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Abstract 2959: Glycogen synthase kinase 3-β expression in prostate cancer (PCa) correlates with aggressive pathological features and its blockade with 9-ING-41 inhibits viability of PCa cell lines

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Abstract

Castration-resistant prostate cancer (CRPC) represents a lethal stage of disease with limited treatment options beyond androgen receptor (AR) inhibitors and chemotherapy. GSK-3β is a serine/threonine kinase established as a therapeutic target in several solid tumors. GSK-3β inhibitors reduce prostate cancer cell growth and inhibit AR-V7 transcriptional activity in vitro (Rinnab L et al 2008; Schütz SV et al 2011; Nakata et al 2017). This study aimed to characterize the GSK-3β expression in molecular subtypes of PCa and the antitumor activity of 9-ING-41, a selective small molecule GSK-3β inhibitor currently in phase 1/2 clinical studies (NCT03678883). We hypothesized that GSK3-β expression may correlate with sensitivity to GSK3-β inhibition as well as suppression of anti-apoptotic pathways. We evaluated the expression of GSK-3β in a tissue microarray of 134 specimens of PCa tumors from radical prostatectomies (median age 69, serum PSA 10.5 ± 7.6 ng/ml; grade groups (GG): 18 - GG 1 (13.4%), 67 - GG 2 (48.5%), 29 - GG 3 (21.4%), 7 - GG 4 (5.2%), 13 - GG 5 (9.7%); 72 patients (54.9%) had pT2 tumors, and 52 (39,1%) were pT3. Seven patients (5.7%) had positive lymph node (pN1 disease). ERG expression and PTEN loss were observed in 52% (71/134) and 42%, respectively. The GSK-3β histologic score (% of positive tumor cells multiplied by intensity 0-3) correlated with higher Gleason grade ($p<0.05$), extraprostatic extension (pT3a, $p<0.05$), but not with serum PSA, tumor volume, margin status or size of index nodule. Cases with predominant nuclear localization of GSK-3β (5%; N=7) had higher Gleason score, pathologic stage, and all but one had PTEN loss. The antiproliferative effect of 9- ING-41 in four PCa human cell lines (PC3, DU145, LNCAP and 22rV1) was investigated using Cell-Titer-Glo (CTG) viability assay. 9-ING-41 demonstrated a dose-dependent decrease in proliferation of AR positive (IC50s 0.3 μM LNCAP; 0.8 μM 22rV1) and AR negative cell lines (IC50 0.6 μM PC3, 0.2 μM DU145). 9-ING-41 induced robust apoptosis (cleaved PARP) in LNCAP and PC3 cells, but not in DU145. All four cell lines expressed GSK-3β, the target of 9-ING-41 and its level were not altered by treatment. 9-ING-41 decreased the expression of phosphorylated NF-kβ (Ser536), anti- apoptotic proteins MCL-1 and BCL-2 by western immunoblotting. Interestingly, the most sensitive cell line, DU145, had lower levels of NF-kβ and suppressed both MCL-1 and BCL-2 after exposure to 9-ING-41. Our current work is evaluating the extent of apoptosis versus growth arrest, especially in the DU145 cell line, where PARP cleavage was not observed. We are also evaluating the effects of the 9-ING-41 on cellular targets of GSK-3β as potential markers of drug efficacy. 9-ING-41 has potent anti-proliferative activity against PCa cell lines. These data support the inclusion of patients with CRPC in clinical studies of 9-ING-41 and its further investigation for the treatment of CRPC.