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)

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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

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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

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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.

Table 1: Rates of biopsy-detected PC by treatment and baseline characteristics

	Dutasteride	Placebo	Relative risk reduction, % (95% CI)
Subjects in efficacy population, n	3303	3423	
PCa, n (%)	659 (20.0)	857 (25.0)	22.8 (15.2, 29.7)
Age, years – n (%)			
<65	342 (17.5)	461 (22.5)	24.0 (13.4, 33.4)
⩾65	317(23.5)	396 (28.9)	22.1 (10.8, 31.9)
Family history of PCa, n (%)			
Yes	105 (23.4)	141 (32.3)	31.9 (13.0, 46.7)
No	554 (19.4)	716 (24.0)	21.6 (13.1, 29.3)
Baseline prostate volume tertile, cc, n (%)			
<36.6	268 (25.2)	349 (31.1)	20.3 (7.8, 31.1)
36.6–<51.8	214 (19.6)	250 (22.1)	16.0 (0.3, 29.3)
⩾51.8	169 (15.4)	244 (22.0)	32.1 (18.4, 43.6)
Baseline % free PSA tertile, n (%)			
<13.7	261 (24.0)	346 (29.8)	22.5 (10.4, 33.0)
13.7–<18.6	213 (19.0)	266 (23.4)	20.1 (5.5, 32.4)
⩾18.6	184 (16.8)	244 (21.8)	25.4 (10.8, 37.7)
Number of cores at entry biopsy			
⩽9	377 (22.3)	480 (27.4)	21.6 (11.3, 30.8)
⩾10	282 (17.5)	375 (22.5)	24.3 (12.5, 34.5)

7007 ORAL

Three years of adjuvant androgen deprivation with goserelin in patients with locally advanced prostate cancer treated with radiotherapy: Results at 10 years of EORTC trial 22863

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Background: To confirm if the significant increase in overall and progression-free survival of patients with locally advanced prostate cancer reported at 5 years follow-up with the addition of long term androgen deprivation (LTAD) to external irradiation (RT) (Bolla M et al. N Engl J Med 1997; Lancet 2001) is maintained at 10 years and to assess the impact on cardiovascular and bone toxicity.
Materials and Methods: From 1987 to 1995, 415 patients with locally advanced (T1–2 WHO grade 3 M0 or T3–4 N0–1 M0) prostate cancer aged = 80 years were randomly allocated to combined RT plus LTAD or RT alone, followed by the same hormonotherapy in case of relapse. The whole pelvis was irradiated with photons ⩾10 MV up to 50 Gy (25 fr/5 wks), followed by a boost of 20 Gy (10 fr) to the prostate and seminal vesicles. LTAD consisted in monthly injections of goserilin (Zoladex®) 3.6 mg started on d1 of irradiation continued until progression or maximum 3 years. Comparisons are by intention-to-treat, with Logrank test (2-sided a = 5%). Heterogeneity of results by tumor stage and grade are investigated using a meta-analysis methodology.
Results: Disease and patient characteristics were well balanced in the two groups with median age 71 years. The median follow-up is 9.1 years. 192 of 415 patients have died (112 on RT alone and 80 on RT plus LTAD). LTAD added to RT increased the 10-year overall survival from 39.8% with RT alone to 58.1% (HR = 0.60, CI: 0.45–0.80, P = 0.0004), clinical progression-free survival (PFS) from 22.7% to 47.7% (HR = 0.42, CI: 0.33–0.55, P < 0.0001), distant metastases-free survival from 30.2% to 51.0 % (HR = 0.50, CI: 0.38–0.65, P < 0.0001) and biochemical PFS from 17.6% to 37.9% (HR = 0.43, CI: 0.30–0.60, P < 0.0001). Cumulative prostate cancer mortality at 10 years was 31.0% on RT and 11.1% on RT plus LTAD (HR = 0.38, CI: 0.24–0.60; P < 0.001). The cumulative cardiovascular mortality at 10 years was 11.1% and 8.2% (HR = 1.11, CI: 0.59–2.09, P = 0.75), with and without LTAD, respectively. Two pathological fractures were reported with RT plus LTAD (respectively at 7.2 and 9.9 years after treatment start). In patients with N0-x disease, the survival treatment effect was greater for T3–4 disease, but was independent of differentiation grade.
Conclusion: For patients with locally advanced prostate cancer, three years of LTAD with external irradiation improves overall survival without apparently increasing late cardiovascular toxicity.

Poster presentations (Tue, 22 Sep, 09:00–12:00)
Genitourinary malignancies – Prostate cancer

7008 POSTER

Prospective study evaluating salvage radiotherapy plus 2-year androgen suppression for post-radical prostatectomy patients with PSA relapse

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Background: To determine the efficacy of a combined approach of salvage radiotherapy (RT) plus 2-year androgen suppression (AS) for patients with PSA relapse after radical prostatectomy (RP).
Materials and Methods: A total of 104 patients with PSA relapse after RP were treated with RT plus 2-year AS, as per a phase I/II study. Patients were assigned into three groups: Group1: persistently detectable post-operative PSA (i.e. PSA never declined below 0.2 ng/ml after RP), Group 2: PSA relapse alone after initially undetectable post-operative PSA, and Group 3: PSA relapse with clinically palpable or biopsy proven local recurrence. AS started within 1 month after RT, and consisted of nilutamide for 4 weeks and buserelin acetate depot every 2 months for 2 years. Relapse-free rate including freedom from PSA relapse was estimated using the Kaplan-Meier method. PSA relapse was defined as a rise above 0.2 ng/ml with two consecutive increases over a minimum of 3 months.
Results: See table. All achieved undetectable PSA with the protocol treatment. Relapse-free rate including freedom from PSA relapse for the entire cohort was 90% at 5 years and 75% at 7 years (range: 68–81.1%).

Patient Characteristics and Outcomes

	Group 1	Group 2	Group 3
No. of patients	29	49	26
Median age (years)	60	63	63.5
Pre-operative PSA (ng/ml)			
Median	12	9	9.1
Gleason score (%)			
5	0	4	0
6	10	18	12
7	52	65	69
8–10	38	12	19
Pathological stage (1997 TNM) (%)			
PT2N0	45	61	58
PT3aN0	14	22	23
PT3bN0	41	16	19
PT4N0	4	0	0
Margin status (%)			
Positive	88	45	81
Interval from RP to PSA relapse			
<2 vs. ⩾ 2years (%)	100 vs. 0	59 vs. 41	56 vs. 44
PSA prior to salvage RT (ng/ml)			
Median (mean)	1.2 (2.2)	0.7 (1.4)	1.7 (2.0)
Range (%): 0.06- 0.19	0	6	8
0.2–0.99	41	61	23
1–1.99	28	18	23
2–4.99	24	8	42
> 5	7	6	4
PSA doubling time (months)			
Median (mean)	N/A	7.7 (10.0)	6.2 (12.4)
%: <3 months		5	13
3–<6		29	35
6–<12		38	22
12–<24		24	22
⩾ 24		5	9
Time from RP to RT (months)			
Median	6	34.8	41.6
Total RT Dose (Gy)			
Median (range)	66 (60–70)	66 (60–66)	66 (66)
AS after RT			
% completing 2-year AS	79	88	85
% not completing (median AS duration, months)	21 (17)	12 (21)	15(11)
Follow-up from RT (years)			
Median (range)	6.2 (0.6–8.4)	6.3 (3.7–9.8)	6.7 (2.0–9.3)
Relapse-free and Survival Rates (%)			
5-year relapse free rate	84.7	91.5	91.6
7-year relapse free rate (95% CI)	68.0 (41.6–84.4)	81.1 (62.5–91.1)	75.6 (44.3–90.9)
7-year survival (95% CI)	93.1 (75.1–98.2)	95.9 (84.4–99.0)	88.3 (67.9–96.1)

Conclusion: The combined treatment of salvage RT plus 2-year AS yielded an encouraging result for patients with PSA relapse after RP. A confirmatory study is needed.