models using the Fine and Gray method were adjusted for age, tumour stage, Gleason score and initial PSA.
Results: Distant progression was not significantly reduced by 3 months NADT [HR = 0.89, 95% CI 0.60–1.31; p = 0.55] but was reduced by 6 months NADT [HR = 0.49, 0.31–0.76; p = 0.001]. Interval hazards revealed the presence of two distinct waves of distant progression in men receiving RT alone. The first wave occurred within 7.5 years of randomization. The magnitude of the first wave was not reduced significantly in men receiving 6 months NADT with Gleason scores 8−10 [HR = 0.68, 0.30–1.53; p = 0.35], or those experiencing distant progression as a first competing clinical progression [HR = 0.66, 0.41–1.09; p = 0.11]. In contrast the second wave of distant progressions, which occurred 7.5 or more years after randomisation and usually in men with Gleason scores <8, T stage 2 primaries, was halved by 3 months NADT and almost completely prevented by 6 months NADT.
Conclusions: Variations in androgen dependent distant progression exist in locally advanced PC that have important implications for successful therapy.

7102 ORAL

Association of Benign Prostate Hyperplasia With Prostate Cancer Incidence and Mortality − a Nationwide Cohort Study

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Background: Although benign prostate hyperplasia and prostate cancer share features such as hormonal dependent growth and response to treatment with anti-androgen therapy, benign prostate hyperplasia is generally not considered a pre-malignant lesion. We tested the hypothesis that clinical benign prostate hyperplasia associates with increased risk of prostate cancer incidence and mortality.
Materials and Methods: Using a prospective design with individual participant data from five national registries, we studied 3,009,258 Danish men. We collected prostate cancer diagnoses (n = 53,315), information on prostate cancer mortality (n = 25,459) and ascertained clinical benign prostate hyperplasia through hospitalization (n = 187,591) and/or operation (n = 77,698) in 1980–2006 and use of α-adrenergic receptor antagonists (n = 143,365) and/or use of 5-α-reductase inhibitors (n = 47,465) in 1995–2006.
Prostate cancer was assessed by status of benign prostate hyperplasia using Kaplan–Meier plots of cumulative incidence and Cox proportional hazard ratios, adjusted for potential cofounders, with men without benign prostate hyperplasia as reference group.
Results: For entire cohort studies, multivariate-adjusted hazard ratios for prostate cancer incidence were 2.22 (95% confidence interval 2.13 to 2.31) in men hospitalized and 3.26 (3.03 to 3.50) in men operated for benign prostate hyperplasia, versus general population controls. Corresponding hazard ratios for prostate cancer mortality were 2.00 (1.91 to 2.08) for hospitalization and 7.85 (7.40 to 8.32) for operation. For age-matched cohort studies, corresponding hazard ratios for prostate cancer incidence were 3.04 (2.96 to 3.13) for hospitalization, 2.60 (2.47 to 2.73) for operation, 4.49 (4.33 to 4.65) for α-adrenergic receptor antagonist use, and 2.54 (2.40 to 2.68) for 5-α-reductase inhibitor use.
Conclusion: In Danish men followed for up to 27 years, clinical benign prostate hyperplasia associated with a 2−3 fold increased risk of prostate cancer incidence, and with a 2−8 fold increased risk of prostate cancer mortality.

7103 ORAL

Association of Single Nucleotide Polymorphisms (SNPs) in VEGF Pathway Genes With Progression-free Survival (PFS) and Blood Pressure (BP) in Metastatic Renal Cell Carcinoma (mRCC) in the Phase 3 Trial of Axitinib Versus Sorafenib (AXIS Trial)

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Background: In the randomized, open-label, phase 3 AXIS trial in second-line mRCC (clinicaltrials.gov NCT00678392), axitinib demonstrated a statistically significant improvement in PFS compared to sorafenib (median 6.7 *v* 4.7 months; hazard ratio 0.665, $P < 0.0001$). This study also explored potential associations between germline SNPs in VEGF pathway and genes with PFS and BP-related endpoints.
Material and Methods: DNA samples (n = 263, 36% of patients) from blood were genotyped using Taqman allelic discrimination. Potential associations between SNPs in VEGF pathway genes (*VEGF-A*, *VEGFR1*, *VEGFR2*, *HIF1*α) and PFS were evaluated in the Caucasian subpopulation only (n = 249), as well as between SNPs in *VEGF-A*, *VEGFR1*, and *VEGFR2* with hypertension (Grade 3 or greater) and high BP (at least one diastolic BP [dBP] reading $\geqslant$90 mmHg).
Results: Differences in PFS were seen with *VEGF-A* SNPs rs1570360 (adjusted $P = 0.127$; Cox regression interaction test), rs699947 ($P = 0.058$), and rs833061 ($P = 0.058$). Log-rank tests indicated that potential associations between PFS and genotype for these three SNPs are driven more by differences in PFS among genotypes in the axitinib arm than in the sorafenib arm. For example, the median PFS for *VEGF-A* rs699947 A/A in axitinib-treated patients was 52 weeks (versus 28 weeks for other genotypes; adjusted $P = 0.16$), while no difference in PFS among these genotypes was noted in sorafenib-treated patients (adjusted $P = 0.95$). After adjusting for multiple testing, no statistically significant correlations were observed between SNPs and hypertension or high dBP using logistic regression analysis.
Conclusions: Three *VEGF-A* SNPs were potentially associated with PFS. None of the VEGF pathway SNPs examined was associated with axitinib-related hypertension or dBP. These results support previously reported associations of rs1570360 and rs699947 with overall survival in a trial of a bevacizumab-based regimen (Schneider et al, JCO 2008;26:4672), and association of germline SNPs with efficacy for pazopanib (Xu et al, ASCO GU 2011:303). These exploratory data suggest that specific SNPs might help to explain some of the observed interpatient variability in PFS for RCC patients receiving axitinib therapy. Moreover, germline SNPs might be important tools in the future to guide selection of VEGF inhibitors.

7104 ORAL

Bone Mineral Density Loss and Fractures in the TROG 03.04 (RADAR) Trial

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Clinical trial information: Trial name: TROG 03.04 (RADAR). Australian New Zealand Clinical Trials Registry Number: ACTRN12607000097448
Objectives:
1. To improve prostate cancer specific mortality and PSA progression;
2. To reduce or delay the incidence of bone metastases and prevent leuprolide-induced osteopenia.

Design: Phase 3 randomised controlled trial.
Trial status: Closed to recruitment; Follow-up phase. Trial sponsors: National Health and Medical Research Council (Australia), Health Research Council (New Zealand), Novartis Pty Ltd (Australia).
Background: Prospective bone mineral density (BMD) and fracture data following androgen deprivation (AD) $\pm$ bisphosphonates were endpoints in the RADAR trial for locally advanced prostate cancer (LAPC).
Methods: Between 2003 and 2007 1071 men with LAPC were randomly allocated to short-term (6 months) neo-adjuvant AD using leuprolide and radiation (STAD) either alone, or followed by intermediate term (12 months) AD (ITAD), or accompanied by 18 months of zoledronic acid [4 mg- i.v. q 3 mo] (STADZ), or accompanied by both (ITADZ). Thoraco-lumbar X-rays (TLX) were done on all men before randomisation and 3 years after to document 'silent' fractures, and DEXAs were obtained prior to randomisation, and at 2 and 4 years after in a nested substudy of 200 men. All symptomatic fractures after randomisation were documented too.
Results: Loss of BMD at 2 years was significantly greater in men receiving STAD and ITAD without zoledronic acid. Further changes at four years indicated spontaneous recovery in some men, particularly those treated with STAD and continued loss in others. Use of zoledronic acid also reduced silent TLX fractures in multi-variable models of the BMD data ($p < 0.025$) and in men experiencing symptomatic fractures with osteopenic contribution (n = 28) in the entire study population ($p = 0.056$). Updated data and silent fracture TLX data, currently under review, will also be presented.
Conclusions: Zoledronic acid reduces BMD loss and fractures due to both STAD and ITAD.