e17026 **Publication Only**

PTCH1 and *AXIN2* modulation of AR copy number effects on AR gene overexpression in metastatic castration resistant prostate cancer (mCRPC).

Raymond T. Yan, Jeanne Latourelle, Omar Khalid, Ravi Bharat Parikh, Bruce W. Church; GNS Healthcare Inc., Cambridge, MA; GNS Healthcare, Cambridge, MA; University of Pennsylvania, Philadelphia, PA

Background: Androgen receptor (AR) signaling is a critical pathway in prostate cancer progression. Reactivation of the AR pathway is a key driver in mCRPC. Patients with mCRPC often develop resistance to novel AR signaling inhibitors (ARSIs) such as enzalutamide. AR inhibitor resistance leads to shorter overall and progression-free survival and can be attributed to AR gene amplification with subsequent AR overexpression and androgen-sensitization in prostate tumors. Identifying novel modulators of AR amplification in patients progressing on ARSIs may lead towards potential targets in drug discovery. **Methods:** In this cross-sectional study, an *in silico* patient model was developed on prescribed drug therapies and failed therapies patient information, PSA measures, ~100 mutation variables including somatic, germline, and gain/loss mutations, and ~1K gene expressions data from 275 mCRPC patients obtained from the Tempus database using GNS Healthcare's Causal artificial intelligence technology, REFS. A causal network model was reconstructed based on patient data with inferred effect estimates. The network model was topologically surveyed for biological interactions. **Results:** Causal analysis of this model uncovered two germline mutations, located in *PTCH1* and *AXIN2*, which modify the effect of AR copy number gain (*ARgain+* : copy number 6, *ARgain-* : copy number < 6) on AR gene expression. For *PTCH1*-mutant group, there was a 2-fold increase in AR gene expression in *ARgain+* patients compared to *ARgain-* patients ($p = 2.1e^{-12}$), while only 1.4 fold increase in AR gene expression from the PTCH1 non-mutant group ($p = 6.3e^{-08}$). Similarly, there was a 2-fold increase in AR gene expression in *ARgain+* patients compared to *ARgain-* patients ($p = 7.2e^{-16}$) for the *AXIN2*-mutant group, while only one-fold increase in AR gene expression with the *AXIN2* non-mutant group ($p = 0.001$). The C to T missense mutation in codon 3746 in *PTCH1* and codon 148 in *AXIN2* have higher prevalences, 55% and 72%, respectively in this mCRPC cohort compared to their population allele frequencies, 38% and 47%, respectively. **Conclusions:** *PTCH1* and *AXIN2* mutations from our analyses is consistent with a literature reported role for Hedgehog signaling and Wnt/-catenin signaling pathways, respectively, influencing the disease progression in castration-resistant prostate cancer. Our findings suggest that the missense germline mutations in *PTCH1* and *AXIN2* predicts response to enzalutamide and other ARSIs in CRPC setting, and propose potential targets for combination therapy to overcome ARSI drug resistance in hormone-refractory prostate cancer. Research Sponsor: None.

mCRPC (N = 275)	Average AR Gene Expression (Std.Dev)			
	PTCH1		*AXIN2*	
AR gain (copy number)	Non-mutated (n = 109)	Mutated (n = 166)	Non-mutated (n = 67)	Mutated (n = 208)
-	13.5 (7.9)	15.1 (8.1)	14.4 (7.4)	14.5 (8.3)
+	32.9 (15.2)	47.4 (18.2)	29.6 (13.9)	43.8 (18.2)