IN BRIEF

PROSTATE CANCER

New nonsteroidal compound for treating CRPC

ODM-204 is a novel nonsteroidal compound that has a dual mechanism of action against CYP17A1 and AR. In vitro, ODM-204 inhibited proliferation of VCaP and LNCaP cells. In vivo, oral administration of this compound significantly reduced VCaP xenograft tumour growth in mice. Oral ODM-204 showed potent inhibition of steroid biosynthesis in rats and monkeys. These data formed the basis of the DUALIDES first-in-man study of ODM-204 in castration-resistant prostate cancer (CRPC).

ORIGINAL ARTICLE Oksala, R. et al. Discovery and development of ODM-204: a novel nonsteroidal compound for the treatment of castration-resistant prostate cancer by blocking the androgen receptor and inhibiting CYP17A1. *J. Steroid Biochem. Mol. Biol.* https://doi.org/10.1016/j.jsbmb.2018.02.004 (2018)

PROSTATE CANCER

Pembrolizumab effective in PD-L1-positive disease

The results of the nonrandomized phase Ib KEYNOTE-028 trial of pembrolizumab in advanced solid tumours have been reported. Eligibility criteria were advanced prostate adenocarcinoma, unsuccessful standard therapy, measurable disease using RECIST 1.1, and PD-L1 expression in ≥1% of tumour or stroma cells. In total, 23 patients were included, 4 of whom had partial responses and 8 of whom had stable disease. Median progression-free survival was 3.5 months and median overall survival was 7.9 months. The adverse effect profile was acceptable, with 14 men experiencing treatment-related adverse events.

ORIGINAL ARTICLE Hansen, A. R. et al. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. *Ann. Oncol.* https://doi.org/10.1093/annonc/mdy232 (2018)

KIDNEY CANCER

PEERfect scores for RCC

Investigators have identified and validated the peak early-phase enhancement ratio (PEER) radiographic measurement for accurately differentiating CD117$^+$ renal oncocytoma from CD117$^+$ chromophobe renal cell carcinoma (RCC). Retrospective analysis revealed the most reliable variable for tumour differentiation was the tumor:cortex PEER using multiphase CT. In prospective validation, PEER had 100% accuracy in differentiating tumours.

ORIGINAL ARTICLE Amin, J. et al. Identification and validation of radiographic enhancement for reliable differentiation of CD117(+) benign renal oncocytoma and chromophobe renal cell carcinoma. *Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-18-0252 (2018)

KIDNEY CANCER

Germline mutations in RCC

A new study published in *JAMA Oncology* has assessed the prevalence of cancer-related germline mutations in 254 patients with advanced renal cell carcinoma (RCC). Overall, 41 participants had germline mutations, 14 of whom had mutations in syndromic RCC-related genes; the most frequently mutated genes were *CHEK2* and *FH*. Patients with non-clear-cell RCC were more likely to have an RCC-associated gene mutation and 10.0% of these patients had a mutation that could aid therapy decisions. Clinical guidelines for genetic testing would have missed 37.5% of patients with RCC-associated gene mutations.

ORIGINAL ARTICLE Carlo, M. I. et al. Prevalence of germline mutations in cancer susceptibility genes in patients with advanced renal cell carcinoma. *JAMA Oncol.* https://doi.org/10.1001/jamaoncol.2018.1986 (2018)

KIDNEY CANCER

Oncometabolite mechanism unravelled

Building on observations that L-2-hydroxyglutarate (L-2-HG) levels are often elevated in renal cell carcinoma (RCC) owing to loss of L-2-HG dehydrogenase (L2HGDH), a new study now offers mechanistic insight into this oncometabolite.

The authors first investigated the contribution of L-2-HG to malignant phenotypes through pharmacological or genetic modulation of L2HGDH expression. In non-transformed renal epithelial cells, L2HGDH knockdown and treatment with L-2-HG octyl ester markedly increased cell proliferation and migration. Conversely, genetic restoration of L2HGDH expression in RCC cells reduced migration in vitro and suppressed tumour growth in xenograft mouse models.

The mechanisms underpinning L-2-HG accumulation in the context of L2HGDH loss were then investigated. Biochemical studies in L2HGDH-deficient RCC cells indicated that L-2-HG is generated by the direct reduction of α-ketoglutarate (α-KG) via malate dehydrogenase 2 (MDH2) and that glutamine (rather than glucose) is the predominant carbon source for α-KG and, therefore, L-2-HG. Accordingly, glutaminase inhibition and MDH2 knockdown substantially reduced RCC cell migration in an L-2-HG-dependent manner, and glutaminase inhibition suppressed tumour growth in vivo, suggesting that the glutamine–MDH2 axis promotes L-2-HG accumulation and aggressive phenotypes.

Interestingly, transcriptomic and functional experiments revealed that

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PROSTATE CANCER

miR-96 influences RARγ expression

The microRNA (miR)-96–retinoic acid receptor-γ (RARγ) signalling axis influences androgen receptor (AR) signalling and disease progression in prostate cancer, according to new research.

"We undertook pancancer analyses using TCGA data of the nuclear receptor superfamily and found that RARγ was uniquely and commonly downregulated in prostate cancer," explains Moray Campbell, corresponding author.

RARγ knockdown in nonmalignant and malignant prostate cancer cell lines increased cell viability and substantially altered gene expression in the absence of exogenous ligand. Further analysis showed that RARγ function regulates the function of AR. Chromatin immunoprecipitation sequencing showed that the RARγ cistrome is enriched at active enhancers of genes that are enriched for AR binding and are associated with aggressive disease.

In nonmalignant cells, stable knockdown of RARγ resulted in inhibition of the antiproliferative effects of dihydrotestosterone (DHT) treatment and reduced the sensitivity of the DHT-dependent transcriptome, specifically in AR target genes and genes that interact with the AR pathway.

In silico prediction identified the miR-96-182-183 cluster as one of the most commonly upregulated in prostate cancer. In vitro, miR-96 levels were increased and *RARG* levels reduced in malignant cells. miR-96 overexpression reduced RARγ levels (which was reversed by antagomiR-96 treatment in combination with an miR-96 mimic) and increased cell viability. In a mouse model, *Rarg* expression reduced and miR-96 expression increased in line with prostate