PROSTATE CANCER

CRYO COMBO
AUGMENTS ICI

Cryoablation could be used to augment the effect of immune checkpoint inhibition (ICI) in prostate cancer, according to a preclinical study.

ICI has shown only moderate efficacy in prostate cancer, despite FDA approval in other malignancies. However, an abscopal effect has been proposed. Benzon and colleagues studied this potential effect using a combination of cryoablation and ICI. After establishing synchronous grafts in FVB/NJ mice, the mice received anti-PD1 (10 mg/kg), anti-CTLA4 (1 mg/kg), or a control antibody with or without adjuvant cryoablation of the larger tumour graft and with or without neoadjuvant degarelix. Although cryoablation of the larger tumour delayed growth acceleration in the untreated graft, with a nearly eightfold reduction in mortality, the combination of PD1 blockade and cryoablation did not have a synergistic effect compared with cryoablation alone. However, cryoablation did seem to synergize with anti-CTLA4, delaying growth acceleration and decreasing mortality fourfold compared with cryoablation alone. Depletion of CD3⁺ or CD8⁺ cells completely neutralized the beneficial effects of the combination, suggesting that the effect is T cell-dependent. Trimodal therapy using degarelix, PD1 blockade, and cryoablation almost doubled tumour growth delay and survival in 25% of treated mice compared with bimodal therapy with degarelix and cryoablation, also in a T cell-dependent manner.

Further studies will determine whether trimodal therapy (androgen ablation, cryoablation, and PD1 blockade), or combined cryoablation and low-dose anti-CTLA4, could have a role in prostate cancer treatment.

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ORIGINAL ARTICLE Benzon, B. et al. Combining immune check-point blockade and cryoablation in an immunocompetent hormone sensitive murine model of prostate cancer. *Prostate Cancer Prostatic Dis.* 21, 126–136 (2018)

SEXUAL DYSFUNCTION

Treating vulvovaginal symptoms

New data, published in *JAMA Internal Medicine*, show that treatment with either vaginal oestradiol tablets or vaginal moisturizer is no better than placebo for relieving vulvovaginal symptoms in postmenopausal women. Thus, shared decision making regarding treatment of these symptoms should consider cost and patients' formulation preference.

This randomized, double-blind, placebo-controlled trial was conducted over 12 weeks in two centres. In total, 302 postmenopausal women reporting at least one moderate-to-severe symptom of vulvovaginal itching, pain, irritation, or dryness at least weekly within the previous 30 days were recruited. Participants were randomly assigned 1:1:1 to receive vaginal oestradiol tablets plus placebo gel, placebo tablets plus vaginal moisturizer, or placebo tablets plus placebo gel. Primary outcome was severity of

most bothersome symptom defined by the participant at enrolment.

Overall, 294 women provided data for primary analysis. Neither treatment reduced most bothersome symptom severity between baseline and 4 or 12 weeks more than placebo. Mean decreases at 12 weeks were 1.2 points to 1.4 points from baseline most bothersome symptom score for all groups. At the clinically meaningful decrease of two points or more, no differences between treatment and placebo were seen. Moreover, no differences between groups were observed in Female Sexual Function Index score (either in total or in any of the six domains). At the beginning of the trial, nearly all women were either frequently or always distressed about sex life. At 12 weeks, almost half of participants were rarely or never distressed. Women in all trial arms reported similar mean treatment satisfaction, but more women who received

“At the clinically meaningful decrease of two points or more, no differences between treatment and placebo were seen.”

PROSTATE CANCER

Macropinocytosis
for proliferation

PTEN-deficient prostate cancer cells survive and proliferate in low-nutrient environments by using macropinocytosis to scavenge extracellular proteins and necrotic debris, according to a new study.

Anabolism and proliferation of cancer cells is fuelled by the upregulation of nutrient acquisition pathways, but as tumours grow, nutrients become limited and tumour necrosis can occur. “Activating mutations in Ras confer resistance to nutrient stress by stimulating scavenging of extracellular protein via macropinocytosis,” says Aimee Edinger, an author on the new paper. “PI3K activity is necessary for macropinocytosis downstream from Ras, and so we hypothesized that prostate cancer cells deficient in PTEN (which opposes the PI3K pathway) might also exhibit macropinocytosis and resistance to nutrient stress.”

“increased uptake was consistent with internalization via macropinocytosis”

The researchers showed that neither PTEN-knockout nor PTEN-wild-type murine embryonic fibroblasts (MEFs) took up the macropinocytotic cargos dextran and bovine serum albumin (BSA) in complete medium. However, in low-nutrient medium, dextran and BSA uptake was greatly increased in PTEN-knockout MEFs. The increased uptake was consistent with internalization via macropinocytosis.

The study also showed that PTEN loss alone is not enough to drive macropinocytosis: AMPK activation is also needed for PTEN-deficient MEFs to form macropinosomes and proliferate