index are being developed. Pegylated doxorubicin and Nab paclitaxel are just two examples of such development. In addition newer molecules targeting microtubules like Eribulin and Epothilones have demonstrated increased efficacy and different safety profile.
Targeted therapies are an addition to the armamentarium of agents to fight breast cancer. But when used as monotherapy without chemotherapy have led to modest responses and benefits to patients. Overall, the results of trials with chemotherapy in combination with molecular-targeted therapies have been superior than targeted agents administrated alone.
Chemotherapy is an integral and irreplaceable part of the treatment of breast cancer. But there is a need for agents with better therapeutic index and agents overcoming the resistance to existing chemotherapeutic drugs. Targeted therapies do play an important role in a subgroup of patients in combination with to chemotherapy.

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Targeted regimes without cytotoxics – are they ready for prime time?

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Current context/presentation goal: Chemotherapy has been shown to improve outcome both in early and advanced breast cancer. Nevertheless, chemotherapy is associated with a broad array of side effects that significantly alter the quality of life. One of the research goals in the next years will be to decrease the number of patients treated with cytotoxic agents. There are two ways to decrease indications of chemotherapy: i. to identify patients who do not get benefit from such treatment, ii. to substitute cytotoxic treatment by targeted agents, that do not exhibit toxicity.
In the presentation, we will focus only on Her2-overexpressing breast cancer, and will discuss whether targeted approaches without cytotoxics could improve outcome.
Her2 signalling in breast cancer: Her2 overexpression occurs in around 10% of early breast cancer. Overexpression is related to gene amplification, and leads to the activation of intracellular kinase pathways. Her2 is though to mediate oncogenesis of such cancers. Interestingly, several additional molecular events are sometimes observed in this subset of cancers. These events could mediate resistance to Her2-inhibitors. These molecular events include PI3KCA mutations (Stemke-Hale et al, Cancer Res. 2008 Aug 1;68(15):6084−91), IGF1R overexpression (Nahta et al, Breast Cancer Res. 2006; 8(6): 215.), PTEN loss (Nagata et al, Cancer Cell. 2004 Aug;6(2):117−27). These data suggest that Her2-overexpressing breast cancer is an umbrella that includes several molecular entities, some of them being highly sensitive to Her2-inhibitors, while other ones are resisting to this kind of approach.
Efficacy of Her2 inhibitors as single agents: Two Her2 inhibitors (Trastuzumab, Lapatinib) have been developed until now. When used in the first line metastatic setting, the two agents exhibit the same range of efficacy. In the phase II reported by Vogel et al (JCO 2002 Feb 1;20(3):719−26), trastuzumab was associated with a 35% objective response rate in patients with Her2-overexpressing breast cancer. Interestingly, 7 out of 85 patients with Her2+++ breast cancer have presented a complete clinical response. In the phase II reported by Gomez et al (JCO 2008 Jun 20;26(18):2999–3005), lapatinib was associated with a 24% response rates.
New generation of HER inhibitors are being developed. In phase II trials performed in patients previously treated with trastuzumab, neratinib/trastuzumab (ASCO 09) and trastuzumab-DM1 (ASCO 09) were associated with 28 and 32% response rates respectively. Interesting, the neratinib/trastuzumab combination was associates with 7% complete response. Altogether, the phase II trials performed with targeted therapy alone suggest that a subset of patients with Her2-overexpressing breast cancer is highly sensitive to Her2-inhibition alone. Adding other targeted agents, including pertuzumab (Baselga et al, ASCO 07, Abstract No:1004) or everolimus (Andre, ASCO 08, Abstract No:1003) could increase efficacy in biomarker-selected population.
Unfortunately, there is no data about whether such high level of efficacy translates into long term PFS in the metastatic setting.
Looking at pCR rates in patients treated with targeted agents in the preoperative setting could be a possible way to get information about whether targeted agent could substitute chemotherapy. Unfortunately, there are only a few studies that evaluated Her2-inhibitors without chemotherapy in the preoperative setting. The NeoALTTO program will provide some relevant information regarding this question. In this trial, Her2-inhibitors are being provided for 6 weeks before combining them with chemotherapy. Since biopsies are being done at day 14, and radiological assessment at week 6, this trial will provide informations about whether some patients are highly sensitive to Her2 inhibition and whether these patients could be characterized in terms of biological profile.
Combining Her2 inhibitors with chemotherapy: Lessons from randomized trials: Five trials (Piccart-Gebhart et al, NEJM 2005 Oct 20;353(16):1659−72; Romond et al, NEJM 2005 Oct 20;353(16):1673−84; Joensuu et al, NEJM2006 Feb 23;354(8):809−20, Spielmann SABCS 2007, Slamon SABCS 2007) have evaluated the efficacy of trastuzumab in the adjuvant setting. All these trials included adjuvant chemotherapy. Although there is some debate about whether combined arm could be more effective than sequential arm, there is no doubt that using trastuzumab alone after chemotherapy is effective in a subset of patients. Such data reinforce the concept that a subset of patients could be treated with Her2-inhibitor alone.
Chemotherapy-free regimen in the metastatic setting: Lessons from randomized trials: Two randomized trials (Kaufman et al. Ann. Oncol 2006;17(suppl. 9): abstract LBA2; Johnson, SABCS 2008) have evaluated whether a combination between Her2 inhibitor and endocrine therapy is more effective than endocrine therapy alone. The two trials reported a benefit of using Her2 inhibitor. Interestingly, in the EGF30008 trial, the lapatinib/letrozole arm was associated with a median PFS at 8 months, a number in range with PFS observed in trials combining taxanes + Her2-inhibitors.
Conclusion: The current data suggest that a subset of patients with Her2-overexpressing breast cancer is highly sensitive to targeted approach, and could be spared from chemotherapy. This subset of patients should be identified soon using biomarker studies from preoperative trials. In the daily practice, it is not yet recommended to use targeted agents without chemotherapy. One potential exception could be elderly patients with Her2-overexpressing/ER-positive cases without visceral involvement. The discussion about how to provide evidence for equivalency between targeted approaches and cytotoxic regimen will be done during presentation.

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Role of maintenance chemotherapy in advanced breast cancer

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Advanced/Metastatic Breast Cancer (MBC) is considered an incurable disease. First line chemotherapy in patients with MBC is associated with a median disease free survival between 5−12 months, and a median overall survival (OS) between 24−36 months. In general, it can be said, that patients who respond to chemotherapy present a better OS than non-responders. However, treatment duration remains controversial. Should we continue treatment until disease progression or should we stop it once a positive response or stabilization of the disease has been achieved? Different strategies of maintenance chemotherapy have been used in randomized clinical trials to answer this question. A good inclusion criteria for maintenance chemotherapy would be patients with HER-2 (−) tumors, negative hormone receptor tumors or hormone refractory patients. In HER-2 (+) patients the use of trastuzumab until progression appears to be clinically justified, as well as the use of endocrine therapy in hormone receptor (+) tumors following chemotherapy. Over the last 20 years, ten randomized clinical trials have been published comparing short vs. long duration treatment in MBC patients. Seven of these studies did not use new agents such as taxanes or pegilated liposomal adriamycin (PLA). Overall, these trials have shown a consistent benefit in terms of better time to progression (TTP) for the maintenance arm, but only one has shown an improvement in OS and, in one data on this parameter are still pending. In conclusion, maintenance chemotherapy may be a reasonable approach to obtain better TTP but a modest benefit in OS according to a recent meta-analysis. Further trials with current agents/regimens are required in order to obtain evaluable-relevant clinical new data to help us in decision making to justify a change in clinical practice. Any clinical trial should have quality of life as a secondary end-point since added extra toxicity is a major concern in any form of maintenance treatment

Scientific Symposium (Wed, 23 Sep, 09:00−11:00)
New targets for ovarian cancer

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Biology of tumor angiogenesis and potential biomarkers of angiogenesis

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In 2004 Avastin was approved as the first anti-angiogenic drug for human use. Additional anti-angiogenic compounds were approved since, and clinical use has demonstrated that they provide survival advantage to metastatic renal cancer and, in combination with chemotherapy, to advanced colorectal, breast, and non-small lung cancers. Many clinical