IN BRIEF

PROSTATE CANCER

Mismatch mutations: aggressive but sensitive

A retrospective study has investigated the characteristics of patients with metastatic prostate cancer with germline and somatic mismatch repair (MMR) mutations. These patients demonstrated surprisingly durable responses to standard hormonal therapies and 50% of men who received PD-1 inhibitors also demonstrated a >50% PSA response at 12 weeks. Thus, despite being an aggressive tumour type, MMR-mutated advanced prostate tumours also seem to be particularly sensitive to hormonal and anti-PD-1 therapy.

ORIGINAL ARTICLE Antonarakis, E. S. et al. Clinical features and therapeutic outcomes in men with advanced prostate cancer and DNA mismatch repair gene mutations. *Eur. Urol.* https://doi.org/10.1016/j.eururo.2018.10.009 (2018)

BLADDER CANCER

MicroRNA signature aids diagnosis

MicroRNAs (miRNAs) in urine have potential for noninvasive diagnosis of bladder cancer. Expression of 384 different miRNAs was analysed in urine samples from patients with bladder cancer. After elimination, six miRNAs (let-7c, miR-135a, miR-135b, miR-148a, miR-204 and miR-345) were identified that distinguished cancer from controls with an AUC of 92.9%. Together these miRNAs could be used as a signature for bladder cancer diagnosis from urine samples.

ORIGINAL ARTICLE Hofbauer, S. L. et al. A urinary microRNA (miR) signature for diagnosis of bladder cancer. *Urol. Oncol.* https://doi.org/10.1016/j.urolonc.2018.09.006 (2018)

INCONTINENCE

Mirabegron MIRACLE cure for male incontinence?

The MIRACLE study is a randomized, double-blind, placebo-controlled, parallel comparison phase IV study to test the effect of mirabegron in men with overactive bladder (OAB). In total, 464 men were randomized to receive 50 mg of mirabegron or placebo. The change in mean number of micturition episodes was similar between groups, but significant improvements were observed in various OAB symptom scores. No significant adverse effects were associated with mirabegron treatment.

ORIGINAL ARTICLE Shin, D. G. et al. Mirabegron as a treatment for overactive bladder symptoms in men (MIRACLE study): efficacy and safety results from a multicenter, randomized, double-blind, placebo-controlled, parallel comparison phase IV study. *Neurourol. Urodyn.* https://doi.org/10.1002/nau.23852 (2018)

PROSTATE CANCER

AR variants in CTCs correlate with outcomes

Expression of the androgen receptor (AR) splice variants (AR-Vs) AR-V7 and ARv567es has been noted in circulating tumour cells (CTCs) in men with prostate cancer. Using a novel digital droplet PCR assay, AR-Vs were assessed in CTCs of patients receiving docetaxel or cabazitaxel in the TAXYNERGY trial. Overall, 67% of patients were AR-V7$^+$, 42% were ARv567es$^+$, 54% were double positive and 9% were double negative. PSA50 response rates were higher in variant-negative men than variant-positive men for both AR-Vs. Median progression-free survival was 12.02 months for AR-V7$^-$ men versus 8.48 months in AR-V7$^+$ men, and 12.71 months for ARv567es$^-$ patients versus 7.29 months in ARv567es$^+$ patients. Expression of AR-Vs in CTCs influences outcomes with taxane therapy, and absence of both variants is associated with maximal responses.

ORIGINAL ARTICLE Tagawa, S. T. et al. Expression of AR-V7 and ARv567es in circulating tumor cells correlates with outcomes to taxane therapy in men with metastatic prostate cancer treated in TAXYNERGY. *Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-18-0320 (2018)

KIDNEY CANCER

Hyperpolarized MRI illustrates metabolic response to therapy

A recent article in *Cancer Research* has described the use of an integrated platform using [1-^{13}C]pyruvate combined with hyperpolarized MRI to visualize the in vivo effect of mTOR inhibition in metastatic clear cell renal cell carcinoma (ccRCC).

The manipulation of metabolic processes by malignant cells — in particular the Warburg effect, whereby oxidative phosphorylation is rerouted through anaerobic glycolysis — is a hallmark of cancer. The PI3K–mTOR axis controls glycolysis via both transcriptional and post-translational modification of glycolytic enzymes; thus, the effects of drugs that interrupt the pathway ought to be visible using imaging to visualize glycolytic flux.

Dong and colleagues used an integrated hyperpolarized MRI technique to investigate the effect of mTOR inhibition in vitro and in vivo on patient-derived xenograft models and ccRCC JHRCC12 and JHRCC228 cell lines.

First, cell lines were treated with rapamycin, in order to determine whether they were sensitive to mTOR inhibition. Cellular proliferation was suppressed in both JHRCC12 and JHRCC228 models in vitro illustrating on-target inhibition, although a complete response to rapamycin was observed in JHRCC228 cells, whereas JHRCC12 demonstrated only a partial, dose-dependent response.

Previous data show that with targeted inhibition of signalling pathways, changes in hyperpolarized lactate in vivo act as noninvasive indicators of early changes in tumour metabolism. Accordingly, T2-weighted ^{1}H images with corresponding HP MRI overlay

PROSTATE CANCER

A new class of AR antagonists?

Development of a novel class of androgen receptor (AR) antagonists, which seem to be active even in the presence of AR mutations, has been described in a recent study.

AR antagonists are a common therapeutic option for men with prostate cancer; however, many cancers become resistant and the presence of mutant ARs in some patients means that tumours can bypass inhibition. AR antagonists with novel structures could help to prevent this problem.

Roell and colleagues analysed compounds based on methyl anthranilate, an extract of the saw palmetto plant that has previously been shown to antagonize the AR. Structure–activity relationships were assessed using the androgen-dependent prostate cancer cell line LNCaP, which was treated with the compounds alone to analyse AR activation and also in combination with an AR agonist (R1881) to investigate AR antagonism.

Several of the compounds were able to bind to and inhibit the effect of R1881, with activity varying with chemical structure. As the AR antagonists currently in use are halogenated, the authors investigated the effects of halogen-substituted anthranilic acid esters. Halogen substitution at the benzene ring of the lead structure considerably increased the inhibitory effect.

In addition to antagonism of R1881, some compounds also antagonised AR in competition with DHT and could inhibit wild-type AR and AR mutants. In particular, one compound (28) inhibited not only the wild-type AR but also the AR-mutants AR-T877A, AR-F876L and AR-W741C. By contrast, enzalutamide treatment activated AR-F876L, suggesting that compound 28 acts via a different mechanism to enzalutamide.

Treatment of LNCaP cells with putative antagonist compounds reduced cell growth, probably by inducing senescence, as suggested