Podium Session 1: Oncology – Prostate
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POD-01.01

5-Alpha Reductase Inhibitors Diminish the Rate of Progression in Men with Low-risk Prostate Cancer on Active Surveillance

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Introduction and Objectives: 5-alpha reductase inhibitors (5ARIs) have been shown to prevent prostate cancer in two large randomized controlled trials. No prior work has shown the effect of 5ARIs on those already diagnosed with low risk prostate cancer. Our goal was to determine the effect of 5ARIs on pathologic progression in men on active surveillance for prostate cancer.

Methods: This was a single institution retrospective cohort study comparing men taking a 5ARI versus no 5ARI while on active surveillance for prostate cancer. All men had at least two biopsies. Inclusion criteria for active surveillance were PSA <10 ng/mL, clinical stage T1c/T2a, Gleason score $\leq$6, and $\leq$3 cores positive with no more than 50% of a core involved at initial diagnostic biopsy. Pathologic progression was evaluated and defined as Gleason score >6, or maximum core involvement >50% or >3 cores positive on a follow-up prostate biopsy. Univariate, multivariate and Kaplan-Meir analyses were conducted.

Results: A total of 288 men on active surveillance met the inclusion criteria. The median follow-up was 38.5 months (IQR 23.6-59.4) with 93 men (32%) experiencing pathologic progression and 96 men (33%) abandoning active surveillance. Men taking a 5ARI experienced a lower rate of pathologic progression (18.6% vs 36.7%, p=0.004) and were less likely to abandon active surveillance (20% vs 37.6%, p=0.006). The median time to progression was longer in the 5ARI group (42.5 months) compared to the non-5ARI group (31.5 months; p=0.026). On multivariate analysis, lack of 5ARI use was most strongly associated with pathologic progression (OR 2.98, 95% CI 1.5 – 5.9) followed by age and baseline maximum percentage involvement of any biopsy core.

Conclusions: 5ARIs were associated with a significantly lower rate of pathologic progression and abandonment of active surveillance.

POD-01.02

Long-term Outcome of Randomized Trial between Cryoablation and External Beam Therapy for Locally Advanced Prostate Cancer (T2c-T3b)

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Introduction and Objective: Our primary objective is to assess and compare the survival outcomes between cryoablation (CRYO) and External Beam Radiation Therapy (EBRT) in locally advanced prostate cancer (T2c-T3b).

Methods: Patients with cT2c-cT3b prostate cancer (CaP)(PSA <25 ng/mL, negative metastatic evaluation on CT and bone scan), initially recruited for the trial from 1999 to 2002, were randomized to either primary CRYO (Cryocare System, Endocare Inc., Irvine, CA, USA) or EBRT (66 Gy in 33 fractions, administered at 2 Gy per day, 5 days a week for 6.5 weeks, directed at the prostate, seminal vesicles, and peri-prostatic region). All patients received neoadjuvant hormonal therapy (HT) for 3 months prior and continued for 3 months after the procedures. Patients underwent regular trans-rectal ultrasound and biopsy till 24 months of follow-up (at 3, 6, 12, 18, 24 months for CRYO and at 18, 24 months for EBRT) and as clinically indicated thereafter. Biochemical failure was based on the Phoenix criteria (PSA nadir + 2 ng/dL). Biochemical disease-free survival (bDFS), disease-specific survival (DSS) and overall survival (OS) were analysed with Kaplan-Meier curve.

Results: Median follow-up was 105.2 (higher EBRT dose for patients with locally advance CaP). 62 patients completed the trial. Preoperative demographic and clinicopathological characteristics of both groups were comparable. Prostate volume before therapy was smaller in the CRYO group (31.3 mL vs 40.9 mL) ($p\leq$0.01). There was greater reduction in prostate volume in the CRYO group after intervention (–54% vs 34%) ($p\leq$0.01). DSS and OS were comparable between both groups. The 8-year bDFS rate was significant lower in the CRYO group (17.4% vs 59.1%) (p=0.01), however median time to bDFS was not significantly different (Figure 1).

Conclusion: This randomized trial showed that CRYO was inferior in attaining bDFS close to 9 years in patients with locally advanced CaP (cT2c-T3). A recent randomized trial for more localized CaP showed favorable outcome with CRYO cancer. CRYO may be more suited for less bulky CaP or longer neoadjuvant HT is required for optimal bDFS.

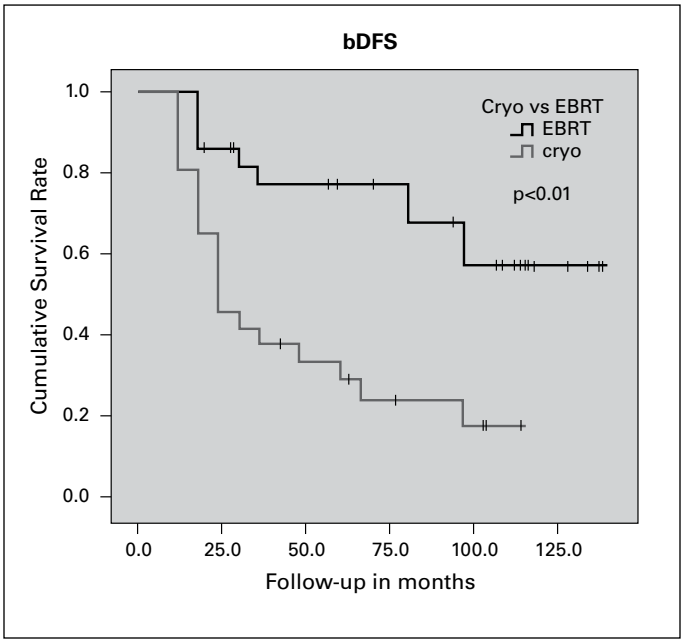

Fig. 1. POD-01.02

POD-01.03

A Phase III Randomized Trial Comparing Intermittent versus Continuous Androgen Suppression for Patients with PSA Progression after Radical Therapy (NCIC CTG PR.7/SWOG JPR.7/CTSU JPR.7/ UK Intercontinental Trial CRUKE/01/013)

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Background: In men with PSA recurrence after radical radiotherapy (RRT), previous phase 2 trials of intermittent androgen deprivation (IAS) have demonstrated that quality of life (QoL) is improved in the off treatment interval. Effects on survival are unknown. In this randomized phase 3 trial, we compared IAS vs continuous androgen deprivation (CAD) to test for non-inferiority of IAS with respect to overall survival (OS).

Methods: Eligible men had rising PSA >3.0 ng/mL >1 year post RRT, either initial or salvage, for localized prostate cancer. Patients could receive up to 1 year of neo/adjuvant androgen deprivation therapy (ADT) completed >1 year prior. Stratification factors were time since RRT (>1-3 vs >3 years), initial PSA (<15 vs >15), prior radical prostatectomy and prior ADT. IAS was delivered for 8 months in each cycle with restart when PSA reached >10 ng/mL off treatment. Primary endpoint was OS; secondary endpoints included time to castrate resistance, QoL, cholesterol/HDL/LDL, duration of treatment/non-treatment intervals, time to testosterone and potency recovery. The independent DSMC recommended halting the trial after a planned interim analysis demonstrated that a pre-specified stopping boundary for non-inferiority was crossed.

Results: 1386 patients were randomized to IAS (690) or CAD (696) arms. Arms were balanced for important baseline factors. Median follow up was 6.9 years. IAS patients completed a median of 2 x 8 month cycles (range: 1-9). 524 deaths were observed (268 on IAS vs 256 on CAD). Median OS was 8.8 vs 9.1 years on IAS and CAD arms, respectively (HR 1.02, 95%CI 0.86-1.21; p for non-inferiority [HR IAS vs CAD ≥1.25] = 0.009). The IAS arm had more disease related (122 vs 97) and fewer unrelated (134 vs 146) deaths. Time to castrate resistance was statistically significantly improved on the IAS arm (HR 0.80, 95%CI 0.67-0.98; p=0.024). IAS patients had reduced hot flashes, but otherwise there was no evidence of differences in AEs, including myocardial events or osteoporotic fractures. IAS patients had better QoL in the domains of physical function (p<0.01), fatigue (p<0.01), urine problems (p = 0.01), hot flashes (p<0.01), desire for sexual activity (p<0.01) and having an erection (p<0.01).

Conclusions: In men with PSA recurrence after RRT IAS is not inferior to CAD with respect to OS. IAS was associated with an improvement in time to castrate resistance and QoL.

POD-01.04

Intergroup Randomized Phase III Study of Androgen Deprivation Therapy (ADT) + Radiation Therapy (RT) in Locally Advanced Prostate Cancer (CaP) (NCIC-CTG, SWOG, MRC-UK, INT: T94-0110; NCT00002633

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Background: The impact of radiotherapy on overall survival (OS) in men with locally advanced CaP is unclear. The SPCG-7 trial recently showed a benefit to RT for CaP specific mortality. Our primary objective was to assess the effect of RT on OS when added to lifelong ADT in men with locally advanced CaP.

Methods: Patients with T3/T4 (1057) or T2, PSA >40 µg/L (119) or T2 PSA >20 µg/L and Gleason ≥8 (25) and N0 /NX, M0 prostate adenocarcinoma were randomized to lifelong ADT (bilateral orchiectomy or LHRH agonist) with or without RT (65-69 Gy to prostate ± seminal vesicles with or without 45Gy to pelvic nodes). The primary endpoint was OS and secondary endpoints included disease specific survival (DSS), time to disease progression and quality of life.

Results: 1205 patients were randomized from 1995 to 2005, 602 to ADT and 603 to ADT+RT (well balanced with respect to baseline characteristics). A protocol specified 2nd interim analysis on OS was performed in Aug 2009 (data cut-off Dec 31st 2008). The DSMC recommended release of the results to the Trial Committee for publication. The median follow-up is 6.0 years and 320 patients have died (175 ADT and 145 ADT+RT). 10% of patients had no follow-up data beyond 2006. The addition of RT to ADT significantly reduced the risk of death (Hazard Ratio (HR) 0.77, 95% CI 0.61-0.98, p=0.033). 140 patients died of disease and/or treatment (89 on ADT and 51 on ADT+RT) The disease specific survival HR was 0.57 (95% CI 0.41-0.81, p=0.001) favoring ADT+RT. The 10 year cumulative disease specific death rates were estimated at 15% with ADT+RT and 23% with ADT alone. Grade ≥2 late GI toxicity rates were similar in both arms (proctitis, 1.3% ADT alone, 1.8% ADT+RT).

Conclusions: The trial results indicate a substantial overall survival and disease specific survival benefit for the combined modality approach (ADT+RT) in the management of patients with locally advanced prostate cancer with no significant increase in late treatment toxicity. In view of this data combined modality therapy (ADT+RT) should be the standard treatment approach for these patients.

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POD-01.05

Denosumab Treatment for Prolonging Bone Metastasis-Free Survival in Men With Castrate-Resistant Prostate Cancer: Results of a Phase 3, Randomized, Double-Blind Trial

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Introduction and Objective: Men with castrate-resistant prostate cancer (CRPC) are at increased risk for developing bone metastasis, which can result in pain and bone-related complications called skeletal-related events (SREs). This study assessed the ability of denosumab (XGEVA™), which is approved in the United States for the prevention of SREs in patients with advanced cancer and bone metastasis, to prolong bone metastasis–free survival (BMFS) in men with CRPC who were at increased risk of developing bone metastasis.

Methods: Adult men with non-metastatic CRPC at high risk for developing bone metastasis (PSA value ≥8.0 ng/mL obtained ≤3 months before randomization and/or PSA doubling time ≤10.0 months) and total serum testosterone levels of <50 ng/dL were randomized 1:1 in a blinded manner to receive monthly subcutaneous (SC) denosumab 120 mg or monthly SC placebo. Stratification was by PSA risk group and prior/current chemotherapy for PC. Calcium and vitamin D supplements were strongly recommended. The primary endpoint was bone metastasis-free survival (BMFS) as determined by time to first bone metastasis or death from any cause. Bone metastasis was confirmed by an independent central reading facility using radiography, computed tomography, or MRI in a blinded fashion. This trial was event driven, with the first patient enrolled in February 2006.

Results: A total of 1432 subjects were enrolled. Denosumab significantly improved median time to BMFS by 4.2 months compared with placebo (hazard ratio [HR] 0.85; 95% CI: 0.73, 0.98; *P*=0.03), and significantly improved time to first occurrence of bone metastasis. Overall survival was similar between treatment groups. Rates of adverse events (AEs) and serious AEs were generally similar between groups.

Conclusions: In patients with CRPC, denosumab significantly prolonged BMFS and delayed time to bone metastasis.

POD-01.06

A Phase III, Double-Blind, Randomized, Parallel Group, Placebo-Controlled Study of Oral Fosamax®, 70 mg Once-a-Week, for the Prevention of Androgen Deprivation Bone Loss in Non-Metastatic Prostate Cancer

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Background: Androgen deprivation therapy (ADT) induces loss of bone mineral density (BMD) and increases the risk of fractures in patients with prostate cancer. We sought to determine whether a weekly dose of alendronate, an oral bisphosphonate, could reduce this unwanted side effect.

Objective: To assess whether once weekly oral alendronate therapy would maintain or improve bone mineral density in men initiating ADT for localized prostate cancer.

Methods: In this multi-center, double-blind, randomized, placebo-controlled study, hormonally naïve prostate cancer patients initiating ADT with leuprolide acetate (Lupron®) 30 mg intramuscularly every 4 months were randomized to receive either oral alendronate 70 mg once-weekly or placebo for one year. Both groups received daily calcium (equivalent to 500 mg elemental calcium) and vitamin D (400 IU) supplementation daily. Changes in BMD and bone marker levels were assessed.

Results: One-hundred ninety-one subjects were enrolled to the trial with 186 randomized to receive either alendronate (84 patients - 45%) or placebo (102 patients - 55%). The primary outcome measure was the percent change from baseline to end of study in spine BMD. The alendronate group demonstrated a mean spine BMD increase of 1.7% compared with -1.9% in the placebo group ($p<0.0001$). Alendronate also increased the BMD at the hip (percent change 0.7%) compared with those receiving calcium and vitamin D alone (percent change -1.6%). However this change was lost ($p=0.631$) after adjusting for centre ($p=0.007$) and baseline hip BMD ($p<0.0001$). Median urinary NTX values decreased by 3.5% in the alendronate group and increased by 16.5% in the placebo arm, even after adjusting for centre ($p=0.510$) and baseline urinary NTX ($p<0.0001$). Bone specific alkaline phosphatase (BSAP) decreased a median of 2.25% in the alendronate group, and increased a median of 3.12% in the placebo arm, irrespective of centre or baseline BSAP or other covariates ($p<0.0001$). The safety and tolerability profile was similar for the two treatment groups.

Conclusion: This study showed that weekly oral alendronate prevented bone loss and increased bone mass in addition to decreasing bone turnover in patients initiating ADT for localized prostate cancer, with few related side effects.