IN BRIEF

BLADDER CANCER

Budding prognostic technique for muscle-invasive bladder cancer

A retrospective study of 106 patients with muscle-invasive bladder cancer (MIBC) has shown that tumour budding is an independent predictor of cancer-specific mortality. Tumour buds were identified and quantified on radical cystectomy samples using the hot-spot method. Mean tumour bud count was 32.3 ± 25.9 buds, with 14 buds being the cut-off point according to the receiver operating characteristic. Mean survival for participants with ≤14 buds was 65.9 months, but survival for those with >14 buds was only 18.5 months ($P = 0.003$). In multivariable analysis, number of tumour buds was an independent predictor of mortality. Patients with >14 buds had a 2.27-fold increased risk of mortality and the risk of mortality increased progressively with the number of buds at a rate of 2% per bud. Thus, tumour budding could be used as a predictor of cancer-specific mortality in patients with MIBC.

ORIGINAL ARTICLE Lorenzo Soriano, L. et al. Tumor budding: prognostic value in muscle-invasive bladder cancer. *Urology* https://doi.org/10.1016/j.urology.2019.04.006 (2019)

PROSTATE CANCER

DDR pathway mediates radiosensitization in prostate cancer

New research shows that enzalutamide radiosensitizes both androgen-dependent and androgen-independent prostate cancer. In vitro, treatment with enzalutamide radiosensitized 22Rv1 and DU145 cells, causing decreased colony survival on irradiation. Enzalutamide plus radiation caused an increase in phosphorylated S1981 ATM and radiation-induced γH2AX and 53BP1 foci, suggesting enzalutamide inhibits repair of radiation-induced DNA double-strand breaks. In vivo, enzalutamide treatment plus irradiation caused a decrease in the size of LNCaP-derived xenograft tumours. In a castration-resistant prostate cancer model, enzalutamide plus radiation significantly reduced tumour progression. Enzalutamide plus radiation also inhibited proliferation in a patient-derived xenograft model of prostate cancer. These results suggest that the efficacy of prostate cancer treatment could be enhanced by concurrent administration of enzalutamide and radiotherapy.

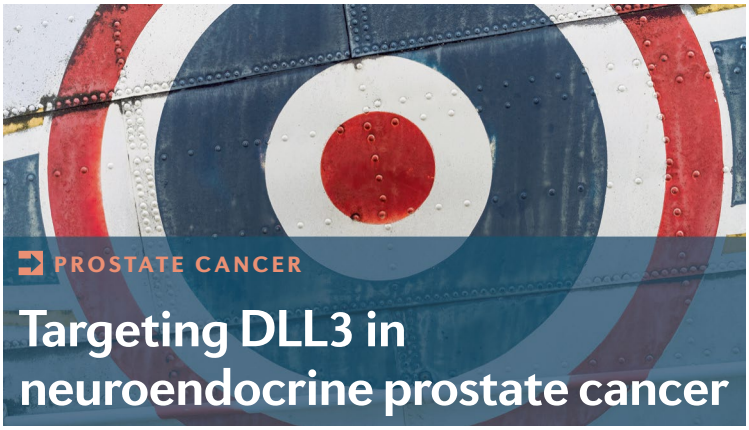
ORIGINAL ARTICLE Sekhar, K. R. et al. Radiosensitization by enzalutamide for human prostate cancer is mediated through the DNA damage repair pathway. *PLOS ONE* **14**, e0214670 (2019)

STONES

Risk of urolithiasis increased with testosterone replacement therapy

A population-based matched cohort study has shown that men who receive testosterone replacement therapy are at increased risk of developing stones. Data from the Military Health System Data Repository were analysed and overall 26,586 matched pairs were included. In total, 659 men who received testosterone replacement therapy experienced a stone-related event, compared with 482 men who did not have testosterone ($P < 0.0001$) at 2 years. No significant difference was observed on the basis of secondary polycythemia, an indirect indicator of increased testosterone levels while on treatment. This risk should be considered when prescribing testosterone.

ORIGINAL ARTICLE McClintock, T. R. et al. Testosterone replacement therapy is associated with an increased risk of urolithiasis. *World J. Urol.* https://doi.org/10.1007/s00345-019-02726-6 (2019)



Credit: RM/Alamy

PROSTATE CANCER

Targeting DLL3 in neuroendocrine prostate cancer

New data show that >75% of castration-resistant small-cell neuroendocrine prostate cancers (CRPC-NE) express the Notch ligand delta-like protein 3 (DLL3), which can be targeted by the antibody–drug conjugate SC16LD6.5 (rovalpituzumab tesirine). Treatment with this agent resulted in complete and durable responses in DLL3$^+$ prostate cancer xenograft models and clinical and radiological responses in a patient in a phase I basket trial.

Prostate cancer treatment with androgen receptor pathway inhibitors can result in drug resistance and the emergence of tumours with neuroendocrine features. These aggressive tumours have molecular similarities to small-cell lung cancers (SCLCs). SC16LD6.5 has shown promising efficacy in early-phase SCLC trials.

In this new study, the researchers investigated DLL3 expression of CRPC-NE and antitumour activity of SC16LD6.5 in DLL3-expressing prostate cancer models. First, the team evaluated DLL3 expression in different prostate tissues. None of the benign and only 0.52% of localized prostate cancer samples were DLL3$^+$. By contrast, 12.5% of CRPC adenocarcinomas and 76.6% of CRPC-NE expressed DLL3, and 10.37% and 63.95% of cells in these samples were DLL3$^+$, respectively. Survival analyses showed that patients with DLL3$^+$ tumours had worse overall survival both from the time of prostate cancer diagnosis (35 months versus 81.5 months) and from the time of metastasis (11.8 months versus 71.6 months).

The timing and mechanisms of neuroendocrine phenotype acquisition in prostate cancer remain unclear. In this study, the team evaluated temporal, intrapatient and interpatient heterogeneity of tumour DLL3 expression. In one patient, the primary tumour at diagnosis was DLL3$^-$, a metastatic bone CRPC adenocarcinoma sample 1 year before death was DLL3$^+$ and all metastases and the primary tumour at autopsy were highly DLL3$^+$ and had small-cell features, indicating acquisition of DLL3 expression with time and treatment resistance. Data from two other patients showed heterogeneity of DLL3 expression and/or small-cell features.

Using cell line and patient-derived prostate cancer xenograft models, the researchers observed complete responses at 35 days after a single dose of SC16LD6.5 in DLL3$^+$ models but no response in DLL3$^-$ models. Notably, in a patient with DLL3$^+$ neuroendocrine prostate cancer receiving SC16LD6.5 every 6 weeks in an ongoing phase I trial, target nodal metastases shrunk from 42 mm to 24 mm and nontarget lesions showed complete or partial responses after 1 treatment cycle, remaining stable and without new lesions after 2 cycles.

The team also tested whether circulating tumour cell (CTC) analysis might enable noninvasive detection of emerging DLL3 expression, which could inform trial eligibility. DLL3 expression status of CTCs and matched metastatic biopsy samples was concordant in 13 of 15 patients (87%).

Clemens Thoma

ORIGINAL ARTICLE Puca, L. et al. Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. *Sci. Transl Med.* **11**, eaav0891 (2019)
FURTHER READING Davies, A. H. et al. Cellular plasticity and the neuroendocrine phenotype in prostate cancer. *Nat. Rev. Urol.* **15**, 271–286 (2018)