IN BRIEF

BPH

Steaming ahead with BPH therapy

The 4-year outcomes of a trial of water vapour therapy using the Rezūm system for lower urinary tract symptoms (LUTS) caused by BPH have been reported. In this randomized, controlled trial, mean International Prostate Symptom Score improvement at the 4-year follow-up point was consistent with the 3-month outcomes at 46.7%. Surgical retreatment rate was 4.4% and no changes in sexual function occurred. Improvements in incontinence scores were maintained over the 4 years. The results of this trial show that the Rezūm system is effective for symptomatic relief of LUTS in men with BPH.

ORIGINAL ARTICLE McVary, K. T., Rogers, T. & Roehrborn, C. G. Rezūm water vapor thermal therapy for lower urinary tract symptoms associated with benign prostatic hyperplasia: 4-year results from randomized controlled study. *Urology* https://doi.org/10.1016/j.urology.2018.12.041 (2019)

BLADDER CANCER

Therapy affected by tumour microenvironment

Gene expression profiling of muscle-invasive bladder cancer (MIBC) could aid treatment selection for patients with this disease. Increased immune infiltration in tumours was associated with improved disease-specific survival (DSS) in patients treated with trimodality therapy. However, increased stromal infiltration was associated with reduced DSS in patients who received neoadjuvant therapy and radical cystectomy. These results suggest that the tumour microenvironment influences treatment outcomes in MIBC.

ORIGINAL ARTICLE Efstathiou, J. A. et al. Impact of immune and stromal infiltration on outcomes following bladder-sparing trimodality therapy for muscle-invasive bladder cancer. *Eur. Urol.* https://doi.org/10.1016/j.eururo.2019.01.011 (2019)

PROSTATE CANCER

PSMA ADC shows promise in advanced disease

Results of the first-in-man, dose-escalation study of a prostate-specific membrane antigen antibody–drug conjugate (PSMA ADC) have been reported. This therapy is designed to bind to $PSMA^+$ cells specifically, internalize and release the drug into the cell. PSMA ADC has shown promise in preclinical models. In this study, the conjugate showed antitumour activity at doses ≤2.5 mg/kg in a cohort of 52 men with metastatic castration-resistant prostate cancer (mCRPC) and toxic effects were acceptable. Thus, this new therapy has promise for treating mCRPC.

ORIGINAL ARTICLE Petrylak, D. P. et al. Phase 1 study of PSMA ADC, an antibody-drug conjugate targeting prostate-specific membrane antigen, in chemotherapy-refractory prostate cancer. *Prostate* https://doi.org/10.1002/pros.23765 (2019)

BLADDER CANCER

Treatment timing well tolerated in bladder cancer

Pembrolizumab can be safely combined with either sequential or concomitant stereotactic body radiotherapy (SBRT) for treating metastatic urothelial carcinoma. New data from a randomized phase I trial reported no dose-limiting toxic effects or grade 4 or 5 adverse events for either combination; one grade 3 adverse event occurred in the concomitant SBRT arm. Overall response rates were 0% and 44.4% in the sequential arm and the concomitant arm, respectively, but the trial was not powered to compare efficacy between treatment arms. Overall, pembrolizumab plus SBRT was well tolerated for treating metastatic urothelial carcinoma.

ORIGINAL ARTICLE Sundahl, N. et al. Randomized phase 1 trial of pembrolizumab with sequential versus concomitant stereotactic body radiotherapy in metastatic urothelial carcinoma. *Eur. Urol.* https://doi.org/10.1016/j.eururo.2019.01.009 (2019)

PROSTATE CANCER

Emerging role for the unfolded protein response

The unfolded protein response (UPR), a survival mechanism induced by endoplasmic reticulum (ER) stress, has been implicated in prostate cancer, but the precise mechanisms are unclear. A new study now reports a novel, therapeutically targetable link between the UPR and MYC oncogene signalling.

A key route of UPR activation is inositol requiring-enzyme 1α (IRE1α)-mediated mRNA splicing of X-box-binding protein 1 (*XBP1*) into XBP1 spliced (XBP1s), an active transcription factor that initiates a UPR transcriptional programme. Following observations that androgens activate IRE1α–XBP1s signalling in prostate cancer, Sheng et al. developed MKC8866, an IRE1α RNase-specific inhibitor that represses *XBP1* splicing. Functional characterization revealed that MKC8866 suppressed tumour initiation capacity in response to mild ER stress in vitro. In tumour xenograft mouse models, MKC8866 monotherapy potently inhibited tumour growth and, when combined with clinically approved drugs (abiraterone, enzalutamide and cabazitaxel), exhibited additive inhibitory or synergistic antitumour effects.

Mechanistic studies revealed that, in addition to the ER stress–UPR pathway, MYC signalling was among the most highly downregulated pathways following *XBP1* knockdown or MKC8866

PROSTATE CANCER

CRPC-specific gene therapy

Gene therapy that can target castration-resistant prostate cancer (CRPC) shows promising preclinical results when tested in vitro and in vivo. In the future, this therapy could be an alternative treatment option for men with this disease.

The virus-like particles (VLPs) of JC polyomavirus (JCPyV), which has been detected in human prostate cells, were used as a vector for a plasmid that was constructed using the PSA promoter so that expression of the thymidine kinase suicide gene only occurred in androgen receptor $(AR)^+$ prostate cancer cells; this plasmid was called PSAtk-VLP.

Confirmation that JCPyV VLPs could enter CRPC cells was obtained using VLPs packaged with green fluorescent protein (GFP) and fluorescence microscopy of treated 22Rv1 cells. The transcriptional targeting of plasmids containing the PSA promoter and GFP was tested using different cell lines, including lung adenocarcinoma, neuroblastoma, bladder cancer and two prostate cancer cell lines: an AR^- cell line (PC3) and 22Rv1 cells, which are AR^+. Fluorescence microscopy showed that the PSA promoter was activated and GFP expression induced only in 22Rv1 cells, owing to the reliance of PSA promoter activation on AR signalling.

Cytotoxic effects were seen only in 22Rv1 cells transfected with a plasmid containing the PSA enhancer–promoter fragment and the thymidine kinase suicide gene treated with ganciclovir and not in other cancer cell types. Similarly, the cytotoxicity of PSAtk-VLPs was specific to 22Rv1 cells on transfection and treatment with ganciclovir.

In vivo, GFP-containing VLPs reached the 22Rv1 cell-derived tumour xenograft site and gene expression was induced after tail vein injection in a mouse model of CRPC, showing that delivery via the blood is feasible. In this xenograft model, tail vein