

The Genitourinary Cancers Symposium

February 2-4, 2012

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Society of Urologic Oncology

– PRESSCAST TUESDAY, JANUARY 31, 12:00 PM ET –

Research From the 2012 Genitourinary Cancers Symposium Highlights New Treatments, Compares Existing Therapies for Prostate Cancer

ALEXANDRIA, Va. – Research on promising new therapies and data on the relative benefits of established treatments for prostate cancer were released today, in advance of the fourth annual Genitourinary Cancers Symposium, being held February 2-4, 2012, at the San Francisco Marriott Marquis in San Francisco, Calif.

The results of five studies were highlighted in a media presscast (press briefing via live webcast):

- [*Vigorous Exercise Linked to Expression of Certain Genes in Early-Stage Prostate Cancer*](#): A study shows that men with early-stage prostate cancer who exercise vigorously at least three hours a week have more than 180 genes that are expressed differently in the prostate than those who did not exercise as intensively. These genes include known tumor suppressor genes and DNA repair pathways, suggesting a number of potential mechanisms by which vigorous exercise may help delay cancer progression, as prior studies have shown.
- [*IMRT Better Than Conformal Radiation Therapy for Reducing Prostate Cancer Recurrence and Side Effects, May Also Be Superior to Proton Beam Therapy*](#): A large comparative effectiveness study shows that men with localized prostate cancer who are treated with intensity modulated radiation therapy (IMRT) are less likely to experience cancer recurrence or significant side effects from treatment than those who receive conventional conformal radiation therapy (CRT). The analysis also found that proton beam therapy, a newer and more costly form of radiation treatment, did not significantly improve outcomes compared to IMRT.
- [*External Beam Radiation Leads to Most Side Effects, Highest Costs of Three Common Prostate Cancer Treatments*](#): An analysis of more than 100,000 prostate cancer patients shows that treatment with external beam radiation therapy (EBRT) resulted in higher long-term toxicities and treatment-related costs than prostatectomy and brachytherapy, two other common treatments for the disease.
- [*Novel Investigational Drug Targeting Bone Metastases Improves Survival for Metastatic Prostate Cancer*](#): A randomized, phase III trial shows that a new radiation-emitting agent aimed at treating bone metastases both improved survival and delayed cancer-related bone problems in men with castration-resistant prostate cancer (CRPC). The agent, radium-223 chloride, is the first alpha particle emitting agent targeting bone metastases shown to improve survival in metastatic CRPC.

– More –

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- [*Study Shows New Targeted Drug Improves Overall Survival in Metastatic Prostate Cancer*](#): An international, randomized phase III trial shows for the first time that an investigational oral drug that halts androgen signaling significantly improves overall survival in patients with metastatic castration-resistant prostate cancer.

“It’s gratifying that two of the presentations reported today provide us with new options to improve survival for patients with advanced castrate-resistant prostate cancer, an especially difficult disease with few effective treatments,” said Nicholas J. Vogelzang, MD, Chair and Medical Director of the Developmental Therapeutics Committee of US Oncology, who moderated today’s presscast. “Just as importantly, today’s studies will help guide our use of several established treatments in the field, ensuring that more patients receive the best possible therapies while avoiding unnecessary side effects and costs.”

Genitourinary cancers include those of the prostate, kidney, bladder and testis, as well as less common cancers such as those of the penis, ureters and other urinary organs. In 2012, more than 390,000 people in the United States are expected to be diagnosed with genitourinary cancers, with more than an estimated 58,000 deaths. The most common genitourinary cancer is prostate cancer, which according to estimates, will be diagnosed in more than 241,000 men in the United States in 2012, and claim more than 28,000 lives.¹

The Genitourinary Cancers Symposium is co-sponsored by the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO) and the Society of Urologic Oncology (SUO).

More information for media: www.asco.org/GUpresskit

Relevant Links From [Cancer.Net](#), the oncologist-approved cancer information website from the American Society of Clinical Oncology:

- [Guide to Prostate Cancer](#)
- [Understanding Radiation Therapy](#)
- [Managing the Cost of Cancer Care](#)
- [Survivorship](#)
- [Late Effects](#)
- [Bone Health During Cancer Treatment](#)
- [Physical Activity and Cancer Risk](#)

¹ American Cancer Society, Cancer Facts and Figures 2012

**General Poster Session C
Friday, February 3, 2012
12:15 PM - 01:45 PM PT**

**Senior Author: June Chan, MD
University of California
San Francisco, CA**

Study Links Vigorous Exercise with Expression of Certain Genes in Early-Stage Prostate Cancer

A study shows that men with early-stage prostate cancer who exercise vigorously at least three hours a week have more than 180 genes that are expressed differently in the prostate gland than those who did not exercise as intensively. These genes include known tumor suppressor genes and DNA repair pathways, suggesting that a better understanding of the molecular effects of exercise may guide development of strategies to prevent or delay cancer progression.

“We previously reported that prostate cancer patients who exercise tend to fare better after a diagnosis of prostate cancer, and now we are trying to understand why,” said senior author June Chan, ScD, associate professor, epidemiology and biostatistics and urology, and the Steven and Christine Burd-Safeway Distinguished Professor at the University of California, San Francisco. “These preliminary findings give us several good leads on which molecular mechanisms may be influenced by physical activity and involved in prostate cancer progression and should be studied more closely in a larger scale study. We hope such data can be used to identify new gene signatures that predict progression and prognosis, which would have a broad impact on many aspects of prostate cancer care.”

In two separate studies last year, Chan and her colleagues reported links between exercise, especially vigorous activity or a brisk walking pace, and a lowered risk of disease progression and death among men with prostate cancer. Physical activity has been reported to offer benefits for other cancers as well, including breast and colorectal cancer. To explore potential molecular mechanisms behind this protective effect, the researchers examined possible correlations between exercise and prostate gene expression patterns in men with low-risk prostate cancer who were undergoing “active surveillance,” rather than active treatment. They used data on gene expression from normal prostate tissue samples in 70 men obtained from an earlier study that had examined the effects of nutritional supplements on the normal prostate. As part of that study, the men completed a questionnaire about their exercise habits, including the amount and intensity of exercise.

The investigators observed 184 significant genes that were expressed differently between those men who participated in more vigorous exercise – such as jogging, tennis or lap swimming – for at least three hours a week and those who reported less intense physical activity, such as walking at any pace. Genes that were more highly expressed in the vigorous activity group included both well-known tumor suppressor genes associated with breast cancer, *BRCA1* and *BRCA2*. Greater expression of molecular pathways involved in cell cycle and DNA repair were also observed in the group participating in more versus less physical activity.

“This was a small study with provocative findings that should be interpreted cautiously and warrant confirmation in a larger study. These preliminary data suggest that DNA repair in the prostate gland is one mechanism through which vigorous physical activity may protect against prostate cancer progression, and there are potentially more,” Chan said. “If our findings are substantiated, and we can determine which molecular differences really matter for disease recurrence, then these signals could be used to improve monitoring of prostate cancer and its response to any intervention.”

Chan’s team hopes to confirm its findings in a larger group of men on active surveillance, as well as examine the effects of physical activity among men who have already experienced cancer recurrence. The investigators are also collaborating to develop new patient education strategies that reinforce the value of physical activity and other healthy lifestyle practices that may improve prostate cancer outcomes.

Abstract #189

Title: Physical activity and prostate gene expression in men with low-risk prostate cancer.

Authors: Mark Jesus Mendoza Magbanua, Erin L Richman, Eduardo V Sosa, Lee Jones, Jeffrey Simko, Katsuto Shinohara, Christopher M. Haqq, Peter Carroll, June M. Chan; University of California, San Francisco, San Francisco, CA; Duke University Medical Center, Durham, NC

Background: Physical activity (PA), in particular longer duration or higher intensity, may reduce the risk of PCa progression and PCa-specific mortality in men diagnosed with clinically localized PCa. However, the molecular mechanism(s) by which PA exerts its protective effect in the prostate remains unknown. We examined the correlation of PA and gene expression patterns in men with low risk prostate cancer who elected to undergo active surveillance.

Methods: Morphologically normal prostate tissue was obtained from men who subsequently participated in a clinical trial focused on nutritional supplements (previously published microarray dataset #GSE27140). Of the original sample (n=84), 70 completed a brief PA questionnaire and were dichotomized based usual PA [e.g. any vigorous PA (yes/no), 3+ h/wk vigorous PA (yes/no)]. Differential expression and pathway (gene set) analyses between groups were performed using Significance Analysis of Microarrays. Genes and gene sets with a false discovery rate ≤ 0.10 and 0.20 were considered significant, respectively.

Results: Gene expression analysis detected 184 significant genes that were differentially expressed between men who performed vigorous PA for 3+ h/wk (n=23) and those who did not (n= 47). Up-regulated genes included the known tumor suppressors, *BRCA1* and *BRCA2*. Furthermore, pathway analysis revealed that cell cycle and DNA repair pathways were positively modulated in men who participated in 3+h/wk vigorous PA vs. not. Consistent with the data on vigorous PA and clinical outcomes in men with PCa, the duration of vigorous PA was important; there were no significant genes detected when comparing men who participated in any vigorous PA to men who did none.

Conclusions: Prostate gene expression and pathway analyses revealed candidate genes and in vivo pathways that may be modulated by participating in 3+ h/wk of vigorous PA. These data provide mechanistic insight into how 3+ h/wk of vigorous PA may offer PCa-specific benefits. Furthermore, understanding the molecular mechanisms by which such PA affects normal prostate gene expression may aid the development of strategies to prevent or delay PCa progression.

Disclosures: Nothing to disclose.

**Oral Abstract Session A
Thursday, February 2, 2012
1:15 PM - 03:05 PM PT**

**Senior Author: Ronald Chen, MD
University of North Carolina
Chapel Hill, NC**

Large Study Suggests IMRT Is Better Than Conventional Conformal Radiation Therapy for Reducing Prostate Cancer Recurrence and Side Effects, May Also Be Superior to Proton Beam Therapy

A large comparative effectiveness study shows that men with localized prostate cancer who are treated with intensity modulated radiation therapy (IMRT) are less likely to experience cancer recurrences or significant side effects from treatment than those who receive conventional conformal radiation therapy (CRT). The analysis also found that a more costly form of radiation treatment, called proton beam therapy, did not significantly improve outcomes compared to IMRT. This study is the first to comprehensively examine the comparative outcomes of patients with prostate cancer treated with these three types of radiation therapy.

“Patients and doctors are often drawn to new treatments, but there have not been many studies that directly compare new radiation therapy options to older ones,” said senior author Ronald Chen, MD, MPH, assistant professor of radiation oncology at the University of North Carolina (UNC) at Chapel Hill and Research Fellow at the Sheps Center for Health Services Research at UNC. “In the past 10 years, IMRT has largely replaced conventional conformal radiation therapy as the main radiation technique for prostate cancer, without much data to support it. This study validated our change in practice, showing that IMRT better controls prostate cancer and results in fewer side effects.”

Comparative effectiveness research is designed to help clinicians and patients make more informed treatment decisions and may also influence the future adoption of new therapies and technologies in medicine overall.

IMRT is a more advanced form of radiation that enables doctors to shape and vary the intensity of the radiation field, delivering an increased radiation dose to the tumor and sparing more nearby normal tissue than is possible with conventional conformal radiation therapy. In proton beam therapy, cancerous tumors are irradiated with high-energy particles called protons. The clinical effect of using protons compared to X-rays (which are used with CRT and IMRT) for prostate cancer is not completely understood, though proton beam radiation is often thought to be able to further spare normal tissue compared to X-rays

In the study, Chen and his team analyzed data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database of more than 12,000 patients with localized prostate cancer who were treated with conventional conformal radiation therapy, IMRT, or proton beam radiation from 2002 to 2007. They examined the proportion of patients who were diagnosed with radiation-related side effects after treatment, including gastrointestinal and urinary problems, erectile dysfunction and hip fractures. They also determined the proportion of patients in each group who required additional cancer treatments after radiation, using this as an indication of cancer recurrence.

The researchers found that after adjusting for demographic, disease and institutional characteristics, patients who received IMRT had fewer gastrointestinal problems diagnosed (rate ratio 0.91, meaning that IMRT reduced gastrointestinal problems by 9 percent) and fewer hip fractures (rate ratio 0.78, or a reduction of 22 percent) than those who received conventional conformal radiation therapy, suggesting that IMRT is a safer radiation technique. They also found that IMRT patients were less likely to require additional cancer treatments (rate ratio 0.81, or 19 percent fewer additional cancer treatments), suggesting that IMRT may offer better cancer control and reduce recurrence.

“Several trials have shown that higher doses of radiation therapy improve disease control, and it is likely that IMRT allowed a higher dose of radiation to be given to the prostate than conventional conformal radiation,

resulting in improved cure rates while simultaneously reducing side effects due to less radiation being given to organs surrounding the prostate,” Chen said.

The investigators also found that patients who received proton therapy had a higher rate of gastrointestinal problems, and did not have significantly improved outcomes compared to IMRT.

“We’ve seen a rapid growth in the number of proton facilities in the U.S. in the past five years, despite its very high costs. Yet with the data we have to date in the published literature, there does not appear to be a clear benefit of proton beam therapy compared to IMRT,” said Chen. “The technology needs to be closely examined through comparative effectiveness research before we adopt it as the ‘next’ treatment for prostate cancer.”

Abstract #3

Title: Comparative effectiveness of intensity modulated radiation therapy (IMRT), proton therapy (PT), and conformal radiation therapy (CRT) in the treatment of localized prostate cancer.

Authors: Nathan Christopher Sheets, Gregg Goldin, Anne-Marie Meyer, Yang Wu, YunKyung Chang, Til Sturmer, Jordan A Holmes, Bryce B. Reeve, Paul Alphonso Godley, William Ruffin Carpenter, Ronald C. Chen; University of North Carolina Hospitals, Chapel Hill, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC; National Cancer Institute, Bethesda, MD

Background: Comparative effectiveness research is urgently needed in prostate cancer because of the rapid adoption of newer and costlier radiation treatments such as IMRT and PT despite limited demonstrated benefit compared to prior technologies. We compared the morbidity and disease control outcomes of IMRT, PT and the older CRT for primary prostate cancer treatment. **Methods:** Population-based study using Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data from 2000 through 2009 for patients with non-metastatic prostate cancer. Propensity score adjustment was used to balance demographic, disease and institutional characteristics. Rates of morbidity (gastrointestinal, urinary, erectile dysfunction, hip fractures) and additional cancer therapy (surrogate for recurrence) were calculated. **Results:** IMRT use increased from 0.15% in 2000 to 95.9% in 2008. In propensity score-adjusted analyses, men who received IMRT vs. CRT were less likely to be diagnosed with GI morbidity (13.4 vs. 14.7 per 100 person-years, $p < 0.001$) and hip fractures (0.8 vs. 1.0, $p = 0.006$), but more likely to be diagnosed with erectile dysfunction (5.9 vs. 5.3, $p = 0.006$). IMRT patients were less likely to receive additional cancer therapy (2.5 vs. 3.1, $p < 0.001$). In a propensity-score matched comparison between PT and IMRT, PT patients had a higher rate of GI morbidity (17.8 vs. 12.2 per 100 person-years, $p < .001$). No significant differences in rates of other morbidities or additional therapies between PT and IMRT. **Conclusions:** IMRT vs. CRT was associated with less GI morbidity and hip fractures, more erectile dysfunction, and less need for additional cancer therapy. This large-scale population-based study is the first to suggest a simultaneous reduction in disease recurrence and morbidity in patients treated with IMRT vs. CRT for localized prostate cancer. Proton therapy did not significantly improve outcomes compared to IMRT, but had increased GI morbidity. These results provide new and long-needed information to decision-makers regarding the currently available evidence on the comparative effectiveness of different RT techniques. **Disclosures:** Nothing to disclose.

Study Finds External Beam Radiation Is Most Toxic, Expensive of Three Common Prostate Cancer Treatments

An analysis of more than 100,000 prostate cancer patients shows that treatment with external beam radiation therapy (EBRT) resulted in higher long-term toxicities and treatment-related costs than prostatectomy and brachytherapy, two other common treatments for the disease. The results provide valuable insight that may influence future decision-making regarding the use of these treatment options.

“Research to date has not given us a clear picture of how each prostate cancer therapy affects men over the long run,” said lead author Jay Ciezki, MD, a staff physician at the Cleveland Clinic. “Our analysis is one of the first to examine the quality of life and financial costs of these three very common prostate cancer treatment strategies for more than five years after treatment. We found that external beam radiotherapy had higher toxicity rates and was the most costly therapy per patient-year. While there are clearly still some high-risk prostate cancer patients who will benefit from external beam radiotherapy, for the approximately 80 percent or more of prostate cancer patients diagnosed with low- and intermediate-risk disease, brachytherapy or prostatectomy may be even more preferable options than we’ve previously assumed for men with low- and intermediate-risk prostate cancer.”

Researchers analyzed data in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database collected between 1991 and 2007; median follow-up was 71 months. They compared treatment-related toxicities and related outcomes among men who received external beam radiation, prostatectomy or brachytherapy (radiation therapy administered through surgically implanted radiation-emitting “seeds”). Because the SEER-Medicare database provides information on cancer diagnoses and outcomes, along with individual patient costs, it allowed the investigators to obtain Medicare reimbursement data for both the initial treatment and any subsequent treatments related to the toxicities. They then calculated the total cost per patient-year for each of the three therapies over time.

“We were able to get a good picture of the long-term costs of patient care and were surprised to see such dramatic differences among the three treatment strategies,” Ciezki said.

In all, records of 137,427 patients were examined, including 59,559 (43 percent) treated with prostatectomy, 60,806 (44.2 percent) who received EBRT, and 17,062 (12.4 percent) who were treated by brachytherapy. Overall, 10,585 (7.3 percent) needed some type of treatment intervention for a therapy-related effect. The researchers were not able to determine the stage of prostate cancer in individual patients included in the study. The study was limited to patients older than 65 with prostate cancer as their only cancer diagnosis.

The investigators found that brachytherapy had the lowest cost per patient-year: \$2,557.36. Prostatectomy came in slightly more expensive, at \$3,205.71, followed by EBRT, at \$6,412.29. EBRT also resulted in the most treatment-related toxicities: 7.1 percent of patients who received EBRT experienced genitourinary toxicity, such as urethral strictures and bladder bleeding, compared to 6.7 percent of those treated with prostatectomy and 3.4 percent of those treated with brachytherapy. Similarly, 1.7 percent of EBRT patients had gastrointestinal effects, compared to only 0.1 percent of prostatectomy patients and 0.3 percent of brachytherapy patients.

The researchers caution that the study findings are preliminary, and they plan to more closely examine the data and the differences they observed, including differences in toxicities found between older and newer techniques, and whether certain types of patients might be predisposed to long-term effects from particular therapies.

Abstract #4

Title: Long-term toxicity and associated cost of initial treatment and subsequent toxicity-related intervention for patients treated with prostatectomy, external beam radiotherapy, or brachytherapy: A SEER/Medicare database study.

Authors: Jay P. Ciezki, Chandana A. Reddy, Kenneth Angermeier, James Ulchaker, Kevin L. Stephans, Rahul D. Tendulkar, Andrew Altman, Nabil Chehade, Eric A. Klein; Cleveland Clinic, Cleveland, OH; Kaiser Permanente, Cleveland Heights, OH; Kaiser Permanente, Cleveland, OH; Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH

Background: Treatment-related toxicity for prostate cancer (CaP) is rarely reported more than 5 years after therapy. We examined the SEER-Medicare linked database with the potential of having 16 years of follow-up data on toxicity requiring procedural intervention.

Methods: The SEER-Medicare database was queried for CaP patients treated with prostatectomy (RP), external beam radiotherapy (EBRT), or brachytherapy (PI) between 1991-2007. We identified procedural billing codes associated with toxicity-related treatments. We obtained information on the Medicare reimbursement rates for the initial treatment and any toxicity-related interventions. We then computed the cost per patient-year within each treatment modality over time.

Results: A total of 137,427 patients who were 65 years or older at the time of CaP diagnosis and who had CaP as their only cancer diagnosis were retrieved from the SEER/Medicare database: 59,559 (43.3%) treated with RP, 60,806 (44.2%) treated with EBRT, and 17,062 (12.4%) treated with PI. No patient received combined therapy. The median follow-up is 71 months. Overall, 10,585 (7.3%) patients experienced a toxicity requiring intervention. Within treatment modalities, the percentages receiving toxicity-related intervention were: RP 6.9%, EBRT 8.8%, and PI 3.7%. The gastrointestinal (GI) and genitourinary (GU) toxicity comparisons are listed in the table. Dilatation of a urethral stricture was the most common GU toxicity (3.6% of all patients) while cauterization of rectal bleeding was the most common GI toxicity (0.8% of all patients).

Conclusions: The long-term toxicity and cost per patient-year of the major prostate cancer treatment modalities differ. EBRT is the most toxic and most costly.

Treatment Modality	Number within modality (% of total)	Percent of Treatment Group with GU Toxicity	P-Value	Percent of Treatment Group with GI Toxicity	P-Value	Average Cost per Patient-Year (\$)	P-Value
Prostatectomy	59,559 (43.3)	6.7	< 0.0001	0.1	< 0.0001	3205.71	<0.0001
External Beam	60,806 (44.3)	7.1		1.7			
Brachytherapy	17,062 (12.4)	3.4		0.3			

Disclosures: Nothing to disclose.

**General Poster Session A
Thursday, February 2, 2012
11:45 AM - 01:15 PM PT**

**Lead Author: Oliver Sartor, MD
Tulane Cancer Center
New Orleans, LA**

Study Finds Investigational Drug Targeting Bone Metastases Improves Survival for Metastatic Castration-Resistant Prostate Cancer

A randomized, phase III, multi-national study shows that a novel radiation-emitting agent that targets bone – and aimed at treating bone metastases – both improved survival and delayed cancer-related bone problems in men with metastatic castration-resistant prostate cancer (CRPC). The agent, radium-223 chloride (Ra-223), is the first alpha particle emitting drug developed to target bone that has been shown to improve survival in metastatic CRPC.

“As recently as two years ago, we had very few options for patients with this particularly difficult form of advanced prostate cancer,” said lead author A. Oliver Sartor, MD, Laborde Professor of Cancer Research at the Tulane University School of Medicine in New Orleans and medical director of the Tulane Cancer Center. “Now we have a handful. But Radium-223 is the first treatment to both reduce adverse skeletal-related events (SREs) and improve survival, making this a particularly promising therapeutic option.”

Prostate cancer is considered castration-resistant when growth continues despite extremely low levels of testosterone.

Radium-223 is a novel agent that directly targets bone metastases, delivering short bursts of high-energy alpha radiation. In the trial, called ALSYMPCA, Sartor and his colleagues randomized 922 patients with progressive, CRPC with bone metastases to receive Ra-223 plus best supportive care or placebo and best supportive care. An interim analysis of 805 patients showed that Ra-223 significantly improved median overall survival compared to placebo (14.0 months versus 11.2 months). As a result, the trial was ended early. Additionally, the time to the first SRE was significantly delayed (median time to SRE was 13.6 months vs. 8.4 months in the placebo group). Best supportive care involves treatment to address the symptoms of cancer, rather than to improve the overall disease outcomes; it includes therapies such as antibiotics, analgesics, radiation therapy for pain from bone metastases, and corticosteroids. SREs include bone fracture, spinal cord compression, external beam radiation to bone and bone surgery.

“These findings will help us to increasingly individualize advanced prostate cancer treatment, with a novel agent that can extend our patient’s lives,” Sartor said.

He said that further research is planned to examine the effectiveness of combining Ra-223 with other drugs. Studies are needed to determine whether Ra-223 is effective in combination with newly available immunotherapies, hormonal therapies, and chemotherapy. In addition, other investigators have already begun testing Ra-223 in patients with breast cancer who have bone metastases, and plans are underway for clinical studies of Ra-223 in other cancers.

Abstract # 9

Title: Radium-223 chloride impact on skeletal-related events in patients with castration-resistant prostate cancer (CRPC) with bone metastases: A phase III randomized trial (ALSYMPCA).

Authors: A. Oliver Sartor, Daniel Heinrich, Svein Inge Helle, Joe M. O'Sullivan, Sophie D. Fossa, Ales Chodacki, Tomasz Demkow, John P. Logue, Mihalj Seke, Anders Widmark, Dag Clement Johannessen, Sten Nilsson, Peter Hoskin, Arne Solberg, Nicholas David James, Isabel Syndikus, Nicholas J. Vogelzang, C. Gillies O'Bryan-Tear, Minghua Shan, Chris Parker; Tulane Cancer Center, New Orleans, LA; Akershus University Hospital, Lorenskog, Norway; Haukeland University Hospital, Bergen, Norway; Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Ireland; Radiumhospitalet, Oslo, Norway; Hospital Kochova, Chomutov, Czech Republic; Centrum Onkologii-Instytut im Skłodowskiej-Curie, Warsaw, Poland; Christie Hospital, Manchester, United Kingdom; Centrallasarettet Växjö, Växjö, Sweden; Norrlands University Hospital, Umeå, Sweden; Ullevål University Hospital, Oslo, Norway; Karolinska Universitetssjukhuset, Stockholm, Sweden; Mount Vernon Hospital Cancer Centre, Middlesex, United Kingdom; St. Olavs Hospital,

Trondheim, Norway; Cancer Research UK Clinical Trials Unit, Institute for Cancer Studies, Birmingham, United Kingdom; Clatterbridge Centre for Oncology, Wirral, United Kingdom; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Algeta ASA, Oslo, Norway; Bayer HealthCare Pharmaceuticals, Montville, NJ; The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom.

Background: Radium-223 chloride (Ra-223) is a 1st-in-class alpha-pharmaceutical targeting bone metastases (mets) with high-energy alpha-particles of short range (<100 µm). ALSYMPCA, a phase III, double-blind, randomized, multinational study, compared Ra-223 plus best standard of care (BSC) vs placebo (pbo) plus BSC in patients (pts) with bone mets in CRPC. The primary endpoint was OS; secondary endpoints included skeletal-related events (SREs).

Methods: Eligible pts had progressive, symptomatic CRPC with ≥ 2 bone mets on scintigraphy & no known visceral mets; were receiving BSC; & either previously received docetaxel, were docetaxel ineligible, or refused docetaxel. Pts were randomized 2:1 to receive 6 injections of Ra-223 (50 kBq/kg IV) q4 wks or matching pbo and stratified by prior docetaxel use, baseline alkaline phosphatase level, and current bisphosphonate use.

Results: 922 pts (Ra-223, n = 615; pbo, n = 307) were randomized from 6/2008-2/2011. Based on data from a planned interim analysis (n = 809), unblinded June 2011, Ra-223 significantly improved OS in pts with CRPC with bone mets vs pbo (median OS 14.0 vs 11.2 mo, respectively; two-sided P = 0.00185; HR = 0.695; 95% CI, 0.552-0.875). SREs were lower in the Ra-223 vs pbo group, & time to 1st SRE was significantly delayed (median time to SRE 13.6 mo vs 8.4 mo, respectively; P = .00046; HR = .610; 95% CI, .461-.807).

Conclusions: Ra-223 significantly delayed time to 1st SRE and SRE components, except surgical intervention. These reductions in SREs, particularly SCC, are noteworthy. Ra-223 is an effective therapy with a highly favorable safety profile & may provide a new standard of care for treatment of CRPC pts with bone mets.

SRE Component	No. (%) of Events		Time to Event (Ra-223 vs Pbo)	
	Ra-223 N=541	Pbo N=268	P value*	HR (95%CI)
Pathologic Bone Fracture	20 (4)	18 (7)	.013	.45 (.24-.86)
Spinal Cord Compression (SCC)	17 (3)	16 (6)	.016	.44 (.22-.88)
External Beam Radiotherapy	122 (23)	72 (27)	.0038	.65 (.48-.87)
Surgical Intervention	9 (2)	5 (2)	.69	.80 (.27-2.4)

*Not adjusted for multiplicity

Disclosures: **Oliver Sartor, MD**, Consultant or Advisory Role with Algeta; **Daniel Heinrich, MD**, Consultant or Advisory Role with Algeta; **Sophie D. Fossa, MD**, Consultant or Advisory Role with Bristol-Meyers Squibb and sanofi-aventis, Honoraria from Amgen and sanofi-aventis, Expert Testimony on behalf of Amgen and sanofi-aventis; **Sten Nilsson, MD**, Consultant or Advisory Role with Algeta, Honoraria from Algeta; **Peter Hoskin, MD, MRCP, FRCR**, Research Funding from Algeta; **Nicholas David James, MD, PhD**, Consultant or Advisory Role with Algeta, Research Funding from Algeta; **Nicholas J. Vogelzang, MD**, Employment/Leadership Position with US Oncology, Consultant or Advisory Role with Amgen, Bayer, Boehringer Ingelheim, Celgene, Clinical Care Options, Johnson & Johnson, Dendreon, Eisai, Genentech, GlaxoSmithKline, Millennium, Veridex, Cougar Biotechnology, Centocor Ortho Biotech, Takeda, Novartis, Pfizer, Honoraria from Amgen, ArQule, Bayer, Clinical Care Options, Johnson & Johnson, Dendreon, Genentech, Lilly, Veridex, WILEX, US Oncology, Cougar Biotechnology, Centocor Ortho Biotech, Novartis, Pfizer, sanofi-aventis, Research Funding from Algeta, ArQule, Johnson & Johnson, GlaxoSmithKline, Takeda, Tokai, Veridex, WILEX, US Oncology, Cougar Biotechnology, Centocor Ortho Biotech, Millennium, Novartis, Pfizer; **C. Gillies O'Bryan-Tear, MRCP**, Employment/Leadership Position with Algeta, Stock Ownership with Algeta; **Minghua Shan, PhD**, Employment/Leadership Position with Bayer; **Chris Parker, MD, MRCP**, Employment/Leadership Position with Algeta, Honoraria from Bayer.

General Session II
Thursday, February 2, 2012
10:15-11:45 AM PT

Lead Author: Howard Scher, MD
Memorial Sloan-Kettering Cancer Center
New York, NY

Study Shows New Targeted Drug Improves Overall Survival in Metastatic Prostate Cancer

A randomized phase III international trial shows for the first time that an investigational oral drug that halts androgen signaling significantly improves overall survival in patients with metastatic castration-resistant prostate cancer (CRPC). The drug, MDV3100 could become another key component in the oncologists' arsenal against this difficult-to-treat form of prostate cancer.

“MDV3100 works differently than other agents for metastatic castration-resistant prostate cancer,” said lead author Howard I. Scher, MD, Chief of the Genitourinary Oncology Service and D. Wayne Calloway Chair in Urologic Oncology at Memorial Sloan-Kettering Cancer Center in New York. “This drug targets a unique aspect of the malignant process, blocking a biological mechanism that enables tumors to resist other therapies and grow – and it worked far better than we expected when we set out.”

Prostate cancer is considered castration-resistant when tumor growth continues despite hormonal therapies that lower testosterone levels. Testosterone works through the androgen receptor to promote cell growth. According to Scher, MDV3100, developed by Charles Sawyers and Michael Jung, was designed to interfere directly with androgen receptor signaling by preventing androgens – or male sex hormones like testosterone – from binding to androgen receptors in the tumor, a key step in promoting prostate cancer growth. The drug also limits the ability of the androgen receptor to get to the nucleus and bind to DNA, subsequent steps in androgen receptor function. The action of the drug blocks cell growth and results in prostate cancer cell death.

In the study, called AFFIRM, 1,199 men with metastatic CRPC were randomized to receive either MDV3100 or placebo. All patients had cancers that continued to progress despite previous hormonal therapy and docetaxel chemotherapy. After a planned interim analysis, researchers found that median overall survival was 18.4 months for patients treated with MDV3100 and 13.6 months for those receiving placebo. Treatment with MDV3100 prolonged life by 4.8 months and reduced the risk of death by 37 percent compared to placebo. As a result, the trial was halted early, and patients in the placebo arm were offered the drug.

The researchers also found the median radiographic progression-free survival was 8.3 months for those given MDV3100 versus 2.9 months for placebo. This means that MDV3100 significantly slowed the progression of bone metastases, the primary site of prostate cancer spread and a major cause of morbidity, and other metastases. Additionally, almost 30% of patients had complete or partial responses to MDV3100 treatment on imaging as compared to 1.3% in the placebo group.

MDV3100 treatment also resulted in a substantial impact on level of prostate-specific antigen, or PSA. PSA reductions of 50% or greater from baseline were observed in 54.0 % of MDV3100 patients versus 1.5% of placebo patients and 90% or greater from baseline in 25% of patients vs. 1% of placebo patients. Finally, MDV3100 increased the time to PSA progression by 5.3 months, from – 3.0 months in the placebo group to 8.3 months in the MDV3100 treated group.

Importantly, MDV3100 was well-tolerated in the AFFIRM study. The most common adverse events occurring more frequently in the MDV3100 group ($\geq 2\%$) than in the placebo group included fatigue, diarrhea and hot flushes. These were generally mild and did not result in dose-reduction. “The next challenge is finding the best way to maximize how we use MDV3100, which may be in sequence or in combination with other treatments. But for now, we think this once-daily oral drug could be a valuable new option for certain patients with cancer that progresses, despite standard hormone therapy and chemotherapy – a type of prostate cancer that has historically been extremely unresponsive to therapy,” Scher said.

MDV3100 is also being evaluated in patients with CRPC who have not yet been treated with chemotherapy or hormonal therapy, the standard initial treatment to lower testosterone. The latter approach has the potential provide similar treatment benefits as traditional hormonal therapy but would not lower androgen levels. “This would potentially be a more favorable option for patients’ quality of life, enabling men to avoid hot flashes and other side effects typically experienced during hormonal therapy,” Scher said.

Abstract #LBA1

Title: Effect of MDV3100, an androgen receptor signaling inhibitor (ARSI), on overall survival in patients with prostate cancer postdocetaxel: Results from the phase III AFFIRM study.

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Background: MDV3100, a novel androgen receptor signaling inhibitor (ARSI), competitively inhibits binding of androgens to the androgen receptor (AR), inhibits AR nuclear translocation, and inhibits association of the AR with DNA (Tran et al, Science. 2009;324:787). MDV3100 was selected for development based on activity in prostate cancer model systems with overexpressed AR, and was active in a Phase 1-2 trial enrolling pre- and post-chemotherapy treated patients with progressive castration resistant disease (CRPC) (Scher et al, Lancet. 2010;375:1437). The AFFIRM trial evaluated whether MDV3100 could prolong overall survival (OS) in men with CRPC who progressed following docetaxel based chemotherapy. **Methods:** In this randomized, double-blind, placebo-controlled, multinational Phase 3 study (NCT00974311), patients who had received ≤ 2 regimens of docetaxel-based chemotherapy were randomized 2:1 to MDV3100 160 mg/day or placebo. Treatment with corticosteroids was allowed but not required. Patients were stratified by baseline ECOG performance status and mean brief pain inventory score. The primary endpoint was OS. Other efficacy endpoints included radiographic progression-free survival (PFS), time to first skeletal-related event, time to prostate-specific antigen (PSA) progression, and circulating tumor cell count conversion rate. **Results:** 1,199 patients were randomized between Sep 2009 and Nov 2010. Based on a planned interim analysis at 520 death events, the Independent Data Monitoring Committee (IDMC) recommended the study be unblinded and placebo patients offered MDV3100 due to a significant OS benefit ($P < 0.0001$; hazard ratio 0.631). The estimated median OS was 18.4 months for MDV3100 treated compared to 13.6 months for placebo treated men, a median OS difference of 4.8 months. Data to be available include PFS, time to PSA progression, and safety. **Conclusions:** MDV3100, a novel ARSI, significantly improves OS in men with post-docetaxel treated CRPC reducing the risk of death by 37% relative to placebo. The IDMC determined the risk:benefit of MDV3100 was favorable and recommended the Phase 3 AFFIRM trial be unblinded. **Disclosures:** **Howard I. Scher, MD**, Consultant or Advisory Role with Medivation, Research Funding from Medivation; **Fred Saad, MD, FRCS**, Consultant or Advisory Role with Medivation, Honoraria from Medivation, Research Funding from Medivation; **Mary-Ellen Taplin, MD**, Consultant or Advisory Role with Medivation, Research Funding from Medivation; **Kurt Miller, MD**, Consultant or Advisory Role with Medivation, Astellas Pharma, Honoraria from Astellas Pharma; **Peter Mulders**, Consultant or Advisory Role with Astellas Pharma, Novartis, Amgen, Honoraria from GlaxoSmithKline, Novartis and AstraZeneca, Research Funding from Bayer and Pfizer; **Mohammad Hirmand, MD**, Employment/Leadership Position with Medivation; **Bryan Selby**, Employment/Leadership Position with Medivation; **Johann Sebastian De Bono, MD**, Employment/Leadership Position with Institute of Cancer Research, Consultant or Advisory Role with Medivation, Astellas Pharma and Johnson and Johnson, Honoraria from Astellas Pharma, Medivation and Johnson and Johnson.

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