7004 ORAL

Final results of a randomized phase II study of OGX-011 (OGX) in combination with docetaxel (DOC)/prednisone versus docetaxel/prednisone in patients with metastatic castration resistant prostate cancer (CRPC)

K.N. Chi[1], S.J. Hotte[2], E. Yu[3], D. Tu[4], B. Eigl[5], I. Tannock[6], F. Saad[7], S. North[8], J. Powers[9], E. Eisenhauer[9]. *[1]BC Cancer Agency, Medical Oncology, Vancouver BC, Canada; [2]Juravinsky Cancer Centre, Medical Oncology, Hamilton ON, Canada; [3]University of Washington, Medical Oncology, Seattle WA, USA; [4]NCIC - Clinical Trials Group, Biostatistics, Kingston ON, Canada; [5]Tom Baker Cancer Centre, Medical Oncology, Calgary AB, Canada; [6]Princess Margaret Hospital, Medical Oncology, Toronto ON, Canada; [7]Centre Hospitalier de l'Université de Montréal, Urology, Montreal QC, Canada; [8]Cross Cancer Institute, Medical Oncology, Edmonton AB, Canada; [9]NCIC - Clinical Trials Group, IND Program, Kingston ON, Canada*

Background: Clusterin is a cytoprotective chaperone protein associated with CRPC progression. OGX is a 2'-methoxyethyl antisense that potentiates chemotherapy in xenografts and inhibits clusterin expression in humans at doses of $\leqslant$640 mg.
Methods and Methods: Patients (pts) with CRPC and chemo-naive received docetaxel (DOC) 75 mg/m^2 q3w + OGX 640 mg IV weekly + prednisone (Arm A) or DOC + prednisone (Arm B) in a single stage randomized phase II design (clinicaltrials.gov identifier: NCT00258388). Primary endpoint was PSA response rate (RR). Progression free survival (PFS) and overall survival (OS) were secondary endpoints. Planned sample size was 40/arm to test the hypothesis (true PSA RR <40% vs. >60%) with 10% β and 10% α for Arm A and to estimate the true PSA RR with an accuracy that half-width of the 90% CI <13% if true PSA RR = 40% for arm B.
Results: 82 pts (41 Arm A, 41 Arm B) were randomized from 09/05−12/06. All pts are off therapy and 58 have died. One pt was ineligible but included in survival analysis. Baseline characteristics were similar: median age 69 (49−87), PSA >100 μg/L in 51%, Hgb $\geqslant$100 g/L in 98%, alk phos > ULN in 44%, LDH > ULN in 36%, ECOG performance status (PS) 0:1 in 51%:49%, bone/lymph node/other metastases in 85%/62%/37%. Median cycles for Arm A and B was 9 and 7. Adverse events associated with OGX included fatigue, fever, rigors, diarrhea and rash. Mean serum clusterin change from baseline by day 1 cycle 2 was −18% in Arm A and +8% in Arm B (P = 0.0005). PSA RR was 58% (90% CI 43−71%) for Arm A and 54% (90% CI 40−67%) for Arm B. PSA declines at 12 weeks of any/>30%/>50% was observed in 87%/65%/45% (Arm A) and 68%/58%/34% (Arm B). PSA/objective disease progression as best response occurred in 0%/4% (Arm A), and 7%/17% (Arm B). PFS for Arms A and B was 7.3 (5.3−8.8) and 6.1 months (3.7−8.6). Median OS for Arms A and B was 23.8 (16.2-∞) and 16.9 months (12.7−25.8) (unadjusted HR = 0.61 [0.36−1.02], P = 0.06). Variables predictive of OS on multivariate analysis: PS 0 vs. 1 (HR = 0.28 [0.15−0.53], P < 0.0001), presence of non-bone/nodal metastasis (HR = 2.13 [1.20−3.77], P = 0.01) and treatment assignment (HR = 0.49 [0.28−0.85], P = 0.012).
Conclusions: The PSA RR in the DOC/OGX arm met criterion for further study, however the PSA RR in the control arm appeared similar. OGX reduced serum clusterin and OS appears superior with DOC/OGX. Given the OS results, this combination warrants further evaluation and a phase III trial is planned. Supported by a grant from the Canadian Cancer Society.

7005 ORAL

Overall survival in men with and without prevalent vertebral fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer

M. Smith[1], B. Egerdie[2], P. Sieber[3], T.L.J. Tammela[4], F. Saad[5], C. Ke[6], B. Leder[7], R. Dansey[8], C. Goessl[9]. *[1]Massachusetts General Hospital, Genitourinary Medical Oncology, Boston MA, USA; [2]Urology Associates, Urologic Medical Research, Kitchener ON, Canada; [3]Urological Associates, Lancaster Limited, Lancaster PA, USA; [4]Tampere University Hospital, Surgery, Tampere, Finland; [5]Centre Hospitalier de l'Université de Montréal, Urology & Oncology, Montreal QC, Canada; [6]Amgen Inc, Biostatistics, Thousand Oak CA, USA; [7]Massachusetts General Hospital, Endocrine Unit, Boston MA, USA; [8]Amgen Inc, Global Development, Thousand Oaks CA, USA; [9]Amgen Inc, Clinical Research, Thousand Oaks CA, USA*

Background: Androgen deprivation therapy (ADT) is well-established for treating prostate cancer, and is complicated by bone loss and increased fracture risk, including vertebral fracture. In non-cancer populations, vertebral fractures may be asymptomatic or have functional consequences (eg, loss of height, kyphoscoliosis, and impaired respiratory mechanics), and are prognostic for subsequent fractures and increased long-term mortality (Hasserius et al, Osteoporos Int 2003; Bliuc et al, JAMA 2009). As there are no data available on this association in men with prostate cancer, we performed an analysis of overall survival (OS) and prevalent vertebral fracture (PVF) at baseline in 1468 men with nonmetastatic prostate cancer on ADT enrolled in a phase 3, randomized, placebo-controlled study of denosumab.
Methods: OS during 36 months of treatment was analyzed by presence or absence of radiographically-confirmed PVFs in the overall population (median age: 75 years; median ADT duration: 20.5 months), and was adjusted for stratification factors of age (<70 vs $\geqslant$70 years) and ADT treatment duration ($\leqslant$6 vs >6 months). We also analyzed OS by placebo treatment (n = 734; mean age: 76 years; median prior duration of ADT: 20.4 months) or denosumab treatment (n = 734; mean age: 75 years; median prior duration ADT: 20.8 months). PVFs were assessed by lateral spine radiographs of T4−L4 vertebrae at baseline in a blinded fashion by a central reader using the Genant vertebral fracture scoring system.
Results: PVFs were present in 22% (329/1468) of subjects enrolled at baseline. The on-study death rate was higher for subjects with PVFs compared with those without PVFs, 7.6% (25/329) vs 5.1% (53/1035; HR = 1.57; p = 0.062). After adjusting for age group and ADT duration, the death rate remained higher in subjects with PVFs compared with those without PVFs (HR = 1.55; p = 0.07). Within each treatment arm, on-study death rate for subjects with PVFs compared with those without PVFs was 9.2% (16/174) vs 4.6% (23/504) with HR = 2.14, p = 0.019 for placebo, and 5.8% (9/155) vs 5.7% (30/531) with HR=1.09, p = 0.81 for denosumab. The hazard ratio (PVF: without PVF) adjusted for age group and ADT duration was placebo: HR = 2.13, p = 0.021; denosumab: HR = 1.08, p = 0.84.
Conclusion: In conclusion, men with prostate cancer on ADT who had PVF at baseline appeared to have shorter overall survival.

7006 ORAL

Effect of baseline characteristics on prostate cancer rates and risk reduction in the Reduction by Dutasteride of prostate Cancer Events REDUCE) trial

G. Andriole[1], O. Brawley[2], L. Gomella[3], M. Marberger[4], F. Montorsi[5], C. Pettaway[6], C. Teloken[7], T. Tammela[8], D. Tindall[9], R. Rittmaster[10]. *[1]Washington University School of Medicine, Division of Urologic Surgery, St Louis, USA; [2]Emory University, Winship Cancer Institute, Atlanta, USA; [3]Thomas Jefferson University, Kimmel Cancer Center, Philadelphia, USA; [4]University of Vienna, Department of Urology, Vienna, Austria; [5]Universita' Vita Salute San Raffaele, Department of Urology, Milan, Italy; [6]University of Texas, Anderson Cancer Center, Houston, USA; [7]Federal Medical School FFCMPA, Department of Urology, Alegre, Brazil; [8]Tampere University Hospital, Division of Urology, Tampere, Finland; [9]Mayo Medical School, Department of Urology, Rochester, USA; [10]GlaxoSmithKline, Urology Medical Development, Research Triangle Park, USA*

Background: The REDUCE trial (sponsored by GlaxoSmithKline) evaluated the dual 5α-reductase inhibitor (5ARI) dutasteride in prostate cancer (PCa) risk reduction. Overall, dutasteride decreased biopsy-detectable PCa incidence (the primary endpoint) by 23% vs. placebo (P < 0.001) without an increase in high-grade (Gleason 7−10) cancers (Andriole, AUA 2009).
Materials and Methods: REDUCE was a 4-year, international, double-blind, placebo-controlled, randomised study to evaluate the efficacy and safety of dutasteride in reducing the risk of biopsy-detectable PCa (Trial no. NCT00056407). Entry criteria included serum PSA 2.5−10.0 ng/mL (age 50−60) or 3.0−10.0 ng/mL (age > 60), and a negative prostate biopsy within 6 months prior to study entry. Study-mandated, 10-core biopsies occurred after 2 and 4 years; for-cause biopsies could be performed at anytime. We report the PCa relative risk reduction (Mantel-Cox) according to subjects' baseline characteristics.
Results: 8121 subjects had a negative entry biopsy confirmed by central pathology and took at least one dose of study drug (efficacy population). This analysis is based on the 83% of men in the efficacy population who had at least 1 biopsy (n = 6726). PCa rates by baseline characteristics are shown in Table 1, and are consistently between 22% and 32% relative risk reduction.
Conclusions: Dutasteride's ability to reduce the risk of biopsy-detectable PCa was consistent across many baseline characteristics. These results confirm the utility of dual 5AR inhibition to improve the natural history of PCa in men at increased risk of developing the disease.