Transcriptomic-Clinical Risk Stratification to Guide Abiraterone Treatment Intensification in High-Risk Prostate Cancer: A Combined Analysis of NRG/RTOG 9202, 9413, 9902, and 0521

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BACKGROUND: Outcomes for a subset of patients with localized, high-risk (HR) prostate cancer (PCa) remain poor when treated with radiation therapy (RT) and androgen deprivation therapy (ADT). Observations from STAMPEDE have provided evidence that patients with clinical very high-risk (VHR) features derive benefit from the addition of abiraterone acetate and prednisone (AAP) to their treatment package. It is yet unknown if AAP intensification may benefit other patients outside of the STAMPEDE-defined subset.

METHODS: This is a secondary analysis of all available pre-treatment biopsy samples from four predominantly HR trials: NRG Oncology/RTOG 9202, 9413, 9902, and 0521. Decipher GC score was generated from samples with adequate tissue based on a locked and validated risk model measuring RNA expression from 22 genes (Veracyte, San Diego, CA). The primary endpoint was metastasis-free survival (MFS), and secondary endpoints were overall survival (OS) and distant metastases (DM). The primary objective was to determine if a specific subgroup of HR patients had sufficiently poor prognoses to derive a clinically meaningful benefit from AAP intensification. The prognostic impact of GC was evaluated via hypothesis testing [H_0:(s)$HR_{GC}=1$;H_a:(s)$HR_{GC}\neq 1$] for MFS and OS, utilizing Cox proportional hazards models, and DM utilizing a Fine and Gray model for hypothesis testing. GC score was analyzed both as a continuous variable as well as a categorical variable: ≤ intermediate risk (IR, <0.6), HR (0.6-0.85), and VHR (>0.85).

RESULTS: Overall, 448 patients from 4 RCTs with a median follow-up of 10.4 years (Q1-Q3: 9.1-11.8) were included. The median PSA was 22.8 ng/mL (Q1-Q3: 10.3-44.7), and median GC was 0.72 (Q1-Q3: 0.56-0.86). Within this cohort, 34%(n=152) of patients fulfilled the NCCN/STAMPEDE VHR criteria, 65%(n=293) had GC ≥HR, and 26%(n=115) were in both of these groups. A significant prognostic impact of GC score as a continuous variable (per 0.1) was seen for the primary endpoint, MFS ($HR_{adjusted}$ 1.19 [95% CI: 1.11-1.29], p<0.001), as well as both secondary endpoints, DM ($sHR_{adjusted}$ 1.32 [95% CI: 1.15-1.51], p<0.001) and OS ($HR_{adjusted}$ 1.18 [95% CI: 1.09-1.27], p<0.001). A corresponding analysis utilizing GC category yielded statistically significant prognostic effects on all endpoints (all p<0.05).

The median survival time(MST) in years for MFS for the ≤IR, HR, and VHR Decipher GC risk categories were 14.0 (95%CI: 12.2-16.3), 10.4 (95%CI: 8.7-12.1), and 9.3 (95%CI: 7.8-15.2), respectively. The corresponding MSTs for OS were 14.6 (95%CI: 12.2-17.1), 10.8 (95%CI: 9.8-13.9), 11.3 (95%CI: 10.3-not applicable), respectively. The survival distribution of the Decipher GC HR and VHR group were similar to the published STAMPEDE VHR control arm (RT+ADT), whereas GC ≤IR was observed to have a better prognosis.

CONCLUSIONS: Our findings suggest a new clinical population whose prognosis is sufficiently poor that AAP intensification may produce a clinically meaningful benefit. This may approximately double the patient population potentially eligible for AAP intensification.

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