Aberrant HER2 signaling is a therapeutic target in a subset of castration-resistant prostate cancer

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Background

• While most men with metastatic prostate cancer (PCa) initially respond to androgen-deprivation therapy and second-line hormonal agents, resistance is ultimately universal and subsequent survival is limited.

• HER2 is a transmembrane receptor tyrosine kinase. HER2 dimerization (primarily with HER3) initiates signaling to promote cellular processes critical to survival, proliferation, and metastasis.

• HER2 signaling in PCa promotes androgen receptor (AR) transcriptional activity and contributes to persistent AR signaling in a subset of castration-resistant prostate cancer (CRPC).1,3

• Aberrant HER2 signaling in metastatic CRPC (mCRPC): HER2 amplification is rare in PCa, but increased HER2 mRNA expression is found in 10% of the Stand Up To Cancer (SU2C) mCRPC cohort.4

• In addition, the HER2 splice variant d16HER2, which results in a self-dimerizing, constitutively active protein, has been identified in 7% of mCRPC samples in the SU2C cohort and in circulating tumor cells from 6/15 (40%) patients with mCRPC (unpublished data).

• In a trial of neoadjuvant abiraterone at our institution, approximately 20% of abiraterone-resistant PCa showed increased HER2 signaling, as detected by phospho-ErbB3 immunohistochemistry (IHC).1

• Here, we present preclinical and clinical data to support signaling via canonical HER2/HER3 interactions and the d16HER2 variant as potential oncogenic drivers of CRPC. We also show preclinical evidence that enhanced HER2 signaling may be targeted with irreversible HER2-targeted inhibitors to inhibit tumor growth.

Methods

Preclinical Studies:

• Human-derived VCaP prostate cancer xenografts were serially biopsied prior to castration, at castration-resistance, and after resistance to abiraterone + enzalutamide (Abi/Enza).

• Biopsies were submitted for RNA sequencing and RT-PCR, IHC, and reverse-phase protein array (RPPA) for gene/protein expression changes.

• Castration-resistant VCaP and LuCaP-70CR xenografts were treated with reversible EGFR/HER2 tyrosine kinase inhibitor (TKI) lapatinib (100 mg/kg) or irreversible pan-HER TKIs afatinib (20 mg/kg) or neratinib (20 mg/kg).

Clinical Studies:

• Transcript levels of total HER2 and d16HER2 variant were determined for TCGA and SU2C PCa datasets.4,5

• IHC for phospho-HER2 (Tyr1221/1222) and phospho-HER3 (Tyr1289) (Tyr1289) were performed on metastatic samples from 49 heavily-treated mCRPC patients and compared to 18 hormone-naive patient prostatectomy samples.

HER2 TKIs Inhibit CRPC Growth

• Castration-resistant VCaP and LuCaP-70CR xenografts rapidly become resistant to lapatinib within 5 days, while irreversible pan-HER TKI inhibited tumor growth for at least 15 days.

Conclusions

• HER2 overexpression and d16HER2 expression are associated with PCa progression, castration-resistance, and resistance to second-line hormonal therapy with abiraterone/enzalutamide.

• HER2-targeted therapy with irreversible TKIs is more effective at inhibiting CRPC growth than the reversible TKI lapatinib.

• Our data suggest that a subset of CRPC with aberrant HER2 signaling representing 20-25% of mCRPC patients may have molecularly treatable disease with HER2-targeted therapy.

• Further studies to investigate potential treatment with an irreversible pan-HER TKI such as neratinib in biomarker-selected mCRPC patients after resistance to abiraterone and/or enzalutamide is warranted.

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References

2. Shiota et al., Oncotarget 2015.
4. Robinson et al., Cell 2015.