**Report of NRG Oncology/RTOG 9601, A Phase III Trial in Prostate Cancer: Anti-androgen Therapy (AAT) with Bicalutamide During and After Radiation Therapy (RT) in Patients Following Radical Prostatectomy (RP) with pT2-3pN0 Disease and an Elevated PSA**

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**Purpose/Objective(s):** To test if long term AAT when combined with RT in patients with prostate cancer (PC) will improve overall survival and other cancer control outcomes.

**Materials/Methods:** Post-RP patients with pT3pN0 or with pT2pN0 (and also positive margins) who had or developed elevated PSA levels from 0.2 to 4.0 ng/ml were randomized on a phase III, double-blinded, placebo-controlled trial of RT + placebo (64.8 Gy in 36 fractions of 1.8 Gy) vs RT + AAT (24 months of bicalutamide, 150mg daily) or placebo during and after RT. The primary end-point is overall survival. The trial design required 725 patients and provided 80% power to detect a reduction in death rate by at least 28.5% and a 1-sided significance level of 0.046.

**Results:** From 3/98 to 3/03, 761 eligible patients (median age 65) were randomized to RT + AAT (384) or RT + placebo (377). 248 patients (33%) were pT2pN0 and 513 patients (67%) were pT3pN0. 671 patients (88%) had a PSA nadir after RP of < 0.5 ng/ml. 649 patients (85%) had an entry PSA value of <1.6, 112 patients (15%) had an entry PSA of 1.6-4. Median follow up was 12.6 years. The actuarial overall survival at 10 years was 82% for RT plus AAT and 78% for RT + placebo and a hazard ratio of 0.75 (95% CI: 0.58-0.98) with a 1-sided p-value of 0.018 (2-sided p-value = 0.036). PSA progression was defined as a PSA > 0.5 ng/ml in patients whose treatment resulted in an undetectable PSA or, if not, when the PSA rose 0.3 ng/ml above the entry PSA. Freedom from PSA Progression (FFP) estimated at 10 years was 46% for RT + AAT and 30% for RT + placebo (p < 0.001). The 12-year incidences of PC central-reviewed deaths were 2.3% for RT + AAT and 7.5% for RT + placebo (p<0.001).The cumulative incidence of metastatic PC at 12 years was less in the RT + AAT arm, 14% (51 patients), vs 23% (83 patients) in the RT + placebo arm (p<0.001). Late Grade III and Grade IV toxicity were similar in the AAT and placebo arms. By category the combined Grade III plus Grade IV toxicities for RT +AAT and RT +placebo were: for bladder 7.0% vs 6.7%, bowel 2.7% vs 1.6%. Gynecomastia (mostly all Grades I and II) differed significantly by treatment arm, 70% and 11%. In the RT +AAT arm Grade III was the highest liver toxicity observed which occurred in <1% of patients.

**Conclusion:** The addition of 24 months of AAT with 150mg daily of bicalutamide during and after RT significantly improved the long term overall survival and FFP and reduced the incidence of metastatic PC and PC death without adding significantly to radiation toxicity.