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Us TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

July 2008

HIGHLIGHTS FROM THE 2008 ANNUAL MEETINGS OF THE AMERICAN UROLOGICAL ASSOCIATION (AUA) AND AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)

NEW ANALYSIS BOOSTS FINASTERIDE'S PROSTATE CANCER VALUE

A new analysis of data from a key prostate cancer study strengthens the view that finasteride, formerly sold as Proscar® but now available generically may be a valuable weapon to prevent prostate cancer, researchers reported last month at the 2008 AUA meeting. The initial results of that study were announced in 2003.

The extensive reanalysis of the data showed that finasteride reduced a man's risk for developing prostate cancer by about 30 percent. That compares to the initial finding that it reduces the risk by about 25 percent.

Initially, researchers cautioned that men developing prostate cancer on finasteride were more likely to have high-grade cancers that could theoretically spread quickly even if tumors were small. But the new analysis showed that the drug may actually reduce the risk of high-grade tumors, said Dr. Ian Thompson, lead investigator from the University of Texas Health Sciences Center at San Antonio, Tx.

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ACTIVE SURVEILLANCE STILL VIABLE FOR SOME PROSTATE CANCERS

During 30 months of follow-up, the need for intervention could be predicted by characteristics of the first and second biopsy, Scott E. Eggener, MD, of the University of Chicago, said at the American Urological Association (AUA) meeting held in Orlando, FL. Specifically, the number of positive cores in the first and second biopsies and the finding cancer in the second biopsy identified men with an increased likelihood of stopping surveillance favoring treatment, Dr. Eggener said.

"Every single day patients come to doctors' offices wondering whether they need treatment, whether they should be subjected to the side effects of treatment, which can be with them for decades," Dr. Eggener said in an interview. "This is just another piece of data to use when counseling them. For highly select patients, active surveillance seems to be a safe, reasonable, feasible option, but doctors need to know there is a low but real risk of dangerous progression," he added.

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ADJUVANT RADIATION SHOWS PROMISE FOR HIGH-RISK SURGERY PATIENTS

Adjuvant radiation significantly reduces the risk for biochemical recurrence in men with advanced (pT3) disease, according to the latest data from Southwest Oncology Group trial 8794, a significant, long-term study.[1]

"This is an answer we've been waiting for a very long time," presenter Gregory P. Swanson, MD, associate professor of radiation oncology, urology and radiology at the University of Texas Health Science Center at San Antonio, TX told Medscape Urology. The randomized study hypothesized that adjuvant radiotherapy improves disease-free survival in patients with surgical stage C (T3N0M0) carcinoma of the prostate. The primary end point was metastasis-free survival.

"We asked ourselves, for high-risk patients after surgery, can we do something more?" Dr. Swanson said. "The benefit of radiation after surgery is not a new concept for oncologists — it's a new concept for urologists. But the long-term benefit was un-

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KENNEDY HAS MAJOR CANCER BILL IN SENATE

Kennedy had already begun work on an overhaul of the 1971 National Cancer Act when his tumor was diagnosed, and advocates hope the fact that he fell victim to this disease will generate public support and lend new urgency to the need to update the bill.

"People think of Ted Kennedy as a fighter and as someone who has always been there for everyone," said Daniel E. Smith, president of the American Cancer Society Cancer Action Network, the American Cancer Society's advocacy arm. "The fact that he now is fighting this disease is a jolt. It's a wake-up call to everyone." The 76-year-old has been a prominent and passionate advocate of cancer research and other health care issues throughout his long tenure in the Senate.

He's been instrumental in promoting biomedical research, AIDS research and treatment, a national bone marrow donor registry and anti-tobacco bills. "With his legacy in health care, this could be an incredible crowning achievement for him," said Hala Moddelmog, a breast cancer survivor and president and CEO of the cancer-fighting foundation Susan G. Komen for the Cure. "I really think people will rally behind it, I really do. I think they already were starting to - and this will just bring it home to people."

Kennedy, who worked closely with Republican Sen. Kay Bailey Hutchison of Texas, plans to file the legislation in the coming weeks, an aide said. The bill seeks to improve coordination of cancer research, prevention and treatment while giving more money to the National Cancer Institute and other public research agencies.

Kennedy's family has been touched by cancer over the years - two of his children, Kara and Edward Kennedy Jr., are cancer survivors. The senator threw himself into their care, finding the best medical advice and treatment options for them.

A few weeks ago, Kennedy and Hutchison teamed up with cancer survivor Lance Armstrong at a Senate hearing and a news conference calling on Congress and the country to step up

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PROSTATE CANCER VACCINE LINKED TO IMPROVED SURVIVAL IN SMALL TRIAL

About half the patients had increased PSA doubling time and about 70% had anti-PSA T-cell responses associated with tumor destruction, reported David Lubaroff, PhD, of the University of Iowa in Iowa City. No patient had a vaccine-related adverse event. "We've evaluated the vaccine in only a small number of patients, but at this point, we are very encouraged," said Dr. Lubaroff at the 2008 American AUA meeting held in Orlando, FL.[1] Dr. Lubaroff reported that 55% of the 32 patients in the study outlived nomogram-predicted survival. The increase in survival after a single vaccine dose ranged from two months to 47 months.

Immunization with an anti-PSA vaccine has been hypothesized to have more potency compared with active nonspecific or adoptive/passive immunotherapy. In previous studies, the adenovirus/PSA vaccine induced a stronger anti-PSA response than did other viral PSA vaccines. Moreover, incorporation of a collagen matrix into the vaccine enhanced the anti-PSA immune response.

"Immunization of mice with the adenovirus/PSA vaccine in matrix can induce anti-PSA responses even in the presence of high-titer antiadenovirus antibodies," said Dr. Lubaroff. "This is significant because most humans have pre-existing levels of antiadenovirus antibodies as a result of prior natural exposure to the virus."

A total of 32 patients with stage D2/D3 prostate cancer received vaccine doses of 106 to 108 plaque-forming units/mL. All patients had disease progression following first- and second-line therapy. They were randomized to receive the vaccine in aqueous suspension or in the collagen matrix suspension. At the two lowest dose levels, three patients each received the aqueous or matrix formulation. Ten patients each received the highest dose of the aqueous or matrix formulation. Patients were evaluated at 24 hours, 14 and 21 days, and at two, four, eight, and 12 months after vaccination.

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KENNEDY

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the fight against cancer. The events were aimed at building support for the bill. "This is personal for all of us," said Armstrong, who has worked closely with Kennedy on the bill. When Kennedy's diagnosis was revealed, Armstrong said renewing the fight against cancer would be a good way to honor the senator.

"The timing of this news comes just as Sen. Kennedy is leading the creation of bipartisan legislation to renew the fight against a killer that claims more than 560,000 American lives every year. And in honor of Sen. Kennedy, the time for a national call to action in the war against cancer is now."

NewDx Digest, 28 May 2008

FINASTERIDE PREVENTION

(Continued from page 1)

Researchers also concluded the cancer cases finasteride prevented were "clinically significant" in that they were the same type that are currently treated with radiation or surgery.

"Conceivably, every man when he turns 55, if prostate cancer is of concern to him -- if he's having the PSA checked on a regular basis -- his doctor probably should at least tell him that he can reduce his risk by about 30 percent by taking finasteride," Thompson said in a telephone interview.

The new analyses released at the 2008 Annual AUA meeting in Orlando, FL were recently published in the journal *Cancer Prevention Research*.

The study involved 18,882 men with an age of 55 and up who did not have prostate cancer when the research began. One group was given finasteride and the rest were given a placebo for seven years to see whether or not the drug prevented the disease.

"I wish I had known then what I know now because it would have been a home run when it was first published, and when the drug was not generic. Unfortunately, now the drug is generic, so there's nobody to actually take the drug to the FDA (US Food and Drug Administration for approval for prostate cancer prevention)," Thompson said.

Reuters, 19 May 2008

AMGEN REPORTS POSITIVE DATA AT ASCO FOR DENOSUMAB IN CANCER PATIENTS

Amgen (NASDAQ: AMGN) today announced results from two denosumab studies concerning prostate cancer patients. A Phase 2 study of metastatic patients previously treated with IV bisphosphonates found that denosumab normalized a key marker of bone resorption at a significantly greater rate than that seen with continuation of IV bisphosphonates, and also patients receiving denosumab experienced fewer skeletal-related events (SREs). A separate retrospective analysis comparing the results of this study to another Phase 2 study of patients never treated with an IV bisphosphonate revealed that the effect of denosumab on bone turnover markers was similar regardless of previous exposure to bisphosphonates. These results were presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO).

Phase 2 Data of Patients Previously Treated with IV Bisphosphonates

The study evaluated patients whose urinary N-telopeptide (uNTx) levels had not normalized despite treatment with IV bisphosphonates. The primary endpoint of patients with uNTx <50 at week 13 was achieved by 71 percent of patients in the denosumab arms compared with 29 percent in the IV bisphosphonate arm ($p<0.001$). In addition, denosumab induced suppression of uNTx levels faster than IV bisphosphonate (9 days versus 65 days, respectively).

At week 25, denosumab treatment was associated with fewer on-study SREs (8 percent) than were seen in those receiving IV bisphosphonate therapy (20 percent). Skeletal-related events include fractures, radiation or surgery to bone, and spinal cord compression.

The adverse event profile of denosumab was similar to that of advanced cancer patients receiving treatment, and balanced across treatment arms. The most common adverse events included bone pain, nausea, anemia, constipation, and asthenia. No neutralizing anti-denosumab antibodies were observed.

"Skeletal-related events can be a devastating complication of bone metastases," said Karim Fizazi, M.D., Ph.D., Head of the Department of Medical Oncology, Institut Gustave-Roussy, Villejuif, France. "Elevated markers of bone resorption are routinely accepted indicators of poor outcomes for our advanced cancer patients. So it was encouraging to see that in this study, denosumab was able to further suppress bone turnover in patients previously on bisphosphonates, and that denosumab patients also reported fewer skeletal-related events."

Comparison of Phase 2 Data on Bone Turnover Markers of IV Bisphosphonate-Treated Versus Bisphosphonate-Naïve Patients

In a comparison of the effect of denosumab on bone turnover markers in

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'EQUIVOCAL' ANTIOXIDANT EFFECTS IN CANCER THERAPY

While some studies have shown antioxidants can reduce the occurrence of clinically significant side effects, there is also evidence they can lead to lower tumor control, according to Brian Lawenda, MD of the Naval Medical Center San Diego, and colleagues. Until the safety issue is sorted out, oncologists and patients should be leery of the combination of radiation (RT) or chemotherapy with antioxidants, Dr. Lawenda and colleagues wrote online in a commentary in the *Journal of the National Cancer Institute*.[1] "Without strong safety data, it should be discouraged," Lawenda said, adding he and his colleagues have urged more research on the question.

The difficulty is that RT and some forms of chemotherapy -- e.g., anthracyclines and platinum-based agents, act by creating free radical damage in tumor cells. Antioxidants prevent or reduce such damage. But the extent and effect of the possible interactions of various drugs, RT regimens and antioxidants has not been clearly defined, they said.

Dr. Lawenda and colleagues studied published randomized clinical trials in which antioxidants were used with either form of cancer treatment. Generally, they said, the trials were small but a few of those that tested RT plus antioxidants had several hundred patients and one had 1,451. That study, reported in 2006, was a meta-analysis of 14 randomized controlled trials testing the antioxidant amifostine (Ethyol®) in patients with various cancers. The analysis showed significant reductions ($P<0.001$) in a range of side effects, including a 63% reduction in the risk of developing mucositis and an 85% reduction in the risk of acute pneumonia. At the same time, there was no difference in control rates, Lawenda and colleagues said.

On the other hand, a 2005 study randomized 540 RT patients with head and neck cancer to get placebo or the antioxidant α-tocopherol, with or without the antioxidant β-carotene. Those who received both antioxidants had a 38% reduction in severe, acute side effects, which was significant at $P<0.05$, the researchers said. But the benefit was coupled with reductions of 29% and 56% in local tumor control rates for α-tocopherol and α-tocopherol plus β-carotene, respectively.

All told, researchers found 9 studies testing RT with and without antioxidants and found data from a limited number of them that suggests antioxidants during RT decreases tumor control and shortens survival. Researchers found 16 trials of antioxidants with chemotherapy, the largest of which had 250 patients. But because most of the studies were small, it was difficult to draw definitive conclusions either way, the researchers said.

The key clinical message, Dr. Lawenda said, is that doctors and their patients need to communicate about the use of antioxidants, especially because many such compounds are readily available and are widely publicized as having cancer-fighting benefits. "We're saying to patients to be very careful about information coming out of the lay press," he said. And doctors, for their part, should be careful to ask patients about their antioxidant use and counsel them about the state of the science.

1. *Lawenda BD, et al. J Natl Cancer Inst 100: 773-83, 2008.*

MedPage Today, 27 May 2008

EXTERNAL BEAM RADIATION FOR PROSTATE CANCER HIKES RISK OF SECONDARY CANCERS

Naeem Bhojani, MD, of the University of Montreal, Canada and his colleagues studied 10,333 men treated with external beam radiation therapy (EBRT, 4,137 patients) or radical prostatectomy (6,196 patients) and identified men subsequently diagnosed with secondary malignancies. They identified 92 bladder cancers, 82 lung cancers, and 228 rectal cancers. After adjusting for age, baseline comorbidities, and year of treatment, EBRT predisposed to a threefold higher rate of bladder cancer and a nearly twofold higher rate of lung and rectal cancer.

"The increased rate of secondary malignancies after EBRT should be considered in localized prostate cancer treatment decision-making," they conclude.

Renal & Urology News, 23 May 2008

ADJUVANT RT

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known. The only way to answer this was a randomized study."

Eligible patients had clinical stage A or B (T1 or T2) cancer confined to the prostate, or clinical stage C (T3N0M0) cancer outside the prostate, with at least 1 of the following factors: seminal vesicle involvement, cancer inked surgical margin, or extension beyond prostatic capsule. Patients were randomized within 16 weeks of surgery.

Of the 431 patients enrolled, 425 were eligible. Half the eligible patients ($n = 214$) were given radiation and half ($n = 211$) received no treatment. The untreated group consisted of 67% white and 20% African American men, and had a median age of 65.8 years. The group receiving treatment had a median age of 64.1 years and consisted of 72% white and 19% African American.

The primary end point was positive. Radiation significantly reduced recurrence by all parameters and increased metastatic disease-free and overall survival. At 15 years out, metastasis-free survival was 49% in the treated group and 40% in the untreated group ($P = 0.021$). "But that's not all," Dr. Swanson said. "With the survival curve, the P value was .031 and, at 15 years, 50% of radiation of patients had survived," compared with 39% of the untreated group. At 10 years, the percentage of those who did not have a relapse in PSA levels was 52% in the treated group and 26% in the untreated group. "Radiation really pushed that back," Dr. Swanson said.

Any downsides — the long-term effects of radiation — are minor, such as urinary and rectal irritation, which seem to improve over time, and a possible increase in urinary leakage or scarring, Dr. Swanson said.

Brantley Thrasher, MD, chairman of the department of urology at the University of Kansas, in Lawrence, who was not involved with the study, cautioned physicians who learn about the successes of adjuvant radiation not to overtreat patients. "People are asking about how pragmatic it is to treat everyone,'' Dr. Thrasher said. "Why not

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PSA TESTING MIGHT NOT BE NEEDED IN OLDER MEN

In fact, the probability of prostate cancer death and high-risk disease declined steadily in those men, Anna E. Kettermann, of Johns Hopkins, reported at the 2008 American Urological Association meeting.[1] In contrast, a PSA level of 3 ng/mL or greater was associated with an increased probability of developing high-risk prostate cancer. "Men who have a PSA level below 3 ng/mL at age 75 to 80 are unlikely to develop aggressive prostate cancer during their remaining life, and for these men, PSA testing might be safely discontinued," said Kettermann.

The findings came from an analysis of data on 849 participants in the Baltimore Longitudinal Study on Aging. Investigators calculated each man's probability of developing high-risk prostate cancer in five-year increments, beginning at ages 60 to 65, stratified by PSA cutoff points of <1 ng/mL to >3 ng/mL. High-risk prostate cancer was defined as death from prostate cancer, a PSA value greater than 20 ng/mL, or a prostate biopsy Gleason score of 8 or higher at diagnosis.

The study population comprised 727 men who did not have prostate cancer and 122 who did -- 35 had aggressive disease and 87 were alive with cancer or had died of other causes. The entire cohort had been followed for a median of 10 years, during which time they had a median of four repeat PSA tests. The median PSA level was 1.2 ng/mL in men who had high-risk prostate cancer, 1.3 ng/mL in those who had lower-risk prostate cancer, and 0.7 ng/mL in those who remained free of prostate cancer. Overall, 18 patients died of prostate cancer, and 17 others had high-risk disease. All 35 had PSA values that exceeded 3 ng/mL at some point during follow-up. None of the remaining 87 patients with lower-risk prostate cancer or those who remained free of prostate cancer had PSA levels that exceeded 3 ng/mL during follow-up.

"Our analysis showed that the probability of high-risk prostate cancer increased with PSA value," said Kettermann.

1. *Carter HB, et al. Urol 179(suppl): 600, 2008 (Abstract 1751).*

MedPage Today, 23 May 2008

DENOSUMAB

(Continued from page 3)

two Phase 2 trials, one trial involving patients previously treated with IV bisphosphonates versus a second trial involving patients not previously treated, denosumab was found to suppress bone resorption to a similar extent, regardless of prior bisphosphonate exposure. This side-by-side comparison of changes in serum-C telopeptide (sCTx), a marker of bone breakdown, from baseline to week 25, showed that at the six months time point, denosumab suppressed bone resorption by 85 percent in bisphosphonate-naïve patients compared with 80 percent in patients with prior exposure to IV bisphosphonates. In patients previously treated with IV bisphosphonates, denosumab suppressed bone resorption by 80 percent compared with 45 percent in patients who continued on IV bisphosphonates.

In this comparison, the incidence of serious adverse events was similar across treatment groups in both studies and events were consistent with a population of patients with advanced cancer, and patients treated with IV bisphosphonates.

"Because denosumab specifically targets RANK Ligand, we believe it works in a different way from other bone loss and destruction treatments," said Roger Dansey, MD, Global Development Leader for Denosumab Oncology at Amgen. "Results from the denosumab oncology program presented thus far are encouraging and we look forward to results from additional clinical trials in the bone loss and SRE settings."

The scientific information discussed in this news release related to Amgen's product candidates is preliminary and investigative. Such product candidates are not approved by the US FDA, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidates. Further, the scientific information discussed in this news release relating to new indications for products is preliminary and investigative and is not part of the labeling approved by the FDA for the products. The products are not approved for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

AMGEN news release, 31 May 2008

INTERIM PHASE 1/2 DATA OF IPILIMUMAB IN PROSTATE CANCER PRESENTED AT ASCO ANNUAL MEETING

Medarex, Inc. announced interim results from a Phase 1/2 trial of ipilimumab, an investigational oncology immunotherapy, as monotherapy or in combination with radiotherapy (RT) in patients with metastatic castration resistant prostate cancer (mCRPC). Data presented showed that ipilimumab monotherapy or in combination with RT was clinically active and generally well-tolerated.

Preliminary evidence of anti-cancer activity showed that 21 percent of patients (7 of 33) experienced decreases in PSA serum levels of over 50 percent, with median duration of PSA responses of 4.8 months. This included one patient treated at the highest dose with a complete response (measured by both PSA and RECIST criteria) ongoing over one year. Two additional patients had PSA reductions of more than 30 percent within 12 weeks of treatment.

The interim results were described in an oral presentation by investigator Tomasz Beer, MD, the Grover C. Bagby Endowed Chair for Prostate Cancer Research and Associate Professor of Medicine from Oregon Health & Science University Cancer Institute, at the 2008 Annual ASCO meeting (Abstract #5004).

"These initial data in patients with metastatic castration resistant prostate cancer demonstrated preliminary antitumor activity, including durable response, and is suggestive of a safety profile at the optimal ipilimumab regimen similar to that observed in our melanoma program," said Geoffrey M. Nichol, MBChB, Senior Vice President of Product Development at Medarex. "Radiotherapy is routinely used for palliative treatment in patients with metastatic castration resistant prostate cancer and bone metastases, and these data encourage further exploration of the ability of tumor antigen release by RT to serve as an immune-supportive

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ACTIVE SURVEILLANCE

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To better define the clinical environment of active surveillance, investigators at 3 academic medical centers retrospectively reviewed prospectively collected data on 262 prostate cancer patients who had opted for active surveillance between 1991 and 2007. Men included in the analysis were 75 or younger, had clinical stage T1-2a cancer, a biopsy Gleason score of 6 or less, a PSA value of 10 ng/mL or less, 3 or fewer positive cores at initial diagnosis, at least 2 biopsies before the start of active surveillance, and no active treatment for at least 6 months after the second biopsy.

During a median follow-up of 29.7 months, 43 patients underwent primary treatment—either RP, radiation treatment or androgen deprivation therapy. Of the 43 patients who had primary treatment, 26 underwent RP. Of those, 13 had a Gleason score of 7 or greater, and 24 (92%) had organ-confined cancer. The actuarial probability of remaining on active surveillance was 95% at one year, 91% at two years, and 75% at five years.[1]

One man developed lymph node metastases and another had skeletal metastases after a 6-month PSA rise. The man with bone involvement had gone 3 years without a prostate biopsy.

"One of the basic tenets of active surveillance is that primary treatment can be delayed or even obviated," said Dr. Eggener. "When patients do undergo treatment, that treatment needs to be effective. If the treatment is not effective, you are failing the patients."

Factors associated with primary treatment revealed only 2 predictive factors: a greater number of positive cores on the first and second biopsy combined and cancer in the second biopsy.

"There is a low but very real risk of developing metastatic disease and losing the window of curability," said Dr. Eggener.

Limitations of the study noted by the authors included a short median follow-up and use of a non-standardized management strategy.

AUA abstract 183.

MedPage Today, 20 May 2008

PCA3 COULD BE USEFUL IN SELECTING PROSTATE CANCER PATIENTS FOR ACTIVE SURVEILLANCE

The urine test for the PCA3 gene, already marketed for use in diagnosing prostate cancer, could also be useful in prognostication. It might have clinical application in selecting men with low-grade and low-volume tumors who would be suitable candidates for active surveillance, say researchers writing in the May issue of the Journal of Urology (*J Urol* Vol. 179, pp 1804-8, 2008).

This latest study, by Hiroyuki Nakanishi, MD and colleagues from the University of Texas MD Anderson Cancer Center suggests that the test can be used to differentiate men who require immediate treatment for their prostate cancer from men who could be followed with active surveillance.

Dr. Nakanishi and colleagues investigated results from 96 men who underwent a radical prostatectomy. The results show a significant correlation between PCA3 level in urine before the operation and the severity of cancer that was found in the removed tissues.

The PCA3 score was significantly different in men having low-volume (less than 0.5 cc) and low-grade (Gleason score of 6) cancer than in men who were found to have significant cancer, the researchers report.

This latest study expands on previous work "in an important way," comments Leonard Marks, MD, from the Geffen School of Medicine at UCLA. Last year, Dr. Marks and colleagues reported that the test was useful in men with high PSA levels but negative biopsies. At that time, Medscape Oncology reported that PCA3 was shown to be useful in differentiating men who needed to undergo further biopsies from men who did not.

In an editorial comment that accompanies the new study, Dr. Marks said: "These results must be regarded as preliminary, but if they are validated in definitive trials, PCA3 testing could become an important tool to help us decide not only who should undergo biopsy, but also who should undergo treatment."

A second editorial comment from Adam Kibel, MD, from Washington University School of Medicine also emphasizes that further work is needed. Low PCA3 levels in urine correlated strongly with smaller tumors and a lower pathological Gleason score. "However, while these associations are extremely interesting and encouraging, it remains to be proven that patients with low PCA3 can be safely observed," he wrote. "Further analyses from "watchful-waiting" trials will be critically important before any marker, including PCA3, can be accepted as a marker for indolent prostate carcinoma.

But such a marker is needed, both editorialists agree, because a proportion of men have clinically indolent disease that does not require treatment.

Medscape, 12 May 2008

US TOO SEEKS BOARD MEMBER APPLICATIONS

Us TOO is pleased to announce the annual public call for nominations to the Us TOO International Board of Directors. The Board Membership Committee, chaired by Fred Mills, will review and evaluate nominees and submit recommendations to the full Board for approval at its December 2008 Board meeting.

Selection criteria includes items such as the candidate's relationship to Us TOO's purpose, its membership criteria ("…any man diagnosed with prostate cancer, a member of such a man's family or significant other, or any person involved in or interested in support or treatment of any such patients…"), familiarity with an Us TOO chapter, ability to think globally, skills or experience deemed beneficial to the work of Us TOO and commitment to Us TOO's purpose and mission.

Letters of nomination with a vita or resume should be sent by August 31, 2008 to Thomas Kirk, President/CEO, Us TOO International, 5003 Fairview Avenue, Downers Grove, IL 60515 or e-mail tom@ustoo.org.

GRASSLEY'S WAR ON CANCER PATIENTS—EDITORIAL

The news did not make it to the front pages, but on February 28th a powerful member of the U.S. Senate launched an attack on the Food and Drug Administration, the drug companies and the desperate cancer patients they treat.

Charles Grassley (R., Iowa), ranking member of the Senate Finance Committee, requested that the Government Accountability Office launch an inquiry into whether the FDA behaved appropriately in granting the "accelerated approval" of Avastin, a drug for treating women with metastatic breast cancer. Mr. Grassley's action will have a catastrophic effect on America's ability to develop new drugs.

At issue is the concept of "surrogate endpoints" and the FDA's "accelerated approval" regulations. In the 1980s, at the height of the AIDS epidemic, AIDS activists were livid at the slow pace of development of new drugs to fight HIV. They lobbied heavily for changes in the law to allow an expedited pathway for the approval of new drugs for any disease deemed serious or life-threatening. The historic results were new laws and regulations that created an accelerated approval mechanism by which a drug could be allowed on the market if it showed early evidence of an effect on a surrogate endpoint.

For cancer, examples of surrogate endpoints are tumor shrinkage or a delay in the disease's progression. This kind of measurement – as opposed to an assessment of a drug's impact on a patient's overall survival – has dramatically increased the pace of cancer clinical trials. It also has won near-universal acceptance within the cancer community. The FDA does require follow-on studies to assure that surrogate findings show clinical benefit. But if all cancer clinical trials were required to show a survival benefit from the get-go, progress in cancer-drug development would slow to an absolute crawl.

Enter Mr. Grassley. It seems not a week goes by without him making a public accusation of evil doings within the drug industry or the FDA. Yes, Mr. Grassley did some good after the Vioxx® episode, by focusing on the woeful manner in which postmarketing drug safety is managed and regulated by the FDA. But he and his staff should have kept their eyes on the ball. In the case of Avastin, the senator implied in his GAO request that something sinister occurred during the FDA's premarket deliberations, and that surrogate endpoints were the new bogeyman. Nothing could be further from the truth.

In February, the FDA approved Avastin® despite a 5-4 vote by its Oncology Drugs Advisory Committee (ODAC) not to recommend approval. Meetings of this advisory committee address the most vexing issues that exist in cancer-drug development. The advice is usually helpful but never binding. Everyone who works at the FDA knows that the public only sees a fraction of what FDA insiders consider when they make their final decisions on products.

In the case of Avastin, additional data emerged late in the review process, after the ODAC meeting, that strongly supported accelerated approval. It became clear that Avastin had an enormous impact on the surrogate endpoint known as "progression-free survival." PFS is such a powerful measure that it is actually used as the basis for full approval in many cancer indications.

As part of the accelerated approval letter, the FDA also placed some of the most stringent postmarketing requirements in history for the drug's sponsor to gain full approval. No standards were lowered, and many women may now live much longer without their disease progressing.

The damage done by Mr. Grassley's decision to make an issue of this decision cannot be understated. Having served at the FDA during the Congressional hearings over the Imclone/ Martha Stewart insider trading scandal, I can attest to how an action like this GAO inquiry will resonate within the halls of FDA. An extremely cautious and protective bureaucracy will respond to such intimidation by being even more protective.

The senator is demanding a full-scale review of each and every product ever approved, and is asking for a rejudgment by GAO "to ensure that drugs approved on surrogate endpoints are both safe and effective."

You can bet these bully tactics will have an effect. Look for greater demands by the FDA for cancer programs to not use the accelerated approval pathway. Just a few weeks ago, Medarex Inc. announced that the FDA will renege on a commitment to grant accelerated approval of a new product for skin cancer if its clinical trial showed benefit using the PFS endpoint. The FDA ordered a change toward the much stricter endpoint of overall survival, adding years to the time it will take to evaluate the drug's efficacy.

U.S. cancer-drug development stands on a precipice overlooking a new dark age in which each new product's development is longer and costlier than the last. Companies may decide it is not financially viable to even bother developing new drugs, and the pipeline for new products to treat cancer could slow even more. Mr. Grassley's legacy could be thousands of additional cancer deaths.

Advocates for all patients affected by Grassley's antidrug company demagoguery – including cancer patients, Alzheimer's patients and AIDS patients – must make their voices heard.

Dr. Thornton is a former medical officer in the Office of Oncology Products at the Food and Drug Administration. He volunteers as president of the Sarcoma Foundation of America.

Wall Street Journal, 29 May 2008

CANCER VACCINE

(Continued from page 2)

The patients' median age was 71, and their median PSA level at enrollment was 128 ng/mL. The patients were followed for a median of 12 months, and they had a median survival of 18 months. There were documented anti-PSA antibody responses in 34% of patients, anti-PSA T-cell responses in 68%, and an increased PSA doubling time in 46%. The most common adverse events were localized erythema/ ecchymoses (nine patients) and cold- or flu-like symptoms (five).

A phase 2 trial of the vaccine has already begun and will focus on efficacy in men with advanced prostate cancer.

1. Lubaroff DM, et al. J Urol 179(suppl): 184, 2008, abstract 526.

MedPage Today, 19 May 2008

IPILIMUMAB

(Continued from page 5)

intervention in combination with ipilimumab as a potentially important treatment option for these patients."

The Phase 1/2 trial was conducted to evaluate the safety and preliminary anti-tumor activity of escalating doses of ipilimumab (3, 5 or 10 mg/kg) every three weeks for up to four doses, with and without a single dose of focal RT administered to target bone lesion (s) prior to the first dose of ipilimumab. The dose escalation portion of the trial enrolled 33 patients with mCRPC and with bone metastases. Additional patients are enrolling in the expansion cohort of 10mg/kg ipilimumab in combination with RT.

Adverse events related to ipilimumab were generally manageable and consistent with immune-related adverse events (irAEs) previously reported in other clinical trials of ipilimumab. Grade 3/4 events included diarrhea/colitis (5 patients), rash (1 patient) and elevated liver enzymes (2 patients). No new patterns or frequency of adverse events emerged in patients receiving the combination of ipilimumab and RT.

PRNewswire/FirstCall, 2 June 2008

ENTHUSE (ENDOTHELIN A USE) TRIAL NOW OPEN

AstraZeneca has opened a new Phase III trial program of an investigational endothelin A (ETA) receptor blocker for hormone resistant prostate cancer (HRPC). Phase II results support further studies of its effectiveness in men with advanced prostate cancer.

The study drug specifically targets ETA receptors (not ETB receptors) and may inhibit tumor cell proliferation and survival and blocks formation of new blood vessels and bone metastases. Phase III trials that are now recruiting in the US will test the drug as monotherapy and in combination with chemotherapy against non-metastatic and metastatic disease. The Phase III trial program, ENTHUSE (ENDOTHELIN A USE), is open to men with:

- HRPC metastatic to bone with mild or no symptoms and rising serum PSA levels (n=580);
- Non-metastatic HRPC with rising serum PSA levels (n=1500); and
- Progressive, metastatic HRPC with rising PSA levels where docetaxel therapy is indicated (n=1044).

Go to <www.clinicaltrials.gov> and search for the key word "ENTHUSE" for more information about these trials.

ADJUVANT RT

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wait on a very low-level PSA bump? That is always going to be an argument on [trial] 8794." With 30% to 40% of patients, the cancer won't recur — without any treatment, said Dr. Thrasher, who recommended waiting for that slight "bump" in PSA before treatment. "These are compelling data, don't get me wrong, but I am not treating everyone," he said.

But Ian M. Thompson, MD, lead investigator and chair of the department of urology at the University of Texas Health Science Center at San Antonio, called the study findings a "homerun." "To improve survival by almost 2 years is extreme." Thompson said. "This is really a remarkably big deal."

Funding was provided by a grant from the National Cancer Institute. The researchers have disclosed no relevant financial relationships.

1. *Presented May 20, 2008 at the AUA Annual Meeting in Orlando, FL*

Medscape, 20 May 2008

Editor's note: An earlier study presented at the ASCO GU Symposium showed that the rate of PSA rise after biochemical recurrence related to success of adjuvant RT.

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