external domain, leading to the more active truncated p95 form of the HER2 receptor or the inhibition of HER2 receptor mediated neo-angiogenesis. Only recently, antibody-dependent cellular cytotoxicity (ADCC) has raised significant interest as it might explain the activity of trastuzumab beyond progression (TBP). By binding via immunoglobulin fragment C receptor (FCGR) the to the HER2 receptor, trastuzumab attracts natural killer cells, which become activated and release substances that perforate the tumor cell and promote tumor cell death in concert with a new cytotoxic or targeted agent. Polymorphisms of the FCGR was found to correlate with different levels of activity of trastuzumab which supports this concept.
The GBG26 trial has demonstrated that TBP works clinically. 156 patients that were progressing during trastuzumab treatment received further chemotherapy with capecitabine alone or together with continuing trastuzumab. A significant increase in response and clinical benefit rate, a significant prolongation of time to progression and a trend towards longer overall survival was observed for those patients continuing trastuzumab. The combination of trastuzumab and capecitabine increased only the rate of anemia, but no other toxicity was more frequent compared to capecitabine alone. This result is supported by various retrospective observational studies. Again treatment beyond progression was superior, sometimes even led to significant differences in overall survival compared to patients continuing TBP. However, there was always uncertainty in these observational studies, why trastuzumab was continued or not.
Further prospective trials are supporting this concept. The EGF 100151 trial investigated lapatinib in a similar setting. 399 patients received capecitabine with or without lapatinib resulting in a significant increase in response rate and progression-free survival. Especially brain metastasis appeared less frequent in the combination treatment. The lapatinib combination was associated with more diarrhea and skin reactions. The EGF104900 study explored treatment with lapatinib with or without trastuzumab in heavily and trastuzumab pretreated patients. Again, TBP achieved a longer progression-free survival. A phase II study (BO17929) reported higher efficacy for the combination of trastuzumab and pertuzumab in trastuzumab pre-treated patients compared to a low clinical activity of pertuzumab alone in a preceding study. Currently a head to head comparison of trastuzumab and lapatinib in combination with capecitabine is planned in trastuzumab pre-treated patients.
In conclusion in vivo data and clinical evidence support the concept of TBP, which represents a paradigm shift in oncology, where usually all treatments are discontinued in the event of tumor progression. A continues blockade of HER2 throughout all stages of breast cancer has therefore to be considered.

139 INVITED

Antiangiogenic drugs – quo vadis?

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Angiogenesis has been deemed an attractive target for the potential treatment of cancer for several decades. Following the biological definition and molecular identification of vascular endothelial growth factor (VEGF), agents targeting this ligand and its receptor have been developed and resulted in improvements in progression-free and/or overall survival in several tumour types. Though proof of principle has been demonstrated, the therapeutic effects are moderate.
Efforts to identify predictive markers to improve the therapeutic index and thereby the practical feasibility of this approach, remain a challenge. Levels of receptor, ligand, or polymorhisms of the same have not clearly defined the utility of VEGF targeted therapy and continuing efforts directed at expression arrays and functional imaging are subjects of intensive research.
Angiogenesis is a complex, multi-factorial process and further improvements in efficacy are likely to require agents targeting multiple pathways in addition to VEGF (e.g. Tie – and Tie-2) though consequent increases in toxicity must be anticipated. Vascular disrupting agents and competitive substrate analogues of nitric oxide synthase are also in clinical development.
The VEGF dependence of 'micrometastatic' disease has recently been raised as an issue following presentation of the results of the C08 trial in colorectal cancer. More prolonged suppression of the 'angiogenic switch' may be required to have a significant, long-term effect on the risk of disease recurrence in the adjuvant setting.

140 INVITED

Combinations of endocrine agents and new targeted drugs: where do we stand ?

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Endocrine Therapy, the oldest targeted therapy for the treatment of breast cancer, has been available for more than a century by now. Only recently, other targeted options against growth factor receptors or VEGF have become available for routine clinical use. Mostly, these agents have been developed in combination with a chemotherapy backbone. Yet, the majority of breast cancers is endocrine responsive and combinations with endocrine therapy also have the potential of being less toxic than those with chemotherapy. Moreover, preclinical evidence also suggests that resistance to endocrine therapy may be mediated by growth factor receptors such as EGF-R and HER2. Consequently, combinations of endocrine therapy and HER1 or HER2 have so far been best explored regarding their clinical utility.
In a randomized phase II trial, Osborne et al. (SABCS 2007) showed that combined tamoxifen and gefitinib rendered a slightly better median PFS than tamoxifen alone; this finding was later supported by Christofanilli et al. (ASCO 2008) using anastrozole and gefitinib.
In the phase III Tandem trial (Mackey et al SABCS 2006), patients receiving anastrozole and trastuzumab had a significantly increased median PFS compared to those treated by anastrozole alone (4.8 vs. 2.4 months). Yet, the response to aromatase inhibitor (AI) monotherapy was disappointingly low in this HER2 positive population. Evaluating letrozole and lapatinib vs. letrozole alone, Johnston et al (SABCS 2008) showed a significantly increased median PFS (8.2 vs. 3.0 months) for the combination in a randomized phase III first line trial in HER2 positive disease. No significant difference was seen in HER2 negative disease. Again, the PFS rate in the AI alone arm suggests that endocrine therapy alone may not be sufficiently effective in triple positive disease. Data of the ELECTRA first line trial combining letrozole and trastuzumab are expected at the end of 2009. In the annually updated evidence-based AGO guidelines (www.ago-online.de), the combination of AI + trastuzumab and letrozole + lapatinib are considered as therapy options in HER2 positive disease.
Recently, combinations of endocrine therapy with other targeted agents such as the mTOR inhibitor RAD001 have proven to be effective in the neoadjuvant setting (Baselga et al, SABCS 2007). Unfortunately, there is so far no predictive marker indicating patients who will mostly likely benefit from this therapy. An ongoing GEICAM-GBG trial is currently evaluating letrozole + bevacizumab in the first line setting.
Only recently, combinations of endocrine therapy and targeted agents have become available for clinical use in breast cancer. Yet, so far, therapeutic benefits are mostly modest, and it is still unclear which patients will benefit more from combing a targeted therapy with an endocrine backbone and where a chemotherapy backbone would be most appropriate. Nevertheless, further evaluation of such combinations will be most important given the large percentage of endocrine responsive breast cancer and the favourable safety profile of endocrine therapy.

Scientific Symposium (Tue, 22 Sep, 14:45−16:45)
Locally-advanced rectal cancer

141 INVITED

Rectal cancer staging: which method is optimal?

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There is a challenging task for radiologists in helping to improve the therapeutic management of rectal cancer patients. With more tailor made treatment strategies for different risk groups and for the good responders after neoadjuvant treatment there is a growing need for an accurate imaging selection tool.
The pretreatment assessment of local tumor spread includes the determination of the depth of tumor growth in the rectal wall, the circumferential resection margin at TME, the depth of tumor invasion in surrounding pelvic structures, and the nodal status. US, CT and MRI are being used for staging of rectal cancer, each one with its own power and weaknesses.
After preoperative chemoradiation often advanced tumors drastically shrink so the debate now is whether less extensive surgery can be done for the responders or whether even surgery can be omitted in the complete responders. This is only an option if imaging after chemoradiation can accurately select the responders from the non responders and the partial responders from the complete responders.
Learning objectives of the lecture:
1. To understand the evidence in imaging of rectal tumors.
2. To understand what is the best imaging method for rectal cancer staging and restaging.
3. To understand future directions in rectal cancer imaging.