378 Invited

Targeting ER and signalling pathway

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The last few years has seen a significant increase in the number of novel targeted therapeutic agents entering clinical development for breast cancer. These have followed in the footsteps of targeted endocrine therapies against ER which since the 1980's have contributed to significant gains in breast cancer survival. HER2 targeted therapies (ie trastuzumab) have delivered significant improvements in disease-free and overall survival in early breast cancer. However, not all HER2 positive cancers respond to this therapy, and several approaches are now being developed to enhance blockade of HER2 signalling and overcome trastuzumab resistance. Promising strategies include improved antibodies (ie. 2C4 or pertuzumab) that bind at different extracellular sites to disrupt HER2 hetero-dimerisation, HSP90 inhibitors (ie. 17-AAG) that interfere with client HER2 protein processing, or small molecule tyrosine kinase inhibitors (ie. lapatinib) that target both HER2 and EGFR. Another important area of translational breast cancer research has been the use of various signal transduction inhibitors (STIs) to enhance the benefit of endocrine therapy that targets ER, specifically by overcoming and/or preventing de-novo/acquired resistance. The recognition of the role played by EGFR and HER2 in cross-talk activation of ER signalling has been confirmed by pre-clinical studies showing that various STIs give additive or synergistic effects when combined with endocrine agents. Activation of the PI3-K/Akt pathway has also been associated with resistance to either estrogen deprivation or tamoxifen, and inhibitors of mTOR (a downstream target of Akt) can restore tamoxifen sensitivity in breast cancer cells. Inhibitors of IGFR which activates Akt cell survival pathways are also in early stage development for breast cancer. Strategies to combine endocrine agents with various targeted therapies are being explored in both early stage (neoadjuvant) and metastatic settings. The EGFR tyrosine kinase inhibitor gefitinib combined with the aromatase inhibitor anastrozole for 4−6 weeks induced greater inhibition of Ki-67 than with gefitinib alone in a double-blind placebo controlled pre-operative study in 56 women with ER+ve and EGFR+ve primary breast cancer. In metastatic disease a randomised phase II study (TAnDEM) has reported that the addition of trastuzumab to the aromatase inhibitors anastrozole significantly improved time to disease progression in ER+ve HER+ve advanced breast cancer. A phase III study of the mTOR inhibitor temsirolimus with letrozole in metastatic disease was stopped early due to lack of efficacy over letrozole alone, although a neoadjuvant study of RAD-001 (everolimus) with/without letrozole recently reported some additional benefit for the combination. Biomarker studies associated with these trials remain important in attempting to select appropriate patients for these novel targeted agents, especially for the combination of STIs with ER targeting. Ongoing studies in both advanced breast cancer and in the pre-operative setting continue to study the pharmacodynamic effects of these novel agents, in particular trying to define molecular signatures that may predict response.

379 Invited

Targeting HER family

Abstract not received.

380 Invited

Synthetic lethal approaches to the treatment of cancers with DNA repair defects

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About one in nine women in the Western world develop cancer of the breast and at least 5% of these cases are thought to result from a hereditary predisposition to the disease. Two breast cancer susceptibility (BRCA) genes have been identified and mutations in these genes account for most families with four or more cases of breast cancer diagnosed before the age of 60. Women who inherit loss-of-function mutations in either of these genes have an up to 85% risk of breast cancer by age 70. As well as breast cancer, carriers of mutations in BRCA1 and BRCA2 are at elevated risk of cancer of the ovary, prostate and pancreas. The genes are thought to be tumour suppressor genes as the wild-type allele of the gene is observed to be lost in tumours of heterozygous carriers. Both BRCA1 and BRCA2 have significant roles in the maintenance of genome integrity via roles in the repair of DNA damage via homologous recombination. The specific DNA repair defect in BRCA-mutant cells provides opportunities for novel therapeutic approaches based on selective inhibition of functionally interacting repair pathways, in particular by inhibition of the enzyme PARP. Here I will describe recent work defining determinants of sensitivity and resistance to PARP inhibitors, as well as the application of the synthetic lethal approach to other cancer types.

Selected publications

Turner N, Tutt A, Ashworth A (2004) Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 4: 814–819.

Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434: 917–921

Lord, C.J., Garrett, M.D. and Ashworth, A. (2006) Targeting the double-strand DNA break repair pathway as a therapeutic strategy. Clin Cancer Res, 12, 4463–4468.

Iorns, E., Lord, C.J., Turner, N. and Ashworth, A. (2007) Utilizing RNA interference to enhance cancer drug development. Nat Rev Drug Disc, 6, 556–568.

Edwards, S., Brough, R., Lord, C.J., Natrajan, R., Vatcheva, R., Levine, D.A., Boyd, J., Reis-Filho, J.S. and Ashworth, A. (2007) Resistance to Therapy caused by Intragenic Deletion in BRCA2. Nature, In press.

Friday, 18 April 2008 14:00–16:00

SENONETWORK MEETING

Breast units: Time to define the standards

381 Invited

The pathology report: what do we really need to know?

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Background: It is not so long ago that a pathology report on a breast cancer read "Adenocarcinoma of the breast" or "Spheroidal cell carcinoma of the breast" with no reference to prognostic factors and no report on margins. Surgeons did not request this information or dissect the axilla to assess nodal status. In the UK, one could still see occasional reports like this in the early 1980's although more enlightened clinicians were beginning to realise that cancers were not all the same and that tailored treatment might be more effective.

The advent of breast cancer screening made the assessment of prognostic factors mandatory and increasing use of anti-oestrogenic therapy lead to the assessment of receptors. Today there are many factors which are required for prognostic and therapeutic planning. Pathology data are essential for entry into decision making systems which are used by many oncologists to decide on chemotherapy.

Mandatory Information: Standard factors have been used now for a number of years to predict prognosis. The most useful are tumour size, tumour grade (Elston & Ellis), tumour type and nodal status. These factors have been combined into prognostic indices such as the Nottingham Prognostic Index (NPI) and have been used since the 1980's. Other factors which may not be as important for prognosis, may have an effect on local recurrence. These are margin status, vascular invasion and the presence of an extensive in-situ component.

Breast cancer was one of the first cancers to have targeted therapy for some tumours and assessment of the hormone receptor status is necessary to avoid unnecessary anti-oestrogen therapy. This was originally the preserve of biochemists but the advent of immunohistochemistry and the production of high quality antibodies for the assessment of receptor status moved the test into the routine pathology laboratory and the oestrogen receptor status also became an essential part of the pathology report. Due to the known increase in hormone sensitivity with tumours which are oestrogen and progesterone receptor positive, many laboratories assess both of these receptors routinely.

More recent development of humanised antibodies to the human epidermal growth factor receptor type 2 (HER-2) has made the assessment of HER-2 status an essential part of the pathology report. While some units assess this on all cancers, others only perform the test on the patients who may be eligible for trastuzumab (Herceptin) therapy.

Other markers: Other prognostic markers have been assessed in the past and are assessed in some units today. Examples of these are proliferation markers such as S-phase fraction, or MiB1, markers of invasiveness such as urokinase (uPA), uPA inhibitors such as plasminogen activator inhibitor (PAI-1), angiogenesis and angiogenic factors and other growth factor receptors such as epidermal growth factor receptor (EGFR). None of these are regarded as front line markers necessary to predict