# Symposia

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## Anti-HER2 monoclonal antibodies

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Breast carcinomas express high levels of ErbB receptors, such as the EGF (ErbB1) receptor and the closely related HER2 (ErbB2) receptor, and their overexpression is associated with a more agressive clinical behaviour. Monoclonal antibodies, tyrosine kinase inhibitors and other ErbB receptor targeted approaches can inhibit breast cancer growth and have moved to the clinic. The single agent clinical trials with trastuzumab, a monoclonal antibody that targets HER2, provided proof-of-concept of the activity of growth factor receptor targeting for the treatment of breast cancer. Furthermore, trastuzumab prolonged overall survival, the most important and elusive goal in metastatic breast cancer, in patients treated initially with trastuzumab and chemotherapy compared with patients treated with chemotherapy alone. Recently, a series of clinical trials have further enhanced our knowledge on how to maximize the clinical use of trastuzumab: only tumors with high level of HER2 overexpression as determined by immunohistochemistry (HER2 3+) or gene amplification appear to benefit from trastuzumab therapy; the activity of single agent trastuzumab in the first line setting is excellent and at least as high as any conventional chemotherapy agent in HER2 positive patients; a series of well tolerated and active combinations of chemotherapy and trastuzumab are emerging. In particular weekly taxane + trastuzumab and weekly vinorelbine + trastuzumab fulfill these requimements; a new q 3 week dosing schedule may become available in the future if ongoing studies confirm similar efficacy to the q week regimen. Available data suggests an optimal pharmacokinetic profile taking in consideration its very prolonged half-life; and finally and most important, adjuvant studies with trastuzumab are currently underway both in the United States (NSABP-B31, Intergroup study) and in Europe (HERA trial and BCIRG). Another anti-HER2 antibody, designated 2C4, might be active in cases of not dramatic HER2 overexpression where HER2 may act as a very potent heterodimer partner of other ErbB receptor family members. Novel antibody-based molecules such as intracellular antibodies, bispecific antibodies, and antireceptor antibody fusion molecules are also entering clinical trials.

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## Monoclonal antibodies anti-angiogenesis

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The use of inhibitors of angiogenesis has been the focus of the development of a number of novel therapies. While small molecule inhibitors of angiogenesis have focused on specific targets such as the tyrosine kinase pathway for vascular endothelial growth factor, this has the disadvantage of not inhibiting both of the receptors for VEGF signaling. In contrast, antibodies that block the activity of VEGF can inhibit signaling through all relevant receptors. Two monoclonal antibodies have been developed as specific inhibitors of VEGF-induced angiogenesis. rHuMAbVEGF is a IgG antibody which inhibits all isoforms of VEGF. Phase I trials have demonstrated safety of the molecule through doses of 10 mg/kg both alone and in combination with chemotherapy. Minimal evidence of anti-tumor activity defined by minor responses and disease stabilization were seen. Subsequent phase II studies in combination with chemotherapy have been conducted in patients with non-small cell lung cancer colorectal cancer. Adverse events seen in these studies have included a higher than expected rate of thromboembolic events as well as an apparent increased risk of tumor bleeding for a specific subpopulation of lung cancer patients. In both studies, an apparent improvement in either response rates of progression-free survival compared to randomized placebo controls was seen though the sample sizes were inadequate to make these differences statistically significant with adequate power to accept the benefit as real. As a result, subsequent phase III randomized, placebo-controlled trials are planned or ongoing. Single agent studies in patients with refractory cancer have also been conducted, specifically in breast cnacer and prostate cancer. The preliminary results of the breast cancer trial was presented previously and demonstrated a propensity for the development of hypertension in ~25% of the patients treated. Objective responses to single agent therapy were seen, indicating that there may be a role for primary anti-angiogenic therapy in patients with specific refractory cancer. The second humanized antibody, HuMC833 is an IgG4k for which the phase I trial incorporating imaging and biopsy was recently reported. This phase I trial importantly demonstrated the variability of anti-angiogenic response to therapy as measured by PET flow scans both within the same as well as different tumors. This highlights the importance of developing surrogate markers for the activity in clinical therapy.

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## Antibody blockade of the epidermal growth factor receptor combined with radiation

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The Epidermal Growth Factor Receptor (EGFR) has emerged as a key molecular target for modulation in cancer therapeutics. Epithelial tumors comprise approximately two-thirds of all human cancer and a correlation between overexpression of EGFR and clinically aggressive malignant disease has been established for many cancers. The initial rationale underlying EGFR signal interruption as an anti-cancer strategy involved proliferative growth inhibition. However, more recent studies now confirm the capacity of EGFR down-regulation to modify cellular radiosensitivity, chemosensitivity, apoptosis, invasion capacity, angiogenesis and DNA damage repair. The favorable interaction profile for EGFR blocking agents combined with radiation and/or selected chemotherapy drugs has stimulated clinical trials in diverse anatomic sites including head and neck, colorectal, pancreatic and lung. Monoclonal antibodies (mAbs) directed against the EGFR show great promise in preclinical and early clinical trial results for a spectrum of epithelial tumors. The most mature development to date for EGFR mAbs is that of C225 which is a chimeric mAb to the EGFR. A fully humanized mAb to the EGFR has also been developed (ABX-EGF), and a mAb directed against the most commonly expressed mutant form of the EGFR (EGFRvIII) in human tumors has been established (mAb 806). Preliminary results and current development status for these agents are reviewed. The spectrum of cellular and biological effects which follow molecular blockade of the EGFR is enlarging, and reflect the central role of this receptor in regulating epithelial cell behavior. Potential advantages and disadvantages of accomplishing EGFR blockade using the mAb approach compared with the use of tyrosine kinase inhibitors are previewed. Molecular inhibition of EGFR signaling in combination with radiation or chemotherapy represents a highly promising investigational arena. An update regarding current translational research efforts and early clinical trials is provided.

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## Monoclonal antibodies for therapy of solid tumors

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The therapeutic potential of monoclonal antibodies for cancer became soon evident after the original description of the hybridoma technique in 1975. Nevertheless, it took almost two decades of inconclusive clinical trials before more consistent positive treatment effects were reported. Several explanations for these impressive failures have been discussed, among them inaccessibility of antigenic cells within solid tumor tissue, inadequate target structures, cellular heterogeneity due to genomic instability, immunogenicity of the antibody – to name a few. The nature of the targets, – be it a growth factor receptor or an adhesion molecule –, as well as "humanization" of the effector portion of the antibody both seem to play a critical rôle for therapeutic efficacy. My review will focus on recent results of antibody trials showing efficacy in combination with defined chemotherapeutic agents. Recently, also novel antibody formats such as single-chain bispecifics are