abnormalities were observed in 11.3% AA vs 8.9% placebo, and cardiac disorders were observed in 15.9% AA vs 11.7% placebo patients.
Conclusions: AA statistically significantly prolonged median OS in patients with mCRPC who have progressed post-docetaxel. With longer follow-up, the magnitude of the treatment effect of AA on OS increased and no new safety issues were detected. The OS benefit demonstrated across subgroups was generally consistent with that seen in the overall patient population. Clinical benefit was maintained in older patients and in those with visceral disease. The present results further confirm the benefit provided by AA in patients with mCRPC.

7001 ORAL

Abiraterone Acetate Improves Functional Status in Patients With Metastatic Castration-resistant Prostate Cancer (mCRPC) Post-docetaxel − Results From the COU-AA-301 Phase 3 Study

S. Harland[1], J.S. de Bono[2], C.M. Haqq[3], J.N. Staffurth[4], Y. Hao[5], D. Gagnon[6], C. Liu[3], C.N. Sternberg[7], A. Molina[3], H.I. Scher[8]. *[1]UCL Cancer Institute, Oncology, London, United Kingdom; [2]The Institute for Cancer Research, Royal Marsden Hospital, Sutton, United Kingdom; [3]OrthoBiotech Oncology Research & Development (A Unit of Cougar Biotechnology), Los Angeles CA, USA; [4]Cardiff University, Velindre Hospital, Cardiff, United Kingdom; [5]Johnson & Johnson Pharmaceutical Services, Global Strategic Marketing & Market Access, Raritan NJ, USA; [6]Thomson Reuters, Strategic Consulting Healthcare, Santa Barbara CA, USA; [7]San Camillo and Forlanini Hospitals, Department of Medical Oncology, Rome, Italy; [8]Memorial Sloan Kettering Cancer Center, Genitourinary Oncology Service, New York NY, USA*

Background: Abiraterone acetate (AA) is a potent, selective androgen (CYP17) biosynthesis inhibitor, shown in the COU-AA-301 trial to improve overall survival (HR = 0.646) in mCRPC progressing after docetaxel (D). Here we retrospectively assess the impact of AA on patient-reported functional status in that study.
Material and Methods: COU-AA-301 is an international, randomised, double-blind study of AA (1 g QD) + prednisone (P; 5 mg BID) vs placebo + P in mCRPC post-D. Functional status was assessed at baseline, Cycles 4, 7, 10, and treatment discontinuation using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. All analyses were conducted using responder definitions of clinically significant changes (improvement/decline compared to baseline) in eligible patients; definitions were based on literature [Cella D, et al. Value Health 2009;12:124−9] and distribution-based calculations.

FACT-P measure	AA N = 797	Placebo N = 398	p Value
FACT-P total score			
Improvement, n/eligible (%)	268/563 (48)	87/273 (32)	<0.0001[a]
Time to decline [median], days	363	253	<0.0001[b]
Physical WB			
Improvement, n/eligible (%)	285/616 (46)	83/295 (28)	<0.0001[a]
Time to decline [median], days	339	240	<0.0001[b]
Social/Family WB			
Improvement, n/eligible (%)	158/292 (54)	63/130 (49)	0.284[a]
Time to decline [median], days	168	89	0.397[b]
Emotional WB			
Improvement, n/eligible (%)	80/147 (54)	24/62 (39)	0.0380[a]
Time to decline [median], days	424	226	<0.0001[b]
Functional WB			
Improvement, n/eligible (%)	212/487 (44)	83/249 (33)	0.0076[a]
Time to decline [median], days	337	169	<0.0001[b]
FACT-G Scale			
Improvement, n/eligible (%)	235/568 (41)	78/283 (28)	<0.0001[a]
Time to decline [median], days	424	274	<0.0001[b]
Prostate Cancer Subscale			
Improvement, n/eligible (%)	321/554 (58)	101/255 (40)	<0.0001[a]
Time to decline [median], days	262	142	<0.0001[b]

[a] Chi squared test; [b] Log-rank test.

Results: 797 patients were randomized to AA and 398 to placebo, with respective median treatment durations of 8 and 4 months. Baseline FACT-P scores (for all 7 measures) were similar between groups. AA significantly improved functional status from baseline at each assessment and delayed time to decline in the majority of FACT-P measures, except the social/family well-being (WB) subscale where there was no difference (Table).
Conclusions: In post-D mCRPC, therapy with AA + P yields significantly greater improvements in patients' functional status and forestalls functional decline, compared to P alone. The extent of these benefits is likely to be considered important to patients.

7002 ORAL

Time to Disease-related Pain After Sipuleucel-T in Asymptomatic Patients With Metastatic Castrate Resistant Prostate Cancer (mCRPC): Results From 3 Randomized Phase III Trials

E.J. Small[1], C.S. Higano[2], P.W. Kantoff[3], J.B. Whitmore[4], M.W. Frohlich[5], D.P. Petrylak[6]. *[1]UCSF Comprehensive Cancer Center, Urologic Oncology, San Francisco CA, USA; [2]University of Washington, Medical Oncology, Seattle, USA; [3]Dana-Farber Cancer Institute, Division of Solid Tumour Oncology, Boston, USA; [4]Dendreon Corporation, Biometrics, Seattle, USA; [5]Dendreon Corporation, Clinical Affairs, Seattle, USA; [6]Columbia University Medical Center, Division of Hematology Oncology, New York, USA*

Background: Sipuleucel-T, an FDA-approved therapy for men with asymptomatic or minimally symptomatic mCRPC, has a demonstrated survival benefit. In addition to survival data, 3 completed Phase III, randomized, controlled trials sponsored by Dendreon Corp. also collected data on time to disease-related pain (TDRP).
Materials and Methods: Studies D9901 (NCT00005947) and D9902A (NCT01133704) enrolled only asymptomatic pts; TDRP was a secondary endpoint. Pain status was collected until disease-related pain or 4 weeks following disease progression, whichever occurred first. The IMPACT study (NCT00065442) originally enrolled only asymptomatic pts with a co-primary endpoint of TDRP; it was later amended to include minimally symptomatic pts and to remove the TDRP endpoint. Pts were treated with 3 infusions of sipuleucel-T or control at approximately 2-week intervals, and were then followed for safety and clinical endpoints. Pain status for pts enrolled prior to the amendment was collected until disease-related pain was observed. TDRP was assessed in all studies by pain logs and adjudicated by blinded independent reviewers. TDRP was analyzed using the Kaplan–Meier (KM) method and log rank test; hazard ratio (HR) was derived from an unadjusted Cox regression model. Analyses were based on all randomized pts on D9901 (n = 127) and D9902A (n = 98), and on IMPACT pts randomized prior to the amendment (n = 203).
Results: TDRP results were: D9901 HR = 0.68, D9902A HR = 1.39, and IMPACT HR = 0.80. Integrated results were HR = 0.84 ([95% CI: 0.64, 1.12]; P = 0.24). Separation in the KM curves was seen at approximately 6 months. Median TDRP was 5.6 vs 5.3 months. At 12 months 39.3% of sipuleucel-T vs 18.9% of control pts were estimated to be pain-free. Significant independent baseline predictors of earlier TDRP were higher PSA, higher alkaline phosphatase, lower age, bisphosphonate use, and prior radiation therapy. When adjusted for these clinical factors, the adjusted treatment HR = 0.80 ([95% CI: 0.60, 1.08]; P = 0.14).
Conclusions: The trend towards a delay in TDRP beginning 6 months after randomization is consistent with the potentially delayed anti-tumour effect of immunotherapy. These data provide support for a potential effect of sipuleucel-T on a clinically relevant endpoint proximal to the demonstrated benefit in overall survival. Lack of statistical significance could be due to limited sample size, high rate of censoring, or delayed treatment effect.

7003 ORAL

Denosumab and Bone Metastasis-free Survival in Men With Castrate-resistant Prostate Cancer − Subgroup Analyses From an International, Double-blind, Randomized, Phase 3 Trial

S. Oudard[1], M. Smith[2], L. Karsh[3], B. Egerdie[4], P. Van Veldhuizen[5], F. Gómez-Veiga[6], D. Dearnaley[7], Z. Ye[8], R. Dansey[9], C. Goessl[9]. *[1]Georges Pompidou Hospital, Medical Oncology, Paris, France; [2]Massachusetts General Hospital Cancer Center, Genitourinary Medical Oncology, Boston, USA; [3]The Urology Center of Colorado, Clinical Research Department, Denver, USA; [4]Urology Associates/Urologic Medical Research, Medical Research, Kitchener, Canada; [5]Kansas City VA Medical Center, Hematology and Medical Oncology, Kansas City, USA; [6]Hospital Universitario Juan Canalejo, Urology, A Coruña, Spain; [7]Royal Marsden Hospital, Institute of Cancer Research, Sutton, United Kingdom; [8]Amgen Inc., Gobal Biostatistical Sciences, Thousand Oaks, USA; [9]Amgen Inc., Hematology/Oncology, Thousand Oaks, USA*

Background: Bone metastases are common in men with castrate-resistant prostate cancer (CRPC). Suppression of osteoclast activity by inhibiting RANKL, the key mediator of osteoclast survival, may inhibit release of growth factors from bone and delay onset of bone metastasis. We assessed the ability of denosumab (XGEVA™), a fully human monoclonal anti-RANKL antibody, to prolong bone metastasis-free survival in men with

CRPC by patient subgroups (ClinicalTrials.gov; NCT00286091; Sponsored by Amgen Inc).
Methods: Men with non-metastatic CRPC at high-risk for bone metastasis (PSA value ⩾8.0 ng/mL and/or PSA doubling time ⩽10.0 months) were randomized 1:1 to receive either monthly subcutaneous denosumab 120 mg or placebo. Calcium and vitamin D supplements were encouraged. Enrollment began February 2006; primary analysis cut-off was July 2010, when >660 men had bone metastasis or died. The primary endpoint was time to first bone metastasis or death from any cause, i.e. bone metastasis-free survival. Here we assessed time to bone metastasis-free survival by patient subgroup including baseline PSA risk group (a) dual risk factors: PSA ⩾8.0 ng/mL + PSA doubling time ⩽10.0 months vs (b) single risk factor: PSA <8.0 ng/mL + ⩽10.0 months or ⩾8.0 ng/mL + >10.0 months, Gleason score (2−7 or 8−10), age (<75 years old or ⩾75 years), ethnicity (white or other), and geographic location (North America, Europe, or rest of world).
Results: 1432 men were enrolled; 716 in each arm. Denosumab significantly increased median bone metastasis-free survival by 4.2 months compared with placebo (29.5 and 25.2 months, respectively; Hazard Ratio [HR] 0.85 [0.73–0.98], $P = 0.03$). This benefit on bone metastasis-free survival was consistently observed among all patient subgroups (range of HRs 0.79–0.95). Denosumab also delayed time to symptomatic bone metastasis (0.67 [0.49–0.92]; $P = 0.01$). Primary results including efficacy and safety have been presented previously (Smith et al, AUA 2011).
Conclusion: Denosumab significantly prolonged bone metastasis-free survival compared with placebo among all men, with consistent results observed among subgroups of disease and demographic variables. This is the first large, clinical trial to demonstrate that targeting of the bone microenvironment significantly delays onset of bone metastases.

7004 ORAL

Pain Outcomes in a Randomized Phase 3 Clinical Trial of Denosumab Vs Zoledronic Acid (ZA) in Patients With Solid Tumours and Bone Metastases

L. Fallowfield[1], R. von Moos[2], D. Patrick[3], C.S. Cleeland[4], D.H. Henry[5], V. Hirsh[6], K. Zarogoulidis[7], W. Ying[8], Z. Cong[9], H. Yeh[10]. *[1]University of Sussex, Cancer Research UK, Brighton, United Kingdom; [2]Kantonsspital Graubünden, Oncology, Chur, Switzerland; [3]University of Washington, Health Services, Seattle, USA; [4]University of Texas, Symptom Research Division of Internal Medicine, Texas, USA; [5]Pennsylvania Hospital, Joan Karnell Cancer Center, Philadelphia, USA; [6]McGill University Health Centre, Oncology, Montreal, Canada; [7]Aristotle University of Thessaloniki G. Papanikolaou Hospital, Pulmonary Department, Thessaloniki, Greece; [8]Amgen Inc., Biostatistics, Thousand Oaks, USA; [9]Amgen Inc., Health Economics, Thousand Oaks, USA; [10]Amgen Inc., Clinical Research, Thousand Oaks, USA*

Background: Bone metastases in patients with advanced cancer commonly cause pain and can lead to skeletal-related events (SREs). Denosumab is a fully human monoclonal antibody against RANK Ligand that delayed or prevented SREs more effectively than ZA in patients with solid tumours and bone metastases in a randomized phase 3 clinical trial (Henry D et al, *J Clin Oncol*. 2010. Abstr 9133). We present here the pain outcomes for patients with solid tumours. Patients with breast or prostate tumours were not enrolled in the trial (sponsored by Amgen Inc., ClinicalTrials.gov identifier NCT00330759).
Methods: Eligible patients received 120 mg of denosumab SC or 4 mg of ZA IV every 4 weeks in a randomized, multinational, double-blind, double-dummy trial. Patient-reported pain was assessed with the Brief Pain Inventory (0: no pain-10: pain as bad as can be imagined) at baseline (BL), day 8, and before each monthly visit. Analgesic use was assessed by the 8-point Analgesic Quantification Algorithm (AQA). Analyses included time to moderate/severe pain (>4 points), proportion of patients with no/mild pain (0−4) at BL reporting moderate/severe pain by visit, time to clinically significant worsening of pain (⩾2-point increase from BL), time to clinically significant improvement in pain (⩾2 point decrease from BL), and proportion of patients shifting from no or low analgesic use (AQA ⩽ 2) at BL to strong opioid use (AQA ⩾ 3) by visit.
Results: At BL, mean worst pain scores were 4.9 points (SD=2.8) for the denosumab group (N = 799) and 5.2 points (SD=2.9) for the ZA group (N = 797). Patients with no/mild pain at BL (n = 596) experienced a delay in median time to moderate/severe pain with denosumab treatment (144 days) compared with ZA treatment (112 days) (HR 0.81, CI: 0.66−1.0, $P = 0.0499$). The proportion of patients with no/mild pain at BL reporting moderate/severe pain on study was lower at each visit with denosumab treatment than with ZA treatment. Denosumab-treated patients also experienced a delay in clinically significant worsening of pain compared with ZA-treated patients (median: denosumab 143 days, ZA 119 days; HR 0.86, CI: 0.74–0.99, $P = 0.0392$). The time to clinically significant improvement in pain was similar between treatment groups. Compared with ZA, a lower proportion of patients receiving denosumab shifted from low or no analgesic use to strong opioid use at each visit.
Conclusion: In patients with solid tumours, denosumab delayed the time to increased pain severity compared with ZA. Also, a lower proportion of patients receiving denosumab required increased analgesic use over time.

Poster Discussion Presentations (Mon, 26 Sep, 11:00−12:00)

Genitourinary Malignancies − Prostate Cancer

7005 POSTER DISCUSSION

PSA Measurement at the Fifth Week of Radiotherapy Is an Independent Predictor of Failure in Intermediate Risk Prostate Cancer Patients

R. de Crevoisier[1], T. Messai[2], P. Wibault[2], A. Bridier[2], P. Blanchard[2], J.D. Ospina[3], M. Bakkour[2], A. Bossi[2]. *[1]Centre Eugène Marquis INSERM642, Ille et vilaine, Rennes, France; [2]Gustave-Roussy, Ile de France, Villejuif, France; [3]INSERM 642, Ile et Vilaine, Rennes, France*

Background: The objective was to identify early predictor of recurrence during exclusive radiotherapy for intermediate risk prostate cancer patients.
Material and Methods: A total of 240 patients of median age 71 years (range: 50−83 years) received exclusive external beam radiotherapy (EBRT) for intermediate prognostic group prostate cancer (D'Amico classification). T stages were: stage 1 (45%) and stage 2 (55%). Gleason scores were: scores ⩽6 (57%) and score 7 (43%). Mean pre-treatment PSA (PSA0) value was 11 ng (range: 1.4−20). All the patients received a total dose of 70 Gy in 7 weeks, either in 2.0 Gy/fraction, 5 fr/week (n = 53) or 2.5 Gy/fr, 2.0 Gy/ week (n = 187). PSA was also measured at the fifth week after treatment started (PSA5). Cox regression and log-rank test were used to analyze the impact of the following variables on biochemical failure (BF: nadir + 2 ng/ml) and clinical failure (CF) (metastases): T stage, Gleason score, PSA0, PSA5, PSA ratio (PSA5/PSA0) and dose/fraction.
Results: Median follow-up was: 58 months (range: 6–235). Five year BF and CF rates were 28% (95% CI: 23%-33%) and 5.5% (95% CI: 2%-9%), respectively. Median PSA5 was 8 ng (range: 0.8−30) and median PSA ratio was 0.72 (range: 0.14−3.7).
In univariate analysis, PSA5 was found significant on BF ($p < 0.01$; odds ratio =1.13). Neither the PSA0, PSA ratio as continuous variable, T stage, the Gleason score and the dose/fr were found as predictors for BF. PSA ratio >0.8 increased significantly the risk of BF($p = 0.01$; odds ratio =2.0). In multivariate analysis, PSA ratio >0.8 remained the only predictor of BF ($p = 0.03$; odds ratio =2.3).
As there are only 13 events of CF, multivariate analysis was not feasible. In univariate analysis, neither the PSA0, PSA ratio as continuous variable, T stage nor the Gleason score were found as predictors for CF. However, PSA5 ($p = 0.01$; odds ratio =1.13) as well as PSA ratio >0.8 had a significant impact on CF (logrank test: $p = 0.04$).
Conclusions: PSA measured at 5th week of radiotherapy and PSA ratio (PSA5/PSA0) can be use as simple early predictor of recurrence among intermediate risk prostate cancer patients receiving exclusive radiotherapy. "Bad responders" (PSA ratio >0.8) could receive "intensified" treatment like androgen deprivation combined with high dose radiotherapy.

7006 POSTER DISCUSSION

Predictive Models of Rectum Toxicity in Prostate Cancer Radiotherapy

R. De Crevoisier[1], J. Zhu[2], J.D. Ospina[2], E. Le Prisé[3], A. Bossi[4], T. Messai[4], K. Gnep[3], V. Beckendorf[5], F. Polet[5], A. Simon[2]. *[1]Centre Eugène Marquis Inserm U642, Département de Radiothérapie, Rennes, France; [2]Inserm U642, Laboratoire Traitement du Signal et de l'Image, Rennes, France; [3]Centre Eugène Marquis, Département de Radiothérapie, Rennes, France; [4]Institut Gustave Roussy, Département de Radiothérapie, Villejuif, France; [5]Centre Alexis Vautrin, Département de Radiothérapie, Nancy, France*

Background: In case of prostate 3D conformal radiotherapy (3DCRT): - To identify patients and treatment predictors of rectal toxicity; - To compare the performance of different Normal Tissue Complication Probability (NTCP) models for predicting rectal toxicity.
Materials and Methods: A total of 439 patients (pts) received 3DCRT for localized prostate cancer to a median total dose of 78 Gy (range: 70 to 80 Gy), 2 Gy/fraction. Pts were selected based on the availabilityof dose-volume histograms (DVH). Median age was 67 years (45−78). History of abdominal or pelvic surgery, anticoagulant therapy (ACT) and diabetes were observed in 30%, 15% and 6% of pts, respectively. Tumour prognostic groups (D'Amico classification) were: good (7%),medium (65%)