HER2-Mediated Mechanisms of Resistance to Androgen Deprivation Therapies in Advanced Castration-Resistant Prostate Cancer (CRPC)

Joshua W. Russo[1], Olga Voznesensky[1], Carla Calagua[1], Huihui Ye[2], David Einstein[1], Manoj Bhasin[3] and Steven Balk[1]

[1]Department of Medicine, Hematology/Oncology Division; [3]Bioinformatic and Systems Biology Unit; Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA; [2]Department of Pathology, UCLA Medical Center, Santa Monica CA.

Background: In an effort to identify additional drivers of AR and pro-survival signaling in advanced castration-resistant prostate cancer (CRPC), I have developed an androgen deprivation therapy (ADT)-resistant PCa model system that consists of a VCaP xenograft resistant to long-term combined therapy with abiraterone (Abi) plus enzalutamide (Enza) (AER VCaP xenograft). My initial work has identified increases in HER2 signaling as these tumors progress through castration resistance onto Abi+Enza resistance that can be targeted with recently developed covalent HER2 receptor tyrosine kinase inhibitors (RTKi's), resulting in xenograft tumor regression. These results have been extended to clinical material and active HER2 signaling has been identified in a subset of metastatic CRPC tumors.

Methods: VCaP xenografts were generated from cultured VCaP cells transplanted into mice. Tumors were serially biopsied prior to castration (Pre-Cx), at tumor relapse (CRPC), and following tumor relapse on combined Abi/Enza therapy (AER). Biopsies were submitted for RNA sequencing, immunohistochemical (IHC) staining, and reverse-phase protein array (RPPA) validation of protein expression changes. For kinase inhibitor studies, mice with castration-resistant xenografts were treated with daily intraperitoneal injection of afatinib or lapatinib or daily oral gavage of neratinib. Clinical CRPC biopsy specimens were acquired under an IRB approved protocol and underwent IHC for pHER2, pHER3, and NRG1.

Results: The AER VCaP xenograft model is resistant to long term combined therapy with Abi plus Enza as indicated by continued tumor growth and continued expression of the AR target genes. AER tumors exhibit increased HER2 signaling evidenced by increased expression of pHER3 and pHER2, as well as increased downstream AKT phosphorylation compared to Pre-Cx VCaP xenografts. Similarly, there were increases in a constitutively active splice form of HER2, d16HER2, as tumors progressed. While transcription levels of the HER3 ligand, NRG1, did not increase globally with progression, there was a strong, but heterogeneous intratumoral expression of the ligand. Treatment of castration-resistant xenograft models with the covalent HER2 inhibitors afatinib and neratinib caused tumor regression while noncovalent inhibitor lapatinib did not. Finally, IHC staining of clinical metastatic CRPC biopsies identified colocalized pHER2/pHER3 staining in 18% of cases with an additional 8% of cases displaying positivity for pHER2 alone.

Conclusions: These results suggest that a subset of CRPC utilizes HER2 signaling and might respond to therapies targeting HER2. Significantly, tumors with upregulated HER2 signaling (possibly d16HER2-driven) show greater responses to irreversible inhibitors such as afatinib and neratinib. HER2 might still be a viable target in the CRPC setting with the use of more effective HER2 inhibition or better patient selection.

Conflicts of Interest: None

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