Nature Reviews Urology | Published online 20 January 2016; doi:10.1038/nrurol.2016.12

PROSTATE CANCER

Co-targeting mTOR and AR-Vs is efficacious for CRPC

A group of researchers from the British Columbia Cancer Agency have demonstrated that targeting the mTOR pathway, and the full-length androgen receptor (FL-AR) and androgen receptor variants (AR-Vs) together, is effective at inhibiting castration-resistant prostate cancer (CRPC) cell growth *in vitro* and *in vivo*.

In vitro investigations using enzalutamide-resistant and androgen-independent LNCaP95 cells revealed that combined treatment with BEZ235 (an inhibitor of PI3K and mTOR) and EPI-002 (an AF-1 antagonist, which blocks the activity of FL-AR and truncated AR species) significantly reduced cell growth compared with each as a monotherapy. The same was also true of everolimus in combination with EPI-002. Treatment with BEZ235 in the absence of androgen increased levels of FL-AR, and UBE2C protein levels were reduced by EPI-002. BEZ235 monotherapy significantly increased the luciferase activity of PSA, ARR3 and probasin in androgen-treated cells, an effect that was blocked by both EPI-002 and enzalutamide. BEZ235 treatment in the presence of androgen did not increase FL-AR activity, but in LNCaP cells it significantly inhibited AR-N-terminal domain (AR-NTD) transactivation.

EPI-002 and enzalutamide reduced the expression of *KLK3*, *TMPRSS2* and *FKBP5*, which are FL-AR-regulated genes. BEZ235 increased androgen-induced and androgen-independent expression of *PSA* and in the absence of androgen EPI-002, but not enzalutamide, blocked this effect. Treatment with BEZ235 also induced a twofold increase in *AR-V7* levels in the absence of androgen; this increase was blocked by treatment with EPI-002.

In vivo, castrated mice with xenografted tumours treated with a combination of BEZ235 and EPI-002 had significantly reduced tumour volumes compared with mice given either as a monotherapy.

These results indicate that targeting both the mTOR pathway and the AR-NTD to inhibit FL-AR and AR-Vs could have a therapeutic advantage in treating CRPC.

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ORIGINAL ARTICLE Kato, M. *et al.* Co-targeting androgen receptor splice variants and mTOR signaling pathway for the treatment of castration-resistant prostate cancer. *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.CCR-15-2119 (2015)
FURTHER READING Lu, J., Van der Steen T. & Tindall, D.J. Are androgen receptor variants a substitute for the full-length receptor?. *Nat. Rev. Urol.* **12**, 137–144 (2015)