LBA5000 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Clinical outcomes in patients with castrate-refractory prostate cancer (CRPC) metastatic to bone randomized in the factorial trapeze trial to docetaxel (D) with strontium-89 (Sr89), zoledronic acid (ZA), neither, or both (ISRCTN 12808747).

Nicholas David James, Sarah Pirrie, Darren Barton, Janet Elizabeth Brown, Lucinda Billingham, Stuart I. Collins, Adam Daunton, Alison J. Birtle, Prabir Ranjan Chakraborti, Daniel Ford, Syed A. Hussain, Helen Jones, Ann Pope, Emilio Porfiri, John Martin Russell, Andrew Stanley, John Staffurth, Duncan McLaren, Chris Parker, James Wylie; Cancer Research UK Clinical Trials Unit, School of Cancer Sciences, Birmingham, United Kingdom; Cancer Research UK Experimental Cancer Medicine Centres, Leeds and Sheffield, United Kingdom; Cancer Research Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, United Kingdom; Cancer Research UK Institute for Cancer Studies, University of Birmingham, Birmingham, United Kingdom; West Midlands Strategic Health Authority, Birmingham, United Kingdom; Rosemere Cancer Centre, Royal Preston Hospital, Preston, United Kingdom; Derby Royal Hospital, Derby, United Kingdom; Queen Elizabeth Hospital, Birmingham, United Kingdom; University of Liverpool, Liverpool, United Kingdom; University Hospital Birmingham NHS Foundation Trust, Birmingham, United Kingdom; School of Cancer Sciences, University of Birmingham, Birmingham, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; City Hospital, Birmingham, United Kingdom; Velindre Cancer Centre, Cardiff, United Kingdom; Department of Oncology, Edinburgh Cancer Centre, Edinburgh, United Kingdom; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom

The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Sunday, June 2, 2013, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2013, issue of *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

5001 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Efficacy and safety of enzalutamide (ENZA) monotherapy in hormone-naive prostate cancer (HNPC).

Matthew Raymond Smith, Michael Borre, Per Rathenborg, Patrick Werbrouck, Hendrik Van Poppel, Axel Heidenreich, Peter Iversen, Edwina Baskin-Bey, Frank Perabo, De Phung, Bertrand Tombal; Departments of Hematology and Oncology, Massachusetts General Hospital Cancer Center, Boston, MA; Department of Urology, Århus University Hospital, Skejby, Denmark; Department of Urology, Herlev Hospital, Herlev, Denmark; Department of Urology, AZ Groeninge Kortrijk, Kortrijk, Belgium; Department of Urology, University Hospitals Leuven, Leuven, Belgium; Department of Urology, RWTH University, Aachen, Germany; Department of Urologuy, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; Astellas Pharma Global Development, Inc., Staines, United Kingdom; Astellas Pharma Global Development, Inc., Leiderdorp, Netherlands; Department of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Background: In locally-advanced prostate cancer, the antiandrogen bicalutamide (Bic) is used to maintain quality of life relative to castration therapy (LHRHa), but efficacy as a monotherapy is limited. ENZA is an oral androgen receptor (AR) inhibitor with higher AR–binding affinity vs Bic, and it prevents nuclear translocation, shows no DNA binding, and induces apoptosis. ENZA was approved in the US after prolonging overall survival in post-docetaxel metastatic castration resistant prostate cancer. This phase 2 study assessed ENZA monotherapy in patients (pts) with HNPC and noncastrate testosterone (T) ≥230 ng/dL. **Methods:** Pts with any stage HNPC (ECOG PS 0, life expectancy >1 y) requiring hormonal therapy received ENZA 160 mg/d for 25 wks. Primary endpoint was PSA response (≥80% decline at wk 25). Other endpoints were endocrine levels, pharmacokinetics, safety, and metabolic changes (body composition, bone biomarkers, lipids, and glycemic profiles). **Results:** 67 pts were enrolled. Median age was 73 y; 39% had metastases, 36% and 24% had prior prostatectomy and radiation, respectively. ENZA levels reached steady state after ~4 wks. Mean changes in metabolic outcomes at wk 25 included: –0.24% total body bone mineral density (BMD), –4.15% lean body mass, 6.85% fat body mass, 14.75% bone alkaline phosphatase, 4.55% total cholesterol, 6.48% triglycerides, –1.98% A1c, –0.10% fasting glucose, and 45.06% HOMA-IR. At wk 25, PSA response was 93% (62/67; 95% CI, 86%–99%); median PSA decrease was –99.6%. Mean T and estrogen increased 114% and 72%, respectively; other endocrine increases were observed, the highest was 185% for luteinizing hormone. Most common treatment-emergent AEs were grade 1 and included gynecomastia (36%), fatigue (34%), nipple pain (19%), and hot flush (18%). Five pts had serious AEs (none drug related). **Conclusions:** ENZA monotherapy achieved a high PSA response rate and marked PSA decline with efficacy similar to castration. In contrast to castration, BMD remained stable and metabolic variables (fat body mass, lipid and glycemic profiles) were not substantially impacted with ENZA monotherapy over the 6 month study period. Endocrine changes and AEs were consistent with potent AR inhibition. Clinical trial information: NCT01302041.

5002 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Double-blind randomized trial of aflibercept versus placebo with docetaxel and prednisone for treatment of metastatic castration-resistant prostate cancer (mCRPC).

Ian Tannock, Karim Fizazi, Sergey Ivanov, Camilla Thellenberg-Karlsson, Aude Flechon, Iwona Anna Skoneczna, Francisco Jorquera Orlandi, Gwenaelle Gravis, Vsevolod Matveev, Sevil E. Bavbek, Thierry Gil, Luciano S. Viana, Osvaldo Aren, Oleg Karyakin, Tony Elliott, Alison J. Birtle, Emmanuelle Magherini, Daniel Peter Petrylak, Bertrand Tombal, Mark Rosenthal, VENICE Investigators; Princess Margaret Hospital, Toronto, ON, Canada; Institut Gustave Roussy,, Villejuif,, France; Scientific Center for X-ray Radiology, Moscow, Russia; Umeå University Hospital, Umeå, Sweden; Centre Léon Bérard, Lyon, France; Institute of Oncology, Warsaw, Poland; OncoMed Pharmaceuticals, Inc, Providencia, Chile; Department of Medical Oncology, Institut Paoli Calmettes, INSERM UMR 891, Marseille, France; NN Blokhin Russian Cancer Research Center, Moscow, Russia; Istanbul University Oncology Institute, Istanbul, Turkey; Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; Barretos Cancer Hospital, Barretos, Brazil; Instituto Nacional del Cancer, Santiago, Chile; Medical Radiological Research Center, Obninsk, Russia; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; Sanofi R&D, Vitry-sur-Seine, France; Yale University Medical Center, New Haven, CT; Department of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; Royal Melbourne Hospital, Parkville, Australia

Background: Docetaxel/prednisone is standard first-line chemotherapy for men with mCRPC. Aflibercept is a recombinant human fusion protein that binds A and B isoforms of Vascular Endothelial Growth Factor and Placental-derived Growth Factors, thereby inhibiting angiogenesis. **Methods:** We performed an international double-blind randomized trial (known as VENICE) which recruited men with mCRPC, adequate organ function and no prior chemotherapy. Men were treated with docetaxel (75mg/m^2 intravenously every 3 weeks) and oral prednisone (5mg twice daily) and randomized 1:1 to receive aflibercept (6 mg/kg) or placebo, intravenously every 3 weeks. The primary endpoint was overall survival: 873 deaths were required to detect a hazard ratio (HR) of 0.8 with 90% power. **Results:** A total of 1,224 men were randomized, 612 in each arm. Median age was 68 years and baseline characteristics were well balanced between arms. Participants received a median of 8 (aflibercept) and 9 (placebo) cycles of therapy. Median relative dose intensity was $>$0.93 for aflibercept, placebo and docetaxel. At final analysis, median follow-up was 35 months and 873 pts had died. Median survival was 22.1 months (95.6% CI: 20.3-24.1 months) in the aflibercept arm and 21.2 months (95.6% CI: 19.6-23.8 months) in the placebo arm (stratified HR = 0.94; 95.6% CI: 0.82-1.08, p=0.38). Pre-defined secondary endpoints for aflibercept and placebo arms were similar, including PSA response rate (68.6% and 63.5%), time to first skeletal-related event (median: 15.3 and 15.0 months), and progression-free survival (median: 6.9 and 6.2 months). Quality of Life analysis using FACT-P and a trial-specific module will be reported. Higher incidence of grade 3-4 gastrointestinal disorders, hemorrhagic events, hypertension, fatigue, infections and fatal adverse events (5.6% vs. 3.3%) was observed in the aflibercept arm. **Conclusions:** Aflibercept in combination with docetaxel/prednisone given as first-line chemotherapy for men with mCRPC did not lead to an improvement in survival and added toxicity. Trial Registration**:** NCT00519285. Funding: Sanofi and Regeneron Pharmaceuticals, Inc. Clinical trial information: NCT00519285.

5003 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Correlation of ^{18}F-fluoride PET response to dasatinib in castration-resistant prostate cancer bone metastases with progression-free survival: Preliminary results from ACRIN 6687.

Evan Y. Yu, Fenghai Duan, Mark Muzi, Jeremy Gorelick, Bennett Chin, Joshi J. Alumkal, Mary-Ellen Taplin, Ben Herman, Celestia S. Higano, Robert K Doot, Donna M Hartfeil, Phillip G. Febbo, David A. Mankoff, Department of Defense Prostate Cancer Clinical Trials Consortium and American College of Radiology Imaging Network; University of Washington/Seattle Cancer Care Alliance, Seattle, WA; Brown University, Providence, RI; University of Washington, Seattle, WA; Duke University, Durham, NC; Oregon Health & Science University Knight Cancer Institute, Portland, OR; Dana-Farber Cancer Institute, Boston, MA; Department of Radiology, University of Washington, Seattle, WA; American College of Radiology Imaging Network, Philadelphia, PA; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of Pennsylvania, Philadelphia, PA

Background: Dasatinib is a SRC kinase inhibitor that decreases bone turnover in men with metastatic castration-resistant prostate cancer (mCRPC). ^{18}F-fluoride PET was used to evaluate differential response between normal and tumor bone to dasatinib. **Methods:** Patients with bone mCRPC underwent dynamic ^{18}F-flouride PET imaging prior to and 12 weeks after dasatinib treatment. Up to 5 bone metastases with matching normal bone regions were selected for analysis by SUV_{max}, K_i, $K_1$and Patlak flux. Their pre-treatment values and change from pre-treatment to post-treatment values were evaluated via generalized estimating equations to predict skeletal-related events (SRE) and via Cox proportional hazards modeling to predict progression-free survival (PFS) with Prostate Cancer Working Group 2 criteria, overall survival and time to SRE. **Results:** Eighteen patients treated with dasatinib underwent baseline ^{18}F-flouride PET imaging; 12 had follow-up scans allowing assessment of changes due to therapy. Median age for all patients was 69 (range 48-86) years. Significant decrease in SUV_{max} ($p=0.0002$) occurred in bone metastases with dasatinib while significant increases in Patlak flux ($p=0.0033$) occurred in normal bone. Significant differences in changes from tumor bone compared to normal bone in response to dasatinib were noted for SUV_{max} ($p<0.0001$). Of 18 patients, 17 have either met progression criteria or death by the time of this analysis. Decrease in tumor bone SUV_{max} ($p=0.019$), K_i($p=0.022$), and Patlak flux ($p=0.034$) from pre-treatment to post-treatment correlates with longer PFS. **Conclusions:** ^{18}F-fluoride PET indicates differential effect of dasatinib on tumor compared to normal bone in men with mCRPC. In patients undergoing pre- and post-dasatinib ^{18}F-fluoride PET imaging a decrease in bone mCRPC fluoride uptake in response to treatment correlates with PFS. Clinical trial information: NCT00936975.

5004 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

ERG rearrangements and association with clinical outcome in patients (pts) receiving abiraterone acetate (AA): Results from the COU-AA-302 study in chemotherapy (chemo)-naïve metastatic castration-resistant prostate cancer (mCRPC).

Gerhardt Attard, Johann Sebastian De Bono, Weimin Li, Arturo Molina, Thomas W. Griffin, Thian San Kheoh, Deborah Sokol Ricci, Kathy Zelinsky, Dana E. Rathkopf, Howard I. Scher, Charles J. Ryan; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Janssen Research & Development, LLC, Raritan, NJ; Janssen Research & Development, LLC, Los Angeles, CA; Memorial Sloan-Kettering Cancer Center, New York, NY; Helen Diller Family Comprehensive Cancer Center, University of California-San Francisco, San Francisco, CA

Background: *ERG* rearrangements result in androgen receptor-modulated up-regulation of *ERG* and may predict for AA response in mCRPC. Concordance has been shown between *ERG* status in archival samples and fresh CRPC biopsies (Attard et al., *Cancer Res*. 2009;69:2912). In this prospectively defined biomarker sub-study, the association between *ERG* subtypes and clinical outcome in chemo-naïve mCRPC pts receiving AA was evaluated. **Methods:** COU-AA-302 is a randomized double blind study of AA (1 g) + prednisone (P) (5 mg BID) vs placebo + P in chemo-naïve mCRPC. Fluorescence in situ hybridization (FISH) assays to evaluate *ERG* subtypes (Attard et al., *Oncogene*. 2008;27:253) were conducted on 524 archival prostate tissue samples (365 biopsies, 107 RPEs, 44 TURPs, 3 bone marrows, 5 lymph nodes) from 497 pts. Clinical outcome measures included radiographic progression-free survival (rPFS) (central [CEN] and investigator [INV] reviewed), time to PSA progression (TTPP), and PSA $\geq$ 50% decline. Cox regression was used to evaluate association with time to event endpoints and Cochran-Mantel-Haenszel for PSA response. **Results:** 337 of 497 pts with tumor samples had evaluable FISH results. An *ERG* rearrangement was present in 117 of 337 (35%) pts. 112 pts were class Edel, 50 were 2+Edel (interstitial deletion with duplication of fusion sequences) and 18 were ESplit. A trend for an association with greater improved rPFS (CEN) and TTPP in 2+ Edel pts treated with AA + P vs *ERG* non-rearranged was observed (22 months [m] vs 16 m [HR: 0.59, 95% CI: 0.30-1.16], p = 0.12, and 14 m vs 8 m [HR: 0.68; 95% CI: 0.41-1.15], p = 0.15, respectively). No differences in 2+ Edel vs *ERG* non-rearranged were observed in the P-alone arm. No association between any *ERG* sub-class and either rPFS [INV] or PSA $\geq$ 50% decline in either treatment arm was observed. **Conclusions:** This represents the largest study to date to molecularly characterize CRPC pts participating in a therapeutic phase 3 trial. These data suggest that chemo-naïve mCRPC pts with a 2+ Edel rearrangement may derive a slightly greater benefit from AA and P than other pts. Clinical trial information: NCT00887198.

5005 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Prolaris: A novel genetic test for prostate cancer prognosis.

Michael K. Brawer, Jack M. Cuzick, Matthew R. Cooperberg, Gregory P. Swanson, Stephen J. Freedland, Julia E. Reid, Gabrielle Fisher, Jerry S. Lanchbury, Alexander Gutin, Steven Stone, Peter Carroll, Transatlantic Prostate Group; Myriad Genetics and Laboratories, Inc., Salt Lake City, UT; Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, London, United Kingdom; University of California, San Francisco, San Francisco, CA; University of Texas Health Science Center at San Antonio, San Antonio, TX; Duke University Medical Center and Durham VA Medical Center, Durham, NC

Background: The natural history of prostate cancer is highly variable and difficult to predict. Improved tools are needed to match treatment more appropriately to a patient's risk of progression. Therefore, we developed an expression signature composed of genes involved in cell cycle progression (Prolaris) and tested its utility in prostate cancer. **Methods:** We developed an expression signature composed of 31 cell cycle progression and 15 housekeeper genes. An expression score (Prolaris score) was derived as the mean of all cell cycle progression genes. The signature was tested at disease diagnosis in two conservatively managed cohorts from the UK (N=337 and 349), after radical prostatectomy in two cohorts from the U.S. (N=366 Scott & White Hospital, TX and 413 USCF, CA), and after external beam radiation therapy (N=141) in a cohort from Durham VA Medical Center. All studies were retrospective. **Results:** The cell cycle progression signature was a highly significant predictor of outcome in all five studies. In conservatively managed patients, the Prolaris score was the dominant variable for predicting death from prostate cancer in univariate analysis ($p = 6.1 \times 10^{-22}$ after diagnosis by TURP, and $p = 8.6 \times 10^{-10}$ after diagnosis by needle biopsy). In both studies, the Prolaris score remained highly significant in multivariate analysis making it a stronger predictor of disease-specific mortality than other prognostic variables. After prostatectomy, Prolaris predicted biochemical recurrence (BCR) in univariate analysis (S&W $p = 5.6 \times 10^{-9}$; UCSF $p= 2.23 \times 10^{-6}$) and provided additional prognostic information in multivariate analysis (S&W $p = 3.3 \times 10^{-6}$; UCSF 9.5×10^{-5}). After radiation therapy, Prolaris predicted BCR (Phoenix) in univariate ($p=0.0017$) and multivariate analysis ($p=0.034$). In all five studies the HR per unit change in the Prolaris score was remarkably similar, ranging from 1.89 to 2.92, indicating that the effect size for the Prolaris score is robust to clinical setting and patient composition. **Conclusions:** The Prolaris test predicts prostate cancer outcome in multiple patient cohorts and diverse clinical settings. In all cases, it provides information beyond clinicopathologic variables to help differentiate aggressive from indolent disease.

5006 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Identification of polo-like kinase 1 (PLK1) in aggressive prostate cancer by paradigm analysis.

Phillip G. Febbo, Theodore C. Goldstein, Robert Baertsch, Jack Youngren, Yulia Newton, Adrian Bivol, Eric Jay Small, Joshua M. Stuart; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Department of Biomolecular Engineering, University of California, Santa Cruz, Santa Cruz, CA; University of California, San Francisco, San Francisco, CA; Helen Diller Family Comprehensive Cancer Center, University of California-San Francisco, San Francisco, CA

Background: Integrative analysis that combines expression data, copy number variation, sequence, and epigenetic data with thousands of known biological interactions can help identify strong biological associations and novel "genotype to phenotype" associations. **Methods:** We performed multi-dataset differential expression analysis with Statistical Analysis of Microarrays (SAM) and gene set enrichment analysis (GSEA) across 10 publicly-available PCa microarray datasets to identify genes and pathways differentially expressed between local (n=471) and metastatic (n=220) PCa. We used PARADIGM, an integrated pathway analysis method, on PCa tumor samples with mRNA expression, copy number variation, and TMPRSS2:ERG fusion status data to infer differential fusion gene-related "activities" for pathway features (genes, protein complexes, etc) within a "Superimposed Pathway" representing a comprehensive collection of genetic interactions currently containing 20,314 known interactions among 16,362 concepts representing 6916 proteins, 7345 complexes, 1449 families, 55 RNAs, 15 miRNAs and 582 processes. **Results:** Out of the 7571 genes tested (those genes having data in two or more studies), the meta-analysis on gene expression revealed 210 (1.8% FDR) positively associated with PCa metastasis and 403 (0.94% FDR) negatively associated genes (threshold was $p<0.001$, 2-tailed Student's t-test). GSEA highlighted cell proliferation, cell cycle control, and DNA damage repair pathways with metastatic tumors. The PARADIGM analysis identified a network containing 914 features connected by 1137 edges. PLK1 was identified as both highly expressed in metastatic PCa and as one of the fourteen hubs in the largest (596-feature) sub-network identified by PARADIGM. PLK1 was also associated with high Gleason Sum and recurrent disease in independent local PCa datasets. **Conclusions:** Using an approach pioneered by members of our SU2C/PCF supported PCa Dream Team, integrated analysis across multiple PCa datasets associates PLK1 activity with aggressive PCa and suggests it may provide a novel treatment target for at least a genetic sub-set of advanced PCa.

5007 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Metformin use and all-cause and prostate-cancer-specific mortality among diabetic men.

David Margel, David R. Urbach, Lorraine Lipscombe, Chaim Bell, Girish Kilkarni, Peter Austin, Anthony Michael Joshua, Neil Eric Fleshner; University of Toronto, Toronto, ON, Canada; University of Toronto, Department of Surgery, Division of General Surgery, Institute of Medical Sciences, Toronto, ON, Canada; St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; Division of Urology, Department of Surgical Oncology, Princess Margaret Hospital, Toronto, ON, Canada; Institute of Clinical and Evaluative Sciences, University of Toronto, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada

Background: To evaluate the association between cumulative duration of metformin use after prostate cancer diagnosis and all-cause and prostate cancer-specific mortality among diabetic patients. **Methods:** We used a population-based retrospective cohort design. Data were obtained from several Ontario health care administrative databases. Within a cohort of men over the age of 66 with incident diabetes who subsequently developed prostate cancer, we examined the effect of duration of anti-diabetic medication exposure, after prostate cancer diagnosis, on all-cause and prostate cancer-specific mortality. Crude and adjusted hazard ratios were calculated using a time-varying Cox proportional hazard model to estimate effects. **Results:** The cohort consisted of 3,837 patients. Median age (interquartile range IQR) at diagnosis of prostate cancer was 75 (72-79) years. During a median (IQR) follow up of 4.64 (2.7-7.1) years, 1,343 (35%) died, and 291 patients died of prostate cancer (7.6%). Cumulative duration of metformin treatment, after prostate cancer diagnosis, was associated with a significant decreased risk of prostate cancer-specific and all-cause mortality in a dose-dependent fashion. The adjusted hazard ratio, for prostate cancer-specific mortality was 0.76 (95% confidence interval, 0.64-0.89) for each additional six months of metformin use. The association with all-cause mortality was also significant but declined over-time from a HR of 0.76 in the first 6 months to 0.93 between 24-30 months. There was no relationship between cumulative use of other anti-diabetic drugs and either outcome. **Conclusions:** Increased cumulative duration of metformin exposure after prostate cancer diagnosis was associated with decreases in both all-cause and prostate-cancer-specific mortality among diabetic men.

5008 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

A double-blind, placebo RCT evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer: The U.K. National Cancer Research Network (NCRN) Pomi-T study.

Robert J. Thomas, Madeleine M A Williams, Harbiner Sharma, Aasem Chaudry, Patricia Bellamy; Bedford and Addenbrooke's Cambridge University NHS Hospital Trusts, Bedford, United Kingdom; Bedford Hospital NHS Trust, Bedford, United Kingdom; Cranfield University, Bedfordshire, United Kingdom

Background: Polyphenol-rich foods such as pomegranate, green tea, broccoli and turmeric have demonstrated anti-neoplastic effects in cell lines and animal models. Although some have been investigated in small phase II studies, this combination had never been evaluated within an adequately powered nationally certified RCT. **Methods:** 203 men, average age 74 yrs, had localised prostate cancer, 59% managed with active surveillance and 41% with watchful waiting (progressive PSA relapse following previous radical interventions). They were randomised to receive a b.d. oral capsule containing a blend of pomegranate seed, green tea, broccoli and turmeric or an identical placebo for 6 months. The groups were statistically balanced in terms of gleason grade, body mass index (BMI), treatment category and fasting cholesterol although there was a difference in average age at baseline; 71.8 yrs in the food supplement group (FSG) versus 76.4 years in the placebo group (PG). Four men withdrew after randomisation. **Results:** The median rise in PSA in the FSG was 14.7% (95% CI 3.4-36.7%) versus 78.5% in the PG (95% CI 48.1-115.5%) (63.8% difference, ANCOVA analysis of covariance, $p=0.0008$). 46% of men had stable or lower PSA at trial completion in the FSG versus 14% in the PG (32% difference, chi^2, $p=0.00001$). There were no significant differences in PSA% change within the predetermined subgroups (age, gleason grade, treatment category, BMI). There were no differences in cholesterol, blood pressure, blood sugar or c-reactive protein. 24% men recorded events in the FSG and 34% in the PG (non significant). Mild gastro-intestinal effects were (17%) in the FSG but 8% of these reported an improvement in stool quality. **Conclusions:** This study found a statistically significant short-term favourable effect on the percentage rise in PSA in these men managed with observation following intake of this specific food supplement. Although many men would see this as useful addition to their self help strategies, future trials should look at the longer-term clinical benefits particularly in terms of preventing medical intervention. Clinical trial information: 81263.

5009 **Poster Discussion Session (Board #1), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Long-term safety and efficacy analysis of abiraterone acetate (AA) plus prednisone (P) in metastatic castration-resistant prostate cancer (mCRPC) without prior chemotherapy (COU-AA-302).

Dana E. Rathkopf, Matthew R. Smith, Johann Sebastian De Bono, Christopher Logothetis, Neal Shore, Paul L. De Souza, Karim Fizazi, Peter Mulders, Paul N. Mainwaring, John D Hainsworth, Tomasz M. Beer, Scott A. North, Yves Fradet, Thomas W. Griffin, Youn Choi Park, Thian San Kheoh, Eric Jay Small, Howard I. Scher, Arturo Molina, Charles J. Ryan; Memorial Sloan-Kettering Cancer Center, New York, NY; Massachusetts General Hospital Cancer Center, Boston, MA; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; The University of Texas MD Anderson Cancer Center, Houston, TX; Carolina Urologic Research Center, Myrtle Beach, SC; University of Western Sydney School of Medicine, Ingham Institute, Liverpool, Australia; Institut Gustave Roussy, University of Paris Sud, Villejuif, France; Radboud University Medical Centre, Nijmegen, Netherlands; Haematology and Oncology Clinics of Australia, Brisbane, Australia; Sarah Cannon Research Institute, Nashville, TN; Oregon Health & Science University Knight Cancer Institute, Portland, OR; Cross Cancer Institute, Edmonton, AB, Canada; Laval University, Québec, QC, Canada; Janssen Research & Development, LLC, Los Angeles, CA; Janssen Research & Development, LLC, Raritan, NJ; Helen Diller Family Comprehensive Cancer Center, University of California-San Francisco, San Francisco, CA

Background: AA, a CYP17 inhibitor, prolongs the lives of men with progressive pre- or post-chemotherapy treated mCRPC with a favorable safety profile (Rathkopf et al. ASCO-GU 2013. Abstr 5). This post hoc analysis examines the safety and tolerability of long-term treatment (≥ 24 mos) in study COU-AA-302. **Methods:** 1,088 pts were randomized 1:1 to AA 1000 mg + P 5 mg po BID vs placebo + P. Co-primary endpoints were radiographic progression-free survival (rPFS) and OS. Median times with 95% CI of the end points were estimated using the Kaplan-Meier (KM) method. Post hoc analysis of adverse events (AEs) was performed at pre-specified interim analysis (IA3) (55% OS events). **Results:** At a median follow-up = 27.1 mos (IA3): rPFS HR (95% CI) = 0.53 (0.45, 0.62), $p < 0.0001$ and OS was improved over P [0.79 (0.66, 0.96), $p = 0.0151$]; the latter did not reach the pre-specified efficacy boundary ($p = 0.0035$). All secondary endpoints favored the AA arm (Rathkopf et al. ASCO-GU 2013. Abstr 5). The incidence rate of selected AEs by duration of exposure is shown below (Table). There was no clinically relevant increase in the incidence rate of AEs with longer exposure using AA + P versus P alone; although pts on treatment for ≥ 24 mos may have had greater tolerability. The percentage of patients who came off study due to an AE was 8% (AA) versus 6% (P). **Conclusions:** The updated IA3 of COU-AA-302 in pts without prior chemotherapy confirms the delay in progression and prolongation of life with a favorable safety profile including pts treated for ≥ 24 mos with AA + P or P. Clinical trial information: NCT00887198.

	AA + P				P			
			Grade (%)					
Exposure time, mos	N	All	1 / 2	3 / 4	N	All	1 / 2	3 / 4
Cardiac disorders								
< 3	542	6	5	1	540	5	4	1
12–15	302	5	3	1	184	8	7	1
≥ 24	154	7	6	1	76	9	9	0
Fatigue								
< 3	542	19	18	1	540	17	16	1
12–15	302	8	7	1	184	8	8	0
≥ 24	154	8	8	0	76	4	4	0
Hyperglycemia								
< 3	542	4	2	1	540	4	4	1
12–15	302	3	2	0	184	3	2	1
≥ 24	154	1	1	0	76	4	1	3
Hypertension								
< 3	542	8	7	1	540	8	6	2
12–15	302	5	4	1	184	3	2	2
≥ 24	154	2	1	1	76	1	1	0
Osteoporosis								
< 3	542	1	1	0	540	2	1	0
12–15	302	1	0	0	184	2	2	0
≥ 24	154	3	3	0	76	4	4	0
Weight gain								
< 3	542	2	1	0	540	2	2	0
12–15	302	1	1	0	184	0	0	0
≥ 24	154	2	2	0	76	1	1	0

5010 Poster Discussion Session (Board #2), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Relationship of baseline PSA and degree of PSA decline to radiographic progression-free survival (rPFS) in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC): Results from COU-AA-302.

Charles J. Ryan, Anil Londhe, Arturo Molina, Matthew R. Smith, Johann Sebastian De Bono, Peter Mulders, Dana E. Rathkopf, Fred Saad, Christopher Logothetis, Karim Fizazi, Howard I. Scher, Eric Jay Small, Shannon Matheny, Thian San Kheoh, Thomas W. Griffin; Helen Diller Family Comprehensive Cancer Center, University of California-San Francisco, San Francisco, CA; Janssen Research & Development, LLC, Raritan, NJ; Janssen Research & Development, LLC, Los Angeles, CA; Massachusetts General Hospital Cancer Center, Boston, MA; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Radboud University Medical Centre, Nijmegen, Netherlands; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Montreal, Montreal, QC, Canada; The University of Texas MD Anderson Cancer Center, Houston, TX; Institut Gustave Roussy, University of Paris Sud, Villejuif, France

Background: Abiraterone acetate (AA), an androgen biosynthesis inhibitor, prolongs overall survival (OS) in mCRPC patients and is approved for use in this population. The relationship of PSA kinetics to rPFS was evaluated in an exploratory analysis of patients from COU-AA-302, a randomized phase III study of AA in chemotherapy-naive mCRPC patients. **Methods:** 1,088 patients were randomized 1:1 to AA (1 g) + prednisone (P) (5 mg BID) or P alone. rPFS and OS were co-primary endpoints. rPFS was defined as time to first occurrence of bone scan progression by PCWG2 criteria, progression by CT/MRI by modified RECIST 1.0 criteria, or death from any cause; PSA changes were not a factor in determining rPFS. Quartiles of baseline PSA and % PSA decrease from baseline to nadir were analyzed. Stratified Cox regression models were used with factors for treatment, PSA outcomes, and baseline covariates performed at 55% of OS events. **Results:** 54/546 patients (10%) in AA + P arm achieved undetectable PSA vs 14/542 patients (3%) in the P arm; at median follow-up of 27.1 mos, radiographic progression was observed in 28% (AA + P) vs 50% of patients (P). There was a consistent trend of decreasing hazard of progression with decreasing baseline PSA and increasing % PSA decline (Table). Treatment effect of AA + P vs P with decreasing baseline PSA or % PSA decline remained significant ($p=0.001$) after adjusting for other factors (PSA, LDH, alk phos, hemoglobin, bone metastasis) in the model. **Conclusions:** rPFS was positively associated with the magnitude of PSA decline and inversely associated with baseline PSA. These effects remained after correcting for covariates. In all analyses, treatment with AA led to rPFS outcomes superior to P. Clinical trial information: NCT00887198.

	Baseline PSA (ng/mL) by quartile	HR[a] for progression (95% CI)	P value	% PSA decline	HR[b] for progression (95% CI)	P value
1	< 16	0.49 (0.41, 0.57)	< 0.001	No ↓	1.00 (reference)	-
2	16 - < 40	0.58 (0.46, 0.74)	< 0.001	0 - < 50	0.75 (0.60, 0.93)	0.008
3	40 - < 106	0.75 (0.60, 0.94)	0.012	50 - < 90	0.40 (0.33, 0.50)	< 0.0001
4	≥ 106	1.00 (reference)	-	≥ 90	0.22 (0.17, 0.28)	< 0.0001

[a] vs ≥ 106; [b] vs no ↓

5011 Poster Discussion Session (Board #3), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

A prognostic model for predicting overall survival in metastatic castrate-resistant prostate cancer (mCRPC) men treated with second-line chemotherapy.

Susan Halabi, Chen-Yen Lin, Eric Jay Small, Andrew J. Armstrong, Ellen B. Kaplan, Daniel Peter Petrylak, Cora N. Sternberg, Liji Shen, Stephane Oudard, Johann Sebastian De Bono, A. Oliver Sartor; Department of Biostatistics and Bioinformatics, Duke University and Alliance Statistical and Data Center, Durham, NC; Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC; University of California, San Francisco, San Francisco, CA; Duke Cancer Institute, Durham, NC; Duke University, Durham, NC; Yale University Medical Center, New Haven, CT; Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy; Sanofi-Aventis, Malvern, PA; Department of Medical Oncology, Georges Pompidou European Hospital, Paris, France; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Tulane Cancer Center, New Orleans, LA

Background: Although several prognostic models for overall survival (OS) have been developed and validated in men with chemotherapy naïve mCRPC, this work sought to develop and validate a prognostic model to predict OS in men who had progressed following first-line chemotherapy, and were receiving second line chemotherapy. **Methods:** Data from a phase III trial of cabazitaxel plus prednisone compared to mitoxantrone plus prednisone in mCRPC men who had developed progressive disease following first-line chemotherapy (TROPIC trial) were used. The TROPIC data was randomly split into training (n=507) and testing (n=248) sets. A separate data set consisting of 488 men previously treated with docetaxel who were randomly assigned to either satraplatin and prednisone or placebo and prednisone (SPARC trial), was used as a second testing set for external validation. Adaptive Lasso selected nine baseline prognostic factors of OS. A predictive score was computed from the estimated regression coefficients and used to classify patients into low ($<$-1.25) and high ($\geq$-1.25) risk groups in the two testing sets. The model was assessed on the testing sets for its predictive accuracy using area under the curve (AUC). **Results:** The 9 prognostic variables in the final model included: ECOG performance status, time since last docetaxel use, measurable disease, presence of visceral disease, pain, duration of prior hormonal use, hemoglobin, prostate specific antigen and alkaline phosphatase. The median OS in the TROPIC testing set were 11 and 16 months in the high and low risks, respectively, with a hazard ratio (HR) 2.3 (p-value$<$0.0001). The median OS in SPARC were 11 and 20 months in the high and low risk groups, respectively (HR=2.0, p$<$0.0001). The AUC for this model was 0.73 (95 CI 0.68-0.72) and 0.70 (95 CI 0.72-0.74) on the two testing sets (TROPIC, and SPARC), respectively. **Conclusions:** A prognostic model of OS in the post-docetaxel second line chemotherapy mCRPC setting was developed and externally validated. This model can be used to select patients to participate in clinical trials on the basis of their prognosis. Prospective validation is needed.

5012 **Poster Discussion Session (Board #4), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": Data from >600 patients in the control arm of the stampede trial (NCT00268476).

Noel W Clarke, Nicholas David James, Malcolm David Mason, Daniel M. Aebersold, David Paul Dearnaley, Johann Sebastian De Bono, Chris Parker, Mahesh Parmar, Alastair WS Ritchie, J. Martin Russell, Melissa Ruth Spears, George N. Thalmann, Matthew Robert Sydes, STAMPEDE Investigators; Department of Urology, The Christie NHS Foundation Trust, Manchester, United Kingdom; University of Birmingham, Birmingham, United Kingdom; Cardiff University, Cardiff, United Kingdom; University of Bern, Bern, Switzerland; Institute of Cancer Research/Royal Marsden Hospital, Sutton, United Kingdom; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; MRC Clinical Trials Unit, London, United Kingdom; Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom; Department of Urology, University Hospital, Bern, Switzerland

Background: STAMPEDE (www.stampedetrial.org) recruits men with newly-diagnosed or rapidly relapsing prostate cancer (PCa) that is metastatic (M1) or high-risk locally advanced, all commencing long-term androgen ablation therapy (AAT) for the first time. This is now the largest therapeutic RCT in PCa. We report survival outcomes for newly-diagnosed M1 control arm men in order to inform future trials in this setting. **Methods:** Newly-diagnosed men with M1 disease in the trial's control arm (standard of care: AAT alone for at least 2yr), diagnosed up to 6 months prior to randomisation, were identified from trial records in Dec-2012. We report overall survival (OS) and failure-free survival (FFS) from randomisation by primary disease characteristics. **Results:** 3703 men were recruited to STAMPEDE Oct-2005 to Dec-2012, including a control arm cohort of 630 M1 men with newly-diagnosed disease. This cohort has median age at randomisation 66yr (quartiles 60-71), median PSA 105 (quartiles 34-379) IU/l; metastases to bone only (B) 393 (62%), soft tissue only (ST) 78 (13%) or bone and soft tissue (B+ST) 159 (25%). ST was mainly lymph nodes. Median time from diagnosis to randomisation is 69 days (max 180 days). Median duration of AAT prior to randomisation is 46 days (max 105 days). There were 129 deaths, of which 111 were from PCa. Median OS from randomisation is 42 months, with 2-yr OS 74% (95%CI 68, 78) in this cohort; B 77% (95%CI 71, 83), ST 85% (95%CI 70, 93), B+ST 57% (95%CI 45, 68). Median FFS is 12 months, driven by rising PSA; 2-yr FFS 32% (95%CI 27-37). Median time from FFS event to death was 22 months. Additional data on relapse therapies will be presented. **Conclusions:** Survival, and particularly FFS, remains relatively poor for men presenting with M1 disease starting long-term AAT, despite potential access when castration-resistant (CRPC) to docetaxel and other newer therapies. Better first-line therapy is required; STAMPEDE will report many comparisons in the future. Different M1 patterns may vary prognostically. Men with M1 disease will now spend most time in a state of CRPC, which has important implications for clinicians and trialists. Clinical trial information: NCT00268476.

5013 **Poster Discussion Session (Board #5), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

A prognostic model for predicting overall survival (OS) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate (AA) after docetaxel.

Kim N. Chi, Thian San Kheoh, Charles J. Ryan, Arturo Molina, Joaquim Bellmunt, Nicholas J. Vogelzang, Dana E. Rathkopf, Karim Fizazi, Philip W. Kantoff, Jinhui Li, Johann Sebastian De Bono, Howard I. Scher; British Columbia Cancer Agency, Vancouver, BC, Canada; Janssen Research & Development, LLC, Los Angeles, CA; Helen Diller Family Comprehensive Cancer Center, University of California-San Francisco, San Francisco, CA; Hospital del Mar, Barcelona, Spain; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Memorial Sloan-Kettering Cancer Center, New York, NY; Institut Gustave Roussy, University of Paris Sud, Villejuif, France; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Janssen Research & Development, LLC, Raritan, NJ; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: COU-AA-301 was a multinational, randomized, controlled, phase III trial comparing AA + prednisone (P) (n = 797) versus placebo + P (n = 398) in mCRPC pts post-docetaxel. Using data from that trial, we developed a prognostic model for predicting OS in pts treated with AA post-chemotherapy, with a focus on readily assessable clinical parameters. **Methods:** The analyses used data from pts treated with AA in the COU-AA-301 trial for whom relevant baseline data were available (n = 729). Baseline variables were assessed for association with OS through a univariate Cox proportional hazards regression model. High/low values for accepted normal ranges were used for laboratory parameters. The Cox proportional hazards regression was used with a stepwise procedure to identify independent prognostic factors for OS. The model was subject to sensitivity analyses and the C-index was utilized as a measure of model accuracy. **Results:** The following risk factors were associated with a poor prognosis: ECOG performance status (only pts with scores of ≤ 2 were eligible for this trial) of 2 (HR = 2.19, $p < 0.0001$), presence of liver metastases (HR = 2.00, $p < 0.0001$), time from start of initial LHRH agonist therapy to start of AA treatment ≤ 36 months (HR = 1.30, $p = 0.0078$), low albumin (HR = 1.54, $p < 0.0001$), high ALP (HR = 1.38, $p = 0.0016$), and high LDH (HR = 2.31, $p < 0.0001$). Patients were categorized into 3 risk groups (good prognosis, n = 369; intermediate prognosis, n = 321; poor prognosis, n = 107) based on total number of risk factors and median OS calculated for each group (table). The C-index was 0.74 (95% CI: 0.68, 0.80). **Conclusions:** This prognostic model uses readily available clinical parameters to conveniently assess risk for mCRPC pts previously treated with docetaxel and initiating treatment with AA + P. If validated, the model will be useful in clinical practice and clinical trials. Clinical trial information: NCT00638690.

Number of risk factors	Median OS, mos (95% CI)	HR (95% CI)
0 or 1 (good)	21.3 (19.4, 27.1)	-
2 or 3 (intermediate)	13.9 (11.7, 14.8)	2.30[a] (1.89, 2.81)
4 to 6 (poor)	6.1 (4.8, 7.2)	6.19[a] (4.76, 8.05)

[a]Versus patients with good prognosis.

5014 Poster Discussion Session (Board #6), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Effect of corticosteroid (CS) use at baseline (CUB) on overall survival (OS) in patients (pts) receiving abiraterone acetate (AA): Results from a randomized study (COU-AA-301) in metastatic castration-resistant prostate cancer (mCRPC) post-docetaxel (D).

Robert B. Montgomery, Thian San Kheoh, Arturo Molina, Jinhui Li, Joaquim Bellmunt, Charles J. Ryan, Namphuong Tran, Yohann Loriot, Eleni Efstathiou, Howard I. Scher, Johann Sebastian De Bono; University of Washington, Seattle, WA; Janssen Research & Development, LLC, Los Angeles, CA; Janssen Research & Development, LLC, Raritan, NJ; University Hospital del Mar-IMIM, Barcelona, Spain; Helen Diller Family Comprehensive Cancer Center, University of California-San Francisco, San Francisco, CA; Institut Gustave Roussy, Villejuif, France; Deptartment of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center/Deptartment of Clinical Therapeutics, The University of Athens Greece, Houston, TX; Memorial Sloan-Kettering Cancer Center, New York, NY; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: CS have been used to mitigate mineralocorticoid-related effects and restore sensitivity to AA (Attard et al., *J Clin Oncol*. 2008). Prednisone (P) was also used as an active comparator in the COU-AA-301 (de Bono et al., *N Engl J Med*. 2011) and COU-AA-302 (Ryan et al., *N Engl J Med*. 2013) AA pivotal studies. CUB has also been reported to adversely influence OS in the AFFIRM study, which may reflect an influence on disease biology or unrecognized factors that are not a part of clinically based prognostic models (Scher et al., *Ann Oncol*. 2012). This post hoc exploratory analysis investigated whether CUB is a prognostic factor for OS in mCRPC post-D pts treated with AA + P or P alone. **Methods:** COU-AA-301 is a randomized double-blind study of AA (1 g) + P (5 mg po BID) vs placebo + P in mCRPC post-D. The primary endpoint was OS. All pts had received CS with D therapy. CUB included P (n = 272), dexamethasone (n = 107), and others (n = 110). 797 pts were not on CUB. Median times were estimated by the product-limit method; Cox model was used to obtain the hazard ratio (HR) and associated confidence interval (CI). **Results:** Pts with CUB had worse baseline disease characteristics (including adverse ECOG PS, Gleason score, analgesic score, and LDH) (all $p < 0.05$). Pts receiving CUB had inferior OS; AA + P improved OS independent of CUB. (Table). CUB was an independent prognostic factor in multivariate analysis ($p = 0.03$; HR 1.22 [95% CI: 1.02-1.45]) that was associated with lower baseline androgen levels ($p < 0.0001$). In a stepwise selection model, CUB was not an independent prognostic factor. **Conclusions:** In this study, CUB was not a strong independent prognostic factor in mCRPC post-D pts treated with AA + P or P alone. CUB was associated with worse baseline disease characteristics and inferior OS in this study, in which all pts subsequently received CS. Clinical trial information: NCT00638690.

	No CUB			CUB		
	AA + P n = 537	P n = 260	HR (95% CI) p value	AA + P n =260	P n = 138	HR (95% CI) p value
Median OS, mos	17.3	13.4	0.76 (0.63-0.92) 0.0044	12.7	9.3	0.79 (0.62-1.00) 0.0502

5015 Poster Discussion Session (Board #7), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Evolving patterns of metastatic disease in castration-resistant prostate cancer (CRPC) reported in clinical trials from 1990 to 2011.

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Background: Bone remains the most common site of metastasis in CRPC. With new therapies extending survival in metastatic CRPC (mCRPC), we hypothesized that the incidence of non-osseous metastases is increasing over time. In this study, we evaluated the pattern of metastatic disease in mCRPC as reported in baseline characteristics of prospective clinical trials over 2 decades. **Methods:** We identified all therapeutic studies in patients with mCRPC in Pubmed and ASCO abstracts from 1990-2011. Inclusion criteria included phase 2 or 3 clinical trials in mCRPC with available baseline demographic data and no exclusion of specific site of metastatic disease (except brain). ASCO abstracts were limited to presentations in which data were available online. For each study, demographic data and study-reported sites of non-osseous metastatic disease were recorded (lymph node, visceral, soft tissue, liver). For each type of metastasis, weighted least squares linear regression models were used to evaluate temporal trends. **Results:** We identified a total of 290 eligible studies (270 phase II and 20 phase III) involving 19,110 patients. Of these, 127 studies reported data on non-osseous metastases and prior chemotherapy. There was a significant trend over time ($p=0.001$) of increasing proportions of patients with non-osseous metastasis in both chemotherapy- naïve and treated groups (1.4% per year increase). Increased lymph node, visceral, and soft tissue metastases were seen over the study period. However, the proportion of patients with liver metastasis remained relatively stable **Conclusions:** In this study, we noted an increasing trend of non-osseous metastatic disease in patients with mCRPC over 20 years. This included lymph node, visceral and soft tissue metastatic disease, and this trend was observed in both chemotherapy-naïve and treated patients. Longer survival and new therapies may be changing the clinical presentation of patients with mCRPC.

5016 Poster Discussion Session (Board #8), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

A randomized phase II study evaluating the optimal sequencing of sipuleucel-T and androgen deprivation therapy (ADT) in biochemically recurrent prostate cancer (BRPC): Immune results.

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Background: ADT is a standard treatment for men with BRPC after failure of local therapy, and has immunomodulatory effects. Sipuleucel-T is an autologous cellular immunotherapy approved for asymptomatic/minimally symptomatic metastatic castrate resistant prostate cancer. The STAND trial (NCT01431391) aimed to evaluate optimal sequencing of sipuleucel-T and ADT in men with BRPC at high risk for metastases (*ie* PSA doubling time $\leq$12 mo). **Methods:** Men were randomized (1:1) to Arm 1: sipuleucel-T followed by ADT (2 wks after 3rd infusion); or Arm 2: ADT (3 mo lead in) followed by sipuleucel-T. All men had 3 doses of sipuleucel-T and 12 mo of ADT (45 mg leuprolide SQ at 6 mo intervals). The primary endpoint is cellular immune response (ELISPOT to PA2024 [PAP-GMCSF]). Secondary endpoints are humoral and cytokine responses, product parameters and safety. **Results:** 68 men were randomized. Preliminary data show higher levels of serum cytokines in Arm 2 *vs* Arm 1, with a pattern suggesting a mixed T_H1/T_H2 cellular immune response; elevations were seen in T_H1 (IFNγ, IL 12), T_H2 (IL 4, 5, 10, 13) and T_H17 (IL 17) subsets (all $P<.05$). The increase in T_H1 cytokines was consistent with a trend toward higher PA2024-specific ELISPOT responses 2 wk after the 3rd sipuleucel-T infusion in Arm 2 *vs* Arm 1 (40.5 *vs* 12.8 spots; $P=.086$), suggesting increased T cell activation in Arm 2. Antigen-specific humoral responses were induced in both arms with no differences yet observed between arms. Sipuleucel-T product parameters were roughly equivalent in both arms with APC activation data indicating a robust prime-boost effect. **Conclusions:** While confirmation is required, these preliminary data suggest that tumor-specific T cell responses and broad based immune responses are augmented when sipuleucel-T is given *after* rather than *before* ADT initiation. These data are consistent with preclinical studies showing that ADT enhances T cell activity, and provide preliminary evidence that combining ADT with sipuleucel-T may augment adaptive immunity. Further follow up will determine whether augmented immune responses correlate with clinical parameters (*eg* PSA recurrence). Clinical trial information: NCT01431391.

5017 Poster Discussion Session (Board #9), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Sulforaphane treatment in men with recurrent prostate cancer.

Joshi J. Alumkal, Rachel Slottke, Motomi Mori, Jacob Schwartzman, Julie Nicole Graff, Tomasz M. Beer, Christopher W. Ryan, Dennis R Koop, Ganesh Cherala, Myrna Munar, Jason Frederick Flamiatos, Lina Gao, Erin Tucker; Oregon Health & Science University Knight Cancer Institute, Portland, OR; Oregon Health & Science University, Portland, OR; Oregon Health & Science University Knight Cancer Institute, Portland VA Medical Center, Portland, OR

Background: Diets high in cruciferous vegetables are strongly associated with lower prostate cancer risk. Sulforaphane is a constituent of these foods postulated to harbor the anti-neoplastic activity based on pre-clinical evidence in multiple tumor models. Our own work demonstrates that sulforaphane inhibits HDAC function and suppresses AR signaling in prostate cancer cells (Gibbs, et al *PNAS* 2009). However, the anti-tumor efficacy and safety of sulforaphane in men with prostate cancer was unknown. **Methods:** In this single arm study, we treated patients with biochemical (PSA)-recurrence of prostate cancer with 200 μmol of sulforaphane extracts for up to 20 weeks. The primary endpoint was PSA response rate ($>$50% decline in PSA). Other efficacy endpoints included: maximal PSA decline and percent change in PSA from baseline to end of study. We also analyzed PSA doubling time changes using a mixed effects model. Genotyping for *GSTM1* that contributes to sulforaphane metabolism, sulforaphane pharmacokinetics (PK), and pharmacodynamic (PD) measurements of HDAC inhibition in mononuclear cells (MCs) were also performed. **Results:** Twenty patients were enrolled, and 16/20 (80%) completed the pre-planned 20 weeks of treatment. One patient experienced a PSA decline $>$50%. Thirty-five percent of patients had lesser PSA declines (3% to 20%), and 15% of patients had a final PSA lower than baseline. There was a significant reduction in PSA doubling time (6 months pre-study vs. 9.4 months on-study, $p=.013$). Of note, testosterone levels remained non-castrate in all subjects. PK analysis demonstrated that *GSTM1* null genotype correlated with longer sulforaphane T1/2 (half-life) (2.6 hours for *GSTM1* null vs. 2.1 hours for *GSTM1* intact, $p=0.04$). Sulforaphane treatment also increased histone acetylation in PD assays in MCs. Finally, no grade three adverse events were seen, and only one patient discontinued study treatment for toxicity (grade one GI discomfort). **Conclusions:** Treatment with 200 μmol per day of sulforaphane is feasible, safe, and inhibits HDAC function. This combined with the preliminary observation of PSA modulation, which may indicate biologic activity, provides the basis for dose escalation studies of sulforaphane in men with prostate cancer. Clinical trial information: NCT01228084.

5018 Poster Discussion Session (Board #10), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Prostate-specific membrane antigen antibody drug conjugate (PSMA ADC): A phase I trial in metastatic castration-resistant prostate cancer (mCRPC) previously treated with a taxane.

Daniel Peter Petrylak, Philip W. Kantoff, Anthony E. Mega, Nicholas J. Vogelzang, Joe Stephenson, Mark T. Fleming, Nancy Stambler, Michaela Petrini, Sara Blattman, Robert Joseph Israel; Yale University Medical Center, New Haven, CT; Dana-Farber Cancer Institute, Boston, MA; Brown University Oncology Group, Providence, RI; Comprehensive Cancer Centers of Nevada, The US Oncology Network, Las Vegas, NV; Cancer Centers of the Carolinas, Greenville, SC; Virginia Oncology Associates, Norfolk, VA; Progenics Pharmaceuticals, Inc., Tarrytown, NY

Background: The abundant expression of prostate specific membrane antigen (PSMA) on prostate cancer cells provides a rationale for antibody therapy. PSMA ADC is a fully human antibody to PSMA linked to the microtubule disrupting agent monomethyl auristatin E (MMAE). It binds PSMA and is internalized within the cancer cell where cleavage by lysosomal enzymes release free MMAE, causing cell cycle arrest and apoptosis. A phase 1 dose escalation study of PSMA ADC in taxane-refractory mCRPC has been completed. **Methods:** Patients with progressive mCRPC following taxane-containing chemotherapy and ECOG status of 0 or 1 were eligible. PSMA ADC was administered by IV infusion Q3W for up to 4 cycles. Safety, pharmacokinetics, PSA, circulating tumor cells (CTC), immunogenicity and clinical progression were assessed. Serum PSMA ADC and total anti-PSMA ADC antibodies were measured by ELISA, and free MMAE was measured by LC/MS/MS.The dosing cohorts ranged from 0.4 mg/kg to 2.8 mg/kg. Subjects who benefitted from PSMA ADC were eligible for treatment in an extension study. **Results:** 52 subjects were dosed in 9 dose levels. All subjects received prior docetaxel, 6 also received cabazitaxel and 3 subjects also received paclitaxel. PSMA ADC was generally well tolerated with the most commonly seen adverse events being anorexia and fatigue. 16 patients reported peripheral neuropathies, including 3 with grade 3. Dose limiting toxicities (DLT) seen at 2.8 mg/kg were neutropenia (one death) and reversible elevations in liver function tests (LFTs). Antitumor activity was manifested as reductions either in PSA or in CTCs in approximately 50% of patients at $\geq$ 1.8 mg/kg PSMA ADC. Exposure to PSMA ADC increased with dose and was ~1,000-fold greater than MMAE exposure. There was no accumulation. Conclusion: PSMA ADC in this study was generally well tolerated in subjects with progressive mCRPC, previously treated with taxane. Antitumor activity was seen at doses $\geq$ 1.8 mg/kg. DLTs were neutropenia and reversible LFT abnormalities. The maximum tolerated dose was determined to be 2.5 mg/kg. A phase 2 trial of PSMA ADC in taxane refractory mCRPC has been initiated at 2.5 mg/kg. Clinical trial information: NCT01414283.

5019 Poster Discussion Session (Board #11), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Randomized phase II study with window-design to evaluate anti-tumor activity of the survivin antisense oligonucleotide (ASO) ly2181308 in combination with docetaxel for first-line treatment of castrate-resistant prostate cancer (CRPC).

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Background: In prostate cancer, expression of survivin, a protein that inhibits apoptosis, is associated with resistance to taxanes and poor outcome. LY2181308 reduces survivin expression and consequently is expected to improve activity of taxanes, such as docetaxel. A randomized phase II study was conducted to assess the activity of the combination. **Methods:** Adult patients (pts) with CRPC, ECOG performance status <2, and no bone or CNSmetastases were randomized 1:2 to standard docetaxel/prednisone every 21 days (Arm A) or standard therapy combined with LY2181308 given as a 3-hr IV infusion (Arm B). Analysis was planned and performed after 130 pts progressed or died. This assessment provided a 70% chance of detecting a difference in progression-free survival (PFS) at the 10% significance level. Initially, LY2181308 was given as a loading dose (3 consecutive days) and then as a weekly 3-hr IV maintenance dose. Arm B also included a window treatment with LY2181308 monotherapy equivalent to a 21-day cycle of docetaxel before starting combined treatment. The primary endpoint was PFS. **Results:** This study enrolled 154 pts. The median PFS for Arm B was 8.64 (90% CI, 7.39–10.45) months vs. 9.00 (90% CI, 7.00–10.09) months in Arm A, showing no statistical difference (log rank $p=0.755$). The median overall survival (OS) for Arm B was 27.04 (90% CI, 19.94–33.41) months vs. 29.04 (90% CI, 20.11–39.26) months for Arm A (log-rank $p= 0.838$). The PSA responses ($>50\%$ reduction in PSA) were similar: 56.9% for Arm A and 56.1% in Arm B ($p=0.856$). Most pts had no pain or mild pain at baseline and during the active period. Pts treated in Arm B had a higher frequency of serious and nonserious adverse events (AEs) than those in Arm A. The observed AE and pharmacokinetic (PK) profiles were consistent with the known safety and PK profiles of LY2181308 and docetaxel. **Conclusions:** The addition of LY2181308 to a standard docetaxel/prednisone regimen showed no improvement in PFS, PSA response, and OS in first line CRPC pts. The safety profile of docetaxel and LY2181308 is predictable and consistent with the known safety profiles. Clinical trial information: NCT00642018.

5020 Poster Discussion Session (Board #12), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

A phase I study of the safety and pharmacokinetics of DSTP3086S, an anti-STEAP1 antibody-drug conjugate (ADC), in patients (pts) with metastatic castration-resistant prostate cancer (CRPC).

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Background: Six-transmembrane epithelial antigen of the prostate-1 (STEAP1) protein is a cell-surface antigen overexpressed in human epithelial prostate cancers. The ADC DSTP3086S contains the humanized IgG1 anti-STEAP1 monoclonal antibody linked to the potent anti-mitotic agent MMAE. **Methods:** This study evaluated safety, pharmacokinetics, and pharmacodynamic activity of intravenous DSTP3086S (0.3-2.8 mg/kg) given every 3 weeks (q3w) to pts with CRPC. A traditional 3+3 design was used to determine maximum-tolerated dose, followed by cohort expansion at the recommended Phase II dose (RP2D). Clinical activity was evaluated per PCWG criteria. Dose escalation results are presented. **Results:** Twenty-eight pts were enrolled with a median age of 67 (43-76), all ECOG PS 0-1, and with a median of 7 prior systemic regimens (including a median of 4 hormonal and 3 non-hormonal regimens). Pts received a median of 3 doses (range 1-10) of DSTP3086S. Reversible Grade 3 transaminitis DLTs occurred in one pt each in the 2.25 mg/kg and 2.8 mg/kg cohorts. Serious AEs (SAE) related to study drug (3 total) included one DVT (Grade 3) in the 1.5 mg/kg cohort, as well as one GI hemorrhage (Grade 3) and one sepsis event (Grade 5) in the 2.25 mg/kg cohort. The most common related AEs across all doses were fatigue (36%), nausea (32%), constipation (25%), decreased appetite and diarrhea (each 21%), and musculoskeletal pain and vomiting (each 18%). Exposure for total antibody, free MMAE, and conjugated MMAE was dose proportional. Approximately 60% of the tumor samples assessed showed high STEAP1 expression. CTC reductions were most robust at 2.8 mg/kg; 4/4 patients with unfavorable CTCs at baseline (median of 99, range: 21-205) exhibited CTC conversions from unfavorable to favorable (<5) after a single dose of DSTP3086S. CTC conversions were also observed at lower doses. PSA decreases of $\geq 50\%$ were observed in 1 pt at 2.25 mg/kg, and 2 pts at 2.8 mg/kg who also had PCWG2 radiologic responses. **Conclusions:** DSTP3086S at the RP2D of 2.8 mg/kg q3w has a tolerable safety profile and shows evidence of anti-tumor activity. Enrollment in the expansion cohort is ongoing.

5021 Poster Discussion Session (Board #13), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Safety of radium-223 dichloride (Ra-223) with docetaxel (D) in patients with bone metastases from castration-resistant prostate cancer (CRPC): A phase I Prostate Cancer Clinical Trials Consortium Study.

Michael J. Morris, Hans J. Hammers, Christopher Sweeney, Emmanuel S. Antonarakis, Steve Y. Cho, Neeta Pandit-Taskar, Heather Jacene, Marianne Bloma, Anne-Kirsti Aksnes, C. Gillies O'Bryan-Tear, Jorge A. Carrasquillo; Memorial Sloan-Kettering Cancer Center, New York, NY; Johns Hopkins University, Baltimore, MD; Dana-Farber Cancer Institute, Boston, MA; Algeta ASA, Oslo, Norway

Background: Ra-223, a first-in-class α-emitting pharmaceutical, targets bone metastases (mets) with high-energy α-particles of very short range ($< 100\ \mu m$). D is an approved chemotherapy with demonstrated survival benefit for patients progressing after castrating hormone therapy. We are exploring the hypothesis that simultaneously targeting the tumor and the bone is clinically superior to targeting either alone. We therefore conducted a phase I study of Ra-223 + D in patients with CRPC and bone mets to establish the safety of the combination. **Methods:** Eligible patients had confirmedsymptomaticCRPC with ≥ 2 bone mets and were candidates for treatment with D. Dose escalation followed a 3 + 3 design, with no intrapatient dose escalation or overlapping of cohorts. Patients were to receive 2 combined doses of Ra-223 q6wk + D q3wk (cohort 1: Ra-223/D = 25 kBq/kg /75 mg/m^2; cohort 2: Ra-223/D = 25 kBq/kg /60 mg/m^2; and cohort 3: Ra-223/D = 50 kBq/kg /60 mg/m^2). Dose-limiting toxicity was assessed 6 weeks after first Ra-223 + D injection. Long-term safety data were collected every 3 months after end of study treatment for up to 1 year after start of study treatment. **Results:** 17 patients were treated, 7 each in cohorts 1 and 3 (1 patient in each cohort discontinued early and was replaced), and 3 in cohort 2. There was no discontinuation or delay of Ra-223 due to adverse events, and so far no reports of long-term toxicity during follow-up. 4 cases of febrile neutropenia occurred during study treatment (12 wk): 3 occurred in cohort 1 (1 was 7 days after first Ra-223 + D, and 2 were in the same subject, both occurring 1 wk after first and second doses of D alone [wk 4 and 10]); 1 occurred in cohort 3, 1 week after second Ra-223 + D (wk 7). Other safety data were as expected based on Ra-223 and D monotherapy data. **Conclusions:** The phase IIa regimen of Ra-223 + D utilizes a regimen of D 60 mg/m^2 q3wk $\times$ 10 + Ra-223 50 kBq/kg q6wk $\times$ 5. The regimen is currently being explored in a randomized 2:1 open-label expanded safety cohort comparing Ra-223 + D versus D 75 mg/m^2 alone (standard dose). Clinical trial information: NCT01106352.

5022 Poster Discussion Session (Board #14), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Mortality at 120 days following prostatic biopsy: Analysis of data in the PLCO study.

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Background: With the widespread use of PSA testing for prostate cancer screening in population, more prostate biopsy are being performed and seem set to increase in number. The safety of this diagnostic procedure needs to be ascertained. Only one study evaluated the mortality following prostate biopsy (Gallina et al, Int J Cancer 2008;123:647-52) and reported an increase of 2 deaths per 1,000 biopsies. Our objective was to re-evaluate the risk of death following prostate biopsy in a large, well-conducted randomised trial – the Prostate, Lung, Colorectal and Ovary (PLCO) Study. **Methods:** We extracted data from the PLCO study on all men participating in the study with a follow-up until 31/12/2009. All biopsies performed since randomisation were included. Cause of death was defined by ICD9 classification. **Results:** Among 12,300 prostate biopsies, 36 deaths occurred within120 days: 17/8390 in the intervention arm and 19/3910 in the control group. Only 17 deaths had neoplasm listed as the underlying cause of death. Thirty-two deaths out of 9,124 (0.35%) occurred in the positive biopsy group compared to 4 out of 3,176 (0.13%) in the negative biopsy group. In this latest group, this represents 1.3 deaths per 1,000 biopsies. Deaths occurred in all age groups from 55-69 to 70-74, and there was no difference identified in age between study arms ($p=0.45$) nor between those with a prostate cancer diagnosis and those not ($p=0.73$). **Conclusions:** The mortality rate at 120 days following prostate biopsy of 1.3 deaths per 1,000 biopsies, in a population free of cancer, is a serious concern for the computation of benefit risk associated with PSA testing. This figure is in line with the risk reported by Gallina et al (2008) and is now based on a properly monitored population. This prostatic biopsy mortality would occur earlier than any benefit from a screening program and could reverse any potential gain from screening such as recorded in ERSPC study.

5023 Poster Discussion Session (Board #15), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Prospective evaluation of testosterone (T) recovery and PSA relapse following 18 months of androgen deprivation (ADT) after prostatectomy (RP): Results from the TAX-3501 trial.

Michael Thomas Schweizer, Peng Huang, Cora N. Sternberg, Ronald De Wit, Evelyne Brana Ecstein-Fraisse, Michael W. Kattan, Adam S Kibel, Mario A. Eisenberger; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy; Erasmus MC, Rotterdam, Netherlands; Sanofi, Vitry-sur-Seine, France; Cleveland Clinic Quantitative Health Sciences, Cleveland, OH; Brigham and Women's Hospital/Harvard University, Boston, MA

Background: Surgical adjuvant trials in men with prostate cancer (PCa) employing progression free (PFS) and overall survival (OS) endpoints require large sample sizes and long-term follow-up, challenging planned study completion. Recent adjuvant trials are designed to evaluate PSA progression as the primary study endpoint. Since PSA is T-responsive, a thorough understanding of T recovery kinetics after ADT is needed. **Methods:** TAX-3501 was a randomized phase III adjuvant study post-RP in men with high-risk PCa (n=228) comparing 18 months of hormonal therapy with (CHT) or without (HT) docetaxel either immediately (I) or deferred (D). We analyzed the T recovery data in 108 patients treated with HT who had at least one post-treatment T value. **Results:** After a median post-treatment follow-up of 676 days (d) (interquartile range 478-847 d) 90 (83%) and 64 (59%) of men had T recovery to >150 ng/dL and to baseline respectively. No significant differences in T recovery between groups were observed (Table). The median time to T recovery from the last day of treatment to >150 ng/dL was 306 d (95% CI, 294-345 d) and to baseline was 487 d (95% CI, 457-546 d). The baseline T recovery in the combined docetaxel [i.e. I(CHT)+D(CHT)] and HT arms [i.e. I(HT)+D(HT)] was not significantly different at 458 d (95% CI, 336-529 d) and 535 d (95% CI, 457-749 d) respectively (HR 1.4, P=0.18). After a median total follow-up of 3.4 years(IQR 2.3–3.8 years) 39/228 (17%) patients had PSA progression, metastatic progression occurred in 1 patient. **Conclusions:** Prospective analyses of T kinetics in TAX-3501 indicate that recovery is prolonged after 18 months of HT and PSA relapses occur late. Given that PSA is androgen responsive, concomitant post-HT T monitoring is critical for understanding PSA relapse rates after HT. Further, since the correlation of PSA relapse with PFS and OS in the adjuvant setting remains poorly defined, metastasis-free survival may be a more reliable and meaningful clinical endpoint. Clinical trial information: NCT00283062.

	Recover T >150 ng/dL		Recover to baseline T	
Group	No	Yes (%)	No	Yes (%)
I(CHT)	5	32 (86)	12	25 (68)
I(HT)	3	43 (93)	17	29 (63)
D(CHT)	5	9 (64)	8	6 (43)
D(HT)	5	6 (55)	7	4 (36)
Total	18	90 (83)	44	64 (59)

5024 Poster Discussion Session (Board #16), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Impact of prostate cancer national guidelines on brachytherapy monotherapy practice patterns.

Yolanda Diana Tseng, Alan T Paciorek, Neil E Martin, Anthony Victor D'Amico, Matthew R. Cooperberg, Paul Linh Nguyen; Harvard Radiation Oncology Program, Boston, MA; Department of Urology and Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA; Department of Radiation Oncology, Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston, MA; University of California, San Francisco, San Francisco, CA; Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA

Background: In 1999, the American Brachytherapy Society (ABS) recommended brachytherapy monotherapy (BT) be limited to low-risk prostate cancer, in part because a high-impact 1998 publication suggested that intermediate or high-risk disease had worse outcomes with BT than with external beam radiation (EBRT) or radical prostatectomy (RP). We studied temporal patterns of BT use before and after the 1999 ABS published guidelines as compared with 4 other treatment options. **Methods:** A retrospective analysis was performed of all men with T1c-T3cN0M0 prostate cancer treated definitively in the United States from 1990 to 2011 in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry. Logistic regression was used to estimate adjusted odds ratios (AOR) comparing BT use with other treatment groups between the 1990-1998 and 1999-2011 periods, controlling for age, disease characteristics, and clinic site type. **Results:** 8128 men received BT (n=1117), BT+EBRT (n=313), EBRT alone (n=596), EBRT+androgen deprivation therapy (ADT, n=613), or RP (n=5489) for modified D'Amico low (n=3506), intermediate (n=2938) or high-risk (n=1684) disease. By t-tests, BT patients were younger than either EBRT or EBRT+ADT patients (both $p<0.001$), older than RP patients ($p<0.001$), and had lower risk disease than men in any of the four treatment groups (all Cochran-Mantel-Haenszel chi-square $p<0.001$). BT comprised 6.1% and 16.6% of all treatments in 1990-1998 and 1999-2011, respectively (Pearson $p<0.01$). The odds of BT use remained increased after adjusting for potential confounders (AOR 4.50, $p<0.001$). Increased BT use was seen only among low (AOR 5.06, $p<0.001$) and intermediate-risk patients (AOR 4.59, $p<0.001$). Among men with low or intermediate-risk disease, BT use increased compared with EBRT (AOR_{LOW} 10.00; AOR_{INT} 12.66, both $p<0.001$), EBRT+ADT (AOR_{LOW} 2.90, $p=0.0037$; AOR_{INT} 2.15, $p=0.0041$) and RP (AOR_{LOW} 4.76; AOR_{INT}5.10, both $p<0.001$). **Conclusions:** Despite national guidelines to the contrary, brachytherapy monotherapy for intermediate-risk prostate cancer increased over time relative to other treatments. Further studies are needed to identify factors that contribute to this evidence-practice gap.

5026 **Poster Discussion Session (Board #18), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM**

An exploratory analysis of bone scan lesion area (BSLA), circulating tumor cell (CTC) change, pain reduction, and overall survival (OS) in patients (pts) with castration-resistant prostate cancer (CRPC) treated with cabozantinib (cabo): Updated results of a phase II nonrandomized expansion (NRE) cohort.

Howard I. Scher, Matthew R. Smith, Christopher Sweeney, Paul Gettys Corn, Christopher Logothetis, Nicholas J. Vogelzang, David C. Smith, Maha Hussain, Daniel J. George, Johann Sebastian De Bono, Celestia S. Higano, Eric Jay Small, Jonathan Goldin, Matthew S. Brown, Dana T. Aftab, Mojtaba Noursalehi, Aaron Weitzman, Ethan M. Basch; Memorial Sloan-Kettering Cancer Center, New York, NY; Massachusetts General Hospital Cancer Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Comprehensive Cancer Centers of Nevada, The US Oncology Network, Las Vegas, NV; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Duke Cancer Institute, Durham, NC; The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Fred Hutchinson Cancer Research Center, Seattle, WA; University of California, San Francisco, San Francisco, CA; University of California, Los Angeles, Los Angeles, CA; Center for Computer Vision and Imaging Biomarkers, University of California, Los Angeles, CA; Exelixis, Inc, South San Francisco, CA

Background: The results of 144 pts with metastatic CRPC treated in a phase II NRE cohort with daily cabo 100 mg and 40 mg starting doses have been previously reported. Substantial rates of bone scan improvement, reductions in CTC counts and pain relief were observed. To better understand the implication of these effects, the association with OS was explored. **Methods:** Relevant baseline variables (LDH, BSLA, visceral disease, pain, hemoglobin, CTCs) and post-treatment changes at week 6: ≥30% reduction in BSLA using computer-aided assessment, CTC conversion (>5 vs. 4 or less/7.5 ml of blood), and pain intensity (7 day averaged worst pain score; BPI scale; using an IVR system) were associated with OS in 144 CRPC pts with bone metastasis who progressed within 6 months of docetaxel (D) treatment (≥225 mg/m^2) in either bone or soft tissue. Median OS was compared between responders and non-responders for each of the above outcomes categories using a Cox proportional hazard model. The findings were examined further after adjusting for significant baseline covariates selected from a stepwise Cox regression model. **Results:** See Table. **Conclusions:** Recognizing the limitations of associating response with survival, this retrospective analysis of decreases in BSLA, CTC conversions and reductions in pain intensity support further study in ongoing phase III trials. Clinical trial information: NCT00940225.

Baseline characteristics, N=144.

Median age	66	Sites of disease, %		
Prior therapies, %		Bone	100	
≥2 prior lines therapy including docetaxel	73	Visceral	31	
Cabazitaxel	24	Moderate to severe pain (BPI≥4), %	47	
Abiraterone	43	Median CTC count	37	
Progression <1 mo from last taxane dose, %	36	CTC count ≥5, %	80	
Results				
Median overall survival, mos		10.8 (CI, 9.1-13.0)		
	Univariate analysis		Analysis adjusted for covariates	
Response categories	HR (95% CI)	P	HR (95% CI)	P
Bone scan response	0.62 (0.38-1.00)	0.054	0.47 (0.28-0.79)	0.005
CTC conversion	0.40 (0.21-0.78)	0.007	0.42 (0.19-0.92)	0.031
Pain	0.65 (0.34-1.24)	0.186	0.51 (0.24-1.11)	0.090

5028 Poster Discussion Session (Board #20), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

The genomic relationship among matched prostate cancer foci.

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Background: Cancer management is influenced by how one views progression and how one calculates the risk of metastases and death. For prostate cancer, this is based largely on histologic appearance, or Gleason score. Cancers with a Gleason score of 6 exhibit indolent behavior and are often considered low risk. Despite recommendations supporting active surveillance for Gleason 6 prostate cancer, the vast majority of American patients receive aggressive local therapy, in part based on a presumption that low grade cancer progresses to high grade, lethal disease. **Methods:** To assess the genomic relationship between low and high grade disease, laser capture microdissection was used to isolate concurrent cancer foci from prostates with multifocal disease, and somatic mutations were identified using exome sequencing. The relationship between a Gleason 6 focus and a concurrent Gleason 8 or higher focus was determined for four subjects, and a lymph node metastasis was examined for two of those subjects. **Results:** We obtained an average of 41-fold median coverage of the exome, with an average high confidence mutation rate of 0.8/Mb. Seventy of 79 (0.886) high confidence somatic mutations in low grade disease were private to the low grade foci. For the cases for which a metastatic focus was available, 15 of 80 (0.188) high confidence somatic mutations in the high grade focus were private. Seven of the 80 (0.088) were shared with low grade foci, and 65 (0.813) were shared with metastatic foci. **Conclusions:** The pattern of shared versus private mutations is consistent with early divergence between Gleason 6 and Gleason 8 or 9 disease, and late divergence between Gleason 8 disease and lymph node metastases. These data support a model of parallel evolution of lower and higher Gleason score disease, rather than progression from Gleason 6 to higher Gleason scores.

5029 Poster Discussion Session (Board #21), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Evidence for a field effect in early prostate cancer (PCa): Gene expression profiles in normal-appearing prostate tissue (NT) adjacent to tumor (T) as predictors of clinical outcome.

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Background: We previously identified genes whose expression predicts aggressive PCa (clinical recurrence (cR), prostate cancer death (PCD), adverse pathology) when assessed in histologically heterogeneous tumor foci and in biopsies (Klein ASCO 2012). These results enabled the definition of a multi-gene Genomic Prostate Score (GPS), which has been clinically validated (Cooperberg AUA 2013). There is interest regarding a possible field effect in PCa, i.e. molecular alterations throughout the gland that may influence PCa development. We conducted exploratory analyses to evaluate gene expression, including GPS, in adjacent normal-appearing tissue (NT) for prediction of cR and PCD. **Methods:** Cohort sampling was used to select 127 patients with and 374 without cR from 2,641 patients treated with RP for T1/T2 PCa. Expression of 732 genes was measured by qRT-PCR separately in T and NT (defined as $>$ 3 mm from T) specimens. GPS (0-100 units) was determined using the genes and algorithm from the validation study. Analysis used Cox proportional hazards models and Storey's false discovery rate (FDR) control. **Results:** 410 evaluable patients had paired T and NT. Of the 405 genes which were predictive of outcome in T (FDR $<$ 20%), 289 (71%) showed similar but weaker effects in NT. 47 genes were associated with cR in NT (FDR $<$ 20%), of which 34 also concordantly predicted cR in T (FDR $<$ 20%). GPS assessed in NT significantly predicted time to cR (HR/20 units = 1.8; 95% CI: 1.3-2.4; p$<$ 0.001) and PCD (HR/20 units = 1.9; 95% CI: 1.2-3.0; p = 0.005) but was less predictive than GPS in T (HR/20 units = 4.8 for cR; 95% CI: 3.7-6.2; p $<$ 0.001 and HR/20 units = 6.9 for PCD; 95% CI: 4.4-10.7; p $<$ 0.001). The strongest components of GPS in predicting cR and PCD in NT were stromal response and androgen signaling genes (p $<$ 0.05); proliferation and cellular organization genes did not consistently provide a significant contribution in NT. **Conclusions:** These data indicate that gene expression profiles, including GPS, can predict outcome in NT, albeit more weakly than in tumor. These findings suggest that there is an underlying field effect associated with the development of aggressive PCa.

5030 Poster Discussion Session (Board #22), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Genomic heterogeneity of circulating tumor cells in castration-resistant prostate cancer (CRPC) revealed by single-cell sequencing.

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Background: Circulating tumor cells (CTC) provide an opportunity to sample multiple metastatic tumor sites through a single blood draw – a "fluid biopsy." NextGen DNA sequencing provides the means to obtain detailed genetic information from captured cells prior to and during treatment. Here we demonstrate the use of DNA sequencing to interrogate genome-wide copy number variations (CNV) at the single-cell level in CTC isolated from pts with CRPC. **Methods:** Pre- and post-treatment blood samples were obtained from pts treated at MSKCC. EpCAM+ events were collected singly and in groups by cytometric flow sorting and were subjected to DNA amplification and Illumina NextGeneration sequencing. Parallel samples were assayed using the Veridex CellSearch method to ensure the presence of malignant cells. **Results:** Samples with up to 50 EpCAM+ events analyzed in bulk displayed CNV patterns expected from published CRPC data. Subsequent single cell analyses showed that the method could reliably detect common genomic markers in CRPC, including AR amplification, PTEN and RB1 loss, and the TMPRSS-ERG fusion. Individual genomic CNV profiles obtained from 125 single cells isolated from 15 patients were then analyzed. Using unsupervised clustering, cells from each pt showed a closely related lineage structure, consistent with an evolution from a common ancestor. The degree of genomic heterogeneity within CTC from an individual pt was highly variable, with R^2 correlation coefficients ranging from >0.92 (nearly homogeneous) to <0.75 (mixed populations). Two pts harbored separate subpopulations with both amplified AR and non-amplified AR cells and another displayed mixtures of genetic markers that changed over the course of treatment. **Conclusions:** The observed variation in complexity of CTC populations in CRPC pts underscores the importance of being able to sample and analyze multiple cells from an individual pt on multiple occasions and with real time analytics. Doing so is essential to understand and identify mechanisms of resistance so that they can be targeted effectively. Supported by STARR Cancer Consortium, NCI SPORE in Prostate Cancer; Department of Defense; Prostate Cancer Foundation.

5031 Poster Discussion Session (Board #23), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Evaluation of clinical phenotype, survival, and circulating tumor cell (CTC) enumeration in men with metastatic castration-resistant prostate cancer (mCRPC).

Rhonda Lynn Bitting, Patrick Healy, Susan Halabi, Daniel J. George, Jung Hyun Ko, Andrew J. Armstrong; Duke Cancer Institute, Durham, NC; Duke University Medical Center, Durham, NC

Background: The presence of ≥ 5 CTCs is prognostic for shorter survival in mCRPC men. However, many men have low CTCs despite widespread metastatic disease, suggesting heterogeneity in CTC phenotype or detection. We evaluated the association of baseline CTC enumeration with clinical characteristics and survival in mCRPC men at our institution. **Methods:** CTCs were enumerated with the standard CellSearch method in mCRPC men in a prospective correlative clinical study. The association between baseline CTC count and prostate-specific antigen (PSA), alkaline phosphatase (AP), lactate dehydrogenase (LDH) was explored using the Spearman correlation (r), and the relationship with Gleason sum, sites of metastasis (mets), and prior docetaxel exposure was explored using summary statistics. The overall survival probability (OS) was estimated by the Kaplan-Meier method. **Results:** In our cohort, 59/82 men had prior docetaxel exposure, and the median CTC count was 16.5. There were 25 men with visceral mets, 55 with bone-predominant mets, and 2 with lymph node only mets. We found a weak relationship between CTCs and PSA (r=0.20), but a more moderate and significant association with AP (r=0.48) and LDH (r= 0.50). We found no relationship between CTCs and Gleason sum, site of mets, or prior docetaxel. 66 men died, and the median OS was 11.2 months (95% CI: 9.2, 12.7). OS was improved in patients with <5 CTCs at baseline compared to ≥ 5 (8.9 vs. 16.6 months, HR=0.47 (95% CI: 0.27, 0.80)). CTC enumeration may further stratify outcomes in men with mCRPC and either visceral or bone metastasis as shown in the table below. **Conclusions**: The prognostic significance of CTCs is distinct from other established biomarkers and may reflect a unique biology of metastasis, dissociated in part from androgen receptor activity (as reflected by PSA values) but related in part to bone microenvironment, hypoxia, and tumor burden (as reflected by AP and LDH values). These associations need to be validated in larger trials.

	N	Deaths	Median OS (95% CI)
Visceral mets			6.4 (4.6, 10.0)
CTC <5	5	3	23.7 (4.9, 23.7)
CTC ≥5	20	17	5.6 (3.7, 9.4)
Bone mets			12.8 (9.7, 16.5)
CTC <5	20	17	16.6 (10.8, 19.5)
CTC ≥5	34	28	11.0 (8.2, 14.8)

5032 Poster Discussion Session (Board #24), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Prostate-specific mRNA detection in whole blood as an analytically validated prognostic biomarker for patients with castration-resistant prostate cancer (CRPC).

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Background: Detection of prostate-specific transcripts in blood has been associated with survival, but validated assays are lacking. We analytically validated a qPCR-based assay in CLIA environment to detect prostate cancer enhanced transcripts in whole blood and determine its prognostic significance relative to circulating tumor cell (CTC) enumeration. **Methods:** Blood was collected from patients with progressive CRPC in PAXgene tubes for total RNA extraction. Five genes overexpressed in prostate tissue, *KLK3, KLK2, HOXB13, GRHL2*, and *FOXA1*, were analyzed by RT-qPCR. Each qPCR-reaction was performed in 6 replicates and detection thresholds for each gene were chosen by receiver operator curve analysis. Detection rates were compared to enumeration using CellSearch in an independent data set of 97 CRPC patients and survival associations explored by concordance probability estimate (CPE). **Results:** Two or more genes were detected by qPCR in 53% (51 of 97, 95% CI 43-63%) of patients, and unfavorable CTC counts (≥5cells) were seen in 46% (45 of 97, 95% CI 36–56%). Transcripts were detectable in 21% (11 of 52, 95% CI 8–35%) of patients with favorable CTC counts (≤4). Similar to CTC enumeration, transcript detection predicted overall survival in a proportional hazards model. The predictive accuracy of qPCR detection in combination with CTC enumeration had a CPE of 0.752 (SE=0.038). **Conclusions:** Thisvalidated RT-qPCR assay detects prostate-specific mRNA in whole blood in more patients than CellSearch, is prognostic for survival, and may assess patient risk in conjunction with CTC enumeration. Its clinical utility will be prospectively explored. Supported by NCI SPORE in Prostate Cancer (P50 CA92629); the Department of Defense Prostate Cancer Research Program; Prostate Cancer Foundation; Mr. William H. and Mrs. Alice Goodwin and the Commonwealth Foundation for Cancer Research and The Experimental Therapeutics Center; DoD Prostate Cancer Research Program Physician Research Award W81XWH-09-1-0307.

5033 Poster Discussion Session (Board #25), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Validation of a genomic classifier that predicts metastatic disease progression in men with biochemical recurrence post radical prostatectomy.

Ashley E. Ross, Mercedeh Ghadessi, Elai Davicioni, Anamaria Crisan, Christine Buerki, Nicholas Erho, Anirban Pradip Mitra, Darby J. S. Thompson, Timothy J. Triche, Felix Yi-Chung Feng, Edward M. Schaeffer; Department of Urology, Johns Hopkins Medical Institutions, Baltimore, MD; GenomeDx Biosciences Inc., Vancouver, BC, Canada; University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA; EMMES Canada, Burnaby, BC, Canada; University of Michigan Health System, Ann Arbor, MI

Background: Almost 50,000 men per year will present with biochemical recurrence (BCR) following local treatment for prostate cancer. These men with rising PSAs as the lone indicator of recurrence present a management dilemma due to their varied outcomes with only a proportion developing subsequent metastatic disease. Thus, there is a clear need to improve patient risk stratification in this context. Here, we evaluate Decipher, a genomic classifier (GC) in men with BCR following radical prostatectomy (RP) for its ability to predict metastasis. **Methods:** The 22-marker GC was validated in a prospectively designed case-cohort study of 1,010 clinically high-risk RP patients. 219 patients, including 85 who developed BCR at least 6 months post-RP were subjected to microarray analysis and GC scores were generated. Survival ROC curves, weighted Cox proportional hazards, and decision curves were used to compare the performance of the GC to Gleason score (GS), PSA doubling time (PSAdT) and time to BCR (ttBCR). **Results:** GC scores significantly stratified these men into those who would or would not develop metastasis after BCR (8% versus 40% of patients developed metastasis at 3 years following BCR depending on GC score category, $p<0.001$). The AUC for GC was 0.82 (95% CI, 0.76-0.86), compared to that of GS 0.64 (0.58-0.70), PSAdT 0.69 (0.61-0.77) and ttBCR 0.52 (0.46-0.59). In decision curve analysis, the GC had the highest overall 'net benefit' and in multivariable modeling with clinicopathologic variables, only GC ($p=0.006$) and GS ($p=0.046$) scores were significant predictors of metastasis. **Conclusions:** When compared to clinicopathologic variables, the GC better predicted metastatic progression among men with BCR following RP. While confirmatory studies in additional patient populations are required, these results suggest that use of the GC can allow for better selection of men requiring additional treatment at the time of BCR.

5034 General Poster Session (Board #35A), Mon, 8:00 AM-11:45 AM

Impact of prior docetaxel (D) on sipuleucel-T (sip-T) product parameters in PROCEED patients (pts).

Celestia S. Higano, Andrew J. Armstrong, Matthew R. Cooperberg, Philip W. Kantoff, James Bailen, Raoul S. Concepcion, Vahan Kassabian, Shaker R. Dakhil, Steven E. Finkelstein, Jeffrey L. Vacirca, Robert M. Rifkin, Andrew Sandler, Candice McCoy, James Boyd Whitmore, Robert Claude Tyler, A. Oliver Sartor; University of Washington/Seattle Cancer Care Alliance, Seattle, WA; Duke Cancer Institute, Durham, NC; University of California, San Francisco, San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA; First Urology, PSC, Jeffersonville, IN; Urology Associates, Nashville, TN; Georgia Urology, Atlanta, GA; Cancer Center of Kansas, Wichita, KS; 21st Century Oncology, Translational Research Consortium (TRC), Scottsdale, AZ; North Shore Hematology Oncology Associates, PC, East Setauket, NY; Rocky Mountain Cancer Centers, US Oncology Research, Denver, CO; Dendreon Corporation, Seattle, WA; Tulane Cancer Center, New Orleans, LA

Background: Sip-T is an autologous cellular immunotherapy indicated for asymptomatic or minimally symptomatic mCRPC. The IMPACT trial excluded pts who received D ≤3 months prior to registration. PROCEED is an ongoing, phase IV registry, enrolling pts treated with commercial sip-T. Use of D prior to sip-T is not restricted, so prior D affect on sip-T immune manufacturing parameters can be evaluated. **Methods:** Pts treated with sip-T ≤ 6 mo were eligible to provide informed consent. Sip-T parameters assessed included: total nucleated cell (TNC) count, antigen presenting cell (APC) count ($CD54^+$large cells) and APC activation (upregulation of CD54). **Results:** By Nov. 2012, 108/761 (14%) received D prior to sip-T and had similar median cumulative APC counts (1.83 [Q1, Q3: 1.16, 2.71] vs. 1.82 [1.27, 2.70] x 10^9) and TNC counts (10.16 [7.30, 13.69] vs. 11.47 [8.56, 15.31] x 10^9) vs. D naïve, whereas median cumulative APC activation appeared slightly lower (32.39 [25.05, 41.02] vs. 34.84 [28.71, 42.83]), but was well above the release criterion for each infusion (2.6 fold). The group was then split by Eastern Cooperative Oncology Group Performance Status (ECOG PS) and Gleason scores (Table). **Conclusions:** Pts with D prior to sip-T appeared to have product parameters comparable to pts without prior D, albeit with a slightly lower APC activation. Further analysis showed that pts receiving D within 3 months of sip-T had higher Gleason and ECOG scores. The clinical significance of these findings is unclear, but suggests that APC activation is not impaired following docetaxel. Clinical trial information: NCT01306890.

	D ≤90 d[1]		D >90 d[1]	
N[2]	17		88	
Median time last D use to 1st sipuleucel-T, d	49		409	
Age,[3] yrs	69.0 (65, 78)		71.5 (66, 77)	
PSA,[3] ng/mL	26.6 (9.4, 214.0)		23.3 (4.0, 87.5)	
APC activation[3,4,5]	29.92 (25.94, 40.17)		32.39 (24.70, 41.16)	
ECOG PS 0, %	29.4		70.5	
ECOG PS	0	≥1	0	≥1
APC activation[3,4]	39.01 (28.56, 42.87)	28.06 (17.71, 39.44)	33.67 (29.57, 43.18)	28.14 (17.71, 34.87)
Gleason ≥ 8, %	64.7		51.1	
Gleason	< 8	≥ 8	< 8	≥ 8
APC activation[3,4]	28.09 (26.52, 34.73)	33.63 (17.71, 42.87)	32.14 (26.70, 37.09)	32.38 (23.53, 41.14)

[1] Prior to sip-T. [2] Docetaxel stop date missing for 3 pts. [3] Median (Q1,Q3). [4] Cumulative. [5] Ratio of CD54 molecules post- vs pre-incubation with PAP-GM-CSF.

5036 General Poster Session (Board #35C), Mon, 8:00 AM-11:45 AM

The association between pre-treatment serum 25-hydroxyvitamin D and survival in stage IV prostate cancer.

Pankaj G. Vashi, Digant Gupta, Kristen Trukova, Gwendolyn M Lambert, Carolyn Lammersfeld; Cancer Treatment Centers of America, Zion, IL; Cancer Treatment Centers of America, Schaumburg, IL

Background: Emerging evidence in the literature suggests a positive association between serum 25-hydroxyvitamin D [25(OH)D], a standard indicator of vitamin D status, and survival in certain types of cancer. We investigated this relationship in newly diagnosed stage IV prostate cancer patients. **Methods:** A case series of 54 newly diagnosed stage IV prostate cancer patients underwent a baseline serum 25(OH)D evaluation prior to receiving any treatment at our institution between Jan 2008 and Dec 2010. We defined vitamin D insufficiency as serum 25(OH)D levels of <=32 ng/ml. Patient survival was defined as the time between date of first patient visit and date of death from any cause/date of last contact. Cox regression was used to evaluate the prognostic significance of serum 25(OH)D after adjusting for age, prostate specific antigen (PSA) and functional status. **Results:** Mean age at diagnosis was 59.6 years. During a median follow-up of 23.6 months, 16 deaths occurred. The mean serum 25(OH)D was 30.1 ng/ml, among whom 38 (70.4%) were insufficient in vitamin D (<=32 ng/ml). Mean overall survival was 49.4 months (95% CI: 38.1-60.7). Mean survival was 32.6 months and 62.4 months for patients in <=32 ng/ml and >32 ng/ml groups respectively (p = 0.02). On univariate analysis, patients with levels >32 ng/ml had a significantly lower risk of mortality compared to those with levels <=32 ng/ml (HR=0.19; 95% CI: 0.04-0.87; p=0.03). On multivariate analysis controlling for age, performance status and PSA, patients with levels >32 ng/ml demonstrated significantly lower mortality (HR=0.13; 95% CI: 0.02-1.0; p=0.05) compared to those with levels <=32 ng/ml. **Conclusions:** Higher circulating levels of serum 25(OH)D were positively associated with survival in patients with metastatic prostate cancer. While these results need to be confirmed in prospective clinical trials, our study adds to the growing body of literature on the prognostic role of serum vitamin D in cancer. Given the high prevalence of vitamin D insufficiency in prostate cancer and the fact that this insufficiency is easily correctable by supplementation, we recommend early vitamin D assessment and intervention for a potential impact on patient survival.

5037 General Poster Session (Board #35D), Mon, 8:00 AM-11:45 AM

Impact of concomitant bone-targeted therapies (BTT) on outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) without prior chemotherapy (ctx) treated with abiraterone acetate (AA) or prednisone (P).

Fred Saad, Karim Fizazi, Matthew R. Smith, Thomas W. Griffin, Anil Londhe, Dana E. Rathkopf, Arturo Molina, Charles J. Ryan; University of Montreal, Montreal, QC, Canada; Institut Gustave Roussy, University of Paris Sud, Villejuif, France; Massachusetts General Hospital Cancer Center, Boston, MA; Janssen Research & Development, LLC, Los Angeles, CA; Janssen Research & Development, LLC, Raritan, NJ; Memorial Sloan-Kettering Cancer Center, New York, NY; Helen Diller Family Comprehensive Cancer Center, University of California-San Francisco, San Francisco, CA

Background: BTT can delay symptomatic progression in cancer pts with bone metastases. In a post hoc analysis, we assessed the impact of concomitant BTT on outcomes in a recent large, multinational study in mCRPC pts without prior ctx. **Methods:** COU-AA-302 was a phase III trial in asymptomatic/mildly symptomatic pts with progressive mCRPC and no prior ctx. 1,088 pts were stratified by ECOG performance status (ECOG-PS, 0 vs 1) and randomized 1:1 to AA 1 g or placebo QD, plus prednisone 5 mg BID. Radiographic progression-free survival (rPFS) and overall survival (OS) were primary end points; secondary end points were times to opiate use, ctx, ECOG-PS deterioration, and PSA progression. The effect of concomitant use of BTT on all end points was assessed retrospectively using a stratified Cox regression model with factors for treatment, concomitant BTT, interaction of treatment and BTT, and baseline covariates. All data were obtained from a prespecified interim analysis at 55% OS events. **Results:** Median follow-up at the time of analysis was 27.1 mos. Among intent-to-treat (ITT) pts, 184/546 AA and 169/542 P pts received concomitant BTT for treatment of bone metastases, either zoledronic acid (n = 330), other bisphosphonates (n = 16), denosumab (n = 22), and/or other BTT (n = 5). In these pts, concomitant BTT use was associated with improved OS, time to opiate use for cancer pain, and time to ECOG-PS deterioration (Table). Results were similar in a sensitivity analysis including only ITT pts with bone metastases at baseline. **Conclusions:** In this post hoc, exploratory analysis, concomitant BTT use was associated with delayed symptomatic progression in asymptomatic/mildly symptomatic mCRPC pts. This potential clinical benefit should be investigated in prospective studies. Clinical trial information: NCT00887198.

End point	Hazard ratio[a] (95% CI)	P value
rPFS	0.855 (0.718-1.018)	0.079
OS	0.754 (0.604-0.940)	0.012
Time to opiate use	0.801 (0.651-0.985)	0.036
Time to ctx	0.916 (0.762-1.100)	0.348
Time to ECOG-PS deterioration	0.750 (0.643-0.874)	< 0.001
Time to PSA progression	0.878 (0.750-1.028)	0.105

[a] BTT vs no BTT.

5038 General Poster Session (Board #35E), Mon, 8:00 AM-11:45 AM

Pain analyses from the phase III randomized ALSYMPCA study with radium-223 dichloride (Ra-223) in castration-resistant prostate cancer (CRPC) patients with bone metastases.

Sten Nilsson, A. Oliver Sartor, Oyvind S. Bruland, Fang Fang, Anne-Kirsti Aksnes, Chris Parker; Karolinska University Hospital, Stockholm, Sweden; Tulane Cancer Center, New Orleans, LA; University of Oslo, The Norwegian Radium Hospital, Oslo, Norway; Bayer HealthCare Pharmaceuticals, Montville, NJ; Algeta ASA, Oslo, Norway; The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: Bone metastases (mets), present in > 90% of patients (pts) with CRPC, may cause severe pain. In a phase 2 dose-response study with a single injection of Ra-223, pain response was seen in up to 71% of CRPC pts with painful bone mets (Nilsson 2012). In the phase 3 ALSYMPCA study, which included 921 CRPC pts with bone mets randomized 2:1 to receive 6 injections of Ra-223 (50 kBq/kg IV) q4wk or matching placebo (Ra-223, n = 614; placebo, n = 307), Ra-223 significantly improved overall survival vs placebo (median 14.9 vs 11.3 mo; HR = 0.695) and was well tolerated. Post hoc analyses of pain parameters in ALSYMPCA are presented. **Methods:** The Cox proportional hazards model was used to analyze time to initial opioid use and time to EBRT. Pts with no opioid use at baseline were included in the pain analyses. All pts were included in the analysis for the prespecified endpoint time to EBRT. Concomitant opioid use was recorded from first study drug injection to 12 weeks after last injection. Pain-related QOL was analyzed based on the sum of 4 questions within FACT-P prostate cancer subscale (PCS) (Cella 2009) using ANCOVA. **Results:** Baseline pain characteristics were similar between the treatment groups (approximately 55% of pts had moderate to severe pain and opioid use based on WHO ladder for cancer pain). Time to EBRT was significantly longer with Ra-223 vs placebo (HR = 0.670; 95% CI, 0.525-0.854). Despite a longer observation time, fewer Ra-223 pts (50%) than placebo pts (62%) reported bone pain as an AE. At baseline, 269 Ra-223 pts and 139 placebo pts did not use opioids. Median time to initial opioid use was significantly longer in the Ra-223 group, with a risk reduction of 38%, compared to placebo (HR = 0.621; 95% CI, 0.456-0.846). Fewer Ra-223 pts (36%) than placebo pts (50%) required opioids for pain relief. The QOL pain score indicated reduced pain for Ra-223 pts relative to placebo pts at week 16 ($P = 0.001$). Ra-223 pts had significant pain reduction relative to baseline at weeks 16 ($P < 0.001$) and 24 ($P = 0.001$). **Conclusions:** These results provide consistent evidence that, in addition to prolonging survival, Ra-223 reduces pain and opioid use in CRPC pts with bone mets. Clinical trial information: NCT00699751.

5039 General Poster Session (Board #35F), Mon, 8:00 AM-11:45 AM

A randomized phase II study of cediranib (CED) alone versus CED plus dasatinib (DAS) in patients (pts) with castration-resistant prostate cancer (CRPC).

Anna Spreafico, Kim N. Chi, Srikala S. Sridhar, David C Smith, Michael Anthony Carducci, Peter Kavsak, Tracy S Wong, Lisa Wang, S. Percy Ivy, Som Dave Mukherjee, Christian K. Kollmannsberger, Sebastien J. Hotte; Princess Margaret Cancer Center, Toronto, ON, Canada; British Columbia Cancer Agency, Vancouver, BC, Canada; Princess Margaret Hospital, Toronto, ON, Canada; University of Michigan, Ann Arbor, MI; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Juravinski Cancer Centre, Hamilton, ON, Canada; Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD; BC Cancer Agency, Vancouver, BC, Canada

Background: Activation of the Vascular Endothelial Growth Factor Receptor (VEGFR) and the oncogenic Src pathway has been implicated in the development of CRPC in preclinical models. CED and DAS are multi-kinase inhibitors targeting VEGFR and Src respectively. Phase II studies of CED (Karakunnel et al ASCO 2009) and DAS (Yu et al Urology 2011) in CRPC have shown single agent activity. **Methods:** Docetaxel-preteated CRPC pts were randomized to arm A: CED alone (20 mg/day) vs arm B: CED (20 mg/day) plus DAS (100 mg/day) given orally on 4-week cycles. Primary endpoint was 12 week progression-free survival (PFS) as per the Prostate Cancer Clinical Trials Working Group (PCWG2). Patient reported outcomes were evaluated using Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Present Pain Intensity (PPI) scales. Correlative studies of bone turnover markers (BTM), including bone alkaline phosphate (BAP) and serum beta-C telopeptide (B-CTx) were serially assayed. **Results:** 22 patients, 11 per arm, were enrolled. Baseline demographics were similar in both arms. Median number of cycles = 4 in arm A (range 1-12) and 2 in arm B (range 1-9). Twelve-week PFS was 73 % in arm A vs 18 % in arm B ($p = 0.03$). Median PFS in months (arm A vs B) was: 5.2 vs 2.6 (95% CI: 1.9-6.5 vs 1.4-not reached). Most common grade 3 toxicities were hypertension, anemia and thrombocytopenia in arm A and hypertension, diarrhea and fatigue in arm B. One treatment-related death (retroperitoneal hemorrhage) was seen in arm A. FACT-P and PPI scores did not significantly change in either arm. No correlation between BTM and PFS was seen in both arms A and B. **Conclusions:** Although limited by small numbers, this randomized study showed that the combination of VEGFR and Src targeted therapy did not result in improved efficacy and may be associated with a worse outcome than VEGFR targeted therapy alone in pts with CRPC. Clinical trial information: NCT01260688.

5040 General Poster Session (Board #35G), Mon, 8:00 AM-11:45 AM

Use of bone scans during initial prostate cancer (CaP) workup, downstream procedures, and associated Medicare costs.

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Background: Bone scans are not recommended in the routine workup for patients with apparent low and intermediate risk CaP. We quantified the use of bone scans in low and intermediate risk patients, uses of other imaging and procedures after the bone scan, and costs to Medicare. **Methods:** Patients in the Surveillance Epidemiology and End Results (SEER)-Medicare database diagnosed with CaP from 2004 to 2007 were included. PSA, Gleason score and clinical T stage were used to define D'Amico risk categories. Patients with metastatic disease were included because the decision to order a staging bone scan for patients with apparent low and intermediate risk cancers occurs before knowledge about metastasis. We report use of bone scans from the date of diagnosis to the earlier of treatment or 12 months. In patients who received bone scans, we report use of X-ray, CT, MRI, and bone biopsy following bone scan to the earlier of treatment or 12 months. Cost was estimated using Medicare reimbursement rates. **Results:** 28% and 47% of patients with apparent low- and intermediate-risk prostate cancer received a bone scan (Table); $<1\%$ of these patients were found to have metastatic disease after work-up. A high proportion of patients had other imaging studies or biopsies after bone scan. For low and intermediate risk patients, the combined cost to Medicare of bone scan, X-ray, and bone biopsy as part of initial workup is estimated at $11,000,000 per year. The cost from CT and MRI after bone scan costs Medicare approximately $15,400,000 per year. **Conclusions:** Overuse of bone scans is common in workup of apparent low and intermediate risk CaP, even with an almost 0% risk of metastatic disease. X-rays, bone biopsies, and perhaps additional scans such as CT and MRI may result from bone scan findings, which are mostly false positives for these patients. These unnecessary procedures are costly to Medicare.

Apparent risk group	Low	Intermediate	High
Total number of patients	11,443	16,512	19,821
Percentage receiving bone scan	28	47	62
Percentage with metastatic disease	0.1	0.7	12.1
Percentage receiving scans and procedures after bone scan			
X-ray	20.8	19.6	14.8
CT	43.4	42.3	39.4
MRI	8.5	7.5	7.3
Bone biopsy	0.4	1.0	5.0

5041 General Poster Session (Board #35H), Mon, 8:00 AM-11:45 AM

Phase II trial of intravenous carboplatin (C), oral everolimus (E), and prednisone (P) in docetaxel-pretreated (DP) metastatic castrate-resistant prostate cancer (mCRPC): A Prostate Cancer Clinical Trials Consortium study.

Muthu Kumaran Veeraputhiran, Daniel H. Shevrin, Mark N. Stein, Lance K. Heilbrun, Daryn Smith, Jing Li, Brenda Dickow, Elisabeth I. Heath, Ulka N. Vaishampayan; Karmanos Cancer Institute, Wayne State University, Detroit, MI; NorthShore University HealthSystem, Evanston, IL; Cancer Institute of New Jersey, New Brunswick, NJ

Background: A phase II clinical trial was conducted of the combination of C and E due to the synergy noted. **Methods:** The primary endpoint was time to progression (TTP). Intravenous C at a target AUC of 5 on day 1, and oral E 5mg once daily and P 5mg twice daily were administered in 21 day cycles. PSA was assessed every 21 days and radiologic response was assessed every 3 cycles. Secondary endpoints included overall survival (OS), the correlation of TTP with phosphorylated (p) mTOR, pAKT, p70S6, and circulating tumor cells (CTC). A 1-stage study design assumed: a reference median TTP = 1.5 months; 1-sided alpha = 0.15; and power = 0.90, requiring 26 patients (pts). **Results:** 26 pts enrolled; median age 69 years (range 54-86) ;8 African American and 18 Caucasians. Median pretherapy PSA was 190 ng/ml (range 13 - 2174). 18 pts (69%) each had bone pain and Gleason score > 8. 125 cycles have been administered; median 3 cycles (range 1 - 16). Predominant grade 3 or 4 toxicities were thrombocytopenia in 8 pts, pulmonary embolism in 2 and neutropenia in 3. No treatment related deaths occurred. 4 (15%) had a > 30% PSA decline and 1 had a >90% PSA decline. 8/19 pts had stable disease but no objective responses in MD. The median TTP and OS were 2.5 months (90% CI: 1.8 - 4.3), and 12.5 months (90% CI: 6.7 - 16.1), respectively. Median area under curves were 5.9 (range, 4.3 – 11.0) and 4.5 (range, 4.1 – 7.1) mg/mL*min with C given alone and in combination with E, respectively. E did not influence pharmacokinetics of C. Median baseline CTC (n=18) was 30 (range 0-2372). 5/18 pts had favorable CTC (CTC<5/7.5 mL) pretherapy. Patients with TTP >18 weeks had reduction in post-therapy CTC with a median decrease of 63% (range 11%-100%). Lack of IHC staining for pAKT was noted in 2/2 pts on therapy for > 30 weeks vs increased expression was noted in 8/8 pts on therapy for < 9 weeks. Testing for TSC1 mutation is planned and will be reported. **Conclusions:** The combination was tolerable but revealed modest clinical efficacy. Biomarker evaluations such as pAKT may help identify a subset likely to benefit from mTOR inhibitor strategy in mCRPC. Clinical trial information: NCT01051570.

5042 General Poster Session (Board #36A), Mon, 8:00 AM-11:45 AM

NCIC CTG, IND-205: A phase II study of PX-866 in patients with recurrent or metastatic castration-resistant prostate cancer (CRPC).

Sebastien J. Hotte, Elizabeth A. Eisenhauer, Anthony Michael Joshua, Vikaash Kumar, Susan Ellard, Richard William Gregg, Robyn Jane Macfarlane, Eric Winquist, Vamsee Torri, Joseph D. Ruether, Naveen S. Basappa, Ankineedu Saranya Kakumanu, Scott A. North, Christian K. Kollmannsberger, Anna Tinker, Deepu Mirchandani, Aurelie Tassignon, Diana Felice Hausman, Alison L Allan, Kim N. Chi, NCIC Clinical Trials Group; Juravinski Cancer Centre, Hamilton, ON, Canada; Queen's University, Department of Oncology, Kingston, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada; Cancer Center of Southeastern Ontario, Kingston, ON, Canada; Cancer Centre for Southern Interior, Kelowna, BC, Canada; Cancer Ctr of Southeastern Ontario, Kingston, ON, Canada; QEII Health Sciences Center, Halifax, NS, Canada; London Health Sciences Centre, London, ON, Canada; Allan Blair Cancer Center, Regina, SK, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada; Cross Cancer Institute, Edmonton, AB, Canada; BC Cancer Agency, Vancouver, BC, Canada; Vancouver Cancer Centre, British Columbia Cancer Agency, Vancouver, BC, Canada; BC Cancer Agency, Kelowna, BC, Canada; Queen's University - NCIC CTG, Kingston, ON, Canada; Oncothyreon, Inc., Seattle, WA; London Regional Cancer Program, London Health Sciences Centre, London, ON, Canada; British Columbia Cancer Agency, Vancouver, BC, Canada

Background: PX-866 is an irreversible, pan-isoform inhibitor of Class I PI-3K. Mutations in *PIK3CA* and loss of PTEN activity lead to activation of AKT signaling; alterations in these genes occur frequently in prostate cancers while activation of the PI-3K/AKT signaling pathway is implicated in prostate cancer progression and treatment resistance. Hence, novel inhibitors of the pathway such as PX-866 are of interest. **Methods:** In this multicenter, two-stage, phase II study, docetaxel-naïve CRPC pts received PX-866, 8mg daily on a 6-week cycle. Primary endpoint was lack of progression at 12 weeks (PCWG2 criteria). Secondary endpoints included PSA and objective response rates and change in circulating tumor cells (CTC) during treatment. If $\leq$5 of the first 20 pts were progression free at 12 weeks, the study would stop. Otherwise, 40 pts would be accrued and PX-866 deemed worthy of further study if $\geq$16 pts were progression free at 12 weeks. **Results:** 43 pts were accrued after the criteria to progress to stage 2 were met. Median age was 70, ECOG PS was 0/1/2 in 27/15/1 pts, 23 pts had measurable disease, 24 patients had CTC $\geq$5. Median number of cycles was 2 (range 1–8). Most common adverse events (AE) were diarrhea (27 pts), nausea (25), fatigue (15), vomiting (13), anorexia (15) and grade 1 hypomagnesemia (11); 7 pts discontinued because of toxicity (3 GI, 3 LFTs, 1 fatigue). Grade 3 AEs were diarrhea (5 pts), AST/ALT elevation (4), fatigue (3). 11 patients were progression free at 12 weeks. 16 of the 24 pts with measurable disease were evaluable for response; there were no objective responses but 10 pts had stable disease (2.6-13.9m). One pt had a confirmed PSA response. CTC favorable conversion (from 5 at baseline to $<$5) was observed in 6/24 evaluable patients (25%). Correlative studies are ongoing. **Conclusions:** PX-866 is well tolerated and showed modest activity in CRPC but did not meet a priori benchmarks for further development as a single agent in unselected patients. As androgen receptor inhibition promotes PI3K activity in PTEN-loss PC models, the addition of PX-866 in pts whose PSA is rising on abiraterone may reverse resistance and phase B of the study is underway to test this hypothesis clinically. Clinical trial information: NCT01331083.

5043 General Poster Session (Board #36B), Mon, 8:00 AM-11:45 AM

Value of cell cycle progression (CCP) score to predict biochemical recurrence and definitive post-surgical pathology.

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Background: Prostate cancer (PCA) has a highly variable natural history and better tools are needed to more appropriately match treatment to a patient's risk of progression. A prognostic mRNA expression signature composed of genes involved in cell cycle progression (CCP) has been previously developed. Here, we tested the utility of this signature to predict biochemical recurrence (BCR) and definitive post-surgical pathological stage. **Methods:** The eligible patient population was treated for PCA by radical prostatectomy at a single high volume center (2005-2006). We randomly selected 390 patients for the study. From each patient we prepared a 'simulated biopsy' by removing a tissue cylinder (0.6mm) from the post-surgical FFPE block containing the largest tumor foci. 249 patients remained eligible for analysis after excluding patients for either insufficient tumor in the biopsy, poor quality molecular data, or receiving neoadjuvant therapy. The median follow-up time for patients who did not recur was 60.8 months. 46 patients experienced BCR. CCP scores were generated as in previous studies. Cox PH models and logistic regression were used to evaluate CCP associations with outcome. **Results:** The CCP signature was a highly significant univariate predictor of BCR (HR=2.03; 95%CI: 1.48-2.79; $p=3.1x10^{-5}$). After adjusting for clinical parameters including biopsy Gleason and PSA, the hazard ratio for CCP score remained significant (HR=1.6; 95%CI: 1.15-2.24; p=0.0068). In a multivariate model including PSA, biopsy Gleason, and clinical stage, CCP score was also an independent predictor of pathological stage (pT2 vs. pT3, p=0.029). In this analysis, PSA was the most predictive variable, but CCP score and clinical stage also provided important and non-redundant information. **Conclusions:** The CCP score has predicted PCA outcomes in multiple patient cohorts and different clinical settings. In this study, we have extended the demonstrated clinical utility to a modern patient cohort from Europe, and for the first time, provided evidence that the score can be used to predict definitive post-surgical tumor stage. The CCP expression score is an emerging and important component in evaluating PCA prognosis.

5044 General Poster Session (Board #36C), Mon, 8:00 AM-11:45 AM

The impact of technology diffusion on treatment for prostate cancer.

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Background: Robotic prostatectomy and intensity modulated radiotherapy (IMRT) hold the promise of improving cancer control and minimizing side-effects for patients with prostate cancer, but are associated with significant upfront investments. Many worry that the perceived advantages of these new technologies and the need to recoup start-up costs could shift decision making in favor of local therapy in lieu of expectant management. In this context, we examined the association of market-level technology penetration with receipt of local therapy. **Methods:** We used the Surveillance Epidemiology and End Results (SEER) - Medicare linked database to identify all patients with loco-regional prostate cancer who were treated or managed expectantly from 2003 to 2007 (n=59,241). We measured technology penetration as the number of providers performing robotic prostatectomy or IMRT per population in a market (hospital referral region). We then performed multinomial logistic regression to examine the association of technology penetration with receipt of prostatectomy, radiotherapy, or no local therapy. **Results:** For each 1,000 patients diagnosed with prostate cancer, 171 underwent prostatectomy, 493 radiotherapy, and 336 had no local therapy. Markets with high robotic prostatectomy penetration had higher use of prostatectomy (175 vs. 141 per 1,000 men, p=0.004) but decreased use of radiotherapy (584 vs. 613 per 1,000 men, p=0.046), resulting in a stable rate of local therapy (Table). High versus low IMRT penetration did not significantly impact use of prostatectomy and radiotherapy (Table). **Conclusions:** Increased penetration of robotic surgical technology was associated with more use of prostatectomy and less use of radiotherapy. However, increased penetration of both robotic prostatectomy and IMRT did not change the overall rate of local therapy. Our findings allay concerns that new technology spurs additional local therapy of prostate cancer.

Adjusted number of patients treated per 1,000 diagnosed.

Type of treatment	Robotic prostatectomy penetration			IMRT penetration		
	Low	High	p	Low	High	p
Surgery	141	175	0.004	154	154	0.995
Radiation	613	584	0.046	596	606	0.571
No local therapy	246	241	0.540	250	240	0.263

5045 General Poster Session (Board #36D), Mon, 8:00 AM-11:45 AM

Automated quantum dots *ISH* assay for detection of ERG rearrangement and PTEN deletion in prostate cancer.

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Background: ERG rearrangement and PTEN deletion are the two most common genomic events in prostate cancer. Overexpression of the ERG protein caused by rearrangement of the ERG gene has been frequently associated with more aggressive prostate cancers and a poor prognosis. PTEN genomic deletion and absence of PTEN expression are associated with unfavorable clinical outcome. To detect ERG rearrangement and PTEN deletion simultaneously, we developed a four-color multiplex ISH assay using non-organic quantum dots (QD). The photo-stability and narrow emission spectra of QDs makes them desirable for ultrasensitive and multiplexing ISH applications. The automated QD ISH assay allows adequate delivery of QDs to nuclear targets and reproducible detection of ERG and PTEN gene targets. **Methods:** DNA probes specific for ERG 5', ERG 3', PTEN and CEN 10 were labeled with different haptens, digoxigenin (DIG), dinitrophenyl (DNP), thiazole sulfonamide (TS), or nitropyrazole (NP). QDs with 565, 655, 605 and 525nm wavelengths were conjugated to the anti- DIG, DNP, TS or NP antibodies, respectively. The multiplex QD ISH assay was fully automated on the VENTANA BenchMark ULTRA. FFPE prostate tissue slides were hybridized with the labeled probes. The probes were then detected by the QD-conjugated antibodies and visualized under fluorescent microscope. **Results:** We performed the multiplex QD ISH assay on 386 slides with tissue sections from 10 prostate specimens on 13 BenchMark ULTRA instruments. The 10 cases consisted of either benign prostate tissues or prostate cancer, positive or negative for ERG rearrangement and/or PTEN deletion. 350 (91%) of the slides were successfully stained for all 4 molecular targets. The expected ERG and PTEN status were detected with high reproducibility. **Conclusions:** We developed an automated QD based multiplex ISH assay to simultaneously detect ERG rearrangement and PTEN deletion in prostate cancer. The assay is highly sensitive and reproducible. It enables investigation of potential clinical use of ERG and PTEN as predictive or prognostic markers. In addition, the same technology is expected to enable multiplex in situ detection of other molecular biomarkers using standard clinical specimens.

5046 General Poster Session (Board #36E), Mon, 8:00 AM-11:45 AM

ASP9521, a novel, selective, orally bioavailable AKR1C3 (type 5, 17ß-hydroxysteroid dehydrogenase) inhibitor: In vitro and in vivo characterization.

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Background: Aldo–keto reductase 1C3 (AKR1C3), also known as type 5, 17β-hydroxysteroid dehydrogenase, is reported to be highly expressed in human normal prostate and prostate cancer (PC) and the expression increases along with increasing malignancy or grade of PC. Since AKR1C3 converts the adrenal androgen, androstenedione (AD) into testosterone (T), combination with a GnRH analogue and AKR1C3 inhibitor would be expected to provide total androgen blockade in the treatment of castration-resistant prostate cancer (CRPC). We obtained a lead compound having a non-steroidal scaffold by high throughput screening (HTS) approaches for targeting enzyme activity of AKR1C3. After optimization of the lead compound, we found ASP9521 as a potent, selective, and orally bioavailable AKR1C3 inhibitor. **Methods:** The inhibitory effect of ASP9521 on enzymatic conversion from AD to T by AKR1C3 was evaluated in vitro, and in CWR22R xenograft models. Effect of PSA production and proliferation on LNCaP cells stably expressing AKR1C3 was examined. Pharmacokinetics in various animals were also investigated. **Results:** ASP9521 showed potent inhibitory effect on enzymatic conversion from AD to T by both human AKR1C3 and cynomolgus monkey homologues in a concentration-dependent manner, with IC50 values of 11 and 49 nmol/L, respectively ASP9521 suppressed both AD-dependent PSA production and cell proliferation in LNCaP cells exogenously expressing AKR1C3 in vitro. The bioavailability of ASP9521after oral administration of 1mg/kg were 30% and 78% in rat and dog, respectively. Furthermore, ASP9521 single oral administration of 3 mg/kg suppressed AD-induced intratumoral T production in CWR22R xenografted castrate nude mice, and this inhibitory effect was maintained for 24 h. In addition, ASP9521 was rapidly eliminated from plasma after oral administration while its intratumoral concentration remained high in tumors expressing AKR1C3. **Conclusions:** These preclinical in vitro and in vivo data are consistent with a potent inhibition of 17β-hydroxysteroid dehydrogenase. The results suggest that ASP9521 should be investigated further to elucidate its role as treatment for PC.

5047^ General Poster Session (Board #36F), Mon, 8:00 AM-11:45 AM

A randomized phase II trial of sipuleucel-T with concurrent or sequential abiraterone acetate (AA) plus prednisone (P) in metastatic castrate-resistant prostate cancer (mCRPC).

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Background: Sipuleucel-T and AA + P are FDA-approved for asymptomatic/minimally symptomatic mCRPC. Suppression of the androgen axis can be immunostimulatory and AA suppresses circulating androgen levels; AA plus sipuleucel-T may therefore be synergistic. However P used with AA, which may be immunosuppressive, has not been studied with concurrent sipuleucelET and could impair sipuleucel-T production and/or immunologic response. P11-3 (NCT01487863) is the 1st study to evaluate the combination of sipuleucel-T and AA + P **Methods:** Patients (pts) with asymptomatic/minimally symptomatic mCRPC were randomized (1:1) to sipuleucel-T (3 infusions at approx 2-wk intervals) with up to 26 wks of AA + P (AA 1000mg QD + P 5mg BID) starting 1 day after the 1st sipuleucel-T infusion (concurrent, arm A) or at 10 wks following the 1st sipuleucel-T infusion (sequential, arm B). Endpoints included the effect of AA + P on product (sipuleucel-T) characteristics eg antigen presenting cell (APC) activation, measured as CD54 upregulation (primary endpoint), APC (measured as $CD54^+$ cells) and total nucleated cell (TNC) counts, as well as safety and immunologic responses. **Results:** 31 pts in arm A and 32 pts in arm B completed sipuleucel-T treatment by the interim analysis (Nov 2012). Baseline characteristics were similar in the 2 arms. 60/63 pts received all 3 infusions of sipuleucel-T. No significant differences in median cumulative APC activation, APC count or TNC count were seen between the arms. Increased CD54 upregulation with the 2nd and 3rd treatments were indicative of a prime boost effect in both arms. Similar profiles of antigen-specific humoral and cellular immune responses were generated with no difference in magnitude of response between the arms ($p>0.05$). The incidence of adverse events (AEs) and serious AEs was similar in both arms. **Conclusions:** These data suggest sipuleucel-T can be successfully manufactured during concurrent AA + P. Product potency and prime boost effect were similar to sipuleucel-T alone. Immune responses and AEs were similar in both arms. It is not known if sipuleucel-T will provide similar efficacy with concurrent or sequential AA + P. Clinical trial information: NCT01487863.

5048 General Poster Session (Board #36G), Mon, 8:00 AM-11:45 AM

The ELDORADO study: A phase II randomised study of concurrent weekly docetaxel, IMRT, and ltadt in patients with high-risk prostate cancer.

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Background: Treatment intensification is warranted for 'high risk' prostate cancer. Docetaxel (DO) and radiotherapy (IMRT) may cause dose-limiting GI or GU toxicity. Treating the whole pelvis last (WP-L) versus the whole pelvic lymphatics first (WP-F) could reduce the number of dose delays or omissions of DO. **Methods:** We performed a double-blind, randomized trial, in patients with 'high risk' non-metastatic prostate cancer who had any one of the following: 1) $\geq$ T2c TNM category, 2) Gleason score $\geq$ 8, or PSA $>$ 20 and $<$ 50 μg/L, OR have a greater than 50% risk of recurrence after radical prostatectomy (RP), as predicted by the Kattan nomogram, with no evidence of metastatic disease. Patients receive long-term androgen deprivation therapy (LTADT), and after 4 months of neoadjuvant ADT, receive IMRT and concurrent DO 20 mg/m^2 x 8 weekly infusions. Patients were randomized to receive WP-F followed by a boost to the prostate/prostate bed, or to have WP-L. The primary outcome was to compare the number of DO dose reductions, delays or omissions due to GI or GU toxicity, between arms. Target sample size was 86 patients (pts). **Results:** 98 pts were registered, 88 were randomized, 2 withdrew consent, leaving 42 pts randomized to WP-F, and 44 pts to WP-L. The trial was closed to accrual Feb 2, 2012. Twenty-five pts had previous RP (29%). Seven pts (16.6%) allocated to WP-F had chemotherapy dose reductions/delays versus 3 pts (6.8%) allocated to WP-L , which was not statistically significant (p=0.19). Overall 80.2% of pts received all 8 weekly doses of DO and IMRT (WP-F vs. WP-L: 78.6% vs.81.8%, p=0.9). Actuarial overall survival at 4 years is 96 % (WP-F vs. WP-L: 94% vs.97%, p=0.6). Biochemical relapse-free survival at 4 years is 96.7% (WP-F vs. WP-L: 98% vs.97%, p=0.92). Two patients have needed surgical intervention for Grade $>$ 3 GU toxicity. Cumulative treatment-related grade 3 or 4 GI or GU toxicity was 36%. When patients were last seen, only 2/84 (2.3%) patients had ongoing grade 3 GI or GU toxicity at a median follow up of 2.7 years **Conclusions:** Concurrent use of DO and IMRT is feasible with reasonable toxicity. Sequence inversion does not enhance chemotherapy delivery. Clinical trial information: NCT00452556.

5049^ General Poster Session (Board #36H), Mon, 8:00 AM-11:45 AM

A phase I/II study of cabazitaxel (Cbz) combined with abiraterone acetate (AA) and prednisone (P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed after docetaxel (D) chemotherapy: Preliminary results.

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Background: Both Cbz and AA have demonstrated significantly improved survival in randomized Ph 3 studies in pts with mCRPC and progressive disease after D treatment. Cbz and AA have established non-overlapping adverse event (AE) profiles. A Ph 1/2 study was initiated to investigate the combination of Cbz + AA for the treatment of mCRPC (NCT01511536). **Methods:** Pts with progressive mCRPC after D were enrolled. The primary objectives were to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of Cbz + AA (Ph 1), and the PSA response rate (RR) with this combination (Ph 2). Secondary endpoints included AEs, pharmacokinetics (PK) and efficacy. All pts received oral AA 1000 mg QD and P 5 mg BID. In Ph 1, pts received 1 of 2 dose levels (DL) of Cbz (20 and 25 mg/m^2 IV Q3W) according to a 3+3 design. A 2-cycle DLT observation period was used. Here, we report results of Ph 1. **Results:** Ten pts were enrolled in Ph 1; 9 were evaluable: 3 at DL1 and 6 at DL2 completed 2 cycles without DLTs (total number of cycles = 46). In general, AEs were Grade (Gr) 1/2; the most frequent all-Gr AEs by pt cycle were asthenia (39%), diarrhea (37%; Gr 3 in 1 pt), back pain (26%), nausea (20%), constipation (20%), anemia (17%), decreased appetite (17%) and fatigue (15%; Gr 3 in 2 pts). In the safety population, 0/3 pts at DL1 and 2/7 pts at DL2 experienced Gr 3–4 neutropenia. The MTD was established at the full approved doses of both drugs (Cbz 25 mg/m^2/AA 1000 mg). In 6 pts evaluable for PK (DL1 and DL2), median Cbz clearance (coefficient of variation %) was similar at cycle 1 (Cbz alone: 28.9 L/h/m^2 [11%]) and cycle 2 (Cbz + AA coadministration: 28.6 L/h/m^2 [42%]). In 9 evaluable pts, 55% PSA RR was observed. **Conclusions:** In this Ph 1 study, Cbz in combination with AA appeared to have a manageable safety profile. Gr 3–4 neutropenia was observed in 2 of 10 patients. Daily AA treatment did not affect Cbz clearance; Cbz exposure was comparable to previous studies of Cbz + P treatment. The Ph 2 portion is ongoing at the established MTD. Detailed safety, PK and preliminary efficacy data (Ph 1) will be presented. Clinical trial information: NCT01511536.

5050 General Poster Session (Board #37A), Mon, 8:00 AM-11:45 AM

Clinical outcome (CO) evaluation of very old (≥ 80 years) castration resistant prostate cancer (CRPC) patients (pts) treated with docetaxel (DOC): Preliminary results of an Italian multicenter retrospective study (DELPHI study).

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Background: Since prostate cancer is mainly diagnosed in pts over 65 yrs of age, castration resistance is usually observed in older pts. In the case of very old pts (≥ 80 years), fear of high toxicity degree limit chemotherapy use due to both pts frailty and several comorbidities occurrence. Moreover, if treated these pts usually receive an adapted chemotherapy, often with a weekly schedule, which in TAX327 trial failed to show survival advantage compared to mitoxantrone. The present retrospective study is aimed to assess CO in this very elderly CRPC population. **Methods:** In this multicentric retrospective study, after Ethical Committee approval, we have reviewed the clinical records of all ≥ 80 yrs CRPC pts from participating institutions, treated with DOC in clinical practice, recording the pre and post-DOC clinical history, the DOC treatment details and outcomes. **Results:** To date we collected a consecutive series of 81 pts from 17 Italian hospitals. The median age was 82 yrs (range 80-90). The median baseline PSA was 107 ng/ml (range 3-1597); 81% of the pts had bone metastases, while nodal, lung and liver metastases were observed in 37%, 6%, and 6% of the pts, respectively. Median Cumulative Illness Rating Scale score was 3 (range 0-11), median Activity Daily Living index score was 0 (range 0-5), median Instrumental Activities of Daily Living score was 0 (range 0-5). The DOC was administered on 3-week or weekly schedule basis (41%/59%). A PSA reduction > 50% and an objective response were observed in 74% and 11% of the pts, respectively. Grade 3-4 toxicities were: neutropenia (11%) , fatigue (8%), diarrhea (1%), renal (2%), and febrile neutropenia (1%). The median PFS and OS were 7 mos and 22 mos, while the 1-year PFS and OS rates were 17.3% and 43.9%, respectively. **Conclusions:** This data suggests that DOC treatment, both on 3-week or weekly schedule, is able to produce good survival outcomes, comparable to pivotal trials (18 mos), also in highly selected very older (≥ 80 yrs) CRPC pts.

5051 General Poster Session (Board #37B), Mon, 8:00 AM-11:45 AM

Detecting lower in addition to the highest Gleason score prostate cancer on core biopsy and the risk of prostate cancer-specific mortality.

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Background: We evaluated the risk of prostate cancer-specific mortality (PCSM) following definitive treatment in men with at least one prostate biopsy core with a Gleason score (GS) lower than the highest GS identified. This pattern termed "ComboGS" in a concurrent submission was shown to be associated with a significant reduction in the odds of upgrading at radical prostatectomy (RP). **Methods:** In this validation cohort 666 men with localized or locally advanced prostate cancer, men were diagnosed via a transrectal, ultrasound-guided needle prostate biopsy (median 6, IQR 5-6 cores) and treated definitively between 1989-2000 with either RP or radiation (RT) or RT and hormones (HT) at a regional radiation oncology center. Patients could be referred into this center from 6 community based hospitals in Southeastern Massachusetts and Rhode Island. Community based pathologists from these 6 health care facilities assigned the biopsy GS used for the analyses in this study. Multivariable competing risks regression was performed (Table) to assess the impact of ComboGS on the risk of PCSM adjusting for age, established PC prognostic factors, and treatment. **Results:** After a median follow up of 4.6 years (IQR 2.5-6.7 years), 168 men (25.2%) died, 41 (24.4%) of PC. ComboGS was associated with a decreased risk of PCSM (Adjusted Hazard Ratio (AHR) 0.40, 95% Confidence Interval (CI) 0.19-0.85, p=.017). Estimates of PCSM were significantly lower in men with versus without ComboGS when the highest GS was ≥7 (p<.001) but not 6 or less (p=.71). Specifically these 5-year estimates were 14.4% and 4.8% versus 1.9% and 2.7% respectively. **Conclusions:** In addition to lower odds of upgrading at RP, using an independent data set the ComboGS assessed by community based pathologists serving 6 hospitals was found to also be associated with a decreased risk of PCSM.

Clinical factor		AHR [95% CI]	p
ComboGS			
	Present	0.40[0.19, 0.85]	.017
	Absent	1.0	-
Treatment			
	RT	0.94[0.34, 2.65]	.91
	RP	1.21[0.23, 6.43]	.82
	RT+HT	1.0	-
PSA(log)		2.63[1.71, 4.06]	<.001
Gleason score			
	8-10	10.73[3.57, 32.31]	<.001
	7	3.59[1.27, 10.16]	.016
	6 or less	1.0	-
Tumor stage			
	T3-4	0.67[0.17, 2.68]	.57
	T2	1.12[0.51, 2.46]	.78
	T1c	1.0	-
Age		1.04[0.98, 1.10]	.22

5052 General Poster Session (Board #37C), Mon, 8:00 AM-11:45 AM

First-in-human phase I study of EZN-4176, a locked nucleic acid antisense oligonucleotide (LNA-ASO) to androgen receptor (AR) mRNA in patients with castration-resistant prostate cancer (CRPC).

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Background: EZN-4176 is a third generationLNA-ASO that binds the ligand binding domain of AR mRNA resulting in full length AR mRNA degradation and decreased AR protein expression. **Methods:** Patients (pts) (performance status ECOG≤1) with progressing CRPC were eligible; prior abiraterone and enzalutamide treatment were allowed. EZN-4176 was administered as a weekly (QW) one-hour intravenous infusion. The starting dose was 0.5 mg/Kg with a 4-week dose-limiting toxicity (DLT) period. After determination of the DLT and the maximum tolerated dose (MTD) for weekly administration, a fortnightly schedule (Q2W) was initiated; a 3+3 modified Fibonacci dose escalation design was pursued. PD studies evaluated AR expression in tissue utilizing antibodies to the amino and carboxy-termini of the AR. **Results:** 22 pts were enrolled (median age 70.6 years, range 59 – 84 years). One pt was treated with the Q2W schedule. Two DLTs (G3/G4 ALT/AST elevation) occurred at 10 mg/Kg, which was therefore identified as the MTD for the weekly schedule. Multiple pts treated at 6.5 and 10 mg/Kg (5/9 pts, 55%) developed ≥G2 ALT and/or AST elevation after the first cycle requiring dose reduction and treatment delay. The most frequent adverse events (AEs) all-grades were fatigue (21/22 pts, 95.4%), nausea (10/22 pts, 45.4%), constipation (8/22 pts, 36.3%), AST (8/22 pts, 36.3%) and ALT (10/22 pts, 45.4%) elevation. The most frequent G3/4 AEs were AST (4/22 pts, 18.1%) and ALT (5/22 pts, 22.7%) elevation. Maximum PSA and circulating tumor cells (CTCs) declines are summarized below. There were no objective soft tissue responses. PD studies did not document any knockdown of AR expression **Conclusions:** EZN-4176 has limited antitumour activity in CRPC at its MTD for weekly administration. Safety, PK, PD and efficacy data will be presented. Clinical trial information: NCT01337518.

EZN-4176 dose (mg/Kg QW)	N	PSA decline ≥ 50%	PSA decline ≥ 30%	CTC conversion from baseline ≥5 to <5; (N/Eval. pts)	CTC decline ≥30% (N/Eval. pts)
0.5	3	0	0	0/0	0/0
1	3	0	0	0/0	0/0
2	3	1 (50%)**	0	0/1	0/1
4	3	0	0	0/3	0/3
6.5	3	0	0	1/1 (100%)	1/1 (100%)
10	6	0	0	1/3 (33%)	1/3 (33%)
10 *	1	0	0	0/0	0/0

* EZN-4176 Q2W, **30 days after treatment discontinuation.

5053^ General Poster Session (Board #37D), Mon, 8:00 AM-11:45 AM

Open-label, multicenter study of sipuleucel-T in men with metastatic castrate-resistant prostate cancer (mCRPC) previously treated with sipuleucel-T: Evaluation of antigen presenting cell (APC) activation and ELISPOT data.

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Background: P10-1 (NCT01338012) is a study of sipuleucel-T, an autologous cellular immunotherapy, in men with mCRPC previously treated with sipuleucel-T in PROTECT (NCT00779402). This preliminary analysis of P10-1 evaluates APC activation (a measure of product potency) and immune responses in men retreated with sipuleucelET. **Methods:** Men who received ≥1 infusion of sipuleucel-T in PROTECT and progressed to mCRPC were retreated with 3 infusions of sipuleucel-T. APC activation was assessed by CD54 upregulation. T cell responses to prostatic acid phosphatase (PAP) and PA2024 (PAP-GM-CSF) antigens were assessed by IFN-γELISPOT assay. **Results:** As of October 23, 2012, 7 men were enrolled and received ≥1 infusion. Median time between the third PROTECT infusion and first P10-1 infusion was 9.2 (range: 7.8–10.0) years. APC activation was greater at the first P10-1 treatment vs the last PROTECT treatment (Table). PA2024 and PAP ELISPOT responses were present prior to retreatment, indicating long-term memory (Table 1); based on other studies of sipuleucel-T, ELISPOT responses are not generally present prior to the first treatment (Beer. Clin Cancer Res 2011; Sheikh. Cancer Immunol Immunother 2013). **Conclusions:** This is the first trial to report the feasibility of sipuleucel-T retreatment following treatment in an earlier stage of prostate cancer. These data indicate the presence of existing immunological memory to the immunizing antigen several years after initial treatment. In addition, retreatment with sipuleucel-T appeared to boost product potency compared with prior treatment. Clinical trial information: NCT01338012.

CD54 upregulation and IFN-γ ELISPOT response by infusion.

		PROTECT infusions (treatment)			P10-1 infusions (retreatment)			
		1 (Day 0)	2 (Wk 2)	Final (Wk 4)	1 (Day 0)	2 (Wk 2)	Final (Wk 4)	Post-final (Wk 6)
CD54 upregulation, median (range)		6.2 (4.2–10.5)	14.7 (8.4–20.9)	13.2 (6.4–19.0)	19.8 (11.7–26.2)	20.5 (7.8–31.2)	22.5 (15.8–26.6)	–
IFN-γ ELISPOT/ 300,000 PBMC, median (range)	PA2024	–	–	–	18 (0–386)	187 (0–946)	70 (1–776)	34 (3–1176)
	PAP	–	–	–	21 (0–308)	67 (0–1076)	45 (0–720)	32 (0–1517)

5054 General Poster Session (Board #37E), Mon, 8:00 AM-11:45 AM

Profile study: Genetic prostate cancer risk stratification for targeted screening.

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Background: Prostate cancer (PC) screening is controversial and better approaches are needed, including a better assessment of individualized PC risk. Several studies have identified a number of common single nucleotide polymorphisms (SNPs) that confer a cumulative risk of PC. We have explored the potential role of genetic markers in identifying men who should be selectively targeted for screening in a population with increased risk of PC due to family history (FH) of the disease. **Methods:** PROFILE has been developed as a pilot study. The primary aim is to determine the feasibility of targeted PC screening using prostatic biopsy (PB) and its association with specific genetic profiles in men with FH. Secondary aims are to evaluate the role of PSA and Diffusion Weighted MRI (DW-MRI) as screening tools in this population. From December 2010 men aged 40-69 with FH of PC were invited into the study until 100 men were enrolled. Blood samples were provided for PSA and DNA extraction. The cumulative SNP risk scores for each patient were calculated by summing 59 risk alleles for each locus using the weighted effect as estimated in previous studies (log-additive model). DW-MRI was performed in 50 patients. All participants were asked to undergo a 10 core PB regardless of baseline PSA. Those who declined PB have been excluded from this analysis. Data on side effects and cancer worry were also collected. **Results:** 35% of invited men entered the study. Median age was 53 yrs (40-69) and median PSA was 1.15. Ninety men accepted to undergo a PB as primary PC screening. Twenty-two tumours were found and 45% of them were clinically significant [Median age 64yrs (47-69), median PSA 5.4 (0.91-9.3)]. The predictive performance of DW-MRI, PSA, genetic model and genetic model plus PSA measured by AUC were: 0.85, 0.73, 0.57 and 0.74, respectively. The genetic model performed better in men with PSA$<$3(AUC 0.63). No severe side effect or adverse psychosocial variables were noted. **Conclusions:** Our results indicate that PB is acceptable as a means of PC screening in men with FH of PC. Overall, DW-MRI and PSA were more predictive of PC than the genetic risk score. As more SNPs are found, a larger study is warranted to evaluate their role in the PC screening algorithm.

5055 General Poster Session (Board #37F), Mon, 8:00 AM-11:45 AM

Interim safety analysis of a compassionate-use program (CUP) and early-access program (EAP) providing cabazitaxel (Cbz) plus prednisone (P) to patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel.

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Background: Cbz + P provides a significant survival benefit vs mitoxantrone + P in pts with mCRPC (Phase III TROPIC study [NCT00417079]; hazard ratio 0.70; $p < 0.0001$). These findings supported the initiation of ongoing Sanofi-funded CUP and EAP (NCT01254279) to provide access to Cbz prior to commercialization and to collect real-life safety data. **Methods:** Expected enrollment is ~1600 pts with mCRPC from 250 centers worldwide. Pts receive Cbz (25 mg/m^2 Q3W) + P (10 mg oral QD) until progressive disease (PD), death, unacceptable toxicity, physician/pt decision or Cbz commercial availability. Pts are followed until 30 days after last dose. Granulocyte colony-stimulating factor (G-CSF) use is recommended as per ASCO guidance. **Results:** Interim baseline and safety data from the first 1301 pts treated in 37 countries are now available. Mean age was 68 yrs (22% were ≥ 75 yrs). All pts had an ECOG performance status ≤ 2. Median time from initial prostate cancer diagnosis was 57.6 months and 60% of pts had ≥ 2 metastatic sites; the most common were bone (91%) and lymph nodes (regional 30%, distant 27%). In total, 17% had PD whilst on docetaxel. The median number of Cbz cycles was 6 (range 1–22); median relative dose intensity was 99%. Overall, 837 pts (64%) received G-CSF (n = 123 curative [C], n = 765 prophylactic [P] and n = 99 [C + P]). Of 1142 pts (88%) who discontinued Cbz + P, the most common reasons were PD (44%), adverse event (AE; 27%), physician decision (13%) and commercial availability of Cbz (7%). Grade 3–4 AEs possibly related to Cbz + P occurred in 43% of pts; the most frequent were clinical neutropenia (18%), febrile neutropenia (FN; 7%) and diarrhea (4%). Of 80 pts (6%) with AEs leading to death, the AE was related to Cbz + P in 39 pts (3%). **Conclusions:** These results provide valuable data on Cbz + P treatment in routine clinical practice, confirming the safety results of clinical trials and showing that treatment with Cbz + P is associated with a manageable safety profile. The incidence of FN seems slightly lower than in TROPIC, owing to more frequent use of G-CSF prophylaxis in the CUP and EAP. Clinical trial information: NCT01254279.

5056 General Poster Session (Board #37G), Mon, 8:00 AM-11:45 AM

Clinicopathologic features and clinical outcomes associated with Gleason upgrading from biopsy to radical prostatectomy.

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Background: Gleason score stratifies patients into prognostic categories and is critical in guiding treatment. Previous series indicate that ~25% of patients with low-grade (Gleason $\leq$6) disease on biopsy are upgraded to higher grade disease upon radical prostatectomy (RP). We sought to characterize the clinical and pathologic variables associated with upgrading and investigate its clinical implications. **Methods:** 1,469 prostate cancer patients underwent prostate biopsy and RP, were seen at Dana-Farber Cancer Institute/ Brigham and Women's Hospital (DFCI/BWH), and had tissue specimens reviewed by DFCI/BWH genitourinary pathologists between 1999-2011. Associations between Gleason upgrading and clinical and pathologic variables were assessed using Wilcoxon's non-parametric test and Fisher's exact tests. Log rank test was used to assess association between upgrading and time to biochemical recurrence (BCR). **Results:** Of 1,469 patients, 958 (65%) had biopsy Gleason 6 and 511 (35%) had biopsy Gleason 7. Among individuals with biopsy Gleason 6, 336 (35%) were upgraded to Gleason $\geq$7 upon RP (275 3+4 and 49 4+3) while 622 (65%) remained Gleason 6 at RP. Variables associated with increased risk of upgrading: greater PSA at diagnosis ($p=1x10^{-4}$); age >58 (OR=1.62, $p < 1x10^{-4}$); >1/3 positive biopsy cores (OR=2.1 for 33-50% compared to $\leq$33%, $p < 1x10^{-4}$). In this study the number of cores biopsied was not associated with upgrading. Gleason upgrading was also associated with extraprostatic tissue involvement (OR=1.69, p=0.005). Patients upgraded from biopsy Gleason $\leq$6 to Gleason 7 on RP had a longer time to BCR than those with Gleason 7 on both biopsy and RP, but a shorter time to BCR than those who remained Gleason 6 on RP (adjusted hazard ratio 0.69, 95% CI 0.49-0.98, p=0.03). **Conclusions:** Gleason upgrading from low-grade to higher grade disease is associated with a higher PSA at diagnosis, older age at diagnosis, and a greater number of positive biopsy cores. Clinically, prostate cancers upgraded from Gleason $\leq$6 to Gleason 7 appear to behave differently than those who are not upgraded. These results could have implications in determining ideal candidates for active surveillance.

5057 General Poster Session (Board #37H), Mon, 8:00 AM-11:45 AM

Use of serum markers in prediction of survival in the trapeze factorial trial evaluating docetaxel with zoledronic acid, strontium-89, or both in castrate-refractory prostate cancer (CRPC) metastatic to bone.

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Background: There is emerging interest in the use of bone turnover markers in CRPC to compliment current modalities and aid therapeutic management decisions. We report the preliminary results of investigation into the clinical utility of P1NP, total alkaline phosphatase (ALP) and PSA as parameters of survival in a representative sample of patients from TRAPEZE. **Methods:** Baseline and post treatment (cycle six or end of treatment if sooner) samples were taken from 120 patients equally distributed across the trial arms of TRAPEZE. Absolute and percentage change in the markers were investigated in relation to overall survival (OS) using the Cox Regression model. **Results:** Of the 120 patients, 38(32%) failed to complete 6 cycles. No relationship was observed between P1NP and OS using either absolute or percentage change ($p=0.59$, $p=0.64$). Absolute change in log PSA was significantly related to OS (HR=1.22 (95%CI 1.01, 1.48), $p<0.05$, respectively) however percentage change in log PSA did not reach statistical significance (HR=1.006 (95%CI 0.99, 1.01), $p=0.095$). Absolute change in ALP was found to be inversely related to OS (HR=0.999 (95%CI 0.998, 0.999), $p<0.001$) but percentage change in ALP was not significant ($p=0.89$). When the PSA and ALP models were applied to the entire trial set (757 patients) the predictive value of both absolute and percentage change in log PSA remained highly significant (HR=1.23, $p<0.001$ & HR=1.01, $p<0.001$). In addition the significance of absolute change in ALP also remained (HR=0.999, $p<0.05$). **Conclusions:** Changes in P1NP were not related to OS in CRPC patients metastatic to bone. Absolute change in ALP was inversely related to OS and both absolute and percentage changes in log PSA were also related to OS in this sub-study. When applied to the entire TRAPEZE patient group all remained statistically significant. The utility of changes in ALP and PSA, as prospective markers for studies in CRPC patients metastatic to bone, merit further evaluation.

5058 General Poster Session (Board #38A), Mon, 8:00 AM-11:45 AM

Novel predictive markers of PSA response to abiraterone acetate in men with metastatic castration-resistant-prostate-cancer (mCRPC).

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Background: Abiraterone acetate (AA) prolongs survival in men with mCRPC pre- and post- chemotherapy. To date, clinical predictive biomarkers of response remain poorly characterized. The aim of this retrospective study was to identify and analyze predictors of response to AA in men with mCRPC. **Methods:** All men receiving AA at the Princess Margaret Cancer Centre between November 2009 and December 2012 were reviewed. PSA response rate (RR) was defined according to PCWG2 criteria and assessed 12 weeks after AA start. Potential predictive factors were analyzed using uni- and multivariable logistic regression models. **Results:** In total, 70 patients were evaluable for response: 34 men were chemotherapy naive and had a PSA RR of 44% (95% CI 27-62%); 36 men had prior chemotherapy and had a PSA RR of 33% (95% CI 17-50%). In univariable analysis, pre-treatment lactate dehydrogenase (LDH) level >220 U/L (ULN) and a neutrophil-to-lymphocyte ratio (NLR) >5 were both significantly associated with a lack of PSA response. On multivariable analysis, NLR>5 remained significantly associated with lack of a PSA response (Table 1A). Men were then stratified into three groups according to these two variables. These groups were significantly associated with RRs (Table 1B). PSA RR was not found to be associated with the Gleason score, initial stage, time from initial diagnosis to mCRPC or to AA initiation, prior ketoconazole or docetaxel treatment, pre-treatment alkaline phosphate or PSA doubling time. **Conclusions:** A pretreatment NLR>5 and an LDH>ULN were both strongly associated with a lack of PSA response to AA. These factors may be key in stratifying men into different response groups to AA.

	Univariable analysis			Multivariable analysis		
Variable	Odds ratio (OR) for response	CI %95	P value	OR for response	CI %95	P value
5 < NLR	0.10	0.48-0.02	0.004	0.11	0.55-0.02	0.007
ULN < LDH	0.33	0.92-0.12	0.034	0.40	0.13-1.21	0.1

Patient groups	Description	No. of pts	No. of responders	(%) RR (CI %95)	Response OR (CI %95)
0	ULN, >LDH 5>NLR	19	12	(87-39) 63	Group 2 vs 0: 0.04 (0.004-0.34)
1	ULN > LDH or 5<and NLR ULN <LDH 5>and NLR	34	14	(60-25) 42	Group 2 vs 1: 0.09 (0.01-0.75)
2	ULN, <LDH 5<NLR	17	1	(18-0) 6	p value=0.012

5059 General Poster Session (Board #38B), Mon, 8:00 AM-11:45 AM

Interim safety results of a global early access protocol (EAP) of abiraterone acetate (AA) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) progressing after taxane-based chemotherapy.

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Background: The COU-AA-301 phase 3 trial showed significantly longer overall survival for AA + prednisone (P) than P alone in mCRPC pts refractory to docetaxel. This global EAP was conducted in the same setting to collect additional safety data. **Methods:** Open-label EAP in pts with mCRPC who progressed after 1 - 2 chemotherapy regimens (≥ 1 taxane), resided in areas where AA was unavailable and were ineligible for ongoing clinical trials of AA. Pts received AA (1000 mg PO/d) plus P (5 mg bid) in 28 d cycles until disease progression. Only serious or clinically important adverse events (AEs) were to be reported by investigators. First interim results (clinical cut-off date: December 31, 2011), reported as part of regulatory submissions, are presented. **Results:** 1079 pts from 15 countries were included: N. America (47%), Europe (29%), Australia (13%), Latin America (7%), and Asia (3%). Median age: 70 years (range: 47 – 93); 89% of pts were White. Median treatment exposure, incl. pts still on treatment (285 pts), was ≈ 3 months. 620 pts (58%) received ≥ 4 treatment cycles, 58 pts (5%) received ≥ 8 cycles. 441 pts (41%) reported serious or clinically important AEs, which were treatment-related in 154 pts (14%). Most common grade 3-4 AEs: ↑ ALP (6%), anemia (3%), hypertension (3%), back pain (2%), and fatigue (2%). Grade 3-4 AEs of special interest were infrequent: LFT abnormalities (8%), hypertension (3%), cardiac disorders (2%), hypokalemia (< 1%), fluid retention/edema (< 1%), osteoporotic fractures (< 1%). Main reason for discontinuation (795 pts): disease progression, in 335 pts (31%). 253 pts (23%) discontinued after marketing authorization. Discontinuations due to treatment-emergent AEs, death, or withdrawal of consent were < 6% each. **Conclusions:** The safety profile observed in these EAP interim results was consistent with that in the COU-AA-301 randomized, placebo controlled trial conducted in the same clinical setting. No new safety signals with AA plus P were detected in this expanded patient population, which included pts from Latin America and Asia, i.e. regions that did not participate in COU-AA-301. Clinical trial information: NCT01217697.

5060 General Poster Session (Board #38C), Mon, 8:00 AM-11:45 AM

Hematologic safety of Ra-223 dichloride (Ra-223) in castration-resistant prostate cancer (CRPC) patients with bone metastases from the phase III ALSYMPCA trial.

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Background: In the updated analysis of the ALSYMPCA study, Ra-223 significantly improved median survival by 3.6 mo vs placebo (Pbo) in 921 CRPC patients (pts) with bone mets (HR = 0.695; 95% CI, 0.581-0.832; p = 0.00007) and had a highly favorable safety profile (Parker et al. ASCO 2012). The hematologic safety profile and results from a post hoc analysis assessing prognostic factors for changes in hematologic parameters in ALSYMPCA pts are presented. **Methods:** Pts were randomized 2:1 to 6 injections (inj) of Ra-223 (50 kBq/kg IV) q4wk or matching Pbo and stratified by prior docetaxel (D) use, total alkaline phosphatase (tALP), and current bisphosphonate use.Multivariate regression analysis was performed to explore the relationship of 6 baseline factors (Table) with maximum % change of hematologic parameters from baseline up to 24 wk on treatment (tx). **Results:** The updated analysis included 901 pts (safety population; Ra-223, n = 600; Pbo, n = 301). Overall grade 3/4 AEs were similar between Ra-223 and Pbo groups, with neutropenia in 2% and 1%, thrombocytopenia in 6% and 2%, and anemia in 13% and 13% of Ra-223 and Pbo groups, respectively. Tx with Ra-223, prior D use, extent of disease (EOD) $>$ 6 bone mets, and tALP $\geq$ 220 U/L, but not current bisphosphonate use, were associated with decreases from baseline in hemoglobin (Hb), neutrophils, or platelets; prior EBRT to bone for pain was associated with an increase. The significance of the relationship between baseline factors and changes in hematologic parameters is summarized in the Table. **Conclusions:** Overall, there was a low risk for hematologic AEs with Ra-223 tx in CRPC pts with bone mets. The strongest prognostic factors for decreases in neutrophils and platelets were Ra-223 tx and prior D use. Baseline tALP $\geq$ 220 U/L was a strong predictor of decrease in Hb. Clinical trial information: NCT00699751.

Variable	Hb (p value)	Neutrophils (p value)	Platelets (p value)
Study tx (Ra-223/Pbo)	0.037*	< 0.0001*	< 0.0001*
Current use of bisphosphonates (Y/N)	0.055	0.479	0.408
Prior use of D (Y/N)	0.069	0.007*	< 0.0001*
EOD > 6 mets including superscan (Y/N)	0.010*	0.321	0.006*
Prior EBRT to bone for pain (Y/N)	0.001*	0.019*	0.089
tALP (< 220 U/L/≥ 220 U//L)	< 0.0001*	0.629	0.023*

*p < 0.05.

5061 General Poster Session (Board #38D), Mon, 8:00 AM-11:45 AM

A pilot phase II study of digoxin in patients with recurrent prostate cancer as evident by a rising PSA.

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Background: Hypoxia-inducible factor 1α (HIF-1α) is a novel cancer drug target and inhibitors of hypoxia-response pathway are being developed. Digoxin and other cardiac glycosides were found to inhibit prostate cancer (PCa) growth via the inhibition of HIF-1α synthesis in mouse model. Epidemiologic data showed that use of digoxin in men was associated with a significant lower risk of development of PCa. We hypothesized that therapeutic dose of digoxin could inhibit human PCa growth and disease progression. **Methods:** Open label, non-placebo pilot study. Non-metastatic, biochemically relapsed PCa patients (pts) with prostate specific antigen doubling time (PSADT) of 3 -24 months and no hormonal therapy within the past 6 months were enrolled. All pts had testosterone $>$ 50 ng/dL at baseline. Digoxin was taken daily with dose titration to therapeutic level (0.8 – 2 mg/dl) and pts had routine follow-up that include cardiac monitoring with EKG. The primary endpoint was to evaluate the proportion of patients at 6 month post-treatment that had a PSADT $>$ 200% from the baseline. **Results:** Fifteen pts were enrolled into the study with 13 pts finishing the planned 6 months of treatment. Twenty percent (3/15) of the pts had PSA decrease $>$25% from baseline. At 6 months, 7 of 15 (47%) pts had PSADT $>$ 200% of the baseline PSADT and were continued on study for an additional 24 weeks of treatment. Mean duration of digoxin treatment was 34.5 weeks. Digoxin was well tolerated with possible relation of one grade 3 back pain and one grade 2 hyperglycemia. No pts came off study due to cardiac reasons. Pre-and post-treatment PSA kinetics, vascular endothelial growth factors and other cytokines levels are being determined. **Conclusions:** Digoxin was well tolerated and showed a prolongation in the PSDAT in 47% of the patients. Digoxin may have biologic activity in men with androgen-dependent PCa but further controlled studies are required to confirm the results. Clinical trial information: NCT01162135.

5062 General Poster Session (Board #38E), Mon, 8:00 AM-11:45 AM

A phase I dose-escalation trial of AEZS-108 in taxane- and castration-resistant prostate cancer (CRPC).

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Background: The receptor for luteinizing hormone releasing hormone (LHRH-R) is highly expressed on CRPC cells and is a potential therapeutic target. AEZS-108 is an LHRH-cytotoxic hybrid that covalently couples an LHRH agonist with doxorubicin. We report the completed Phase I trial of AEZS-108 in men with taxane-resistant CRPC. We explored visualization of AEZS-108 internalization into circulating tumor cells (CTCs) exploiting the auto-fluorescence of doxorubicin and also tested LHRH-R expression on CTCs. **Methods:** This was a dose escalation Phase I trial in men with taxane-resistant CRPC to confirm the dose established in a phase I trial in women. Standard 3+3 design was used with planned expansion at the MTD to ensure 6 patients received 2+ courses without DLT. Eligibility criteria included progression of disease despite prior LHRH agonist and taxane therapy. Patients received AEZS-108 every 21 days until progression or unacceptable toxicity. The primary endpoint was safety. CTCs were captured with a novel slot microfilter and identified by PSA and DAPI staining. AEZS-108 internalization was visualized by fluorescence microscopy. **Results:** Eighteen men with a median of 2 prior chemotherapy regimens (range 1-5) and a median PSA of 106.4 ng/mL (range 8.4-1624.0) enrolled from November 2010 to August 2012. The dose was escalated from 160 mg/m^2 to 210 mg/m^2 then to 267 mg/m^2. There were 2 DLTs in the 7 men receiving 267 mg/m^2 (grade 4 neutropenia), prompting de-escalation to 210 mg/m^2 where 1 of 8 men experienced a DLT (grade 4 neutropenic fever), establishing 210 mg/m^2 as the MTD. Significant non-hematologic toxicities included a case of grade 3 nausea. No cardiotoxicity was seen on serial evaluation and 6 patients completed 6 cycles. Internalization of AEZS-108 was consistently visualized in CTCs 1-3 hours after dosing. Maximal PSA response was stable or decreased in 8 of 18 men. **Conclusions:** The MTD of AEZS-108 in men with taxane-resistant CRPC is 210 mg/m^2, which is below the MTD reported in women with refractory endometrial, ovarian and breast cancer. The activity of AEZS-108 was promising in this heavily pretreated population. The Phase II portion is currently accruing. Clinical trial information: NCT01240629.

5063 General Poster Session (Board #38F), Mon, 8:00 AM-11:45 AM

Prognostic factors of survival in patients with metastatic castration resistant prostate cancer (mCRPC) treated with cabazitaxel: Sequencing might matter.

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Background: Recently, several new drugs have demonstrated an overall survival (OS) benefit in patients (pts) with mCRPC. Their use must be optimized to maximize patient outcomes. We evaluated prognostic factors of OS in mCRPC pts treated with cabazitaxel (C), a new taxane developed to overcome docetaxel (D) resistance. **Methods:** Records of 125 consecutive mCRPC pts (median 67 yrs) treated with C (after D) were retrospectively collected in 9 centers (France, n=8; Turkey, n=1). Baseline characteristics, disease history, PSA response, OS and radiological and/or clinical progression-free survival (PFS) were collected. The influence of selected variables on OS was analyzed by multivariate logistic regression. **Results:** At C initiation, 83.3% of pts were ECOG 0-1, 50.8% had an initial Gleason score of 8-10, 62.9% had pain and 84.8% had radiological or clinical progression. Median duration of response to first-line androgen deprivation therapy was 20 months (mo) and 22% received ≥2 prior D lines. New hormonal agents (abiraterone or enzalutamide) were given before C in 33% of pts and after C in 16%. Median number of C cycles received was 6 (range 2-14). A PSA decrease of ≥50% and ≥30% was reached in 41.3% and 48.8% of patients treated with C. Median OS from first C cycle was 13.3 mo and median clinical and/or radiological PFS was 6.5 mo. In multivariate analysis, OS was significantly reduced in pts with ECOG 2 (HR: 6.05), alkaline phosphatase ≥1.5 ULN (HR: 2.64), lymph node involvement (HR: 1.89). Conversely, OS was significantly prolonged in pts with ≥2 prior D lines (HR: 0.35), prior curative therapy (HR: 0.55), a PSA decrease ≥30% with C (HR: 0.21) and in pts treated with abiraterone/enzalutamide after C (HR: 0.37). Median OS from the first D dose was 65 mo in pts treated with abiraterone or enzalutamide after C versus 39 mo in pts receiving these agents before C. **Conclusions:** Patients with ≥ 2 prior D lines, PSA response ≥30% with C and treated with new hormonal agents after C experienced a prolonged OS. Conversely, intake of new hormonal agents before C rather than after was associated with a reduced OS from the first D dose. Prospective randomized trials are needed to confirm these results.

5064 General Poster Session (Board #38G), Mon, 8:00 AM-11:45 AM

Effects on androgen receptor nuclear import by docetaxel, cabazitaxel, abiraterone, and enzalutamide: Potential mechanism for cross-resistance in castration-resistant prostate cancer (CRPC).

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Background: Recent reports have suggested that paclitaxel and docetaxel, which exert their therapeutic activity primarily through inhibition of microtubule function and mitosis, also impair androgen receptor (AR) signaling. AR signaling is the key therapeutic target for the newly available agents abiraterone and enzalutamide. A recent study suggested impaired efficacy of docetaxel when given after progression on abiraterone in patients with CRPC. To identify potential mechanisms of cross-resistance, we investigated whether and to what extent AR nuclear translocation is affected by docetaxel, cabazitaxel, abiraterone and enzalutamide. **Methods:** Hep3B cells stably expressing GFP labeled AR were used for AR translocation studies. Cells were seeded on a cover slip in steroid-stripped medium (DCC) and treated with docetaxel (1 μM), cabazitaxel (1 μM), abiraterone (6 μM) and enzalutamide (1 μM). The anthracenedione mitoxantrone (100 nM) that does not target the microtubule cytoskeleton was used as a control cytotoxic agent. Following incubation for 48 hours, the synthetic androgen R1881 was added to study dynamics of AR nuclear import by time-lapse confocal microscopy. **Results:** Docetaxel and cabazitaxel inhibited R1881 induced AR nuclear translocation with 21% and 34% respectively compared to control, while mitoxantrone did not affect AR transport. Abiraterone inhibited AR translocation with 58% and enzalutamide completely blocked AR translocation. **Conclusions:** These data point towards a role for microtubules in AR nuclear transport and an additional mechanism of taxane activity in CRPC. Docetaxel, cabazitaxel, abiraterone and enzalutamide all interfere with AR nuclear transport, which is a crucial step in AR signaling. Our findings identify and provide insight in a potential mechanism of clinical cross-resistance between the two taxanes currently registered for treatment in CRPC and the novel agents abiraterone and enzalutamide. Further investigations are warranted in order to define if this potential cross-resistance impacts the most suitable treatment sequence for these drugs in CRPC.

5065 General Poster Session (Board #38H), Mon, 8:00 AM-11:45 AM

Outcomes in patients with liver or lung metastatic castration-resistant prostate cancer (mCRPC) treated with the androgen receptor inhibitor enzalutamide: Results from the phase III AFFIRM trial.

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Background: Enzalutamide (ENZA) inhibits multiple steps in the androgen receptor signaling pathway (Tran et al, Science. 2009;324:787). The phase III AFFIRM trial demonstrated that ENZA increased median overall survival (OS) by 4.8 months (P $<$0.001, HR 0.63) vs placebo (PBO) in post-docetaxel mCRPC patients (pts) (Scher et al, NEJM 2012; 367:1187). Here we assess the effect of ENZA on outcomes in pts with liver or lung metastases in the AFFIRM trial. **Methods:** The AFFIRM trial was a phase III multinational, randomized, double-blind study in post-docetaxel mCRPC pts. Randomization was 2:1 to ENZA 160 mg/day or PBO, stratified by baseline ECOG and mean pain score. The primary endpoint was overall survival (OS). Radiographic progression-free survival (rPFS) was a key secondary endpoint. PSA response defined as a decline of $\geq$50% compared to baseline, and soft tissue objective response per RECIST 1.1 were also assessed and reported here. **Results:** Pts with liver mCRPC comprised 11.5% (92/800) of ENZA pts and 8.5% (34/399) of PBO pts. Pts with lung mCRPC comprised 15.3% (122/800) of ENZA pts and 14.8% (59/399) of PBO pts. The median OS for patients with liver and/or lung mCRPC in the AFFIRM trial was 11.4 months (ENZA: 13.4 months; PBO: 9.5 months). Improved outcomes with ENZA treatment were observed in both liver and lung mCRPC pts. **Conclusions:** In the phase III AFFIRM trial, pts with lung mCRPC had higher median OS than pts with liver mCRPC. ENZA resulted in higher response rates in both liver and lung mCRPC pts. OS and rPFS were also improved in both pt groups treated with ENZA. Clinical trial information: NCT00974311.

	Liver mCRPC		Lung mCRPC	
	ENZA (n = 92)	PBO (n = 34)	ENZA (n = 122)	PBO (n = 59)
OS (months)	9.0 (6.4 , 10.7)	5.7 (4.2 , 9.5)	16.5 (12.5 , NM)	10.4 (8.1 , NM)
	HR = 0.697 (95% CI, 0.436, 1.114)		HR = 0.760 (95% CI, 0.493, 1.172)	
rPFS (months)	2.9 (2.8 , 4.9)	2.8 (2.7 , 3.2)	5.6 (5.3 , 8.2)	2.8 (2.7 , 2.9)
	HR = 0.645 (95% CI, 0.413, 1.008)		HR = 0.427 (95% CI, 0.298, 0.612)	
PSA response (%)	35.1 (24.4 , 47.1)	4.8 (0.1 , 23.8)	52.8 (42.9 , 62.5)	4.3 (0.5 , 14.5)
Objective response (%)	14.9 (8.2 , 24.2)	3.3 (0.1 , 17.2)	29.3 (20.6 , 39.3)	4.9 (0.6 , 16.5)

5066 General Poster Session (Board #39A), Mon, 8:00 AM-11:45 AM

Results from a phase I study of enzalutamide in combination with docetaxel in men with prostate cancer.

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Background: Enzalutamide (ENZA) is a novel androgen receptor (AR) inhibitor that prolongs survival in men with metastatic castration-resistant prostate cancer (mCRPC) who had received prior docetaxel (DOC). DOC also prolongs survival in mCRPC and also appears to have anti-tumor effects mediated through the androgen-receptor axis, providing a compelling rationale for combining the two agents. CYP3A4 plays a role in DOC clearance and is induced by ENZA. We therefore conducted a phase I study to explore the PK and safety profiles of this combination. **Methods:** This study (NCT01565928) evaluated the safety and pharmacokinetics (PK) of DOC co-administered with ENZA in men with mCRPC on androgen deprivation therapy. Pts received DOC (75 mg/m^2) by 1-h infusion every 3 weeks with corticosteroids. ENZA (160 mg/d) was started 24 h after the first DOC infusion. Plasma PK samples were collected for 24 h after Cycle (C) 1 and C2 DOC infusions to enable within-subject comparisons of DOC PK ± ENZA. A sample size of 18 pts able to receive ≥ 2 full doses of DOC was specified for PK analyses. **Results:** Twenty-two pts were enrolled, 4 did not receive 2 full doses of DOC. As of 21 Sept 2012, preliminary PK and C1 and C2 safety data were available from 15 pts. The median age was 65 (range 46-80 yrs); 11 had ECOG performance status 1 (vs 0). Prior primary therapy included surgery (n=2), radiation (n=4) or both (n=5); median PSA was 44.7ng/mL (1.9-585). ANC<1000/mm^3 was reported in 14 pts (1 febrile neutropenia), other adverse events in ≥4 pts included fatigue (11), dyspnea (6), alopecia (5), peripheral neuropathy (5), anemia (4) and dysgueusia (4). No seizures were reported. Preliminary PK data (n=15) show similar DOC exposure (within 20%) for DOC in combination with ENZA vs. DOC alone.Final PK and updated tolerability and efficacy data beyond Cycle 2 will be presented. **Conclusions:** In mCRPC pts, ENZA does not appear to affect tolerability of DOC or have a clinically meaningful impact on DOC PK. Clinical trial information: NCT01565928.

5067 General Poster Session (Board #39B), Mon, 8:00 AM-11:45 AM

Factors impacting decision by African American and underserved populations to choose active surveillance in early-stage prostate cancer.

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Background: African-American (AA) men have the highest rates of prostate cancer (PCa) incidence and mortality in the U.S. Screening for PCa with prostate specific antigen (PSA) has allowed detection of early stage disease, but side effects of radical prostatectomy and radiation raise concerns about unfavorable risk:benefit ratios of PSA screening and subsequent therapy. Active surveillance (AS) is an option for early-stage PCa (ESPC), but only 10% of men eligible for AS choose this approach. The 2011 NIH State-of-the-Science Conference promoted the need to enhance decision-making (DM) about AS. In 2012, the U.S. Preventive Services Task Force recommended *against* PSA screening, while encouraging patient DM. Our study examined DM needs by men (N=204; 68% AA; screening PSA within normal limits) and their significant others (SO) (N=181; 65% AA) regarding AS and other ESPC options. **Methods**: This multi-center, mixed methods study (N=402; 51% rural) included 5 sites nationwide. Subjects completed quantitative questionnaires prior to focus groups (FG); 54 FG were held, with separate groups for men and SO. **Results**: After adjusting for education, comorbidities, insurance, age, health literacy, distance to treatment center, willingness to travel, income and numeracy score, AA men were significantly more likely to be influenced by convenience (*OR*: 2.84, 95% CI: 1.42-5.65) compared to Caucasians. Rural residence, however, did not affect DM. In qualitative analysis, numerous themes were identified relevant to choice of AS: physician treatment discussions being limited to their own specialty; confusion due to conflicting sources of information; convenience; worry about untreated cancer remaining and treatment toxicities; and lack of awareness of AS as an option. SO tended to value cure over avoiding side effects. **Conclusions**: While the impact of new PCa screening guidelines is uncertain, for AS to become a viable treatment option, providers will need to discuss along with other therapeutic alternatives. SO are influential in DM and may be less enthusiastic about AS than men. For AA men, AS may be a particularly attractive option given the relative influence of convenience in DM.

5068 General Poster Session (Board #39C), Mon, 8:00 AM-11:45 AM

Efficacy and safety of radium-223 dichloride (Ra-223) in castration-resistant prostate cancer (CRPC) patients with bone metastases who did or did not receive prior docetaxel (D) in the phase III ALSYMPCA trial.

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Background: Ra-223, a first-in-class α-emitter, significantly improved median overall survival (OS) by 3.6 mo vs placebo (Pbo) in CRPC patients (pts) with bone metastases (mets) receiving best standard of care (BSoC) in the ALSYMPCA study (HR = 0.695; 95% CI, 0.581-0.832; p = 0.00007), and had a highly favorable safety profile in the updated ALSYMPCA analysis (Parker et al. ASCO 2012). This predefined subgroup analysis assessed efficacy and safety of Ra-223 in pts who did or did not receive prior D (pD). **Methods:** Eligible pts had progressive, symptomatic CRPC with $\geq$ 2 bone mets; had no known visceral mets; were receiving BSoC; and had received pD, or were unfit for or declined D (npD). Pts were randomized 2:1 to 6 injections of Ra-223 (50 kBq/kg IV) q4wk or matching Pbo and stratified by prior D use, baseline alkaline phosphatase level, and current bisphosphonate use. Survival data were compared using a log-rank test. **Results:** 395/921 (43%) randomized pts had npD (Ra-223, n = 262; Pbo, n = 133); 526/921 (57%) received pD (Ra-223, n = 352; Pbo, n = 174). Median ages were 74 y (npD) and 69 y (pD). In pts with npD, median OS was 16.1 mo in the Ra-223 group vs 11.5 mo in the Pbo group (HR = 0.745; 95% CI, 0.562-0.987; p = 0.039). In pts with pD, median OS was 14.4 mo vs 11.3 mo in the Ra-223 and Pbo groups, respectively (HR = 0.710; 95% CI, 0.565-0.891; p = 0.003). Overall, there was a low incidence of myelosuppression. Incidences of neutropenia and thrombocytopenia were higher in pts with pD vs pts with npD. **Conclusions:** Ra-223 significantly prolonged OS and had a highly favorable safety profile in CRPC pts with bone mets, regardless of whether they had pD or npD. pD pts had a slightly increased rate of grade 3 and 4 bone marrow suppression with Ra-223. Clinical trial information: NCT00699751.

	No prior D		Prior D	
No. (%) of patients with grade 3 or 4 AEs*	Ra-223 n = 253	Pbo n = 130	Ra-223 n = 347	Pbo n = 171
Hematologic				
Anemia	27 (11)	15 (12)	50 (14)	24 (14)
Neutropenia	2 (1)	1 (1)	11 (3)	1 (1)
Thrombocytopenia	7 (3)	1 (1)	31 (9)	5 (3)
Nonhematologic				
Diarrhea	7 (3)	1 (1)	2 (1)	4 (2)
Nausea	2 (1)	2 (2)	8 (2)	3 (2)
Vomiting	1 (0.4)	2 (2)	9 (3)	5 (3)
Constipation†	3 (1)	3 (2)	3 (1)	1 (1)

* Safety population. † No grade 4.

5069 General Poster Session (Board #39D), Mon, 8:00 AM-11:45 AM

Risk of missing advanced stage or high grade tumors during active surveillance (AS) even in favorable-risk prostate cancer (PC).

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Background: Owing to tumor heterogeneity, no standard selection criteria exist among prospective AS cohorts. Generally, men with low-stage, -volume, and -grade PC and low prostate-specific antigen (PSA) are eligible. In our prospective single-institution AS trial, men with early-stage PC were stratified: Gr I (favorable risk), II (pt's choice), or III [competing comorbidities prevent local therapy (Tx)]. We report our experience with Gr I. **Methods:** Eligibility for Gr I: Gleason score (GS) ≤6, 1 positive (pos) core (<3 mm), and PSA <4 ng/mL *or* GS 7 (3+4), 1 pos core (<2 mm), and PSA <4 ng/mL. Monitoring q6mo included PSA, testosterone, and digital rectal exam. All pts had repeat biopsy (re-BX) at 1 y and then on predetermined BX scheme. Later, re-BX was required within 6 mo of study entry per an 11-core BX scheme (also used during AS). Definitive Tx was offered to pts who met reclassification based on clinical, BX (upgrading, ↑ in pos core BX, and/or ↑ tumor length), and/or radiographic progression. Imaging studies [bone/CT scans, endorectal MRI (eMRI)] were at physician's discretion. **Results:** From 2/2006 to 2/2012, 585 pts enrolled; 191 met Gr I criteria (41 before, 150 after re-BX requirement). Median age was 64 y (range, 36–83); 82% were white, 8% African-American, 8% Hispanic, 2% Asian; 4% had cT1a/cT1b, 84% cT1c, and 12% cT2 disease. Most (189/191) had GS 6 [1 had GS 5, and 1, GS 7 (3+4)]. Median PSA was 3.3 (range, 0.2–10). With median follow-up of 36.2 mo (95% CI: 30.6–41.7), 32/191 (17%) were reclassified [20/41 (49%) before and 12/150 (8%) after re-BX requirement]. Of 32 reclassified, 17 were due to GS: 11 to GS 7 (3+4), 4 to GS 7 (4+3), and 2 to GS 8 (4+4). Ten of the 32 reclassified chose Tx [4 radical prostatectomy (RP); 4 radiation; 2 cryotherapy]. RP showed a pT2N0 GS9 (4+5) apical tumor in 1 at 5 y, a pT3aN0 GS7 (4+3) tumor in 1 at 3 y, a pT2N0 GS7 (4+3) tumor in 1 at 1 y, and a T2N0 GS 7 (3+4) tumor in 1 at 2 y. **Conclusions:** Restrictive selection criteria and re-BX at study entry improve clinical risk classification; however, other improvements, including imaging and markers of disease progression could enhance pt selection for AS.

5070 General Poster Session (Board #39E), Mon, 8:00 AM-11:45 AM

Final results of a phase II study of neoadjuvant metformin in prostatic carcinoma.

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Background: Metformin is an inhibitor of the complex 1 in the respiratory chain, and is widely used in diabetes due to its effect on reducing insulin resistance. It has also been recently described to have effects via AMPK on inhibiting the mTOR kinase. Significant preclinical and epidemiological studies suggest its role in chemoprevention. These actions provide significant rationale to evaluate its utility in prostate cancer. **Methods:** Men were required to have histologically confirmed prostate cancer involving at least 20% of at least 1 unfragmented biopsy core. Exclusion criteria included patients who were found to be on treatment with any drug used for the treatment of any form of diabetes, or patients that began treatment for any form of diabetes during the course of the study. Pts were treated with up to 500mg tid of metformin. The primary objectives were to demonstrate safety and tolerability of neoadjuvant metformin administration in men with prostate cancer and to document changes in phospho-AKT signalling indices. **Results:** 24 patients were enrolled with 21 patients evaluable; median age was 64 yrs (range, 45-70 yrs). Baseline characteristics included median PSA 6 ng/mL (range, 3.22-36.11ng/mL). Median duration of drug treatment was 41 days (range 18-81). No grade 3 adverse events were reported during treatment or radical prostatectomy that were related to metformin. Significant pre-and post changes were noted in serum IGF1 ($p=0.02$), fasting glucose ($p=0.03$), BMI ($p<0.01$) and waist/hip ratio ($p<0.01$). There was a trend for a PSA reduction ($p=0.08$). There were no correlations between any metabolic, morphometric or cancer-related serum indices. On a per patient analyses, metformin reduced a computerised relative ki67 proliferation index by an average of 29% (absolute difference of 1.4%) compared to the baseline biopsy ($p=0.006$). P-4eBP1 staining was also reduced as assessed by H-score ($p<0.01$) consistent with the ability of metformin to inhibit mTOR. **Conclusions:** Neoadjuvant metformin is well tolerated prior to radical prostatectomy and shows promising effects on proliferation and signaling indices. Further research is needed to define the clinical utility of metformin in prostate cancer. Clinical trial information: NCT00881725.

5071 General Poster Session (Board #39F), Mon, 8:00 AM-11:45 AM

Association of SPARC expression with metastatic progression and prostate cancer-specific mortality after radical prostatectomy.

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Background: We assessed the expression of the glycoprotein SPARC (secreted protein, acidic, rich in cysteine) in patients with prostate cancer (PCa) treated with radical prostatectomy (RP) and studied its association with adverse clinico-pathological features at RP and long-term clinical outcomes, such as metastatic progression after surgery and cancer-specific death. **Methods:** Tissues from 78 patients with PCa were used to quantify SPARC expression using tissue microarray (TMA) and immunohistochemistry techniques (IHC). Anti-SPARC mouse monoclonal antibody were use to target the protein and for each patients 4 samples of tissue were used for cytoplasmic staining. Staining of each core was reviewed by an uropathologist who assigned a score (score 0-3) to each core and a global score also assigned to each patient (score 0-3). Analyses of the data relied in cross tables, T-test analyses, survival plots and Cox regression models. **Results:** Higher expression of SPARC protein was recorded in patients who develop metastases during follow-up after RP ($p=0.025$) and in patients who died of PCa after RP ($p=0.002$). Median follow-up of the cohort was 9.3 years after RP. At 5 years, 95.5%, 92.0% and 89.3% of patients were metastases-free for SPARC expression score 1, 2 and 3 respectively. For the same categories, 10 years after RP, 82.2%, 77.0% and 69.9% were metastases-free (Log-rank tests all $p\leq0.05$). Similarly, patients with high SPARC expression had worse cancer-specific survival at 5 and 10 years after RP compared to those with low SPARC expression (Log-rank tests all $p\leq0.01$ when score 1 was compared to score 2 or score 3). Finally, advanced stage at RP (T3-T4) [$p=0.04$] and high Gleason sum (8-10) [$p=0.02$] were also associated with higher expression of SPARC. **Conclusions:** High SPARC expression was associated with worse outcomes in men with prostate cancer treated with radical prostatectomy. Men who developed metastatic disease and men who succumbed to prostate cancer had higher levels of SPARC at radical prostatectomy than their counterpart. SPARC may have an important role in the progression of the disease and may eventually help clinician to better ascertain the risk of progression of the disease.

5072 General Poster Session (Board #39G), Mon, 8:00 AM-11:45 AM

Quantifying copy number variations in cell-free DNA for potential clinical utility from a large prostate cancer cohort.

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Background: Prostate cancer (PrCa) is the most frequent non-dermatological malignancy in the male population. Genomic instability resulting in copy number variation (CNV) is a hallmark of malignant transformation. CNV traces from tumors in cell-free DNA (cfDNA) of prostate cancer patients may be identified through massive parallel sequencing (MPS) of serum DNA. These CNV traces may be biomarkers of cancer with clinical applications for screening and follow-up. **Methods:** DNA was extracted from serum of 205 PrCa patients (Gleason 2 to10), 207 age matched male controls (HC), 10 men with benign hyperplasia (BPH) and 10 with prostatitis (PiS). DNA was amplified using random primers, tagged with a unique molecular identifier per sample, sequenced on a SOLiD system and aligned to the human genome (Build 37). Hits were counted in sliding 100kbp intervals and normalized. Using a random-resampling procedure, genomic regions showing copy number variations in cfDNA that distinguish PrCa from HC were selected. A model using 20 cfDNA regions was cross-validated and used as cfDNA biomarker. Receiver operator characteristics (ROC) curves were calculated for assessment of diagnostic performance by means of area under the curve (AUC). **Results:** To assess whether CNVs in cfDNA are indicative of PrCa, the number of regions with significant CNV deviation was counted in a first subset of 82 PrCa. Using only the number of regions as measure resulted in an AUC of 0.81 (0.7 – 0.9, $p<0.001$). Therefore, all samples were used to select regions ($n=80$) in random resampling (50/50). These regions were used to define a highly significant 20-regions model using five rounds of 10-fold cross-validation (AUC: 0.85 ± 0.7; $p< 10^{-7}$). This final model discriminated between PrCa and HC with an AUC of 0.92 (0.87 – 0.95) reaching a calculated accuracy of 83%. Both BPH and PiS could be distinguished from PrCa using the cfDNA CNV biomarker with a predicted accuracy of 90%. **Conclusions:** MPS revealed that only a limited number of chromosomal regions showing CNVs are necessary to achieve statistical separation between prostate cancer and controls. This technique may prove to be clinically useful for screening and follow up of men with prostate cancer.

5073 General Poster Session (Board #39H), Mon, 8:00 AM-11:45 AM

Post-treatment alterations in 18F-dihydrotestosterone (FDHT) and FDG PET/CT in metastatic castration-resistant prostate cancer (mCRPC) treated with cabozantinib.

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Background: Cabo is a multitargeted kinase inhibitor that has demonstrated complete and partial responses in mCRPC as assessed byTc-99 MDP bone scintigraphy. FDG and FDHT PET/CT demonstrate glucose metabolism and androgen receptor binding, respectively. We are exploring these tracers as response biomarkers in mCRPC treated with cabo. **Methods:** Patients (pts) treated with cabo were scanned with FDHT and FDG PET at baseline and after 6, 12, and 24 weeks (wks) of treatment. 5 index lesions were selected at baseline for each PET modality. The hottest slices from each were averaged (SUVmaxavg) and measured on post-treatment scans. The concordance of the post-treatment alterations of the two tracers (rise vs. decline) was examined, as were PSA alterations. **Results:** All 16 pts had FDG avid and 15 had FDHT avid disease. Baseline median FDHTmaxavg was 10.84 (3.52 – 18.52) and FDGmaxavg was 6.26 (2.74 – 14.7). Post-treatment alterations are described (Table). **Conclusions:** Most pts with mCRPC demonstrate diminution of FDHT uptake after 6 and 12 wks of treatment with cabo. These declines are matched by FDG 50-60% of the time, and correlate with PSA declines even less frequently. The etiology of the extent and degree of FDHT declines, and lack of concordance with post-treatment PSA changes, warrant further investigation, and correlation with other imaging modalities and clinical outcomes. Clinical trial information: NCT00588185.

	6 wks, FDG n=16, FDHT n=15	12 wks, n=10	24 wks, n=5
#Pts with decline in FDHTmaxavg	14	10	5
#Pts with decline in FDGmaxavg	8	6	4
#Pts with rise in FDHTmaxavg	1	0	5
#Pts with rise in FDGmaxavg	8	3 (1 no change)	1
Median % change FDHTmaxavg (range)	-62% (-87 – 39)	-60% (-85 – -32)	-34% (-84 – -20)
Median % change FDGmaxavg (range)	1% (-72 – 123)	-17% (-65 – 35)	-24% (-59 – 4)
Pts with new lesions on FDHT PET	2	2	2
Pts with new lesions on FDG PET	8	3	2
Median % change in PSA (range)	42% (-86 – 439)	19% (-84 – 348)	146% (-47 – 355)
Concordance of FDG and FDHT alterations (both rise or both decline)	8/15 (53%)	6/10 (60%)	3/5 (60%)
Concordance of FDHT and PSA alterations (both rise or both decline)	4/15 (27%)	4/10 (40%)	2/5 (40%)
Concordance of FDG and PSA alterations (both rise or both decline)	9/16 (56%)	8/10 (80%)	3/5 (60%)

5074 General Poster Session (Board #40A), Mon, 8:00 AM-11:45 AM

Use of [-2]proPSA and prostate health index (phi) to improve the diagnostic accuracy of prostate cancer compared to t-PSA and %f-PSA in young men (≤ 65 years old).

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Background: Although prostate-specific antigen (tPSA) screening reduced prostate cancer (PCa) mortality recent recommendations do not endorse PSA-screening due to overdiagnosis and overtreatment and the resulting harm afflicted to patients. Screening studies showed the maximum benefit in young men < 65 years of age. tPSA and percent free PSA (%fPSA) lack specifity in the diagnosis of PCa. [-2]proPSA and the prostate health index (phi) improved this diagnostic specifity. Markers to diagnose clinicaly relevant cancers in young men are needed. **Methods:** The clinical performance of [-2]proPSA and phi was evaluated in a multicenter study. A total of 1362 patients scheduled for initial or repeated prostate biopsy (668 with, 694 without PCa, each ≥ 10 core biopsies) were recruited in 4 different sites based on PSA level 1.6 – 8.0 ng/mL WHO-calibrated (2-10 ng/mL classically calibrated). Serum samples taken prior to digital rectal examination (DRE) were measured for the concentration of tPSA, fPSA and [-2]proPSA with Beckman Coulter immunoassays on Access 2 or DxI800 instruments. Phi was calculated as [-2]proPSA/fPSA*$\sqrt{}$tPSA. **Results:** In univariate analysis [-2]proPSA/fPSA (%[-2]proPSA) and phi were the best predictors of PCa detection in patients at initial biopsy (AUC: 0,72 and 0,73) and repeated biopsy (AUC: 0,74 and 0,74). Analysis of the data for men ≤ 65 years of age (n=593) showed that %[-2]proPSA and phi significantly improved PCa dectection (AUC: 0,72 and 0,73) as compared with tPSA (AUC: 0,54) or %fPSA (AUC: 0,62). In the detection of significant PCa (based on PRIAS criteria) %[-2]proPSA and phi demonstrated the best performance in the whole cohort and in young men (≤ 65) years as well (AUC 0,68 and 0,73). **Conclusions:** This multicenter study showed that [-2]proPSA and phi have a superior clinical performance in detecting PCa in the PSA range of 2-10 ng/mL compared with tPSA and %fPSA at initial and repeated biopsies. This superiority is maintained for the detection of PCa in young men (≤ 65 years of age).

5075 General Poster Session (Board #40B), Mon, 8:00 AM-11:45 AM

Efficacy of docetaxel chemotherapy in metastatic prostate cancer (mPC) patients (pts) experiencing early castration resistance (CR).

Olivier Huillard, Laurence Albiges, Jean-Christophe Eymard, Christophe Massard, Mario Di Palma, Bernard J. Escudier, Karim Fizazi, Yohann Loriot; Institut Gustave Roussy, Villejuif, France; Institut Jean Godinot, Reims, France

Background: mPC pts experiencing a short period of sensitivity to initial androgen deprivation therapy (ADT) have an unfavourable prognosis and lower probability of response to 2nd-line endocrine therapy suggestive of androgen receptor (AR) pathway-independent mechanisms of resistance. Recent studies have shown that docetaxel may kill PC cells through AR targeting. We thus investigated whether docetaxel may have efficacy in pts with early CR. **Methods:** Two independent prospective databases (Institut Gustave Roussy and Institut Jean Godinot) of mCRPC pts were analyzed. Early CR was defined as progression within the first year of ADT. The primary endpoint was time to progression (TTP) on docetaxel. Secondary criteria were clinical benefit (decrease in 2 points on a 0-to-10-pain-scale or in dose or type of pain medication), PSA response (decrease $>$ 50% in PSA serum level) and overall survival (OS). Pts with early CR were compared to pts with sensitivity to initial ADT $>$ 1 year (t-test for quantitative data, χ-2 test or Fischer's exact test for qualitative data, Logrank test for TTP and OS). **Results:** 188 pts were selected for analysis. A higher frequency of unfavourable prognostic factors in pts with early CR as compared with others pts was observed with a median PSA serum level of 81 ng/dl (4-8000) vs 35 ng/dl (4-4260) ($p=5.10^{-5}$), presence of visceral metastasis in 11% vs 2% of pts ($p=0.01$) and Gleason score $\geq$ 8 in 63% vs 41% of pts respectively ($p=0.001$). Clinical benefit and PSA response on docetaxel were observed in 84% vs 89% of pts ($p=0.45$) and 67% vs 81% of pts ($p=0.10$) respectively. Median TTP was 6.1 months (95%CI=6-7.5) vs 7.8 months (95%CI=7-8.3) ($p=0.04$). Median OS was 22.4 months (95%CI=17.1–28.6) vs 36.1 months (95%CI=26.3–42.4) ($p=0.002$). **Conclusions:** mPC pts experiencing early CR have more unfavourable baseline prognostic factors, shorter TTP on docetaxel and shorter OS as compared with pts experiencing time to CR $>$ 1 year. However, similar clinical and biological benefits from docetaxel chemotherapy were observed in this subset of pts. Since they have lower probability of response to second-line endocrine therapy, docetaxel appears as the best option after progression on initial ADT.

5076 General Poster Session (Board #40C), Mon, 8:00 AM-11:45 AM

Safety, efficacy, and health-related quality of life (HRQoL) of the investigational single agent orteronel (ortl) in nonmetastatic castration-resistant prostate cancer (nmCRPC).

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Background: Ortl is a selective, non-steroidal, oral 17,20-lyase inhibitor. Due to its lower inhibition of 17α-hydroxylase vs 17,20-lyase, ortl may allow steroid-free dosing. Ortl 300 mg BID was studied in nmCRPC patients (pts). **Methods:** Pts with nmCRPC, PSA $\geq$2 ng/mL (PSA $\geq$8 ng/mL if doubling time $>$8 mo), and testosterone (T) $<$50 ng/dL received ortl 300 mg BID until PSA progression, development of metastases (mets), or unacceptable toxicity. Primary endpoint: the percentage of pts with PSA $\leq$0.2 ng/mL at 3 mo. Secondary endpoints included safety, PSA kinetics, time to mets, and PFS (PSA progression, mets, or death), endocrine and bone markers, bone mineral density (BMD), HRQoL, cardiac and lipid assessments. **Results:** 38 pts enrolled: median PSA 11.7 ng/mL (range 2.6–67.8), T 8.5 ng/dL (1.4–17.3), and ACTH 20 ng/L (n=32; 0–47). Median therapy duration was 12.4 mo (0.7–27.8); 55% of pts were treated $>$12 mo. 6 had dose reduction, 12 discontinued due to adverse events (AEs), including 2 for possible adrenal insufficiency. Gr 3 hypertension occurred in 7 pts (18%); various $\geq$Gr 3 AEs occurred in another 14 pts; 10 pts (26%) had serious AEs. At 3 mo, median T declined 89% to 0.78 ng/dL; median ACTH increased 171%; median cortisol declined 21%, but remained within normal range. 97% of pts had PSA declines; median PSA declined 83%. 18% had PSA $\leq$0.2ng/mL at 3 mo; 32% achieved PSA $\leq$0.2ng/mL as best response. Median time to PSA progression was 13.8 mo. Median PFS was 13.8 mo. Kaplan-Meier estimates of 1 and 2 y mets-free rates were 94% and 69%, respectively; 8 pts developed mets on study. The patient-reported Aging Male Symptoms Scale showed no decrease in overall scores, psychological, somatic, or sexual domains in 37, 34, 25, and 19 pts assessed at visits 2, 4, 7, and 13, respectively. Serum lipids, cardiac assessments, HbA_{1C}, or bone-specific enzymes (N-telopeptide, or BMD) were not adversely affected. **Conclusions:** In pts with nmCRPC, long-term steroid-free ortl was feasible, with clinical activity as reflected by sustained marked declines in PSA and T, and had manageable toxicities, with no adverse effects on HRQoL, cardiac, bone or lipid profiles. Clinical trial information: NCT01046916.

5077 General Poster Session (Board #40D), Mon, 8:00 AM-11:45 AM

Evaluating the hypothalamic-pituitary-adrenal axis (HPAA) in men receiving ketoconazole for castrate resistant prostate cancer (CRPC).

Rahul Raj Aggarwal, Vivian K. Weinberg, Eduardo V. Sosa, Amy M. Lin, Andrea Lynne Harzstark, Eric Jay Small, Lawrence Fong, Andrew Caleb Hsieh, Carl Formaker, Kathryn M. Koepfgen, Evelyn Hang, Terence W. Friedlander, Charles J. Ryan; University of California, San Francisco, San Francisco, CA

Background: Serum adrenal androgen (AA) levels may be prognostic for survival in men with CRPC treated with androgen synthesis inhibitors (ASIs) including ketoconazole (keto) and abiraterone. We hypothesize that up-regulation of the HPAA and adrenocorticotropic hormone (ACTH) may contribute to therapeutic resistance on ASIs. The current study explores the relationship between ACTH, AA, testosterone (T) and estradiol (E) among CRPC patients (pts) treated with ASI + corticosteroids. **Methods:** Phase II study of keto (400 mg TID) + hydrocortisone (HC) (30 mg/day) in pts with CRPC. Pts who achieved ≥ 30% PSA decline from baseline at week 12 continued keto/HC until progression, at which point HC was replaced by dexamethasone (dex). Serum hormone (H) levels were measured (in AM) at baseline and every 4 weeks using standard assays. Statistical tests include Spearman's rank test for correlation between baseline H levels; Wilcoxon matched pairs for baseline vs. week 4 distribution; and Fisher's exact test for associations between H levels (dichotomized at median) with PSA decline. **Results:** Of 30 pts enrolled and 24 evaluable for PSA response, 13 pts (54%) achieved ≥ 30% PSA decline at 12 weeks. Baseline ACTH was positively correlated with DHEA ($r = 0.40$; $p = 0.04$) and cortisol ($r = 0.52$; $p = 0.007$). Change from baseline to week 4 in H levels is shown in table. There was a significant increase in pts achieving a PSA decline of > 30% if there was a decrease in E at week 4 vs. no decrease (83% vs. 18%; $p = 0.003$). Baseline and changes in other H levels were not associated with PSA outcome at week 12. **Conclusions:** ACTH is positively correlated with DHEA and cortisol in CRPC pts. Declines in E may serve as an additional predictive marker of benefit for ASI therapy. These observations require prospective validation. Analyses exploring changes in ACTH at disease progression and impact of substituting dex for HC are ongoing. Clinical trial information: NCT01036594.

Serum hormone	# Evaluable	Median change (range)	P value
ACTH (pcg/mL)	22	4 (-105,72)	0.13
T (ng/dL)	23	2 (< -26,47)	0.16
E (pg/mL)	23	-1 (< -17,18)	0.38
DHEA (ng/dL)	23	-36 (-318,64)	0.01
DHEA-S (mcg/dL)	22	-52 (-196,0)	0.0001
Androstenedione (ng/dL)	21	-13 (<-67,36)	0.06
Cortisol (mcg/dL)	21	4 (-21,28)	0.52

5078 General Poster Session (Board #40E), Mon, 8:00 AM-11:45 AM

Ejaculation frequency and prostate cancer: A large, prospective study with 16 years of follow-up.

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Background: A prospective study in the Health Professionals Follow-up Study (HPFS) cohort published in 2001 found significantly lower risks of prostate cancer (PCa) among men with more frequent ejaculation. Because associations were stronger among men at older ages, which could be indicative of reverse causation (i.e., men ejaculating less because of symptoms associated with PCa) and few advanced cases were included, we conducted an updated study with an additional 8 years of follow up. **Methods:** We included 31,929 men aged 46-81 years from the HPFS who answered ejaculation frequency questions on the 1992 questionnaire. We assessed average frequency per month at three time points: age 20-29, age 40-49, and in 1991 (the year prior to the questionnaire). These data were also combined to estimate average lifetime frequency. Using follow up through January 31, 2008, we used Cox proportional hazards models to estimate relative risks (RR) and 95% confidence intervals (95% CI) for total PCa risk, as well as risk of advanced, lethal, and high-grade (Gleason 8-10) disease. As sensitivity analyses, we also examined associations within a subgroup of highly screened men and a subgroup of men without erectile dysfunction at baseline. **Results:** During 16 years of follow up, 3403 men were diagnosed with PCa; 455 were advanced, 360 were high grade, and 304 were lethal. Three percent of men reported a lifetime average frequency of >21 times per month while 34% reported 4-7 times per month. Compared to a frequency of 4-7 times per month, multivariate RRs for total PCa for men with >21 ejaculations per month were 0.81 (95% CI: 0.71-0.91) for ages 20-29; 0.76 (95% CI: 0.66-0.88) for ages 40-49; 0.68 (95% CI: 0.53-0.86) in 1991; and 0.57 (95% CI: 0.43-0.75) for lifetime average frequency. RRs for advanced PCa were of similar magnitudes at ages 20-29 years and 40-49 years but not statistically significant. Results were similar when we included only highly screened men or men without a history of erectile dysfunction. **Conclusions:** With extended follow up, ejaculation frequency continues to be strongly inversely associated with risk of total PCa. These findings are unlikely to be attributable to underlying disease or screening frequency.

5079 General Poster Session (Board #40F), Mon, 8:00 AM-11:45 AM

Denosumab and zoledronic acid treatment in patients with genitourinary cancers and bone metastases.

Luis Costa, Karim Fizazi, Fred Saad, Janet Elizabeth Brown, Roger Von Moos, Stephane Oudard, Cora N. Sternberg, Vinod Ganju, Kurt Miller, Huei Wang, Tapan Maniar, Ada Braun; Hospital de Santa Maria and Instituto de Medicina Molecular, Lisbon, Portugal; Institut Gustave Roussy, University of Paris Sud, Villejuif, France; University of Montreal Hospital Center, CRCHUM, Montreal, QC, Canada; Cancer Research UK Clinical Centre, Leeds, United Kingdom; Kantonsspital Graubünden, Chur, Switzerland; Georges Pompidou European Hospital, Paris, France; San Camillo-Forlanini Hospital, Rome, Italy; Peninsula Oncology Centre, Frankston, Australia; Charité-Universitätsmedizin Berlin, Berlin, Germany; Amgen, Inc., Thousand Oaks, CA

Background: Phase III trial results showed that denosumab is superior to zoledronic acid (ZA) in preventing skeletal-related events (SREs) in patients with cancer and metastatic bone disease (Lipton et al; 2012, *Eur J Cancer*). Genitourinary (GU) cancers are some of the most commonly diagnosed cancers worldwide. We now compare the efficacy and safety of denosumab (DMAb) or ZA in a subgroup analysis of patients with GU cancers enrolled in the pivotal phase III trials. **Methods:** Patients were randomized 1:1 to receive DMAb (120 mg, SC) or ZA (4 mg, IV, adjusted for renal function) every 4 weeks. Daily calcium and vitamin D supplements were strongly recommended. Time to 1st on-study SRE, using a Cox proportional hazards model, time to 1st and subsequent on-study SRE, using the Anderson-Gill model, and safety were evaluated for the GU subgroup in an ad hoc analysis. **Results:** 2,128 patients (1,052 DMAb; 1,076 ZA) had GU cancers (prostate = 1,901, renal = 155, bladder = 63, and transitional cell = 9). DMAb significantly delayed the time to 1st on-study SRE by 4.0 months compared with ZA (20.7 months vs 16.7 months) in patients with GU cancers (Table). DMAb also significantly delayed the time to 1st and subsequent on-study SRE. Time to disease progression and overall survival were similar between treatment groups. Adverse events (AEs) and serious AEs were reported by similar percentages of patients in both groups (AEs: 96.9% denosumab, 96.8% ZA; serious AEs: 62.8% denosumab, 60.2% ZA). 14.6% of DMAb pts and 15.9% of ZA pts had a renal AE. Hypocalcemia was reported for 12.9% of DMAb patients and 6.2% of ZA patients. There was no significant difference in the incidence of positively adjudicated osteonecrosis of the jaw between the DMAb (2.2%) and ZA (1.6%) groups (p=0.34). **Conclusions:** Among patients with GU cancers and metastatic bone disease, DMAb was superior to ZA in preventing SREs. Clinical trial information: NCT00330759 and NCT00321620.

Effect of DMAb vs ZA on SRE, disease progression, and survival in patients with GU cancers.

Endpoints	Hazard ratio (95% CI)	P value
Time to 1st on-study SRE	0.81 (0.71, 0.93)	0.004
Time to 1st and subsequent on-study SRE*	0.82 (0.72, 0.93)	0.002

* Multiple-event analysis; reported as a rate ratio.

5080 General Poster Session (Board #40G), Mon, 8:00 AM-11:45 AM

Correlation between baseline variables and survival in the radium-223 dichloride (Ra-223) phase III ALSYMPCA trial with attention to total ALP changes.

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Background: In patients (pts) with castration-resistant prostate cancer and bone metastases (mCRPC), total ALP (tALP) has been shown to be a prognostic marker for overall survival (OS) (Cook 2006). Here the prognostic value of tALP and other baseline clinical variables in Ra-223 pts is presented, along with the initial results of an exploratory analysis of changes in tALP seen with Ra-223. **Methods:** Study population included 921 pts (intent-to-treat population) from the ALSYMPCA trial. The Cox proportional hazards model was used to evaluate the prognostic potential of tALP and other baseline variables (albumin, Hb, LDH, ECOG performance status, PSA, and age). Log transformation was done for baseline variables (tALP, PSA, and LDH) with heavily skewed distributions. Baseline variables were assessed for interaction with treatment. To determine changes in tALP from baseline at 12 wk, 708 pts who had tALP measurements at both baseline and 12 wk were included. **Results:** The baseline variables in the Table were significantly associated with OS. Hb was not a significant factor when adjusting for all other covariates and was therefore removed from the final Cox regression model. No significant treatment-by-covariate interactions were detected. After controlling for other variables, higher baseline tALP was significantly associated with an increased risk of death ($p < 0.0001$). At 12 wk, a decline in tALP relative to baseline was seen in 87% (433/497) of Ra-223 pts, compared to 23% (49/211) of placebo pts. The mean percentage change from baseline in tALP at 12 wk was a 32% decline for Ra-223 pts, in contrast to a 37% increase for placebo pts ($p< 0.001$). **Conclusions:** In mCRPC pts, higher baseline levels of tALP were associated with an increased risk of death. With the majority of Ra-223 pts experiencing a decline in tALP at 12 wk, and the marked mean percentage tALP decline in these pts, further analysis to determine a correlation between tALP dynamics and survival is warranted. Clinical trial information: NCT00699751.

Baseline variable	Hazard ratio	P value
Ra-223 treatment	0.783	0.0086
Albumin	0.973	0.0047
Log LDH	3.476	< 0.0001
ECOG PS	1.612	0.0001
Log PSA	1.401	< 0.0001
Log t-ALP	2.046	< 0.0001
Age	1.014	0.0179

5081 General Poster Session (Board #40H), Mon, 8:00 AM-11:45 AM

Association of bone scan index (BSI) with prognostic biomarkers and survival in men with metastatic castration-resistant prostate cancer (mCRPC) enrolled in a prospective randomized controlled trial of tasquinimod.

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Background: Tasquinimod (T) is an oral immunomodulatory and anti-angiogenic agent currently in phase 3 testing in mCRPC. In a randomized, double-blind phase 2 multicenter study, 201 men with mCRPC who received T had improved radiographic PFS vs. placebo (P), with a more pronounced effect seen in men with bone metastases. Given the subjectivity/variability of bone scan measurements, we sought to evaluate the bone scan index (BSI), a quantitative and objective measure of BS activity, over time in this controlled clinical trial. Post-treatment BSI changes were examined given their prior association with survival. **Methods:** In this retrospective analysis, Exini bone™, an automated software package that generates the BSI (percent tumor involvement) from ^{99}Tc BS, was used to calculate BSI over time from BS collected during central review in this randomized trial of T vs. P. Associations between baseline and on-treatment BSI, survival, prognostic biomarkers, and treatment effect were evaluated. **Results:** 108 men contributed baseline scans for BSI analysis that met quality control metrics (74 T vs. 34 P), 85 of whom (57 T vs. 28 P) had at least 1 evaluable follow-up week 12 scan. Median baseline BSI was 0.90% and after 3 months median BSI was 1.21%. In univariate analysis (n=85) baseline BSI correlated with OS (HR 1.41; p=0.01). Both baseline BSI (HR 1.62; p=0.006) and week 12 BSI change (HR 1.95; p=0.002) remained associated with OS after adjustment for bone alkaline phosphatase, PSA, pain score, hemoglobin, and treatment arm. BSI correlated with baseline PSA, LDH, bone alkaline phosphatase, and the number of bone lesions. The increase in BSI at week 12 vs. baseline was slower with T vs. placebo (0.16% vs. 0.26% increase). **Conclusions:** BSI and BSI changes were associated with OS in men with mCRPC in this prospective trial. BSI correlates with known biomarkers of OS, but adds independent prognostic information. While underpowered, a delay in objective radiographic bone scan progression with tasquinimod is suggested and the evaluation of BSI and BSI changes in the context of phase 3 trials of men with mCRPC is warranted. Clinical trial information: NCT00560482.

5082 General Poster Session (Board #41A), Mon, 8:00 AM-11:45 AM

Association of germ-line genetic variation with failure of androgen ablation (AA) in hormone-sensitive advanced prostate cancer.

Manish Kohli, Shannon McDonnell, Graham H. Bevan, Shaun M. Riska, Brian Addis Costello, Sherri Longenbach, Roxana Stefania Dronca, Timothy Jerome Moynihan, Henry Clement Pitot, Fernando Quevedo, Winston Tan, James Robert Cerhan; Mayo Clinic, Rochester, MN; Mayo Clinic, Department of Medical Oncology, Rochester, MN; Mayo Clinic, Jacksonville, FL

Background: We evaluated the association of germ-line variation in 10 candidate genes important in prostate cancer biology (*NKX3-1, JAK2, SLCO2B1, STAT3, CYP19A1, HSD17B4, TRMT11, PRMT3, HSD17B12, NCOA4)* with failure of AA in advanced prostate cancer patients. **Methods:** Patients (N=619) were enrolled for genotyping at the time of AA failure. Candidate genes were selected from the literature and previous pilot studies in smaller cohorts which had identified variation in *TRMT11* and *HSD17B12* to be associated with AA failure. Genes were tagged using single nucleotide polymorphisms (SNPs) from HapMap with minor allele frequency of >5% and $r^2 \geq 0.8$. DNA was extracted from peripheral blood and genotyped using Illumina Veracode platform. The primary endpoint was time to failure on AA, defined as time from initiating continuous AA to two serial PSA increases over the nadir or clinical or imaging based progression, whichever came first. Principal component analysis was used for gene-levels tests. Association with the primary endpoint was assessed using proportional hazards regression models at the gene-level and at the SNP level. For SNP level results we estimated per allele (ordinal model) hazard ratios (HR) and 95% confidence intervals (CI) using Cox regression, adjusted for Gleason score (GS). **Results:** We successfully genotyped 60 SNPs (from 10 genes) in 519 subjects. The median age of the cohort was 71 years (range 43, 92). The GS distribution was 51% subjects with GS≥8; 33% with GS=7 and 17% with GS<7. Median time to AA failure for the cohort was 2.3 years (IQ range: 1.0-4.5). In gene level analyses adjusting for GS, *TRMT11* (p=0.004), *HSD17B12* (p=0.016), and *JAK2* (p=0.044) genes were associated with time to AA failure. Four of the 18 genotyped SNPs in *JAK2* were associated with AA failure after adjustment for GS (Table). **Conclusions:** Variation in the *JAK2* gene is significantly associated with time to AA failure. Validation is needed to develop these as predictive biomarkers for AA in advanced prostate cancer.

JAK2 gene rsIDs	GS adjusted per-allele HR (95% CI)	P value
rs3808850	1.20 (1.04-1.38)	0.010
rs1887429	0.84 (0.72-0.99)	0.032
rs7849191	1.16 (1.01-1.32)	0.034
rs4372063	1.17 (1.03-1.33)	0.014

5083 General Poster Session (Board #41B), Mon, 8:00 AM-11:45 AM

Sera cytokine levels to predict survival in men with progressive castration-resistant prostate cancer.

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Background: Serum cytokines have been proposed as immunologic biomarkers of clinical responses based on their role in tumor biology. Recently, two whole blood mRNA signatures, which included immunomodulatory gene transcripts, were found to be predictive of survival in CRPC. This study explores serum cytokines, measured with analytically valid assays, as prognostic biomarkers in CRCP. **Methods:** Serum was collected from 75 progressive CRPC patients treated at MSKCC. A panel of 10 cytokines (M-CSF, IFN-γ, TNF-α, IL-1 β, IL-4, IL-5, IL-6, IL-10, IL-12 and IL-13) was measured in a CLIA-certified laboratory by clinically validated ELISAs. To create a risk group classification based on the 10 cytokines, a regression tree methodology was used with the intent to maximize the survival differences between risk groups. In addition to the cytokine risk groups, PSA, LDH, albumin, hemoglobin and CTC enumeration were also independently prognostic. The Cox model was developed to determine the factors that jointly predicted survival. The concordance probability estimate (CPE) was used to determine the discriminatory power of this model. **Results:** Among the 10 cytokines, M-CSF (stimulates monocytes and macrophages) and IL-10 (suppresses T-cell-mediated anti-tumor responses), were most predictive of overall survival in a 3 risk-group model. The relative risk for log CTC was 1.78 (95% CI 1.43 – 2.21). The combination of the cytokine risk groups and CTC enumeration provided the best discriminatory power for predicting survival, yielding a discrimination index measured by the CPE equal to 0.77 (se = 0.03). **Conclusions:** A risk group classification, based on two serum cytokines, M-CSF and IL-10, and log CTC measured by analytically valid assays, predicted survival in patients with progressive CRPC. These cytokines may reflect the biology within the tumor microenvironment, and may also serve as biomarker for clinical benefit. Independent validation in a similar cohort of patients is ongoing.

Risk group (pg/mL)	N	Median survival in months (95% CI)	RR (95% CI)
M-CSF ≥ 333.5 and IL-10 ≥ 1.05	33	14.6 (8.6 - 21.1)	1
M-CSF ≥ 333.5 and IL-10 < 1.05	26	23.5 (15.3 - N/A)	0.65 (0.35 - 1.20)
M-CSF < 333.5	16	50.5 (39.5 - N/A)	0.30 (0.09 - 0.94)

5084 General Poster Session (Board #41C), Mon, 8:00 AM-11:45 AM

Aspirin use and mortality in men with localised prostate cancer: A cohort study.

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Background: Cyclooxygenase-2 (COX-2) expression in prostate cancer has been associated with high grade tumours and poorer prognosis. Use of aspirin, a COX-2 inhibitor, has been associated with reduced prostate cancer mortality in some studies. These studies have not, however, provided information on the dose and timing of aspirin use. **Methods:** National Cancer Registry Ireland data was used to identify men with stage I-III prostate cancer (ICD10 C61) diagnosed 2001-2006. Aspirin use in the year preceding prostate cancer diagnosis was identified from linked prescription refill data (General Medical Services) and stratified by dose (low ≤75mg, high >75mg) and dosing intensity (proportion of days in that year with aspirin supply available). Cox proportional hazards models, adjusted for age, smoking status, year of incidence, comorbidity score, Gleason score, tumour size, pre-diagnostic statin use, and receipt of radiation (time varying) were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations between aspirin use and all-cause and prostate cancer-specific mortality. Interactions with tumour characteristics were examined. **Results:** 2,936 men with stage I-III prostate cancer were identified (aspirin users, N=1,131; 38.5%). Median patient follow-up was 5.5 years. In multivariate analyses, aspirin use was not associated with a significant reduction in prostate cancer-specific (HR 0.90, 95% CI 0.68-1.20) or all-cause mortality (HR 0.98, 95% CI 0.84-1.15). In dose response analyses aspirin use was associated with a significantly lower risk of prostate cancer-specific mortality in men receiving >75mg of aspirin (HR 0.59, 95% CI 0.35-1.00, p=0.048) but not ≤75mg aspirin (HR 1.01, 95% CI 0.75-1.37, p=0.938). Stronger associations were also observed in men with higher aspirin dosing intensity or a Gleason score >7. **Conclusions:** Pre-diagnostic aspirin use, measured using objective prescription refill data, was associated with a significant reduction in prostate cancer-specific mortality in men with stage I-III prostate cancer receiving >75mg of aspirin. These results confirm previous findings, and provide important new information regarding the dose of aspirin associated with survival benefit.

5085 General Poster Session (Board #41D), Mon, 8:00 AM-11:45 AM

Phase II trial of single-agent ganetespib (STA-9090), a heat shock protein 90 (Hsp90) inhibitor in heavily pretreated patients with metastatic castration-resistant prostate cancer (mCRPC) post docetaxel-based chemotherapy: Results of a Prostate Cancer Clinical Trials Consortium (PCCTC) study.

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Background: Hsp90 is a molecular chaperone required for the proper folding and activation of numerous client proteins and is critical to cell survival and proliferation. Ganetespib (G), a synthetic small molecule that binds to the ATP pocket in the N-terminus of Hsp90 causes the degradation of cellular proteins and ultimately death of cancer cells dependent on these proteins. G displays potent anticancer activity in prostate cancer cells. **Methods:** Eligible patients were $\geq$ 18 yrs old with ECOG performance status $\leq$ 2. Adequate hepatic, renal, and bone marrow function was required. Patients were treated with G 200 mg/m^2 intravenously once weekly for 3 consecutive weeks followed by 1 off-week. The primary objective was to evaluate the 6-month progression-free survival (PFS). Secondary endpoints included overall safety and tolerability of G and overall survival. Exploratory markers including maspin, cytokeratins 8 and 18, and HDAC1 were obtained pre, during, and post G treatment. We sought $\geq$ 4 patients with $\geq$ 6 months PFS (a success) in Stage 1 of a 2-stage near-optimal Simon design. **Results:** 18 patients were enrolled at 4 institutions. The patients' median age was 68 (range 51-82), 13 were Caucasian, 4 were African American, and 1 was Asian. Median PSA was 210.7 ng/mL (range 25.9 – 3,489 ng/mL). One patient never started therapy. Among the 17 treated patients, the median number of cycles was 2 (range 1-5). The most frequent Grade 3 toxicities were diarrhea (3 patients), fatigue (3), and dehydration (3). Prior therapy included abiraterone (8), sipuleucel-T (4), and other targeted therapy (4). With $<$ 4 successes in Stage 1, the trial was terminated early. Median PFS was 1.9 months (90% CI: 1.7 – 2.7 months); median OS was 10.2 months (90% CI: 2.3 – 18.3 months). Exploratory markers have been evaluated and will be presented. **Conclusions:** Our study represents the first clinical trial of G in treating mCRPC patients. As a single agent therapy, G did not prolong PFS. Combination therapy is a consideration to improve therapeutic efficacy. Clinical trial information: NCT01270880.

5086 General Poster Session (Board #41E), Mon, 8:00 AM-11:45 AM

Vasectomy and risk of lethal prostate cancer: A 24-year prospective study.

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Background: In the United States, 10 to 15 percent of adult men have undergone a vasectomy. There is conflicting evidence whether vasectomy is associated with increased prostate cancer risk. **Methods**: We undertook a prospective study among 49,432 men in the US Health Professionals Follow-up Study. The men were age 40 to 75 years at baseline in 1986 and were followed prospectively for cancer incidence and mortality through 2010; 6,398 incident cases of prostate cancer were diagnosed, including 734 with high grade (Gleason 8 – 10) and 813 with cancer causing death or bony metastasis (lethal). We used cox regression models to calculate hazard ratios (HR, 95% confidence intervals) of the association between vasectomy and incidence of high grade and lethal prostate cancer, adjusting for potential confounders. We examined associations in the total cohort, and in a subset of 12,371 men highly screened by PSA in order to disentangle potential diagnostic bias. **Results**: At baseline, 22 percent of men reported having had a vasectomy. Men who had undergone vasectomy were at increased risk of high-grade (HR 1.23, 95% CI: 1.04-1.47) and lethal (HR 1.20, 95% CI: 1.01-1.43) prostate cancer. In the highly screened cohort, the association was similar for high-grade cancer, and even stronger for lethal disease (HR 1.56, 1.03-2.36). The risk of lethal prostate cancer was higher among men who had a vasectomy before age 38 years compared to at older ages. The increased risks with vasectomy could not be explained by differences in hormone levels, prevalence of sexually transmitted infections, or cancer treatments. **Conclusions**: Data from this study support the hypothesis that vasectomy is associated with a small increased incidence of aggressive prostate cancer defined as high grade cancer and disease causing death or bony metastasis. Differences in diagnostic intensity or confounding bias do not explain this elevated risk.

5087 General Poster Session (Board #41F), Mon, 8:00 AM-11:45 AM

Circulating miR-337-3p as a novel biomarker for prostate cancer.

Manuel Valladares Ayerbes, Vanessa Medina Villaamil, Sara Martinez Breijo, Isabel Santamarina Cainzos, Guadalupe Aparicio, Jose Gonzalez Dacal, Paula Portela Pereira, Dario Vazquez Pazos, Francisco Gomez-Veiga, Luis M. Antón Aparicio; Oncology Service, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain; Biomedical Research Institute, A Coruña, Spain; Urology Service, CHU A Coruña, A Coruña, Spain; Translational Cancer Research Group, Instituto de Investigacion Biomedica A Coruña (INIBIC), Complejo Hospitalario Universitario A Coruña, SERGAS, A Coruña, Spain; Complexo Hospitalario Universitario A Coruña, A Coruna, Spain; Medical Oncology Department, A Coruña, Spain

Background: Recent studies have demonstrated that the aberrant expression of microRNAs (miRNAs)is related with the development of prostate cancer (PCa). Detection of circulating tumor cells (CTC) may provide diagnostic and prognostic information inPCa. The purpose is identifying circulating miRNAs potentially useful for CTC detection in patients with PCa. **Methods:** In the first study phase we examined blood levels of 92 miRNAs in 49 patients grouped in pools by risk classification: low-risk 42.8%, intermediate-risk 22.5% and high-risk 34.7% and healthy volunteers (N=10) using SYBR-green-based microARN RT-qPCR arrays (Exiqon). Prostate cancer diagnosis was obtained by transrectalultrasound guided biopsy of 10 cores, PSA and digital rectal examination was done previously. In the second study phase using quantitative real-time polymerase chain reaction (qPCR) by TaqMan Human MicroRNAAssays (Life Technologies), we compared the expression levels of miRNAs in blood samples from 34 patients of low-risk, 31 of intermediate-risk, 18 of high-risk localized disease and 22 healthy volunteers paired by age with cases. Receiver-operator characteristic (ROC) curve was used. **Results:** Blood samples from patients with low, intermediate, high-risk and healthy controls exhibit distinct circulating miRNA signatures. microRNAsdifferential expressed between risk groups ($p<0.01$) (low, intermediate and high) and control group: 0microARNs upregulated (MU), 12 MU and 68 MU respectively. Highlight the significantlyover-expression in the intermediate risk group and maintained at the high-risk of microRNAs: 337-3p[247 PicTar predictions (PTP)], 330-3p (307 PTP) and 218 (551 PTP). Preliminary results of the second study phase showed that the median level of miRNA,337-3p was significantly higher in patients with high-risk than that in healthy controls ($p=.001$). ROC curve analyses indicated that this blood miRNA may beuseful for discriminating patients with high-risk from healthy controls (AUC=.724). **Conclusions:** miRNAs in the circulation are relatively stable, very accessible, low invasive and easily testable biomarkers. Our preliminary promisingresults suggest miR-337-3p as novel stable blood-based marker for PCa detection.

5088 General Poster Session (Board #41G), Mon, 8:00 AM-11:45 AM

Effects of abiraterone acetate and enzalutamide on muscle and adipose mass in men with metastatic castration-resistant prostate cancer (mCRPC).

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Background: Abiraterone acetate (AA) and enzalutamide (MDV3100), two androgen receptor-directed compounds, have been shown to improve survival for patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after Docetaxel.. Since these drugs might be used at an early-stage in the future, and skeletal muscle (SM) and adipose tissue (AT) are known to be prognosis parameters, the aim of this study was to evaluate the body composition changes in patients with mCRPC treated with AA and MDV3100. **Methods:** Patients included in AFFIRM (n=62 treated with MDV3100 and placebo n=28) and COU-AA-301 (n=24 treated with AA+Prednisone (P)10mg/day and placebo+P n= 13) trials at the Institute Gustave Roussy were included in the analysis. Cross-sectional areas (cm^2) of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and SM were assessed by computed tomography imaging at 3rd lumbar vertebra and were indexed for height (cm^2/m^2) with Slice-O-Matic software V4.3 at baseline, 3, 6 and 12 months of treatment. The data from patients treated with AA or MDV3100 were compared to placebo-patients and tissues changes were compared to baseline. We used the validated sarcopenic definitions as SM index less than 52.4 (cm^2/m^2). **Results:** For all cohort, median age was 69 years (range: 48-83), median weight was 79 kg (range: 47-150) and median BMI was 25.9 kg/m^2(range: 18-46). At inclusion, 74 patients (58%) were overweight or obese (BMI>24.9 kg/m2), and only 2 patients were underweight (BMI<18.5kg/m2). 97 patients (81%) were sarcopenic, and 56 (75%) of overweight or obese patients were sarcopenic. Over 3 months, the patients from the entire cohort lost muscle mass (mean change: 4.5±7.5% (» 0.7 kg of muscle)) (P=0.01) . A non significant loss of SAT -4.6±19.2% and a non significant increase of VAT (+10.7±50.3%) were observed. A similar pattern was observed at 6 months. There was no significant difference between body composition changes in treated groups and placebo. **Conclusions:** Sarcopenia is highly prevalent in patients with advanced CRPC. Unexpectedly, no difference in body composition changes was observed between patients treated with MDV3100 or AA and placebo.

5089 General Poster Session (Board #41H), Mon, 8:00 AM-11:45 AM

The role of advanced genetic testing in the management of prostate cancer post radical prostatectomy.

Edward M. Schaeffer, Ismael A. Vergara, Anamaria Crisan, Nicholas Erho, Mercedeh Ghadessi, Felix Yi-Chung Feng, Elai Davicioni, Ashley E. Ross; Department of Urology, Johns Hopkins Medical Institutions, Baltimore, MD; GenomeDx Biosciences Inc., Vancouver, BC, Canada; University of Michigan Health System, Ann Arbor, MI

Background: The genomic classifier (Decipher, GC) is a prospectively validated assay that predicts clinical metastasis post radical prostatectomy (RP) more accurately than standard clinicopathologic factors. While over 70% of high risk patients tested in a previous validation had low GC scores and good prognosis, patients with high GC scores had a cumulative incidence of metastasis over 25% over the study duration. Among men diagnosed with localized prostate cancer, these most at risk patients may derive the greatest benefit from novel therapies. We thus examined differential expression (DE) of druggable genes that may be targeted in this group. **Methods:** High-density microarray expression profiles of primary FFPE tumor specimens from 764 men treated with RP at the Mayo Clinic (1987-2006) were evaluated. A subset of 323 patients was flagged as high risk of clinical metastasis (mets) by virtue of having GC score $\geq$ 0.4. Enrichment and identification of DE genes as druggable targets were pursued using DAVID and DrugBank. **Results:** Median follow-up of patients was 15.1 years. Among the 323 patients with high GC scores, 62% had mets during follow-up.We identified 2,262 genes DE between mets and non-mets, 230 of which are associated with 331 approved pharmaceuticals and 547 experimental agents. These agents included multiple established anti-neoplastic therapies not currently used to treat prostate cancer such as bortezomib, capecitabine, dasatinib, etoposide, gemcitabine, imatinib, irinotecan, pemetrexed and vinblastine. The two most enriched pathways, spliceosome and ubiquitin-mediated proteolysis, have been proposed previously as therapeutic targets in cancer. **Conclusions:** Advanced genomic testing that includes validated molecular risk scores as well as transcriptome profiling from a single assay may better enable application of directed, multimodal therapy for individual patients with high risk prostate cancer.

5090 General Poster Session (Board #42A), Mon, 8:00 AM-11:45 AM

Evaluating 18F-16B-fluoro-5α-dihydrotestosterone (FDHT) and FDG-PET as a measure of disease progression in metastatic castration resistant prostate cancer (mCRPC).

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Background: Prostate Cancer Working Group 2 defines radiographic progression as new lesions on bone scan. Molecular imaging has potential as a biomarker that reflects both alterations in disease burden and tumor biology. FDG and FDHT PET capture glycolytic activity and androgen receptor (AR) expression and tracer binding, respectively. We examined these tracers in mCRPC patients (pts) at progression (POD) to determine patterns of relapse. **Methods:** mCRPC pts simultaneously enrolled in imaging and therapeutic clinical trials had FDG and/or FDHT PET scans performed at baseline (BL) and within 4 weeks of treatment (rx) discontinuation for protocol-defined POD. BL characteristics, rx, SUVmax, SUVmaxavg (average of 5 index lesions), and presence of new lesion(s) at POD were collected. ΔSUV was calculated relative to BL. **Results:** 44 mCRPC pts (86 BL PET scans, 84 scans at POD) receiving novel anti-androgens (eg, enzalutamide) (n=18), abiraterone (abi) (n=10), chemotherapy-based rx (n=5), prednisone (n=4), or other targeted rx (n=7) were included. Of those with PET POD, 75% (24/32) had > 1 new lesion on FDG-PET and 96% (25/26) had > 1 new lesion on FDHT. New lesions on FDHT were seen in 33% (6/18) of pts on novel anti-androgens as compared with 100% (10/10) on abi. Presence of a new FDG avid lesion was similar for both anti-androgens and abi (56% vs 60%). **Conclusions:** POD on FDG/FDHT is more frequently detected by a new lesion rather than ΔSUV in existing index lesions. This is possibly an underestimate of change as the BL scan and not the post-rx nadir scan were used as a comparator. AR and glycolytic activity at POD may be dependent on individual and treatment factors. Notably, a third of pts on anti-androgens had a new FDHT avid lesion at POD. Full lesional analysis of metastases may enhance our understanding of tumor biology at POD. Clinical trial information: NCT00588185.

	FDG (n=43 pts)	FDHT (n=41 pts)
New lesions at POD	24 (55.8%)	25 (61%)
% ΔSUVmax[a]	-1.02 (-58.2 to 81.1)	-35.2 (-91.2 to 383.0)
% ΔSUVmaxavg[a]	0.84 (-54.9 to 157.2)	-35.9 (-95.0 to164.6)
% pts with worsening SUVmax	46.5%	31.7%
% pts with worsening SUVmaxavg	53.5%	34.1%
% with PET POD (new lesion or worsening SUVmax or SUVmaxavg)	74.4%	63.4%

[a] Median.

5091 General Poster Session (Board #42B), Mon, 8:00 AM-11:45 AM

Overall survival in hormone-resistant prostate cancer patients with different transition of care within the Veterans Affairs (VA) system.

S Scott Sutton, Gowtham A Rao, LeAnn B. Norris, James Hardin, Sandip M. Prasad, Charles L. Bennett; University of South Carolina, Columbia, SC; Dorn VA Medical Center, Columbia, SC; University of South Carolina College of Pharmacy, Columbia, SC; Medical University of South Carolina, Charleston, SC; University of South Carolina College of Pharmacy and Medical University of South Carolina, Columbia, SC

Background: Prostate cancer patients with locally advanced /metastatic disease have a poor prognosis and although hormonal therapy can induce long-term remission, development of hormone-resistant prostate cancer (HRPC) is inevitable. The goal of this study is to evaluate overall survival in HRPC patients with different transition of care in the Veterans Affairs (VA) system. We hypothesized that prostate cancer patients with late referral to medical oncologists were more likely to have decreased overall survival. **Methods:** This is a retrospective, observational analysis of patients enrolled in the Veterans Health Administration system from October 2003 to March 2011. Patients were followed from initial evaluation and treatment by urology until an endpoint of death or the end of the study period. VA patients with a diagnosis of HRPC were identified; prostate specific antigen (PSA), medical and pharmacy records were collected. HRPC was defined as PSA doubling after treatment with hormonal therapy. Transition of care was defined as two encounters with the medical oncology service and at least one encounter was a medical oncologist. Three cohorts were created: patients transitioned to oncology before HRPC, those transitioned to oncology after HRPC, and patients who were never transitioned to oncology. Primary outcome was overall survival (OS). The Charlson score was utilized for comorbidity assessment. Statistical analysis was conducted using chi square test for categorical variables. **Results:** Total number of patients evaluated was 8,281; 2,168 in transition before HRPC (tbHRPC) cohort, 2,052 in transition after HRPC (taHRPC), and 4,061 patients that never transitioned (tnHPRC). The mean ages for the respective cohorts were: 69.35, 69.69, and 71.64. The Charlson comorbidity scores were 3.79 (tbHRPC), 3.06 (taHRPC), and 3.14 (tnHRPC); p-values < 0.05. Mortality rates among the cohorts were 57% tbHRPC, 69% taHRPC, and 62% tnHRPC; p-values <0.001. PSA doubling within 10 months were: 57% tbHRPC, 60% taHRPC, and 54% tnHRPC; p-values < 0.05. **Conclusions:** Overall survival was improved among prostate cancer patients that transitioned to oncology before becoming HRPC.

5092 General Poster Session (Board #42C), Mon, 8:00 AM-11:45 AM

The impact of reducing the frequency of prostate specific antigen (PSA) testing among men on active surveillance for prostate cancer.

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Background: Active surveillance is a management strategy for men with low risk prostate cancer. Most surveillance regimens include routine PSA assessments, typically performed q 3 mos, although recent studies have questioned the utility of short-term PSA kinetics. Moreover, frequent PSA assessments may be associated with repeated intervals of anxiety around the time of testing, decreasing overall quality of life and potentially leading to avoidable interventions. We hypothesized that PSA assessment q 6 mos rather than q 3 mos would yield similar PSA kinetics calculations. **Methods:** We analyzed data from the Prostate Active Surveillance Study (PASS), a prospective, multicenter cohort accruing data and biospecimens from men on surveillance at 9 sites across North America. In PASS, PSAs are measured q 3 mos, with high completeness of data. We included data from men who had at least 5 PSA assessments after diagnosis, separated by $\geq$6 months (most had 10 PSAs separated by 3 months). PSA doubling time (PSADT) was calculated as ln(2) divided by the slope of a regression line drawn through the 5 PSAs. PSADT3 and PSADT6 were defined as the PSADT calculated from q 3 mos and q 6 mos data, respectively; for PSADT6, PSAs between each 6-month measurement were ignored. In each case, PSADT of 0-3 years defined progression, and PSADT $>$ 3 years or declining PSA defined non-progression. **Results:** 161 men had sufficient PSA followup for analysis. 133 had no progression by either PSADT3 or PSADT6, and 16 progressed by both PSADT calculations. 4 and 8 men, respectively, progressed only by the PSADT3 or PSADT6 calculation but not by the other calculation. The κ score for agreement of progression ascertainment between PSADT3 and PSADT6 was 0.68, and McNemar's test indicated no statistically significant difference between the two assessments ($p=0.39$). **Conclusions:** Calculating PSADT using 6-month rather than 3-month PSA assessments does not significantly change ascertainment of PSA progression in men on surveillance. Our finding suggests that surveillance protocols may reduce the frequency of PSA testing, potentially reducing unnecessary biopsy procedures and patient anxiety due to more frequent PSA measurements.

TPS5093 General Poster Session (Board #42D), Mon, 8:00 AM-11:45 AM

CA184-095: A randomized, double-blind, phase III trial to compare the efficacy of ipilimumab (Ipi) versus placebo in asymptomatic or minimally symptomatic patients (pts) with metastatic chemotherapy-naive castration-resistant prostate cancer (CRPC).

Tomasz M. Beer, Christopher Logothetis, Padmanee Sharma, Yohann Loriot, Karim Fizazi, Alberto Bossi, Eugene D. Kwon, Brent McHenry, Paul Gagnier, Winald R. Gerritsen; Oregon Health & Science University Knight Cancer Institute, Portland, OR; The University of Texas MD Anderson Cancer Center, Houston, TX; Institut Gustave Roussy, Villejuif, France; Mayo Clinic, Rochester, MN; Bristol-Myers Squibb, Wallingford, CT; Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Background: Globally, docetaxel remains the standard of care for metastatic CRPC; however, its use may be delayed until pts develop symptoms. The presence of infiltrating leukocytes in CRPC tumors suggests a natural antitumor immune response is occurring. This is supported by an overall survival (OS) benefit reported in men with asymptomatic or minimally symptomatic metastatic CRPC who received sipuleucel-T. Ipi, a monoclonal antibody that binds CTLA-4, augments antitumoral activity of cytotoxic immune cells. Ipi demonstrated OS benefit in two phase III trials for advanced melanoma, with side effects that were managed using product-specific treatment guidelines. In phase I/II trials in metastatic CRPC, Ipi has shown clinical activity (as measured by prostate-specific antigen [PSA] declines and RECIST response) with a similar toxicity profile to that observed in melanoma. This global (149 sites in 24 countries) phase III study (ClinicalTrials.gov identifier: NCT01057810) evaluates Ipi vs placebo in chemotherapy-naïve pts with asymptomatic or minimally symptomatic CRPC without visceral metastases. **Methods:** The primary endpoint is OS; secondary endpoints include progression-free survival, time to pain progression, time to non-hormonal systemic therapy and safety characterization. The study is designed to detect a 9.3-month median difference (HR=0.7) in OS with 90% power and 0.05 two-sided significance. Pts are randomized at a 2:1 ratio to receive Ipi 10 mg/kg every 3 weeks for up to 4 doses or placebo as induction therapy. Eligible pts will receive maintenance therapy of blinded study drug every 12 weeks. The accrual goal is 600 pts randomized. Clinical trial information: NCT01057810.

Inclusion criteria
Metastatic CRPC
Asymptomatic or minimally symptomatic
Progression during prior hormonal therapy
Discontinuation of anti-androgens
Testosterone <50 ng/dl
ECOG performance status 0-1

Exclusion criteria
Liver, lung, or brain metastases
Prior immunotherapy or chemotherapy for metastatic CRPC
Autoimmune disease
HIV, Hep B, or Hep C infection
Pelvic targeted radiotherapy within 3 months of study

TPS5094 General Poster Session (Board #42E), Mon, 8:00 AM-11:45 AM

A phase II trial of cabozantinib (Cabo) in patients (pts) with castrate-resistant prostate cancer (CRPC) metastatic to bone (NCT01428219).

Petros Grivas, Stephanie Daignault, Kathleen A. Cooney, Jon Jacobson, Corrie Yablon, Brian Dale Ross, Thomas L Chenevert, Craig J Galbán, Alnawaz Rehemtulla, Evan T. Keller, Priya Kunju, Rohit Mehra, June Escara-Wilke, Greg Shelley, Kenneth James Pienta, Maha Hussain, David C. Smith; University of Michigan, Ann Arbor, MI; University of Michigan Medical Center, Ann Arbor, MI; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI

Background: MET overexpression predicts prostate cancer invasion and bone metastasis; inhibition of MET/VEGF pathways has synergistic activity in CRPC (Knudsen et al. Adv Cancer Res 2004; Aftab et al. Clin Transl Oncol 2011). Cabo is a small molecule that inhibits multiple receptor tyrosine kinases, including MET and VEGFR2. A phase II randomized discontinuation trial of Cabo showed clinical activity in CRPC, including reduction of soft tissue lesions, prolongation of progression-free survival (PFS), resolution of bone scans, and reductions in bone turnover markers, pain and narcotic use (Smith et al, JCO 2013). To further define the activity of Cabo in pts with CRPC and bone metastases, we launched a phase II trial to characterize the effects of Cabo on bone metabolism and tumor activity in prostate cancer bone lesions. We hypothesize that the clinical activity of Cabo correlates with measurable pharmacodynamic effects on bone micro-environment. **Methods:** After informed consent, chemotherapy-naive pts with progressive CRPC and bone metastases accessible to CT-guided biopsy, adequate performance status/organ function, are treated with Cabo 60 mg once daily. Primary endpoint: proportion of pts progression-free (PF) at 12 weeks. Secondary endpoints: safety, PFS, response proportion/duration, PSA response, PSA time-to-progression. A Simon's two-stage mini-max design permits early termination after the first 27 evaluable pts in case of unfavorable results. Alternatively, up to 46 evaluable pts will be accrued. Cabo would not be of interest if the 12-week PF proportion is <0.45; it would be of definite clinical interest if the 12-week PF proportion is >0.65 (5% type I error, 85% power). Perfusion/diffusion-weighted MRI (parametric response maps) and bone lesion biopsies are required at baseline and 6 weeks after starting Cabo. Doxycycline is administered prior to bone biopsy for bone labeling. Bone cores are sent for dynamic histomorphometry and immunohistochemistry (phospho-MET/MET, phospho-VEGFR2/VEGFR2, phospho-Akt/Akt). Serum is collected at several time-points to measure markers of bone metabolism. 13 of 27 first-stage pts have been enrolled and started Cabo. Clinical trial information: NCT01428219.

TPS5095 General Poster Session (Board #42F), Mon, 8:00 AM-11:45 AM

A phase I study of cabozantinib (Cabo) plus docetaxel (D) and prednisone (P) in metastatic castrate resistant prostate cancer (mCRPC).

Fatima H. Karzai, Ravi Amrit Madan, Andrea Borghese Apolo, Howard L. Parnes, John Joseph Wright, Jane B. Trepel, Melony A. Beatson, Nancy Harold, Anna Couvillon, Seth M Steinberg, Douglas K. Price, James L. Gulley, William Douglas Figg, William L. Dahut; Medical Oncology Branch, National Cancer Institute, Bethesda, MD; Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; National Cancer Institute, Bethesda, MD; Division of Cancer Prevention, National Cancer Institute, Bethesda, MD; National Cancer Institute, Rockville, MD; National Cancer Insitute, Bethesda, MD; Molecular Pharmacology Section, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: In mCRPC, two randomized trials demonstrated an overall survival (OS) benefit with the chemotherapeutic agent D. However, the survival improvement is modest and new strategies are needed to enhance clinical response. D-based combinations have been evaluated as one alternative strategy. Cabo targets multiple tyrosine kinases including c-Met, vascular endothelial growth factor receptor 2 (VEGFR2) and RET. Cabo has shown activity in mCRPC, with resolution of bone lesions on bone scan, regression of soft tissue/visceral disease, and reductions in circulating tumor cells and bone biomarkers (Smith, et al, J Clin Oncol 30, 2012 [suppl; abstr 4513]). We hypothesize the addition of Cabo to D and P, in patients (pts) with mCRPC, will have an acceptable toxicity profile and could lead to improved survival by targeting different cellular pathways simultaneously. This combination therapy may represent a safe and effective strategy to improve the outcome of mCRPC pts treated with D-based chemotherapy. **Methods:** This is a phase I trial to determine the safety profile and the recommended phase II dose of Cabo in combination with D and P. Pts receive a fixed dose of D (75 mg/m2 IV day 1 of each 21 day cycle) and P (5 mg po q12 hours) in combination with Cabo at three escalating doses: dose level 1 is 20 mg, level 2 is 40 mg, and level 3 is 60 mg (all po qdaily). Using a standard 3 + 3 design, three patients will initially be treated at each dose level until the maximum tolerated dose (MTD) has been defined. An expansion cohort will then be enrolled at the MTD. The accrual ceiling for the study, including both the dose escalation and the expansion phases, is set at 24 pts. Secondary objectives include assessments of pharmacokinetics of each agent, evaluation of antitumor activity of the combination therapy, and assessment of changes in molecular biomarkers for receptor tyrosine kinase and angiogenesis pathways, as well as biomarkers for bone metabolism. Restaging with bone and CT scan will be undertaken every 3 cycles. Enrollment at dose level 1 has been completed without dose-limiting toxicity. Accrual is ongoing at the second dose level. Clinical trial information: NCT01683994.

TPS5096 General Poster Session (Board #42G), Mon, 8:00 AM-11:45 AM

A phase II trial of the aurora kinase A inhibitor MLN8237 in patients with metastatic castrate resistant and neuroendocrine prostate cancer.

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Background: NEPC can rarely arise de novo but more commonly arises as a mechanism of resistance in the setting of advanced prostate cancer. Transformation to NEPC is likely promoted by potent hormonal therapies and is currently under-recognized. There is no effective therapy for NEPC and most patients (pts) survive less than one year. We have found that Aurora kinase A (AURKA) and N-myc (MYCN) are significantly overexpressed and amplified in NEPC compared to prostate adenocarcinoma, and cooperate to induce neuroendocrine (NE) differentiation in prostate cancer (Beltran et al, Cancer Disc 2011). In preclinical models, aurora kinase inhibition results in dramatic and preferential anti-tumor activity in NEPC.
Methods: In this single arm, multi-institutional Phase II trial, pts with metastatic prostate cancer need to meet at least one NEPC entry criterion: 1) histologic diagnosis of small cell or NEPC, 2) >50% immunohistochemical staining for NE markers, 3) development of liver metastases in absence of PSA progression, or 4) serum chromogranin >5x normal or neuron specific enolase >2x normal. Study will be open at 10 institutions including PCCTC sites. After a mandatory on-study research biopsy, pts will be treated with MLN8237, an orally administered Aurora kinase A inhibitor at 50 mg twice daily for 7 days repeated every 21 days. The primary endpoint is objective response rate (ORR). Secondary endpoints include overall survival, progression free survival, PSA response rate, circulating tumor cell response, and serum NE marker response to therapy. A number of correlative studies including AURKA, MYCN, AR, and exome and RNAseq are embedded in this trial in order to molecularly define this aggressive and poorly characterized disease. A Simon 2-stage design will be employed with up to 60 subjects providing 80% power to determine if the true ORR is >30% and 95% power if the true ORR is <15%, assuming a 5% level of significance. A subset of at least 20% meeting histologic entry criteria is embedded.

TPS5097 General Poster Session (Board #42H), Mon, 8:00 AM-11:45 AM

Randomized double-blind, comparative study of abiraterone acetate (AA) plus low-dose prednisone (P) plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed, high-risk, metastatic hormone-naive prostate cancer (mHNPC).

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Background: Patients (pts) who initially present with metastatic prostate cancer (MPC) (up to 30% of men in Europe; 4% in US) typically progress to metastatic castration-resistant prostate cancer (mCRPC) with a poor prognosis. Prognostic factors impacting survival include high PSA concentration, high Gleason score, high volume of metastatic disease, and bone symptoms. AA decreases testosterone via CYP17 inhibition and is approved for treatment of mCRPC before and after docetaxel-based chemotherapy. Two recent reports (*J Clin Oncol*. 2012: 30 [suppl. abstr 4521 and 4556]) showed that AA + P in addition to ADT (LHRH agonist) in the neoadjuvant setting led to higher rates of undetectable PSA and complete pathologic response (cPR) or near-cPR in pts undergoing prostatectomy for high risk-localized prostate cancer than with ADT alone, suggesting a potential role for inhibiting extragonadal androgen synthesis prior to emergence of castration-resistance. Because of its benefit in mCRPC, as well as early activity in high risk-localized prostate cancer, AA is being evaluated in high risk mHNPC. **Methods:** Approximately 1,270 men with newly diagnosed (within 3 months of randomization) high risk mHNPC with at least 2 of 3 high risk factors ($\geq$ 3 bone lesions, presence of visceral metastases or Gleason score $\geq$ 8) are being randomized to AA 1000 mg + P 5 mg daily + ADT or ADT alone. Pts are stratified by presence of visceral disease and ECOG PS (0-1 vs 2). Distant metastatic disease must be documented by positive bone scan or CT/MRI. ADT or orchiectomy within 3 mos of randomization is allowed. Continued use of anti-androgens after randomization is not allowed on study. The primary endpoint is overall survival. Secondary endpoints include radiographic PFS, time to next skeletal-related event, PSA progression, and subsequent therapy. Two interim analyses and a final analysis are planned. 300 sites from 36 countries will participate. As of February 4, 2013, one patient has entered screening. Clinical trial information: NCT01715285.

TPS5098^ General Poster Session (Board #43A), Mon, 8:00 AM-11:45 AM

Randomized, double-blind, placebo-controlled proof of concept study of tasquinimod maintenance therapy in patients with metastatic castrate-resistant prostate cancer (mCRPC) who experience response or stabilization during first-line docetaxel chemotherapy.

Karim Fizazi, Axel Heidenreich, Gedske Daugaard, Joaquim Bellmunt, Nathalie Germann, Eric Chetaille; Institut Gustave Roussy, Villejuif, France; University Hospital Aachen, Aachen, Germany; Department of Oncology, Rigshospitalet, Copenhagen, Denmark; University Hospital del Mar-IMIM, Barcelona, Spain; Research and Development, Ipsen, Les Ulis, France

Background: Docetaxel is the standard first-line chemotherapy for mCRPC. Most patients experience disease response or stabilization on docetaxel, although no treatment is currently used to maintain efficacy when docetaxel is stopped. Tasquinimod is an oral, quinoline-3-carboxamide derivative that binds to S100A9, with immunomodulatory, anti-angiogenic and anti-metastatic activity and a manageable safety profile. Tasquinimod demonstrated significantly improved PFS (7.6 v 3.3 mo) in asymptomatic to mildly symptomatic mCRPC (Pili, R. et al. J Clin Oncol 2011; 29: 4022-8) and is in phase III development. The purpose of this study is to assess whether tasquinimod used as a switch maintenance therapy can postpone cancer progression in patients with mCRPC with response or stabilization on first-line docetaxel therapy. **Methods:** Design: Phase II, multinational, randomized, double-blind, placebo-controlled proof of concept study. Patients with mCRPC will be randomly assigned (ratio 1:1) to receive tasquinimod or placebo. Randomization will be stratified by presence of visceral metastases and opioid analgesic use for cancer-related pain. Patient population: 140 male patients aged ≥18 years with histologically documented mCRPC and ECOG performance status 0 or 1 will be randomized. Before study entry, patients should have received ≥6 cycles of docetaxel and not experienced cancer progression according to PSA and RECIST criteria. Recruitment is ongoing. Dosage: Patients will receive a starting dose of 0.25 mg/day tasquinimod or placebo, with escalation to 0.5 mg/day and 1 mg/day based on individual safety and tolerability. Primary endpoint: Radiological PFS including skeletal-related events, from randomization to the date of radiological progression or death due to any cause. Secondary endpoints: Overall survival, symptomatic PFS, quality of life, pharmacokinetics, safety, PFS on next-line therapy, time to PSA progression, and changes in biomarkers over time. Clinical trial information: NCT01732549.

TPS5099^ General Poster Session (Board #43B), Mon, 8:00 AM-11:45 AM

PROSELICA study update: Comparison of two doses of cabazitaxel (Cbz) plus prednisone (P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel (D)-containing regimen.

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Background: Cbz 25 mg/m^2 IV Q3W + P 10 mg PO QD has an established safety profile and significantly improves overall survival (OS) vs mitoxantrone + P in pts with mCRPC previously treated with a D-containing regimen (phase III TROPIC study; NCT00417079; median OS: 15.1 vs 12.7 mos; HR: 0.70; $P < 0.0001$). Pooled data on file suggest that lower Grade 3–4 neutropenia rates are observed with Cbz $<$ 25 vs $\geq$ 25 mg/m^2 (61% vs 74%). In an attempt to further improve the therapeutic index of Cbz in the second-line treatment of mCRPC, PROSELICA (NCT01308580) was designed to assess whether Cbz 20 mg/m^2 is associated with lower hematologic toxicity and has non-inferior efficacy compared with the standard 25 mg/m^{2}dose. **Methods:** PROSELICA is a randomized, open-label, multinational, phase III study comparing the efficacy and tolerability of IV Cbz 20 with 25 mg/m^2, Q3W. Pts with a life expectancy $>$ 6 mos, ECOG PS $\leq$ 2, confirmed mCRPC and prior therapy with a D-containing regimen are eligible. Pts are randomized 1:1 to Cbz dosing arms; all pts receive P 10 mg PO QD and are treated until disease progression, unacceptable toxicity or consent withdrawal (max. 10 cycles). Pts are stratified by ECOG PS, measurable disease and region of the world. The primary endpoint is OS (non-inferiority). Secondary endpoints include safety, progression-free survival (PCWG2 criteria), PSA and pain progression and response, tumor response and health-related quality of life. Cbz PK and pharmacogenomics will be assessed in subgroups. Planned enrollment is 1200 pts. The study started in May 2011; by 31 Dec 2012, 851 pts had been enrolled. 158 sites are enrolling pts. Based on a review of safety and efficacy endpoints, the last Data Monitoring Committee meeting (Dec 2012) recommended continuing the study without change. Clinical trial information: NCT01308580.

Country	Active sites	Pts randomized, n
Argentina	4	15
Australia	14	107
Belgium	14	64
Brazil	12	47
Canada	4	33
Chile	4	17
France	11	116
Germany	9	19
Hungary	5	24
Netherlands	5	35
Peru	7	15
Poland	3	8
Romania	10	42
Russia	9	75
South Africa	5	19
South Korea	5	24
Spain	8	55
Taiwan	2	2
Tunisia	3	9
Turkey	2	9
USA	15	27
UK	7	89
Total	158	851

TPS5100 General Poster Session (Board #43C), Mon, 8:00 AM-11:45 AM

TAXYNERGY (NCT01718353): A randomized phase II trial examining an early switch from first-line docetaxel to cabazitaxel, or cabazitaxel to docetaxel, in men with metastatic castration-resistant prostate cancer (mCRPC).

Emmanuel S. Antonarakis, Paraskevi Giannakakou, Brian J. Kirby, Leonardo V. Nicacio, Mario A. Eisenberger, David M. Nanus, Scott T. Tagawa; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Weill Cornell Medical College, New York, NY; Sibley School of Mechanical and Aerospace Engineering, Cornell University, Ithaca, NY; Sanofi-Aventis, Bridgewater, NJ

Background: Docetaxel is the standard 1st-line chemotherapy for mCRPC, while cabazitaxel prolongs survival after docetaxel progression. The activity of cabazitaxel in the 1st-line setting is unknown, while the molecular mechanisms of taxane sensitivity/resistance have been understudied. Clinically, a ≥30% PSA decline within 3 months predicts survival in docetaxel- and cabazitaxel-treated men. Molecularly, emerging evidence suggests that sensitivity/resistance to taxanes relates to the ability of microtubules to traffic AR into the nucleus. Circulating tumor cells (CTCs) represent a real-time biomarker to assess drug-target engagement (DTE) which may be predictive of clinical outcome, and novel enrichment techniques present opportunities for molecular testing. **Methods:** This is a multicenter phase 2 trial for chemo-naïve mCRPC. 100 men will be randomized (2:1) to 1st-line docetaxel or cabazitaxel. Following 4 cycles, if a ≥30% PSA decline is not achieved, men will switch to the alternative taxane; others will remain on the initial taxane until progression (PCWG2) or unacceptable toxicity. CTCs will be obtained at screening, baseline, after 1 and 4 cycles of chemotherapy, at crossover and at progression to interrogate mechanisms of taxane sensitivity/resistance. CTCs will be enriched via a prostate-specific microfluidic device, enumerated, and analyzed via multiplex confocal microscopy for microtubule bundling and AR localization. TaqMan PCR (and RNA sequencing) will be used to detect AR variants, as preliminary data show that variant ARv567 predicts taxane sensitivity while ARv7 predicts resistance. The primary clinical endpoint of the trial is achievement of a ≥50% PSA reduction during the treatment continuum. The primary molecular endpoint is analysis of DTE in CTCs, and correlation with PSA responses. The study will have 80% power to detect a 25% increase in PSA response rate with tight interclass kappa coefficients for primary biomarkers. Secondary endpoints include radiographic and PSA progression-free survival, objective response rates, overall survival, and safety. Clinical trial information: NCT01718353.

TPS5101 General Poster Session (Board #43D), Mon, 8:00 AM-11:45 AM

The Pacific trial: A randomized phase II study of OGX-427 in men with metastatic castration-resistant prostate cancer (mCRPC) and PSA progression while receiving abiraterone acetate (AA).

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Background: Heat Shock Protein 27 (Hsp27) is a multi-functional chaperone protein that regulates cell signaling and survival pathways implicated in cancer progression and over-expressed in many cancers including prostate, bladder, lung, and breast. In prostate cancer models, Hsp27 complexes with androgen receptor (AR) and enhances transactivation of AR-regulated genes. OGX-427 is a second-generation antisense oligonucleotide designed to inhibit Hsp27 expression with in vitro and in vivo efficacy that increases apoptosis, inhibits tumor growth, sensitizes cells to chemotherapy and inhibits AR activity (Cancer Res 2007;67(21):10455). A phase 2 study of OGX-427 in patients with mCRPC reported preliminary activity with 50% of patients having a $\geq$50% PSA decline during treatment (J Clin Oncol 30, 2012 (suppl; abstr 4514)). The purpose of this study was to evaluate the clinical activity of OGX-427 in patients with mCRPC progressing on AA. **Methods:** In this randomized, phase 2 study, 74 evaluable patients with mCRPC who are currently receiving AA and have PSA progression despite a prior response are randomized 1:1 to receive either OGX-427 (600 mg IV x 3 loading doses in week 1 followed by 1000 mg IV weekly) with AA or continuing AA alone. Additional eligibility criteria include: ECOG performance status $\leq$1, no evidence of radiographic progression, adequate liver/kidney/bone marrow function, and $\leq$1 prior chemotherapy for CRPC. Protocol therapy is continued until disease progression, unacceptable toxicity, or patient withdrawal. Eligible control arm patients may cross over to receive OGX-427 following disease progression. The primary objective of the study is to evaluate the proportion of patients progression-free at Day 60 post randomization. Secondary objectives include comparisons between arms of PSA and disease response, progression free survival, time to disease progression, serial serum levels of Hsp27, and circulating tumor cell enumeration. The study is designed to detect a 25% improvement in the primary endpoint ($\alpha = 0.2$, $\beta = 0.1$). The study was initiated December, 2012. Clinical trial information: NCT01681433.

TPS5102 General Poster Session (Board #43E), Mon, 8:00 AM-11:45 AM

A phase II study of trebananib (AMG 386) and abiraterone in metastatic castration resistant prostate cancer.

Avani Atul Shah, Fatima Karzai, Ravi Amrit Madan, William Douglas Figg, Cindy H. Chau, James L. Gulley, Guinevere Chun, John Joseph Wright, Andrea Borghese Apolo, Howard L. Parnes, William L. Dahut; National Cancer Institute, Bethesda, MD; Laboratory of Tumor Immunology and Biology, Medical Oncology Branch, National Cancer Institute, Bethesda, MD; Molecular Pharmacology Section, National Cancer Institute, National Institutes of Health, Bethesda, MD; National Cancer Institute, National Institutes of Health, Bethesda, MD; National Cancer Institute, Rockville, MD; Division of Cancer Prevention, National Cancer Institute, Bethesda, MD

Background: Preclinical studies support the use of an antiangiogenic approach in the treatment of prostate cancer. Trebananib is a novel peptide-Fc fusion protein that sequesters angiopoeitin 1 and angiopoeitin 2, thereby preventing their interaction with their common receptor Tie2, and inhibiting tumor endothelial cell proliferation and tumor growth. Trebananib is currently in Phase 3 trials for the treatment of ovarian carcinoma and has been shown to have clinical activity in multiple tumor types. Previous studies have demonstrated that in vivo alterations of testosterone levels regulate the expression of vascular endothelial growth factor, fibroblast growth factor, and angiopoietin associated factors. Dual inhibition of the androgen and angiogenic axis represents a novel strategy of combined targeted therapy for patients with metastatic castration-resistant prostate cancer (mCRPC). We hypothesize that the addition of trebananib to CYP17 inhibitor abiraterone and prednisone will increase the median progression free survival (PFS) in chemotherapy-naïve mCRPC. **Methods:** This phase 2 study will evaluate the treatment effect as measured by progression free survival in patients treated with trebananib plus abiraterone/prednisone relative to abiraterone/prednisone alone. 72 patients with progressive, mCRPC will be randomized 1:1 to either study arm. Trebananib is administered intravenously every week, on days 1, 8, 15 and 22 of each 28-day cycle. Abiraterone acetate is taken once daily with prednisone 5 mg twice daily. We have completed the initial run-in phase of trebananib at 15mg/kg and 30mg/kg. The randomized phase of the study will use the 30 mg/kg dose of trebananib with the standard dose (1000 mg) of abiraterone. The primary end point is radiographic PFS. Secondary end points include overall survival, changes in genetic biomarkers related to the androgen and angiogenesis signaling axis, molecular markers of angiogenesis, circulating tumor cells and androgen receptor signaling status in circulating tumor cells before and after treatment. This combination of angiogenesis inhibition and abiraterone has the potential to improve clinical outcomes in front-line therapy for mCRPC. Clinical trial information: NCT01553188.

TPS5103 General Poster Session (Board #43F), Mon, 8:00 AM-11:45 AM

Design of the AFFINITY study: A randomized phase III study of a novel clusterin inhibitor, custirsen, plus cabazitaxel/prednisone (CbzP) versus CbzP alone as second-line chemotherapy in metastatic castration-resistant prostate cancer (mCRPC).

Tomasz M. Beer, Brent A. Blumenstein, Karim Fizazi, Sebastien J. Hotte, Cindy Jacobs, Patricia S. Stewart; Oregon Health & Science University Knight Cancer Institute, Portland, OR; Trial Architecture Consulting, Washington, DC; Institut Gustave Roussy, University of Paris Sud, Villejuif, France; Juravinski Cancer Centre, Hamilton, ON, Canada; OncoGenex Pharmaceuticals, Inc., Bothell, WA

Background: Custirsen enhances chemotherapeutic activity via inhibition of clusterin expression. Clusterin is a cytoprotective, antiapoptotic chaperone upregulated by anticancer therapies that confers treatment resistance. In a phase 2 study, mCRPC patients who had progressed within 6 mos of completing first-line docetaxel (DOC)/prednisone (P) and who were retreated with DOC/P and custirsen had a median overall survival of 15.8 mos. Lowering of serum clusterin level during second-line treatment was associated with significantly longer survival. CbzP has recently shown a survival advantage in patients with prostate cancer that has progressed after DOC therapy. The AFFINITY study was designed to evaluate in a larger study whether adding custirsen to CbzP will further improve survival in this patient population. **Methods:** AFFINITY was initiated in August 2012. Eligible patients in this phase 3, international, multicenter, open-label trial must have received $\geq$225 mg/m^2 of DOC; have progressive disease as defined by RECIST 1.1, bone scan progression, and/or serum prostate-specific antigen level; have metastatic disease of the chest/abdomen/pelvis/bone; have adequate renal and liver function; and have a Karnofsky score $\geq$70%. Patients may have received up to 1 DOC regimen as well as abiraterone and/or enzalutamide. Approximately 630 patients will receive 21d cycles of Cbz (25 mg/m^{2}IV q21d) + P (10 mg PO/d), either alone or with custirsen 640 mg IV given for 3 loading doses and then weekly until disease progression, unacceptable toxicity, or 10 cycles. The primary efficacy measure is overall survival. The secondary measure is proportion of patients alive without disease progression at Day 140 post-randomization. All efficacy analyses are intent to treat. Adverse events of all patients who receive $\geq$1 dose of custirsen or Cbz will be included in the safety analysis. This study is sponsored by Teva BPP R&D, Inc., in collaboration with OncoGenex Pharmaceuticals, Inc. Clinical trial information: NCT01578655.

TPS5104 General Poster Session (Board #43G), Mon, 8:00 AM-11:45 AM

A randomized phase II clinical trial of enzalutamide in combination with the therapeutic cancer vaccine, PSA tricom, in metastatic, castration resistant prostate cancer.

Nishith K. Singh, Joseph W. Kim, Christopher Ryan Heery, William L. Dahut, Anna Couvillon, Myrna Rauckhorst, Sheri McMahon, Jeffrey Schlom, Tito Fojo, Philip M. Arlen, James L. Gulley, Ravi Amrit Madan; Laboratory of Tumor Immunology and Biology, Medical Oncology Branch, National Cancer Institute, Bethesda, MD; Medical Oncology Branch, National Cancer Institute, Bethesda, MD; Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; National Cancer Institute, Bethesda, MD; Laboratory of Tumor Immunology and Biology, Center for Cancer Research, Bethesda, MD

Background: There is a strong rationale to combine therapeutic cancer vaccines with hormonal abrogation in prostate cancer. Androgen abrogation augments T-cell trafficking to prostate, decreases immune tolerance, increases production of naïve thymic T-cells, enhances cytotoxic T-cell repertoire. PSA TRICOM (PROSTVAC) is a therapeutic, viral-vector based, off-the-shelf, cancer vaccine of PSA & 3 co-stimulatory molecules in phase III testing. This was developed at the NCI in collaboration with Bavarian Nordic Immunotherapeutics. It has demonstrated safety and survival benefit in a randomized phase 2 trial of metastatic castrate resistant prostate cancer (mCRPC). Enzalutamide is a modern androgen receptor inhibitor (ARI) approved for the treatment of mCRPC. Data from the clinical trials with these therapies suggest good individual tolerability without any overlapping toxicities. Analysis of previous trials suggests that vaccines may enhance clinical outcomes with ARI. These data form the scientific basis for a combination approach of a cancer vaccine with ARI to control tumor progression in mCRPC. **Methods:** A randomized, phase 2, open-label clinical trial at the NCI will enroll 72 chemo-naïve, minimally symptomatic patients with mCRPC. They will be randomized (1:1) to enzalutamide (160 mg daily) alone, or enzalutamide with PSA TRICOM for treatment until radiographic progression. PSA-TRICOM will be administered in a core phase (with day 1, 15 and 29 then 4 additional monthly boosts) followed by continued boosts every 3 months. The primary end point will evaluate time to progression in each arm with secondary endpoints including overall survival and systemic immune responses (lymphocyte subsets, regulatory T-cells, regulatory T-cell function, cytokines, naïve thymic emigrants). If a therapeutic cancer vaccine can enhance the clinical efficacy of a hormonal agent such as enzalutamide, it may help define a new role for vaccines as an adjuvant to standard therapies. We will also evaluate this combination in a second trial in non-metastatic, castration-sensitive patients where this combination may yield its greatest clinical impact.