

Nature Reviews Clinical Oncology **11**, 123 (2014); published online 11 February 2014;
 doi:10.1038/nrclinonc.2014.23;
 doi:10.1038/nrclinonc.2014.24;
 doi:10.1038/nrclinonc.2014.22

IN BRIEF

BREAST CANCER

Enzalutamide—a new treatment for ER-positive disease

The androgen receptor (AR) is expressed widely in breast cancer and has been proposed as a therapeutic target in patients who do not express the oestrogen receptor (ER). However, its role in women with ER-positive tumours is uncertain. The AR inhibitor, enzalutamide, exerts its effects by preventing nuclear localization of the AR. Now, a study in 192 women with ER-positive breast cancer has shown that the AR:ER ratio is a significant predictive factor for risk of breast cancer. A high AR:ER ratio demonstrated a fourfold increased risk of failure to respond to tamoxifen treatment, and the AR:ER ratio was an independent predictor of disease-free survival and disease-specific survival. In breast cancer xenograft models, enzalutamide was also shown to inhibit oestradiol-mediated cell growth, indicating that this agent could be used to treat AR-positive tumours, regardless of the ER status.

Original article Cochrane, D. R. *et al.* Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. *Breast Cancer Res.* doi:10.1186/bcr3599

PANCREATIC CANCER

Frondoside A enhances the effects of gemcitabine

Pancreatic cancer has a very poor prognosis. Gemcitabine is the current standard therapy, but more-effective treatments are needed. A study in human pancreatic cancer cell lines has shown that the triterpenoid, frondoside A, when combined with gemcitabine, could serve as a promising new treatment approach for treatment of this disease. In an athymic mouse model, tumour growth was significantly reduced with the gemcitabine–frondoside A combination compared with either drug alone, even when gemcitabine was used at the lowest dose tested (4 mg/kg). These results indicate that this combination might provide clinical benefit in patients.

Original article Al Shemali, J. *et al.* Frondoside A enhances the antiproliferative effects of gemcitabine in pancreatic cancer. *Eur. J. Cancer* doi:10.1016/j.ejca.2014.01.002

BREAST CANCER

Overcoming resistance with dual HER2 blockade

Although many treatment advances in breast cancer have been made, resistance inevitably develops. Activating mutations in *PIK3CA* that occur in patients with *HER2* amplification can often confer resistance to anti-*HER2* therapies. Using the SNaPshot assay, researchers have identified ‘hotspot’ *PIK3CA* mutations in cells resistant to the *HER2* inhibitor lapatinib. They showed that the *PIK3CA* mutations partially uncouple PI3K signalling from *HER2*, and that resistance could be overcome by using the pan-PI3K inhibitor BKM120. In mice with *HER2*-amplified tumours, dual *HER2* blockade with trastuzumab and lapatinib resulted in tumour regression, and the addition of BKM120 further improved tumour regression. The combination of PI3K inhibition with dual *HER2* blockage seems to circumvent resistance to *HER2* inhibitors, providing a rationale to further explore this strategy.

Original article Rexer, B. N. *et al.* Direct inhibition of PI3K in combination with dual *HER2* inhibitors is required for optimal antitumor activity in *HER2*+ breast cancer cells. *Breast Cancer Res.* doi:10.1186/bcr3601