(median ~3 months), and in symptoms and quality of life. All men develop resistance to docetaxel, although some may respond to further courses of docetaxel after an interval off treatment. Thus mechanisms of resistance are likely to include unstable (epigenetic) changes in cells as well as more stable genetic changes such as over-expression of drug export proteins or mutations in genes encoding microtubule-associated proteins. Docetaxel has been given with a variety of other agents in attempts to increase efficacy or delay the onset of resistance, but thus far none has been successful. Likewise administration of other chemotherapeutic drugs after progression on docetaxel, including mitoxantrone, epothilones and satraplatin has shown some but limited benefit, consistent with the presence of common mechanisms of resistance to different types of chemotherapy.

We, and others, have shown that some anticancer drugs have limited distribution from blood vessels within solid tumours, and poor drug access is an as yet unexplored cause of drug resistance. We have also shown that accelerating repopulation of surviving tumour cells may occur between cycles of chemotherapy, leading to tumour regrowth even if there is no change in intrinsic sensitivity to the drugs used. Administration of cytostatic molecular targeted agents between doses of cycle-active docetaxel to inhibit tumour cell repopulation, and the use of new generation hypoxia-selective agents used in combination with conventional chemotherapy to complement limited drug distribution, are two promising approaches that will be investigated in clinical trials.

Scientific Symposium (Mon, 21 Sep, 16:15−18:15)
Resistance mechanisms to EGFR and HER2 inhibitors and strategies to overcome them

57 INVITED

A functional genetic approach identifies the PI3K pathway as a major determinant of Trastuzumab resistance in breast cancer

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Background: At present, 1 year of Trastuzumab (Herceptin®) treatment has become part of the adjuvant treatment of women with early stage HER2-positive breast cancer. However, it is still largely unclear why almost half of the breast cancer patients that over-express HER2 is non-responsive to Trastuzumab based therapy or become resistant to Trastuzumab during treatment. Therefore, clinical questions such as how to optimize patient selection or prevent resistance to Trastuzumab-based therapy still await answers.

We present here a method to identify biomarkers associated with non-responsiveness to Trastuzumab in cell culture and demonstrate that these biomarkers have predictive value in a patient cohort treated with Trastuzumab combination therapy.

Material and Methods: As an unbiased approach to identify genes involved in Trastuzumab resistance, we used a large-scale RNA interference genetic screen in the HER2-overexpressing breast cancer cell line BT-474. We have generated a library of 24,000 shRNA retroviral vectors targeting some 8,000 human genes for suppression by RNA interference and developed a technology to rapidly screen such libraries, named siRNA bar code screening.

Results: Of the 8,000 genes tested, we found that only knock down of PTEN conferred resistance to Trastuzumab. Decreased PTEN expression results in hyper activation of the PI3K pathway. Significantly, activating mutations in the gene encoding the p110a catalytic subunit of PI3K (PIK3CA) have been identified in some 25% of primary breast cancers potentially mimicking the effects of PTEN loss. Indeed, overexpression of the breast cancer-derived mutant PIK3CA (H1047R) also conferred resistance to Trastuzumab in cell culture. These findings are consistent with a major role of the PI3K pathway in the development of resistance to Trastuzumab.

Our cell culture experiments led us to investigate whether PI3K pathway activation is able to predict Trastuzumab resistance in the clinic. In a cohort of 55 patients treated for metastatic breast cancer, activation of the PI3K pathway, as judged by the presence of oncogenic PIK3CA mutations or low PTEN expression, was associated with poor prognosis after Trastuzumab therapy. Furthermore, the combined analysis of PTEN and PIK3CA identified twice as many patients at increased risk for progression compared to PTEN alone.

Conclusions: The present work highlights the central importance of PI3K signalling in risk for progression after Trastuzumab-based therapy, which in turn suggests combination therapeutic strategies to treat Trastuzumab unresponsive breast cancer or to prevent emergence of resistance. We are currently analyzing a cohort of 50 patients who received neo-adjuvant Trastuzumab-based therapy to test whether PI3K pathway activation status validates as a biomarker for response prediction in the neo-adjuvant setting.

58 INVITED

Inhibition of IGF signalling as cancer therapy

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Inhibition of growth factor signalling is emerging as one of the most promising therapies for cancer treatment. Many new approaches to disrupting the insulin-like growth factor (IGF) system have been developed and early clinical trials demonstrate promising results. The IGF system is composed of an interlinked network of ligands and receptors functioning in endocrine, autocrine, and paracrine pathways. As with any endocrine system, there are multiple ligands and receptors. Insulin, IGF-I, and IGF-II interact with the type I IGF receptor (IGF1R), insulin receptor (InsR), and hybrid receptors composed of subunits of both IGF1R and InsR. Preclinical data suggest that in order to predict the physiologic consequences of IGF1R inhibition on the cancer phenotype, a more complete understanding of other growth regulatory pathways needs to be defined. For example, IGF stimulation of cancer cells may result in enhanced cell motility and augment metastatic potential. In other cells, IGF may enhance proliferation and survival. These cancer phenotypes are regulated not by the receptor, but by activation of signalling pathways downstream of IGF1R. Since some of the phenotypes, such as inhibition of metastasis, are not easily observable in clinical trials, attention to these downstream signalling events may help develop predictive biomarkers for appropriate selection of patients. Our preclinical data suggest that the insulin receptor substrate (IRS) adaptor proteins are required regulators of IGF1R regulated biology. Moreover, gene expression signatures downstream of these adaptor proteins differ. IGF1R signalling also cooperates with other known growth regulatory pathways such as EGFR/HER2, estrogen receptor, and integrins. As new anti-IGF therapies emerge, attention to downstream signalling events needs careful consideration in order to identify predictive biomarkers and to define successful combination therapies.

59 INVITED

Understanding the genetic basis of resistance to EGFR targeted therapies to personalize colorectal cancer treatment

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Personalized cancer medicine based on the genetic milieu of individual colorectal tumors has long been postulated but until recently this concept was not supported by clinical evidence. The advent of the EGFR-targeted monoclonal antibodies cetuximab and panitumumab has paved the way to the individualized treatment of metastatic colorectal cancer (mCRC). There is clear evidence that mCRCs respond differently to EGFR-targeted agents and that the tumor specific response has a genetic basis. From the initial observation that cetuximab or panitumumab as monotherapy are effective only in 10−20%, of mCRCs, knowledge has being gained on the molecular mechanisms underlying primary resistance to these agents. The role of oncogenic activation of EGFR downstream effectors such as KRAS, BRAF, PIK3CA and PTEN on response to therapy will be discussed. The rapid and effective translation of these findings into predictive biomarkers to couple EGFR-targeted antibodies to the patients that benefit from them will be presented as a paradigm of modern clinical oncology. Unresolved questions such as understanding the molecular basis of response as well the mechanisms of secondary resistance will be discussed as the future fundamental goals in this research field.