of systemic progression (HR=36, 95% CI 26-51) and the best fit model for predicting systemic progression (R²=0.92),” the researchers said.

“Currently there are multiple definitions of biochemical recurrence (BCR), which creates heterogeneity in prostate cancer outcome reporting and secondary treatment decisions. We found that a PSA cut point of 0.4 ng/mL or greater reflects the threshold at which increases in subsequent PSA values become durable and there is the strongest correlation with future systemic progression.”

Karnes and colleagues acknowledged the lack of consensus on a standardized definition of BCR after RP, pointing to several recommended definitions set by the American Urological Association, the European Association of Urology, and the National Comprehensive Cancer Network. “Consideration should be given to a single PSA cut point of 0.4 ng/mL or greater as it reflects an optimal yet simple cut point,” they said.

(Continued on page 4)

Can ‘Smarter’ Use Resurrect PSA Testing?

PSA testing in the US is now in rapid decline, but urologists are attempting to learn whether “smarter” deployment of the prostate cancer screening tool could enhance its usefulness by improving the accuracy of detecting aggressive disease.

In a new study, results of PSA testing of American men at midlife, when in their 40s and 50s, “strongly predicted” future lethal cases of prostate cancer, conclude lead author Mark Preston, MD, a urologist at the Harvard Medical School and Brigham and Women’s Hospital, in Boston, and colleagues.

The approach, which involves establishing a patient’s baseline PSA level, allows for “risk stratification” of screening. The new study was published online 13 June 2016 in the Journal of Clinical Oncology.

Declining use of PSA testing is “problematic” and is a matter of “throwing the baby out with the bathwater,” Dr. Preston said. “PSA is by no means perfect but definitely has value.” His comments are borne out by new data showing that the rate of distant-stage prostate cancers in the US has recently increased, according to a population-based study (Cancer Epidemiol Biomarkers Prev 2016; 25: 259–263).

“We need smarter screening practices based on actual risk, such as baseline PSA level, family history, or race to identify cancers that will cause symptoms or death in time to provide curative treatment,” Dr. Preston said. (Continued on page 4)
Use of the Cell Cycle Progression (CCP) Score for Predicting Systemic Disease and Response to Radiation of Biochemical Recurrence

Koch MO, Cho JS, Kaimakliotis HZ, et al

Cancer Biomark 7 June 2016; Epub ahead of print

Background: Determining the optimal treatment for biochemical recurrence (BCR) after radical prostatectomy (RP) is challenging.

Objective: We evaluated the ability of CCP score (a prognostic RNA expression signature) to discriminate between systemic disease and local recurrence in patients with BCR after RP.

Methods: Sixty men with BCR after RP were selected for analysis based on: 1) metastatic disease, 2) non-response to salvage external beam radiotherapy (EBRT), and 3) durable response to salvage EBRT. CCP scores were generated from the RNA expression of 46 genes. Logistic regression assessed the association between CCP score and patient group.

Results: Passing CCP scores were generated for 47 men with complete clinical and pathologic data. CCP score predicted clinical status when comparing men with metastatic disease or non-responders to salvage therapy to men with durable response (p=0.006). CCP score remained significantly predictive of clinical status after accounting for time to BCR, PSA at BCR, and Gleason score (p=0.0031).

Conclusions: Elevated CCP score was associated with increased risk of systemic disease, indicating that CCP score may be useful in identifying men with BCR who are most likely to benefit from salvage RT.

Do Skeletal-Related Events Predict Overall Survival in Men with Metastatic Castration-Resistant Prostate Cancer?

Howard LE, De Hoedt AM, Aronson WJ, et al

Prostate Cancer Prostatic Dis 5 July 2016 [Epub ahead of print]

Skeletal-related events (SREs) including pathologic fracture, spinal cord compression, radiation to bone and surgery to bone, are common in men with bone metastatic castration-resistant prostate cancer (mCRPC). Men with mCRPC are at high risk of death. Whether or not SREs predict mortality is unclear. We tested the association between SREs and overall survival (OS) in a multi-ethnic cohort of men with bone mCRPC, controlling for key covariates unavailable in claims data such as bone pain, number of bone metastases and PSA doubling time (PSADT).

We collected data on 233 men diagnosed with nonmetastatic CRPC in 2000-2013 at two VA hospitals who later progressed to bone metastases. First occurrence of SRE and OS were collected from medical records. Cox regression models were used to test the association between SRE and OS, treating SRE as a time-dependent variable. We adjusted for age, year, race, treatment center, biopsy Gleason, primary treatment to the prostate, PSA, PSADT, months from ADT to CRPC, months from CRPC to metastasis, and number of bone metastases at initial bone metastasis diagnosis. In a secondary analysis, we also adjusted for bone pain.

During follow-up, 88 (38%) men had an SRE and 198 (85%) died. After adjusting for risk factors, SRE was associated with increased mortality (hazard ratio (HR)=1.67; 95% confidence interval (CI) 1.22-2.30; P=0.001). When bone pain was added to the model, this association was attenuated, but remained significant (HR=1.42; 95% CI 1.01-1.99; P=0.042).

SREs are associated with increased mortality in men with bone mCRPC. Further studies on the impact of preventing SREs to increase survival are warranted.

Mutations Suggest New Prostate Cancer Treatment Options

Almost 12% of men with metastatic prostate cancer (PCa) had germline DNA-repair mutations, a finding that could help guide therapy selection toward nonstandard agents for selected men, genetic sequencing data for 700 men suggested.

The frequency of inherited DNA-repair mutations was almost three times higher than rates observed in men with localized PCa. The findings point to a “clear treatment pathway” involving agents that specifically target DNA-repair defects, such as poly ADP ribose polymerase (PARP) inhibitors, the authors concluded.

“Because the high frequency of DNA-repair gene mutations is not exclusive to an early-onset phenotype and is associated with clinically and histologically aggressive disease, with compelling evidence for therapeutic relevance, it may be of interest to routinely examine all men with metastatic PCa for the presence of germline muta-
Doc Moyad’s What Works & What is Worthless Column, Also Known As “No Bogus Science” Column

“Increase Your Telomere Length By Drinking Cheap_____?!”

Mark A. Moyad, MD, MPH, University of Michigan Medical Center, Department of Urology

Editor’s Note: Us TOO invites certain physicians and others to provide information and commentary for the Hot SHEET to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

Bottom Line:
One of the largest studies to ever address this anti-aging issue showed that significantly greater telomere length (longer life expectancy is associated with greater telomere length) in nurses who drank caffeinated coffee! Is it time to throw out anti-aging supplements that promise the same thing without substantial research? OH YEAH!!! Lifestyle changes rule!!! Viva Caffeinated Coffee!

I have seen just about everything in my lifetime, except the invention of a patient gown that does not expose your glutes to the maximus when you, as a patient, bend over to pick up a pen you dropped while filling out 10,000 pages of worthless redundant paperwork at your local hospital (all this for a sore knee???). Yet, I did not expect this study at all but it makes me happier than a dog trapped in a room full of squirrels! I was sure that I would not write about coffee again for a long time but I could not ignore this one because it was too juicy and fabulous (kind of like grass fed beef or a whole orange)!

Coffee consumption has been linked with many companies have been pushing EXPENSIVE over-the-counter pills that they claim to increase or maintain telomere length so it might be able to make you live longer! Yeah! Not so fast! Now, we have the first major study that suggests when looking at white blood cells and telomere length that caffeinated coffee (not other caffeinated products or decaffeinated coffee – sorry my less energetic readers) was significantly associated with greater telomere length (just two cups a day).

Okay, so now I have a low-
1,102 due to protocol-based reclassification. Other reasons for discontinuations included anxiety, switch to watchful waiting, death, and loss to follow-up. Two-thirds (67%) of the men were treated with either radical prostatectomy (RP) or radiation therapy (RT) after discontinuation. Only 3% received hormonal therapy. Almost half (48%) of the men were still on AS after five years and 27% were on AS at 10 years, the researchers reported online 19 June 2016 in the journal European Urology. The team had pathology data on 360 men who had RP. Of the men who switched to treatment because of protocol-based reclassification, 82 (30%) had favorable pathological outcomes, 85 (34%) had intermediate outcomes, and 100 (36%) had unfavorable outcomes. Mortality from prostate cancer was less than 1% during follow-up.

Because of the higher rate of unfavorable treatment outcomes, the researchers recommended a change in the PRIAS protocol. “Instead of an immediate switch to active treatment if more than two cores are positive, men should receive further investigation to confirm higher-risk disease,” the researchers write. They recommend examination by magnetic resonance imaging because its negative predictive value for Gleason upgrading is near 100%.

They concluded, “Criteria used to recommend a switch to active treatment do not seem selective enough to avoid unnecessary switches to active treatment.”

The Prostate Cancer Research Foundation, Rotterdam, supports the PRIAS study. The authors made no disclosures.

Reuter Health Information 7 July 2016

Is AS Safe in Low-Risk Prostate Cancer?
(Continued from page 1)
Can ‘Smarter’ Use Resurrect PSA Testing?  
(Continued from page 1)

In the new study, which used 30-year data from a large observational trial, the higher the initial PSA value, the greater the risk for a later lethal prostate cancer and, therefore, the greater the need for monitoring. On the other hand, the lower the initial value was, the lesser the risk was of an aggressive cancer, which in some cases means that follow-up testing could eventually be omitted.

“Men with a PSA below 1.0 ng/mL at age 60 (the median for that age) have an incredibly low risk of developing lethal prostate cancer and likely don’t need further screening,” said Dr. Preston. The new results generally confirm findings from two studies of an unscreened Swedish population (Cancer 2011; 117: 1210–1219; and BMJ 2013; 346: f2023). The Swedish studies showed that a single PSA before the age of 50 or 60, depending on the study, predicted long-term risk for a prostate cancer diagnosis and metastases during a median follow-up period of 27 years.

But the US has had wide opportunistic testing, so Dr. Preston and colleagues decided to see whether results of a one-time PSA test at a relatively young age were predictive of prostate cancer—specifically, lethal disease—among American men.

The team conducted a case-control study among men aged 40 to 59 years who gave blood at enrollment into the Physician’s Health Study. That study began in 1982 and now has long-term follow-up data for 22,000 participants. Baseline PSA levels were available for 234 men with prostate cancer and 711 age-matched controls. Seventy-one participants who developed lethal prostate cancer were re-matched to 213 controls.

Among controls, the median PSA level was 0.68, 0.88, and 0.96 ng/mL for men aged 40-49, 50-54, and 55-59 years, respectively. A total of 82%, 71%, and 86% of lethal cases occurred in men with PSA levels higher than the median at ages 40-49, 50-54, and 55-59 years, respectively.

Some of the more specific findings were dramatic. For example, one in seven men with PSA levels > 3.0 ng/mL at age 55-59 years and one in 12 men with PSA levels >2.1 ng/mL at age 50-54 years died as a result of prostate cancer within 30 years, report the study authors. Furthermore, the authors report that when a baseline PSA level was “markedly elevated” (>90th percentile of controls), the cumulative incidence of lethal prostate cancer 30 years later was “substantial,” with rates of 4.5%, 8.4%, and 14.1% for men aged 45-49, 50-54, and 55-59 years, respectively.

The findings were strong enough for the authors to recommend the adoption of such screening. “Risk-stratified screening on the basis of midlife PSA should be considered in men age 45 to 59 years,” they write.

The authors also attempted to use some of their data to determine the needed screening intervals after a baseline PSA assessment. Even when baseline PSA levels were lower than the median, the researchers found that there was a risk of developing lethal prostate cancer in the next 30 years (< 2%). “Although risk was small, it remained present, subsequently systemic progression.

In an accompanying editorial, Jeffrey J. Tosoian, MD, MPH, and Philip M. Pierorazio, MD, of The James Buchanan Brady Urological Institute and Johns Hopkins University School of Medicine Baltimore, MD, strongly disagreed. You can’t determine an acceptable level of clinical risk [post-RP] with a “rigid, one-size-fits-all definition of recurrence,” they said.

“An acceptable level of clinical risk is unique to each patient’s preferences, disease characteristics and overall life expectancy,” the editors wrote. “Clinical management should be based on an individualized approach in which baseline risk can be estimated using any number of simple, clinically validated tools.”

“Findings from this study and others should be included in future studies to validate the accuracy of various PSA thresholds,” Tosoian and Perorazio said. “Until the ideal test emerges, it is important to remain mindful in our application of current standards such as PSA.”

For the study, the researchers used the Mayo prostate cancer registry to identify 13,512 men with cT1-2N0M0 prostate cancer who underwent RP between 1987 and 2010. The median age was 63 years.

“Although PSA monitoring after RP was not standardized, most of the men underwent PSA monitoring for the first two years and semi-annually for the next three years, followed by annual surveillance,” the researchers said. Cox proportional hazard models and the O’Quigley event-R2 test were used to analyze the strength of association between BCR definitions and sub subsequent systemic progression.

Single PSA cut points of 0.2, 0.3, 0.4, and 0.5 ng/mL or greater were tested as were confirmatory PSA value definitions of 0.2 ng/mL or greater. At a median postoperative follow-up of 9.1 (IQR 4.9-14.3) years, a detectable PSA—defined as a value greater than 0.15 ng/mL—developed in 5,041 men. Systemic progression developed in 512 men, the review showed.

“In general, with higher PSA cut point definitions a greater percentage of patients were found to experience systemic progression,” Karnes and colleagues said. “Both confirmatory PSA definitions showed a greater percentage of patients experiencing systemic progression at five and 10 years compared to their corresponding single PSA cut point definition counterparts.”

Standardizing the definition of BCR will be crucial as prostate cancer surveillance transitions to the primary care setting, the researchers noted. “Using a single PSA cut point for BCR would translate into the simplest and most clear definition, allowing for timely referral to specialists and the initiation of secondary treatment.”

There are a number of design and methodology limitations with this study, given its retrospective nature and the fact that it spanned a period of more than 20 years, Karnes and colleagues pointed out. “Our results may also be limited in generalizability as they were derived from a large cohort treated and followed at a single center.”

MedPage Today  
17 June 2016
Can ‘Smarter’ Use Resurrect PSA Testing?
(Continued from page 4)
and so screening should be continued, albeit with longer intervals,” they write. The authors made a recommendation about repeat PSA tests for youngish men with baseline scores below the median. “It seems that baseline PSA level below the median at age 45 years followed by repeat measurements at five-year intervals would capture most lethal cases, given that the 15-year cumulative incidence for lethal prostate cancer at age 40 to 44 years is zero and in the 45 to 49 year age group only 0.07%,” they report.

As good as the data from the Physicians Health Study are, there are still “obvious pitfalls” to any use of the PSA test in younger men, reminds Alexander Kutikov, MD, a urologic oncologist at the Fox Chase Cancer Center, in Philadelphia, PA, who was not involved in the study. “The key challenge is exposing younger men to the risks of biopsy, screening-related anxiety, and potential treatment early in life,” he told Medscape Medical News.

On the other hand, there are benefits of this screening approach, including the obvious one – earlier detection of lethal prostate cancers.

“At least one guideline currently recommends early baseline screening,” said Dr. Kutikov, referring to the 2013 Melbourne Consensus Statement on Prostate Cancer Testing. It advises that “baseline PSA testing for men in their 40s is useful for predicting the future risk of prostate cancer” and says the strategy should be discussed with men.

The Melbourne statement was bolder than Dr. Preston and colleagues in their recom-

Disparities in Treatment of Patients with High-Risk Prostate Cancer: Results from a Population-Based Cohort
Urology 15 June 2016; Epub ahead of print

To assess the variation in primary treatment of high risk prostate cancer (PCa) by different hospital characteristics in the United States.

We used the National Cancer Database (NCDB) to identify patients diagnosed with pre-treatment high-risk PCa from 2004 to 2011. The primary outcomes were different forms of primary therapy or watchful waiting (WW) across different types of hospitals (community, comprehensive cancer community, and academic hospitals). Multivariable logistic regression analyses were used to test for differences in treatment by hospital type.

During the study period, we identified 102,701 men diagnosed with high-risk PCa. Overall, the most common treatment was radical prostatectomy (37.0%) followed by radiation therapy (33.2%) and WW (8.5%). Compared to white men with high-risk PCa, black men had lower adjusted odds ratios for sur-

Mutations Suggest New Prostate Cancer Options
(Continued from page 2)

(Continued on page 6)
Bipolar Androgen Therapy for Men with Androgen Ablation Naïve Prostate Cancer: Results from the Phase II BATMAN study
The Prostate 24 June 2016; Epub ahead of print

We have previously documented a paradoxical anti-tumor effect when castration-resistant prostate cancer patients were treated with intermittent, high-dose testosterone (i.e., Bipolar Androgen Therapy; BAT). Because, an adaptive increase in androgen receptor expression following chronic androgen deprivation therapy (ADT) may underlie this effect, we tested whether men with hormone-sensitive (HS) prostate cancer (PC) would also respond to BAT if given following a six-month ADT lead-in.

Asymptomatic HS PC patients with low metastatic burden or non-metastatic biochemically recurrent disease were enrolled. Following six-months of ADT, those with a PSA <4.0 ng/mL went on to receive alternating three-month cycles of BAT and ADT. BAT was administered as intramuscular testosterone (T) cypionate or enanthate 400 mg on Days (D) 1, 19, and 57. ADT was continued throughout the study to allow rapid cycling from near castrate to supraphysiologic range T following T injections. The primary endpoint was the percent of men with a PSA <4.0 ng/mL after 18 months. Secondary endpoints included radiographic response and quality of life (QoL). Twenty-nine of 33 patients received BAT following the ADT lead-in. The primary endpoint was met, with 17/29 men (59%, 90% confidence interval: 42-74%) having a PSA <4.0 ng/mL at 18 months. Ten patients receiving BAT had RECIST evaluable disease, and eight (80%) objective responses were observed (four complete; four partial). Three patients progressed per RECIST criteria and three had unconfirmed progression on bone scan.

Men treated with six-month of ADT had improved QoL following the first cycle of BAT as measured by the SF-36, FACT-P, and IIEF surveys. BAT demonstrated preliminary efficacy in men with HS PC following six-month of ADT. BAT may improve QoL in men treated with ADT.

Non-Surgically Related Causes of Erectile Dysfunction after Bilateral Nerve-Sparing Radical Prostatectomy
Prostate Cancer Prostatic Dis 2016; 19: 185-190

Background: Erectile dysfunction (ED) represents one of the most common long-term side effects in prostate cancer (PCa) patients treated with bilateral nerve-sparing radical prostatectomy (BNSRP). The aim of our study was to assess the influence of non-surgically related causes of ED in patients treated with BNSRP.

Methods: Overall, 716 patients treated with BNSRP were retrospectively identified. All patients had complete data on erectile function (EF) assessed by the Index of Erectile Function–EF domain (IIEF–EF) and depressive status assessed by the Center for Epidemiologic Studies-Depression (CES-D) questionnaire. EF recovery was defined as an IIEF–EF of ≥22. Kaplan–Meier analyses assessed the impact of preoperative IIEF–EF, depression and adjuvant radiotherapy (aRT) on the time to EF recovery. Multivariable Cox regression models were used to test the impact of aRT on EF recovery after accounting for depression and baseline IIEF–EF.

Results: Median follow-up was 48 months. Patients with a preoperative IIEF–EF of ≥22 had substantially higher EF recovery rates compared with those with a lower IIEF–EF (P <0.001). Patients with a CES-D of <16 had significantly higher EF recovery rates compared to those with depression (60.8 vs 49.2%; P=0.03). Patients receiving postoperative aRT had lower rates of EF compared with their counterparts left untreated after surgery (40.7 vs. 59.8%; P <0.001). These results were confirmed in multivariable analyses, where preoperative IIEF–EF (P <0.001), depression (P =0.04) and aRT (P =0.03) were confirmed as significant predictors of EF recovery.

Conclusions: Preoperative functional status and depression should be considered when counseling PCa patients regarding the long-term side effects of BNSRP. Moreover, the administration of aRT has a detrimental effect on the probability of recovering EF after BNSRP. This should be taken into account when balancing the potential benefits and side effects of multimodal therapies in PCa patients.

Disparities (Continued from page 5)

Tasquinimod Fails to Extend Overall Survival in Prostate Cancer Trial
Tasquinimod significantly improved radiographic progression-free survival (rPFS) but showed no overall survival (OS) benefit in a trial involving chemotherapy-naïve men with metastatic castration-resistant prostate cancer (mCRPC).

As a result, the drug is no longer being developed for this patient population by Active Biotech, which funded the trial.

“The rPFS alone would not move this forward from a regulatory perspective, and so further development in prostate cancer has been discontinued,” stated Dr. Michael Carducci, of the Johns Hopkins University School of Medicine, in Baltimore MD.

Dr. Carducci and colleagues conducted a randomized (Continued on page 8)
P1, Can ‘Smarter Use…” Despite all the controversy over PSA testing, clinicians are continuing to look for strategies that can shift the risk/benefit ratio making testing more appropriate. Preston and co-workers looked at PSA data from men in their 40s and 50s and then were assessed for prostate cancer over a 30 year observational period. The PSA value strongly correlated with later development of prostate cancer. Having a PSA less than 1.0 ng/mL resulted in a very low likelihood of eventually developing prostate cancer. A high percentage of the lethal cancers occurred in men above the median PSA level for their age group. Unfortunately, death from prostate cancer still occurred in some men with a PSA level below the median. Although the concept is appealing, it has many problems. It could result in many men getting biopsies and ultimately treatment because their PSA was above the median. Sadly, without a prospective study, this approach cannot be properly evaluated and the risk/benefit ratio cannot be accurately determined.

The Bottom Line: Risk stratification for PSA testing is well worth investigating, however, unless proper studies are done there is no way to really know if the effort does more good than harm.

P1, “Study Confirms Active…” Another long-term study of active surveillance (AS) provides some additional data about the safety of this approach. The PRIAS study has been following men with only 107 men having data beyond 7.5 years. Thus far, mortality has remained low and of those eventually undergoing radical prostatectomy (RP), one-third had unfavorable pathology. Almost half the men who discontinue AS do so not because of worsening disease but rather due to other reasons. What does all this mean? Unfortunately, the data from this study is still too immature to really know the long-term risk. Optimal follow-up evaluation is still evolving. PSA does not appear to be a good parameter for deciding about getting definitive therapy. How often a biopsy is done, whether it should be done using MRI, and what pathological changes are clearly indicative of more dangerous disease are still unresolved questions. Work is continuing and likely will yield helpful information. Two things are clear. First, AS can be done with a very low risk, and second, some men still will lose out because treatment occurs too late.

The Bottom Line: Data continues to accumulate about the relative safety of AS as a reasonable treatment option for many men with low-risk prostate cancer.

P1, “Single PSA Cut Point…” What PSA level indicates recurrent disease following RP? That is the basis of the study by Karnes et al. who looked at a large cohort of men from a single institution. They found that the best PSA cutoff was greater than 0.4 ng/mL. This is important because many men found to have lower levels are likely to be concerned and often undergo additional therapies even though no studies have clearly shown that undergoing those therapies at such low PSA levels translates into improved survival. This finding does need to be confirmed from other groups of patients but it can provide some useful information for men with a measurable PSA above 0.15 ng/mL that treatment is not always necessary unless it exceeds 0.4 ng/mL.

The Bottom Line: PSA levels less than 0.4 ng/mL after RP may not pose real risk to survival and immediate therapy may not be necessary.

P2, Use of the Cell Cycle…” A rising PSA after RP presents patients and doctors with a real challenge. Is treatment necessary and, if so, is radiotherapy (RT) the right selection? Clearly, some men will have cancer in the prostate bed alone while others may have it elsewhere or in both places. Salvage RT offers a small benefit because many men who get it probably were not ideal candidates. The report by Koch et al. is important because they found that a high cell cycle progression score (CCP) could separate patients into those with more advanced disease. If confirmed with other studies, this test could be used to identify those men most likely to benefit from RT.

The Bottom Line: CCP scores may prove useful for selecting men for RT when they have a rising PSA after RP.

P2, Mutations Suggest New…” Gene mutations may play an important role in progression on prostate cancer in men with biomarker positive compared to biomarker negative patients. We are hearing more about the potential to perform genetic testing on patients with cancer to separate them into different groups that may respond to specific therapies. Using this approach, Nelson and co-workers used a PARP inhibitor olaparib and found a high response rate in men with this genetic marker present. These drugs inhibit the enzyme poly ADP ribose polymerase that is involved in DNA repair. More data are clearly needed but the concept has great potential.

The Bottom Line: Genetic testing may help to separate patients into potential candidates for specific therapies but more data are needed.

P6, Bipolar Androgen…” It would be very interesting to have a conversation with Dr. Charles Huggins, the founder of castration therapy for prostate cancer about the concept of bipolar androgen therapy (BAT), which is giving testosterone after a period of androgen deprivation therapy (ADT). The idea is that ADT has increased androgen receptor (AR) expression making for a paradoxical effect with testosterone stimulation. Schweizer and co-workers tested this hypothesis in a group of men that had been given three-month intervals of ADT and testosterone. Treatment started when the PSA was less than 4.0 ng/mL. They found that 17/29 men had a low PSA after 18 months. The critical question is what exactly does this mean? Were they really helped? That is unclear because they did not measure objective outcomes or survival. Also, they did not report men dropping their PSA as a result of this therapy, only maintaining a low PSA. Therefore it remains uncertain whether they have impacted on the disease itself. Perhaps more data will follow.

The Bottom Line: BAT is a curious concept that needs much greater evidence of a clinical benefit for patients before widespread adoption.
Tasquinimod Fails to Extend Overall Survival (Continued from page 6)

phase 3 trial involving 1,245 men (median age, 71) with mCRPC recruited between 2011 and 2012 at 241 sites in 37 countries.

They randomized men 2:1 to receive tasquinimod (N=832) or placebo (N=413), administered orally at a starting dose of 0.25 mg/day for at least two weeks. If patients tolerated the drug, they escalated to 0.5 mg/day for two weeks, then to 1 mg/day.

Patients who didn’t tolerate the drug could remain in the study at their maximum tolerated dose. They continued treatment until symptomatic disease progression or until poor tolerability.

Patients continued follow-up after treatment ended, with visits every three months or until 727 patients reached the survival endpoint.

Median follow-up was about 30 months in both groups as of the cutoff date of February 13, 2013; 96.1% of patients had discontinued therapy by then, most often for radiographic progression, which occurred in 396 (48%) patients in the tasquinimod group and 258 (62%) patients in the placebo group.

The researchers estimated median rPFS, the primary endpoint, to be 7.0 months for tasquinimod and 4.4 months for placebo, they report in the Journal of Clinical Oncology, online June 13.

However, at final analysis for overall survival, the secondary endpoint, 492 (59.1%) deaths had occurred in the tasquinimod group compared to 238 (57.6%) in the placebo group. Overall survival was 21.3 months with tasquinimod and to 24.0 months with placebo (p=0.25).

More tasquinimod patients discontinued treatment because of adverse events, mostly decreased appetite, fatigue, asthenia, or nausea; 27.6% of tasquinimod patients and 23.6% of placebo patients experienced at least one serious adverse event, mostly renal and urinary disorders, infections/infestations, and blood/lymphatic system disorders.

“The data suggest this single-agent small molecule with potential immunologic/antivascular effects does not extend survival, and with a number of active drugs in this space, further development plans would be limited and risky,” Dr. Carducci told Reuters Health.

Active Biotech announced plans earlier this year to develop tasquinimod for the treatment of multiple myeloma. Several authors reported financial ties to the company, including employment. Reuters Health Information 23 June 2016