IN BRIEF

PROSTATE CANCER

SBRT suitable for early-stage disease

A multicentre study assessed toxicity and survival end points following dose-escalated prostate stereotactic body radiotherapy (SBRT) in 309 patients with low-risk or intermediate-risk prostate cancer. At a median follow-up period of 61 months, rates of grade 3 or higher genitourinary adverse events (AEs) were low (1.3%), and no grade 4 or 5 AEs occurred. The 5-year overall survival and biochemical disease-free survival compared favourably to historical controls.

ORIGINAL ARTICLE Meier, R. M. et al. Multi-center trial of stereotactic body radiotherapy for low- and intermediate-risk prostate cancer: survival and toxicity endpoints. *Int. J. Radiat. Oncol. Biol. Phys.* https://doi.org/10.1016/j.ijrobp.2018.05.040 (2018)

URINARY INCONTINENCE

Mirabegron and solifenacin for OAB

The randomized phase III SYNERGY II study is the first to assess the long-term safety and therapeutic efficacy of mirabegron plus solifenacin versus each monotherapy for overactive bladder (OAB). Over 12 months, the combination was well tolerated, with only a slightly higher frequency of treatment-related adverse events in the combination arm compared with mirabegron and solifenacin alone (49% versus 41% versus 44%, respectively). The combination significantly reduced the mean number of incontinence episodes and micturitions compared with each monotherapy.

ORIGINAL ARTICLE Gratzke, C. et al. Long-term safety and efficacy of mirabegron and solifenacin in combination compared with monotherapy in patients with overactive bladder: a randomised, multicentre phase 3 study (SYNERGY II). *Eur. Urol.* https://doi.org/10.1016/j.eururo.2018.05.005 (2018)

PROSTATE CANCER

Efficacy of a PARP inhibitor combination

A randomized phase II trial reports the clinical efficacy of poly(ADP-ribose) polymerase (PARP) inhibitor olaparib combined with abiraterone in metastatic castration-resistant prostate cancer. At a cut-off date in September 2017, median radiographic progression-free survival was significantly longer in the abiraterone plus olaparib group than in the abiraterone plus placebo group (13.8 versus 8.2 months; HR 0.65, 95% CI 0.44–0.97, $P = 0.034$). Regarding safety, patients receiving the combination therapy had more grade 3 or worse and serious adverse events than those in the placebo arm.

ORIGINAL ARTICLE Clarke, N. et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.* https://doi.org/10.1016/S1470-2045(18)30365-6 (2018)

KIDNEY CANCER

Pazopanib exposure associated with outcomes

A retrospective analysis of the phase III PROTECT study evaluated the relationship between pazopanib exposure in the adjuvant setting and clinical outcomes in renal cell carcinoma. Multivariate analyses revealed that high early (week 3 or 5) or late (week 16 or 20) pazopanib trough concentrations (C_{trough}) were significantly associated with improved disease-free survival ($P = 0.000758$ and $P = 0.000496$, respectively). Notably, the proportion of adverse event (AE)-related discontinuations or grade 3 or 4 AEs (except hypertension) did not correlate with C_{trough}.

ORIGINAL ARTICLE Sternberg, C. N. et al. Pazopanib exposure relationship with clinical efficacy and safety in the adjuvant treatment of advanced renal cell carcinoma. *Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-17-2652 (2018)

PROSTATE CANCER

A new role for ERG

A previously undefined function of *ERG* has been reported in prostate cancer. In the context of *PTEN* and *TP53* alterations when *RB1* is unaltered, ERG can restrict lineage plasticity and maintain antiandrogen sensitivity. Thus, evaluation of concomitant *ERG* fusion status, *PTEN*, *TP53*, and *RB1* alterations could aid treatment strategy.

Data from TCGA revealed considerable co-occurrence of *PTEN* and *TP53* deletions or mutations with *ERG* fusions in men with primary prostate cancer, suggesting that *ERG* fusions cooperate with *PTEN* and *TP53* alteration in AR-positive prostate cancer. Genetically engineered mice with a combination of these alterations were created to analyse this theory.

Double-mutant (*Pten* deletion and *Trp53* deletion and mutation) and double-knockout (*Pten* and *Trp53* deletion) mice developed well-differentiated adenocarcinoma with high AR expression at 8–10 weeks. By 16–20 weeks, AR expression had dramatically reduced in 90% of mice, along with levels of KRT, whereas levels of vimentin had increased. By contrast, 50% of triple-mutant mice (*Pten* deletion, *Trp53* deletion and mutation, and transgenic *ERG*) had well-differentiated AR^{high}–KRT^{high} adenocarcinomas and 50% had AR^{low}–KRT^{low} tumours at 16–20 weeks. AR^{low}–KRT^{low} tumours lacked transgenic *ERG* expression. AR^{high}–KRT^{high} tumours in triple-mutant mice had reduced RB phosphorylation and expression of cell lineage regulators associated with epithelial–mesenchymal transition. RNA-sequencing showed that *ERG* expression upregulated AR pathway genes and luminal lineage genes and downregulated cell cycle and mesenchymal and neuroendocrine lineage genes.

INFECTION

Chlamydia paralyses neutrophils via CPAF

A novel mechanism by which *Chlamydia trachomatis* can evade the human innate immune system has been identified, according to a paper in *Nature Microbiology*.

Neutrophils internalize and kill pathogens via formation of neutrophil extracellular traps (NETs), which capture microbes and prevent spread. Rajeeve and colleagues infected human polymorphic nuclear leukocytes (PMNs) with *Chlamydia* and *Neisseria gonorrhoeae*. Infection of PMNs with *N. gonorrhoeae* triggered NET formation, but NET formation did not occur when PMNs were infected with *Chlamydia*. Interestingly, neutrophils pre-infected with *Chlamydia* did not form NETs and PMN killing of *N. gonorrhoeae* was reduced, suggesting that *Chlamydia* infection prevents *N. gonorrhoeae*-induced neutrophil activation.

This effect could be via the pathogenicity factor chlamydial protease-like activating factor (CPAF). Unlike the wild-type pathogen, infection of PMNs with CPAF-mutant *C. trachomatis* induced NET formation. The mutant pathogen has previously been shown to be less infective than wild-type chlamydia, but even at a low multiplicity of infection (MOI), the CPAF-mutant pathogen induced NETs. Next, the wild-type and CPAF-mutant *Chlamydia* were exposed to PMNs and the PMN lysates used to infect HeLa cells. Survival of wild-type *Chlamydia* after neutrophil attack was increased compared with the mutant, and infection of HeLa cells was only effective using wild-type lysates, suggesting that CPAF absence enables clearance of the primary infection.

Use of GFP–*Chlamydia* showed that it replicated and was biosynthetically