

## **Pathologic responses and their molecular correlates in the phase-II Genomic Umbrella Neoadjuvant Study (GUNS) of genomic-biomarker-directed triplet therapies in high-risk localized prostate cancer**

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### ***Background.***

Androgen deprivation therapy (ADT) and androgen receptor (AR) pathway inhibition (ARPI) are mainstays of treatment for metastatic castration-sensitive prostate cancer (PC) and increasingly used in high-risk localized disease, but pathologic responses remain limited. We conducted a neoadjuvant phase-II trial, the Genomic-biomarker-selected Umbrella Neoadjuvant Study (GUNS, NCT04812366), to test whether genomic-biomarker-directed triplet-therapy sub-protocols (SPs) improve pathologic responses in high-risk localized PC. We report on two SPs: SP 1 (completed), for cancers with AR-associated or otherwise favorable genomics, and SP 2 (interim Stage 1), for cancers with *TP53*, *RB1*, *PTEN*, or *AKT1* genomic alterations, which are associated with aggressive disease and poor outcomes.

### ***Methods.***

Patients received 8 weeks of an ADT/ARPI doublet (LHRHa + apalutamide) followed by assignment to 16 weeks of a biomarker-specific SP based on Tempus' xT DNA and RNA sequencing of diagnostic biopsies. Over two stages, SP 1 enrolled 100 evaluable participants and randomized them to an ADT/ARPI doublet (SP 1A: LHRHa + apalutamide) or triplet (SP 1B: doublet + abiraterone). SP-2 Stage 1 enrolled 48 patients, randomized to an ADT/ARPI doublet (LHRHa + abiraterone) ± docetaxel (SP 2A/2B). Primary endpoint: major pathologic response (MPR; residual cancer burden (RCB) ≤ 1 mm<sup>2</sup> or largest focus diameter ≤ 5 mm). Biopsies were additionally subjected to PTEN immunohistochemistry (IHC). Clinicopathologic, genomic, and transcriptomic associations with MPR/RCB were evaluated using Fisher's exact, chi-squared, or Wilcoxon rank-sum tests and gene set enrichment analysis.

### ***Results.***

*ERG* fusions (35%), *FOXA1*<sup>alt</sup> (22%), *SPOP*<sup>alt</sup> (12%), *TP53*<sup>alt</sup> (19%), and *PTEN*<sup>alt</sup> (15%, plus additional 13% negative by IHC) dominated the GUNS genomic landscape. *TP53*<sup>alt</sup>, *PTEN*<sup>alt(DNA/IHC)</sup>, and ETS gene (e.g., *ERG*) fusions—especially in combination—were associated with adverse cribriform pathologies. In SP 1, triplet ARPI therapy improved the MPR rate (58% vs. 32%, *p* = 0.004, Holm-adjusted *p* = 0.013) and reduced overall RCB (*p* = 0.013, Holm-adjusted *p* = 0.026) compared to doublet therapy. In SP-2 Stage 1, ARPI+docetaxel triplet therapy (SP 2B) improved the MPR rate (*p* = 0.011, Holm-adjusted *p* = 0.033), with RCB trending lower (not significant), compared to ARPI-only doublet therapy (SP 2A). *ERG* fusions tended to be unfavorable, and *SPOP*<sup>alt</sup> and *FOXA1*<sup>alt</sup> favorable, in SP 1, while *PTEN*-deficient tumors with a concurrent ETS fusion had the worst pathologic outcomes in SP 2. Transcriptomically, baseline AR signaling was strongly associated with favorable response to ARPI-only therapy combinations while immunological signatures were unfavorable, but these associations were lost in SP 2B (docetaxel).

### ***Conclusions.***

Biomarker-directed triplet therapies improved pathologic responses in GUNS Sub-protocols 1 (completed) and 2 (Stage 1) compared to ADT/ARPI-only doublet therapies. Genomic and transcriptomic analyses

identified correlates of response, which could refine future treatment strategies. Baseline AR signaling was strongly associated with response to ARPI but not ARPI + docetaxel.

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