

ERG mRNA Expression Predicts Benefit of Anti-androgen Therapy Added to Salvage Radiation in Recurrent Prostate Cancer Patients: A Secondary Analysis of the NRG/RTOG 9601 Phase III Randomized Trial

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Background Anti-androgen therapy (AAT) improves outcomes for recurrent prostate cancer (PCa) but can introduce adverse events. Predictive biomarkers to guide AAT selection are currently lacking. *ERG* is a commonly altered oncogene in PCa; however, its prognostic role remains controversial, and its utility as a predictive biomarker for AAT response has not been established. To evaluate whether *ERG* predicts the clinical benefit of adding AAT to salvage radiation therapy (RT) in recurrent PCa patients, while clarifying its prognostic role.

Methods This study used *ERG* mRNA expression from radical prostatectomy specimens and clinical data from the phase III NRG/RTOG 9601 trial. NRG/RTOG 9601 trial randomized patients to RT with or without 2 years of bicalutamide (abbreviated as AAT+RT vs. RT). Time to progression (TTP), time to distant metastasis (TTDM), PCa-specific survival (PCSS), and overall survival (OS).

Results This N=352 cohort had about 89% White patients, a mean age of 64.5 years, and a median follow-up of 13 years. *ERG* expression was lower in T2-stage tumors (median=0.15 vs. 0.38 in T3, $p=0.0058$) and those with a positive surgical margin (median=0.17 vs. 0.76 in margin negative, $p=0.0021$), and increased with elevated Decipher risk (median=0.12/0.57/0.7 for low/average/high risk, $p=0.0034$). *ERG*-low patients derived prominent clinical benefit from adding AAT, demonstrating a substantial reduction in 15-year failure rates: 50% reduction (AAT+RT vs. RT: 0.42 vs. 0.84) in risk of progression, 65% reduction in both distant metastasis (0.12 vs. 0.34) and PC-specific mortality (0.11 vs. 0.32), and 33% reduction (0.3 vs. 0.45) in all-cause mortality; and persisted after adjusting for risk factors (AAT+RT vs. RT hazard ratios [HRs] ranging from 0.22 to 0.67). Conversely, *ERG*-high patients gained little benefit (covariate-adjusted HRs from 0.7 to 1.02). *ERG* was prognostic only within the AAT+RT arm, where *ERG*-high patients demonstrated a lack of response (*ERG*-high vs. low covariate-adjusted HR, 95% CI: 2.72, 1.7-4.37 for TTP; 4.02, 1.66-9.76 for TTDM; 3.97, 1.28-12.31 for PCSS).

Conclusions *ERG* is a dual treatment-predictive and prognostic biomarker for AAT response in recurrent PCa, identifying *ERG*-low patients as those who would benefit most from AAT-intensification.

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Conflicts of interest

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