No Increase in Overall Survival in Metastatic CRPC with Ipilimumab

Study Did Show, However, Increases in PFS and PSA Rates

Treatment with ipilimumab does not extend overall survival in asymptomatic or minimally symptomatic men with metastatic castration-resistant prostate cancer (mCRPC), investigators have found. The study did, however, show an increase in progression-free survival (PFS) and in PSA response rates in one of the patient subsets.

The study, led by Tomasz M. Beer, MD, chair of Prostate Cancer Research at the Knight Cancer Institute of Oregon Health & Science University, was published online in the Journal of Clinical Oncology. Beer and his colleagues pointed out that while treatment advances in prostate cancer have been made with the introduction of several novel therapeutic agents, the prognosis and long-term outcomes for men with CRPC need to be improved.

Consequently, the team wanted to evaluate the use of ipilimumab, a monoclonal G1 antibody that increases antitumor-cell responses by binding to cytotoxic T-

lymphocyte antigen 4, in men with chemotherapy-naïve mCRPC without visceral metastases.

In a multicenter, double-blind, phase III trial, 399 men were treated with ipilimumab at 10 mg/kg and 199 with placebo every three weeks for up to four doses, followed by ipilimumab at 10 mg/kg or placebo maintenance therapy every 12 weeks for non-progressing patients. The primary endpoint of the trial was overall survival (OS).

At the time of the primary OS

Largest Series to Date Finds HIFU Effective for Localized Prostate Cancer

Hemiablation with high-intensity focused ultrasound (HIFU) appears to be an effective treatment for men with unilateral localized prostate cancer, and preserves erectile function and continence in most patients, according to a new report. The multi-center study in 111 men is the largest study of HIFU-hemiablation published to date, with the longest follow-up, stated Dr. Pascal Rischmann of Rangueil University Hospital in Toulouse, France. The findings were published online October 7, 2016 in European Urology.

“Active surveillance (AS) is the preferred option for men with low-risk disease and radical prostatectomy (RP) is indicated for high-risk patients, but options for prostate cancer patients who fall in between have been limited,” Dr. Rischmann noted.

Focal treatment with HIFU for men with localized disease offers the option of “sparing the prostate without burning the bridge for other treatments,” he explained. “If this management fails, you can do RP if the patient is not too old, and if he is older, then you can do radiation (RT).”

The French Urological Association initiated the new study, which was conducted in 10 different French centers from 2009 to 2015. Control biopsies were available for 101 of the 111 study participants. Average follow-up was 30.4 months.

Among the men with a control biopsy, at one year after treatment, 95% had no clinically significant cancer in the treated

(Continued on page 4)

Custirsen Shows No Survival Benefits in Metastatic Prostate Cancer

A phase III randomized controlled trial of custirsen in combination with cabazitaxel/prednisone in men with previously-treated metastatic, castration-resistant prostate cancer (mCRPC) has shown no significant survival gains compared to cabazitaxel/prednisone alone, according to data presented at the European Society of Medical Oncology (ESMO) 2016 Congress held in Copenhagen. Custirsen blocks production of clusterin, a protein known to be involved in carcinogenesis and tumour growth, as well as contributing to treatment resistance.

“Despite the negative outcome of the trial, the evaluation of custirsen in prostate cancer was conducted on the basis of solid preclinical and clinical evidence supporting anti-tumour activity,” said principal investigator Professor Karim Fizazi, head of the Department of Cancer Medicine at the Institut Gustave Roussy, Villejuif, France.

A previous phase II trial of custirsen combined with chemotherapy in mCRPC suggested clusterin inhibition may lead to improved clinical outcome, and an earlier phase III trial of custirsen combined with docetaxel suggested men with more aggressive cancers may benefit from the combination.

In the AFFINITY trial, 635 men with mCRPC – previously treated with docetaxel–
National Trends in Prostate Biopsy and Radical Prostatectomy Volumes Following the United States Preventative Services Task Force Guidelines against Prostate-Specific Antigen Screening

JAMA Surg. 2 November 2016; Epub

Key Points:
Question: What are the downstream effects of the 2012 US Preventive Services Task Force (USPSTF) recommendation against PSA screening on practice patterns in prostate cancer diagnosis and treatment?

Findings: Among operative case logs from a nationally representative sample of urologists, prostate biopsy and radical prostatectomy (RP) volume decreased by 28.7% and 16.2%, respectively, following the 2012 USPSTF recommendation.

Meaning: These findings represent the downstream effects of the USPSTF recommendation.

Importance: Studies demonstrate that use of PSA screening decreased significantly following the USPSTF recommendation against PSA screening in 2012.

Objective: To determine downstream effects on practice patterns in prostate cancer diagnosis and treatment following the 2012 USPSTF recommendation.

Biases in Recommendations for and Acceptance of Prostate Biopsy Significantly Affect Assessment of Prostate Cancer Risk Factors: Results from Two Large Randomized Clinical Trials

Tangen CM, Goodman PJ, Till C, et al.
J Clin Oncol 7 November 2016; Epub

Purpose: To identify factors related to who undergoes a prostate biopsy in a screened population and to estimate the impact of biopsy verification on risk factor–prostate cancer associations.

Patients and Methods: Men who were screened regularly from the placebo arms of two large prostate cancer prevention trials (Prostate Cancer Prevention Trial [PCPT] and Selenium and Vitamin E Cancer Prevention Trial [SELECT]) were examined to define incident prostate cancer cohorts. Because PCPT had an end-of-study biopsy, prostate cancer cases were categorized by a preceding PSA/digital rectal examination (DRE) prompt (yes/no) and non-cases by biopsy-proven negative status (yes vs. no). We estimated the association of risk factors (age, ethnicity, family history, body mass index, medication use) with prostate cancer and quantified differences in risk associations across cohorts.

Results: Men 60 to 69 years of age, those with benign prostatic hyperplasia, and those with a family history of prostate cancer were more likely, and those with a higher body mass index (≥25), diabetes, or a smoking history were less likely to undergo biopsy, adjusting for age and longitudinal PSA and DRE. Medication use, education, and marital status also
Doc Moyad’s What Works & What is Worthless Column, Also Known As “No Bogus Science” Column

“Glucosamine and Chondroitin supplements could have anti-cancer or anti-inflammatory effects? I WHAT THE _______ I!”

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:
New research from Memorial Sloan Kettering and Harvard and other top-notch (aka “groovy”) medical centers suggests that glucosamine and chondroitin supplements together may have anti-inflammatory properties, and could also reduce the risk of certain cancers such as colorectal cancer from a very large U.S. prospective study of health care professionals!1 Wow! However, the fact that these supplements do NOT appear to increase the risk of ulcers or heart attacks or high blood pressure or even heart failure is why I am so darn excited about these supplements! What?

I like to laugh (aka “chuckle like a clown”) when I hear arthritis “experts” bash some of the low-cost arthritis dietary supplements explaining that they have some mild or moderate evidence and, in some studies, do not work as well as a placebo. Meanwhile, they ignore some of the more interesting clinical trial research that suggests they might slow the progression of arthritis and/or that they have been found to be overall VERY SAFE in clinical trials. That is the point! That is the point that gets MISSED AND DISMISSED (I capitalize for emphasis and attention). The “experts” do not mention the extreme “catch” with the conventional options. I am a big fan of drugs when needed but painkillers are killing and damaging too many in the U.S. and around the world. For example, opioid drugs are the number 1 cause of unintentional drug overdose that leads to death in the U.S. Also, acetaminophen (e.g., Tylenol) is the number 1 cause of acute liver failure in the U.S. Plus, other over the counter (OTC) painkillers, including ibuprofen, are now associated with increases in heart failure (per FDA), heart attacks, high blood pressure, ulcers, etc., even with short-term use. So, if you can find anything that can reduce chronic dependence on high or regular doses of painkillers, then this is a good thing right? For example, weight loss is one of the best ways to reduce the dependence on and dosage of pain killers for arthritis, but as much negativity as I hear about whether or not supplements work for osteoarthritis, I never hear of serious toxicity associated with these dietary supplements such as glucosamine and chondroitin.

Now, in one of the largest credible databases in the U.S., the combined use of glucosamine and chondroitin supplements was “associated with a statistically significant, 23% reduced risk of colorectal cancer.” This finding was also found in some other observational studies. Laboratory evidence supports a potential anti-inflammatory impact of these supplements including the potential to reduce TNF-alpha, IL-6, COX-2, C-reactive protein (CRP), etc. Preliminary lab studies show the ability of these ingredients to suppress prostate cancer growth.2,3 Do I really believe glucosamine and chondroitin prevent and fight cancer? I HAVE NO IDEA! If I were that smart I would be making big money accurately guessing the weights and birthdates and marital fidelity of people at the local carnival, instead of volunteering all the time for cancer newsletters. Again, I think it is amazing that some “experts” that bash these supplements somehow consider them a failure if they cannot beat a prescription or over the counter pain killer for pain relief. They fail to realize that this weakness is also their greatest strength, which is their safety along with some mild to moderate efficacy! And now they are being associated with other health benefits, so today is a wonderful and beautiful day in the Moyad world! This is a world of cheap, effective supplements, objectivity when it comes to drugs and supplements, lifestyle changes when needed, and oh, free beer Monday through Friday and on Saturday and Sunday only 365 days a year!!! Go Cubs (not sure if I mean it, but the headquarters of Us TOO are Chicago-area based, so I thought I would suck up to them so they still like me because I am insecure)!

References:

Exercise Training Improves Quality of Life for Prostate Cancer (PCa) Patients

Investigators led by Riccardo Valdagni, MD, PhD, and Lara Bellardita, PsyD, PhD, of the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, Italy, conducted a systematic review of randomized controlled trials (RCTs) testing lifestyle interventions, such as diet or exercise, for PCa patients. They identified 17 RCTs published 2003 to 2015 involving 1,989 men (aged 65 to 74) from seven countries. Quality of life (QoL) was the main endpoint and was assessed by various tools, such as the generic Short Form 36 Health Survey (SF-36) and the disease-specific Functional Assessment of Cancer Therapy-Prostate scale (FACT-P).

Due to study heterogeneity, meta-analyses could not be performed. Eight studies involved men undergoing androgen deprivation therapy (ADT) – for whom exercise is recommended to reduce adverse effects, three radiation therapy, and one each active surveillance, radical prostatectomy, and radiation plus ADT. The remaining studies included different active treatments. Control groups received standard care or active monitoring. The quality of the evidence was strongest for exercise interventions, which lasted four weeks up to eight years and were supervised by exercise physiologists, specialists, or kinesiotherapists, according to results published in the journal Oncology Hematology. The findings on dietary or combined interventions were less robust, although cutting calories potentially reduces body mass index and thereby improves QoL.

In most studies on physical activity, resistance exercises, (Continued on page 6)
**Ipilimumab Not Beneficial (Continued from page 1)**

analysis, all men had been followed for two years, 83% for three years, and 26% for four years. The median OS was 28.7 months (95% confidence interval [CI], 24.5 to 32.5 months) in the ipilimumab arm compared with 29.7 months (95% CI, 26.1 to 34.2 months) in the placebo arm (Hazard Ratio [HR], 1.1; 95% CI, 0.88 to 1.39; P=0.37). OS was 78% (95% CI, 73% to 82%) at one year in the men receiving ipilimumab and 85% (95% CI, 79% to 89%) in men on placebo; 56% (95% CI, 51% to 61%) and 61% (95% CI, 54% to 68%) at two years; and 41% (95% CI, 36% to 46%) and 40% (95% CI, 32% to 47%) at three years. The median PFS was 5.6 months (95% CI, 5.3-6.3 months) in the ipilimumab arm compared with 3.8 months (95% CI, 2.8-4.1 months) in the placebo arm (HR, 0.67; 95.87% CI, 0.55-0.81). The study also found a higher PSA response rate with ipilimumab (23%) than with placebo (8%).

“Multiple and not easily quantifiable factors may have contributed to the discordant observation of an improvement in median PFS without a significant difference in median OS between study arms,” Beer and colleagues wrote. “These include an insufficient level of antitumor activity in an unselected patient population; an unfavorable effect of AEs [adverse events] or co-morbidities in an older patient population; the type, dose, time of initiation, and duration of subsequent therapies; or other unknown factors.”

A safety analysis found that any-grade treatment-related AEs occurred in 82% of men who received ipilimumab and 49% of men who received placebo. The most common treatment-related AEs (observed in >10% of ipilimumab patients) were diarrhea (43%), rash (33%), pruritus (i.e., itching, 27%), fatigue (24%), nausea (19%), decreased appetite (16%), vomiting (11%), and asthenia (i.e., weakness, 10%). Serious grade 3 or 4 treatment-related AEs occurred in 27% of ipilimumab-treated patients, and 2% of patients in the placebo arm. Diarrhea was the only grade 3/4 treatment-related AE reported in ≥ 10% of the ipilimumab-treated patients. Nine deaths occurred in the ipilimumab arm due to treatment-related AEs, while none occurred in the placebo arm.

“The biggest takeaway [from the study] is that ipilimumab used in unselected patients did not produce a clinical benefit for patients overall,” Beer said in an interview with MedPage Today. “I do think if we better understand which patients harbor tumors that are more responsible to a drug like ipilimumab, it might be possible to demonstrate a clinical benefit, but in unselected patients we just were not able to see that.”

As for the current state of research in the area of prostate cancer immunotherapy, Beer said that while there have been some failures, there has also been a notable success in the development of sipuleucel-T (Provenge).

“It’s a vibrant field,” he added, pointing out that he and his colleagues recently reported in Oncotarget the results of a small pilot study evaluating the anti-PD-1 antibody pembrolizumab in mCRPC patients: “The early results were quite compelling, showing clinical activity of PD-1 inhibition in prostate cancer. This demonstrates continued progress in this area.”

**Custirsen Shows No Survival Benefits in mCRPC (Continued from page 1)**

were randomized to 21-day cycles of custirsen plus cabazitaxel/prednisone or cabazitaxel/prednisone plus placebo, until disease progression, unacceptable toxicity, or 10 treatment cycles.

Researchers saw no significant difference in overall survival (OS) between the custirsen and placebo arms of the study, with a median overall survival of 14.2 and 13.4 months, respectively (p=0.529). The same was observed in the 62% of men who met the criteria for poor prognosis, where median OS was 11.1 and 10.9 months in the custirsen and placebo groups, respectively.

Similar numbers of men in each arm discontinued treatment due to progressive disease – 28.9% in the custirsen arm and 25% in the placebo arm – while 21.9 and 18.9% of men treated with custirsen and placebo, respectively discontinued due to adverse events. The most frequently reported serious adverse events were neutropenia, anemia, fatigue, asthenia (weakness), bone pain, and neutropenia with fever.

“I am obviously disappointed with the results but am proud to have been involved in this program, and we will take the learnings of this trial to advance our knowledge of the disease in the hope to further advance care,” Fizazi said. “Custirsen remains a viable candidate currently being evaluated for the treatment of non-small cell lung cancer, as failure in one tumour type does not predict the outcome of trials in other indications,” he added.

Commenting on the study, Dr. Cora Sternberg, Chief of the Department of Medical Oncology at San Camillo Forlanini Hospital in Rome, Italy, said, “A number of approaches have been investigated to overcome resistance in prostate cancer, including the use of novel taxanes and tubulin inhibitors, and the inhibition of cell survival pathways.”

“Given the results observed using a taxane either as first-line or second-line chemotherapy in CRPC, the hypothesis remains that combination with custirsen may decrease taxane resistance and enhance the survival benefit of taxane therapy,” Sternberg said. “There was a strong rationale for adding custirsen to chemotherapy to overcome resistance but unfortunately the final results were negative. We likely need even more robust biological molecular stratification before launching phase III trials,” Sternberg concluded.

**Attention Veterans!**

Check out our new **Veterans Resource Page** on the Us TOO website:

[www.ustoo.org/Military-Veterans](http://www.ustoo.org/Military-Veterans)

Let us know what you think, what you like, and what you would add at veterans@ustoo.org.
New Prostate Cancer Screening Algorithm Proposed

Investigators have proposed a new approach to prostate cancer (PCa) screening in which a PSA level of 1.5 ng/mL or higher should prompt primary care physicians, who order most PSA screening tests, to consider referring patients to a urologist for further evaluation. Men who have a PSA below 1.5 ng/mL would have a routine follow-up PSA test in five years.

“In our algorithm, we recommend that a biopsy should not be performed unless the risk of an aggressive tumor is significant, and following a thorough discussion of benefits and risks with the patient,” the investigators, led by E. David Crawford, MD, of the University of Colorado, Denver, wrote in *Urology* (Vol. 96, pp. 116-120, 2016). “These discussions should emphasize that the purpose of screening is the early identification of potentially lethal disease, and that in most cases low-risk tumors, if identified, do not require immediate treatment.”

Under their proposed new approach, primary care physicians (PCPs) would refer to urologists those men who have a PSA level of 1.5 ng/mL or higher or abnormal digital rectal examination (DRE) results. Urologists would then explore possible causes for elevated PSA or abnormal DRE results, including PCa, benign prostatic hyperplasia, and prostatitis.

For men suspected of having PCa, urologists would consider ordering genomic tests such as the Prostate Health Index, 4Kscore, or SelectMDx assays. Men deemed to be at a high risk for aggressive cancer would be considered for a high PORTOS (n=196), among men with a high PORTOS (n=39), those who had RT had a lower incidence of distant metastasis than did men who did not have RT, with a 10-year metastasis rate of 5% (95% confidence interval [CI] 0-14%) in men who had RT (N=20) and 63% (34-80%) in men who did not have RT (N=19; hazard ratio [HR] 0.12 [95% CI 0.03-0.41], p <0.0001), whereas among men with a low PORTOS (N=157), those who had postoperative RT (N=78) had a greater incidence of distant metastasis at 10 years than did their untreated counterparts (N=79; 57% [44-67%] vs. 31% [20-41%]; HR 2.5 [1.6-4.1], p <0.0001), with a significant treatment interaction (pInteraction=0.0001). The finding that PORTOS could predict outcome due to RT was confirmed in the validation cohort (N=330), which showed that men who had RT had a lower incidence of distant metastasis compared with those who did not have RT, but only in the high PORTOS group (high PORTOS [N=82]: 4% [95% CI 0-10%] in the RT group [N=57] vs. 35% [95% CI 7-54%] in the no RT group [N=25]) had metastasis at 10 years; HR 0.15 [95% CI 0.04-0.60], p=0.0020; low PORTOS [N=248]: 32% [95% CI 19-43%] in the RT group [N=108] vs. 32% [95% CI 22-40%] in the no RT group [N=140]; HR 0.92 [95% CI 0.56-1.51], p=0.76), with a significant interaction (pInteraction=0.016). The conventional prognostic tools Decipher, CAPRA-S, and microarray version of the cell cycle progression signature did not predict response to RT (pInteraction>0.05 for all).

**Interpretation:** Patients with a high PORTOS who had postoperative RT were less likely to have metastasis at 10 years than those who did not have RT, suggesting that treatment with postoperative RT should be considered in this subgroup. PORTOS should be investigated further in additional independent cohorts.

HIFU & Localized PCa

(Continued from page 1)

lobe, while 93% were free from clinically significant cancer in the untreated lobe. Mean PSA was 6.2 ng/mL at baseline and 2.3 ng/mL at two years after treatment. Radical-treatment-free survival was 89% at two years. The radical treatments included six RPs, three RTs, and two HIFUs. Thirteen percent of men had grade 3 adverse events. At one year, 97% of men had preserved continence, while 78% had preserved erectile function, and there was no decrease in quality of life at one year. Ten U.S. centers offer HIFU for prostate cancer, Dr. Rischmann noted, but second-generation HIFU technology is not yet available in the U.S. The device used in the study, the Focal One from EDAP TMS, makes it possible to evaluate treatment during the procedure using contrast-enhanced ultrasound, he said.

Rischmann et al conclude: “The efficacy of HIFU partial prostate gland therapy should be evidenced by comparative studies conducted vs. standards of care.”

*Reuters Health*
21 October 2016
Prostate Specific Antigen Failure and Risk of Death within Comorbidity Subgroups among Men with Unfavorable-Risk Prostate Cancer Treated in a Randomized Trial


Purpose: Physicians sometimes make management recommendations on the basis of early results from randomized controlled trials (RCTs) relating to reduced PSA failure (PSAF), yet whether this early end point is associated with all-cause mortality (ACM), particularly in men with competing risks, is unknown. Using a validated metric in men treated within the context of an RCT, we aimed to determine whether PSA failure is associated with the risk of ACM stratified by comorbidity score.

Patients and Methods: Between 1995 and 2001, 206 men with localized (T1b to 2b) intermediate- and high-risk prostate cancer (PC) were randomly assigned to receive radiation therapy (RT) or RT and six months of androgen deprivation therapy (ADT). Cox regression analyses were performed to evaluate whether PSAF modeled as a time-dependent covariate was associated with an increased risk of ACM among men with Adult Comorbidity Evaluation-27-defined no or minimal vs. moderate-to-severe comorbidity after adjusting for age, PC prognostic factors, and treatment.

Results: After a median follow-up of 16.62 years, 156 men (76%) died, 29 of whom (19%) died as a result of PC. PSAF was associated with an increased ACM risk among men with no or minimal (adjusted hazard ratio [aHR], 1.59; 95% confidence interval [CI], 1.03 to 2.46; P=0.04), but not moderate or severe comorbidity (aHR, 1.75; 95% CI, 0.76 to 3.99; P=0.19).

Conclusion: Recommending treatment on the basis of reduced PSAF observed from early results of RCTs is unlikely to prolong survival in men with moderate-to-severe comorbidity but may prolong survival in men with no or minimal comorbidity, providing evidence to support discussing the early results with these men.

Impact of Androgen Deprivation Therapy on Overall Mortality in Prostate Brachytherapy Patients with Low Pretreatment Testosterone Levels


To evaluate whether the use of androgen deprivation therapy (ADT) in prostate brachytherapy patients impacts overall mortality (OM) in men with lower pretreatment serum testosterone (ST) levels compared with those with normal or high baseline ST.

From October 2001 to May 2014, 1,916 men underwent brachytherapy and had a pretreatment ST prospectively before initiation of therapy. Median follow-up was 7.2 years. In total, 26% of the men received ADT, primarily men with higher risk disease. OM and prostate cancer-specific mortality (PCSM) were examined to determine whether men with lower baseline ST were at increased risk of mortality when ADT was used, compared with men without ADT.

New Algorithm (Continued from page 5)

transrectal ultrasound-guided prostate biopsy. Men at a low risk for aggressive cancer would be referred to their PCPs for repeat PSA testing in one year.

This algorithm is similar to one that is used for an elevated blood sugar, where an abnormal result triggers another test, such as an A1C hemoglobin test, the investigators stated.

PCPs, who order approximately 90% of PSA screening tests, are confused about the messages they receive regarding PSA, Dr. Crawford’s group stated. “We believe that a simple message using a PSA cutoff of 1.5 ng/mL is reflective of what PCPs often experience with conditions such as mild hypertension and pre-diabetes,” they wrote. “In this paper, we have presented an alternative approach in which screening is performed for men with at least a 10-year life expectancy.”

Previous research has shown that men with a PSA level of 1.5 ng/mL or higher at a younger age are at increased risk for the development of any PCa and significant PCa later in life. Dr. Crawford’s group cited a 2011 study by Hans Lilja, MD, and colleagues showing that approximately 5% of men who had a PSA value of 1.5 ng/mL or higher when blood was drawn at ages 44 to 50 years will be found to have advanced PCa 20 to 25 years later.

The investigators also reported data from BioReference Laboratories, Inc., that demonstrated that approximately 30% of men aged 45 to 70 years have a PSA level of 1.5 ng/mL or above.

Renal & Urology News, 19 October 2016

Exercise Training (Continued from page 3)

such as weightlifting for six months, significantly improved patients’ quality of life, along with mood, fatigue, physical functioning, and sexual functioning. For example, a 2009 study by Segal, et al. found that resistance training provided lasting benefits compared with aerobics involving walking, jogging, or cycling. In addition, a 2007 study by Monga, et al. found that an eight-week cardiovascular exercise program for men with localized PCa treated with radiation improved cardiovascular fitness, flexibility, muscle strength, fatigue, and quality of life.

“...[E]xercises where the body’s musculature has to work against some type of resistance should be particularly proposed for PCa patients,” according to Drs. Valdagni and Bellardita, and colleagues. “Resistance training based on improving muscles strengths was also shown to have positive effects on mood and physical functioning of healthy older men.”

Patient motivation is a key aspect for the success of any program, the investigators noted. They encouraged additional research, especially quality studies on age-based exercise programs.

References:
Renal & Urology News, 26 October 2016
P1, “Largest Series...” The study by HIFU is a good example of the problem with making conclusions in the absence of strict outcome data. Rischmann et al. reported the results of a multi-center trial involving 111 men treated with HIFU hemiablation. With an average followup of only 30 months, 5% had “clinically significant cancer” on repeat biopsy in the treated lobe; however a biopsy was not performed in 10% of the men. In terms of side effects, 22% reported loss of erections at one year. The authors conclude that “hemiablation with high-intensity focused ultrasound (HIFU) appears to be an effective treatment for men with unilateral localized prostate cancer.” The problem here is that their conclusion is based on too short an analysis and an outcome that has questionable value. Is keeping men from more aggressive therapy really a useful measure of a treatment, especially without knowing if it results in a worse outcome than doing immediate therapy? Another weakness is that 7% had clinically significant cancer in the untreated lobe, so the authors did not prove that treating only one lobe is a valid approach.

The Bottom Line: The value of treating only one lobe in men with prostate cancer is completely unknown and this study does not support its use at this time.

P1, “No Increase in Overall...” Ipilimumab is a monoclonal antibody that increases anti-tumor cell responses. In phase II studies, patients appeared to develop a positive response. Consequently phase III trials were initiated. Unfortunately, the results of a recent randomized phase III trial comparing this drug to placebo in men with castrate-resistant metastatic disease found no increase in survival at one, two or three years, and a higher incidence of severe side effects. Importantly, progression-free survival was improved, which again points out the problem with overly interpreting the value of a progression-free response with any new therapy. Other studies are in progress using this drug in combination with other therapies and may yet show a survival benefit. For now, however, this drug is not worthwhile in men with this stage of disease.

The Bottom Line: Ipilimumab does not improve survival in men with metastatic castrate resistant prostate cancer.

P1, “Custirsen Shows No...” Custirsen is a drug that blocks the production of clusterin, a protein that helps cancers survive. Phase II studies have demonstrated a benefit but no evidence of improving survival. Now the results of randomized phase III trial found no improvement in survival in men with recurrent metastatic disease being treated with cabazitaxel and prednisone. This is yet another reason why randomized trials are needed; because using anything less than survival as a definitive outcome may lead to incorrect conclusions about the value of a new drug.

The Bottom Line: Custirsen does not improve survival in men with recurrent metastatic disease who are receiving cabazitaxel.

P2, “National Trends in...” Previous studies have determined that the detection of prostate cancer has declined following the USPSTF recommendation against routine screening in 2012. Although it is too early to know the long-term impact, one might expect that eventually the mortality from this disease might increase. Until that information is available, we are likely to see various measures of what has been changing. The report by Halpern et al. provides further evidence for some of this change. They observed a drop in prostate biopsies and a drop in radical prostatectomies since 2012. However, caution is needed in interpreting these data. One reason is that we do not know whether the decision to do a biopsy changed either because of the use of genetic markers, more restrictive criteria based on age and health, or the use of different PSA criteria. Also, we do not know from this analysis whether the detection of prostate cancer declined significantly. As for the drop in radical prostatectomies, that might be explained by greater use of active surveillance, as has been strongly recommended for low-risk cancers or by an increase in treating men by methods other than radical prostatectomy. As we often say, time will tell whether the net balance of harms and benefits is changing because of the task force’s recommendations.

The Bottom Line: It is too early to determine whether the change in guidance by the USPSTF has been good or bad for society.

P5, New Prostate Cancer...” Can a better approach to screening be undertaken that lowers morbidity while increasing benefit? That is the aim of the report by Crawford, et al. who is proposing a modified algorithm. It starts with doing a PSA and then considering further evaluation for men if the value is greater than 1.5 ng/mL. The reason is that men with a lower PSA have an extremely low likelihood of harboring a dangerous cancer and most, but not all, cancer deaths occur in men with a PSA above that value. The problem is that we have no idea yet of the implications of this approach. Will it save lives? How many men will be treated without benefit? How many men will still die of the disease? Without a formal randomized study, this suggestion puts us back to where we were when PSA was discovered; recommendations are being made without really knowing the consequences. Without a proper study, the US Preventive Services Task Force is unlikely to embrace this suggestion at this time and, without some proper study, it is unclear how men can be adequately counseled.

The Bottom Line: A new algorithm for screening based on evaluating only men with a PSA above 1.5 ng/mL requires definitive data from a randomized trial to know whether it is a worthwhile endeavor.

P5, “Development and...” Randomized studies have shown that postoperative radiation after radical prostatectomy can significantly improve survival in men with a high risk for recurrence. Unfortunately, only 1/9 men benefit, meaning the vast majority are treated (Continued on page 8)
Years ago, studies found that men with metastatic disease who had a low serum testosterone had a lower survival following androgen deprivation therapy compared to those with a normal testosterone. Taira, et al. recently conducted a similar analysis in men receiving brachytherapy and found a similar result; those men with an abnormally low serum testosterone had a worse overall survival and higher prostate cancer mortality compared to men with a normal or elevated testosterone. Is this enough to make a treatment decision going forward? Ideally, a properly conducted study would be undertaken but until that is done it would not be unreasonable to limit ADT to those men with a normal or high testosterone.

**The Bottom Line: A low testosterone level in men receiving brachytherapy may be a reason to avoid ADT because of a lower likelihood of responding.**

**Low Testosterone**

(Continued from page 6)pared with men with baseline normal or higher testosterone. PCSM and OM at 10 years was 0.8% and 22.0%. Age, tobacco use, diabetes, cardiovascular disease, and percent positive biopsies were the strongest predictors of OM. ADT use by itself was not associated with an increased risk of OM on multivariate analysis (P=0.695). However, ADT use in men with lower baseline testosterone was associated with a significantly higher risk of OM (P<0.01). ADT use in men with normal or higher baseline testosterone was not associated with an increased OM risk (P=0.924).

Men with lower baseline testosterone may be at increased risk of premature death when ADT is utilized compared with men with baseline normal or higher testosterone. Further analysis of this potential risk factor is warranted to further identify subsets of men who may be at higher risk of long-term adverse sequelae from ADT.

**Biases in Biopsies**

(Continued from page 2) influenced who underwent biopsy. Some risk factor estimates for prostate cancer varied substantially across cohorts. Black (vs. other ethnicities) had odds ratios (ORs) that varied from 1.20 for SELECT (community screening standards, epidemiologic-like cohort) to 1.83 for PCPT (end-of-study biopsy supplemented with imputed end points). Statin use in SELECT provided an OR of 0.65 and statin use in PCPT provided an OR of 0.99, a relative difference of 34%.

**Conclusion:** Among screened men enrolled in prostate cancer prevention trials, differences in risk factor estimates for prostate cancer likely underestimate the magnitude of bias found in other cohorts with varying screening and biopsy recommendations and acceptance. Risk factors for prostate cancer derived from epidemiologic studies not only may be erroneous but may lead to misdirected research efforts.

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**Doctor Chodak’s Bottom Line**

(Continued from page 7) unnecessarily. Consequently, efforts are underway to separate the responders from the non-responders. One such effort uses a 24-gene analysis to generate a postoperative radiation therapy outcome score or PORTOS. Using this method, Zhao et al. analyzed men who were from one of five non-randomized trials. They found that a high PORTOS score correlated with a significant reduction in the development of metastatic disease from postoperative radiation, whereas those with a low score did not do better with radiation. This method has important potential value if confirmed in a prospective randomized trial. Hopefully those studies will be forthcoming.

**The Bottom Line:** A 24-gene analysis may be able to identify those men most likely to benefit from postoperative radiation.

**P6, “Impact of Androgen...”**

Years ago, studies found that...