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.

191 INVITED

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

F. Andre[1], R. Wolp Diniz[2]. *[1]Institut Gustave Roussy, Unite d'Immunologie ERM0208Institute de la Sante et de la Research Medicale, Villejuif, France; [2]Institut Gustave Roussy, Breast Cancer Group – Research Medicale, Villejuif, France*

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.

192 INVITED

Role of maintenance chemotherapy in advanced breast cancer

P. Gascon[1]. *Hospital Clinic Barcelona, Servei d'Oncologia Media, Barcelona, Spain*

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

194 INVITED

Biology of tumor angiogenesis and potential biomarkers of angiogenesis

C. Ruegg[1]. *[1]University Hospital (CHUV) and University of Lausanne (UNIL), Division of Experimental Oncology, Lausanne, Switzerland*

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

trials testing new molecules, new indications and new combinations are in progress, including in gynecological cancers, including ovarian cancer. Compared to the benefits expected based on preclinical models, patient benefits in term of long-term survival, however, remained modest. Recent experimental results have demonstrated that tumors treated with anti-angiogenic therapies, contrary to initial assumptions, can develop evasive resistance and rapidly progress to become invasive and metastatic. Thus, in spite of the undisputed success of this new therapeutic approach some old questions on tumor angiogenesis have remained unanswered and new ones have emerged. They include the understanding about how anti-angiogenic therapy and chemotherapy synergize, the characterization of the biological consequences of sustained suppression of angiogenesis on tumor biology and normal tissue homeostasis, and the mechanisms of tumor escape from anti-angiogenesis. Bone marrow-derived and tumor-mobilized cells recruited at tumor sites are emerging as critical determinant of resistance to anti-angiogenic therapy and may represent novel therapeutic targets. Furthermore, although it has been suggested that biomarkers of angiogenesis would greatly facilitate the clinical development of anti-angiogenic therapies, so far there are no validated biomarkers of angiogenesis and surrogate biomarkers of anti-angiogenesis. In order to improve the clinical use of available anti-angiogenic drugs and the development of new ones it will be important to challenge some of the basic concepts of tumor angiogenesis biology and the relationship between tumor vessels and tumor cells. In this lecture I will review some of the emerging critical issues in tumor angiogenesis and discuss their impact on the development of anti-angiogenic therapies.

195 INVITED

Clinical experience with antiangiogenic targeting in ovarian cancer

M.A. Bookman[1]. [1]*Fox Chase Cancer Center, Medical Oncology, Philadelphia, USA*

The biology of Vascular Permeability Factor (VPF) was first described in 1983, followed by the demonstration of constitutive expression in ovarian cancer in 1994. This led to efforts at antibody targeting in tumor model systems, with promising control of ascites and tumor growth. VPF is now recognized as Vascular Endothelial Growth Factor (VEGF), and our knowledge of VEGF expression, receptor biology, and signal transduction has expanded considerably over the last 10 years, culminating in successful targeting strategies through ligand sequestration, inhibition of receptor activation, interference with internal signaling pathways, and gene expression. In addition, a variety of other factors have been identified that contribute to a regulatory network of tumor-associated angiogenesis, introducing an array of potential targets and combinations.

The most well-studied agent has been bevacizumab, a monoclonal antibody that sequesters VEGF, as well as aflibercept, an antibody-like protein constructed of VEGF binding domains. Although single-agent activity with bevacizumab in lung, colorectal, and breast cancer was limited, phase III trials in combination with chemotherapy have demonstrated modest improvements in long-term clinical outcomes. Interest in ovarian cancer was accelerated based on phase II trials demonstrating a 20% RECIST response rate in patients with recurrent disease, together with control of ascites. While generally well-tolerated with a predictable toxicity profile, there was initial concern regarding the risk of bowel perforation that appears largely related to patient selection criteria. As a result, single-agent phase II trials were rapidly followed by 2 front-line phase III trials (in combination with chemotherapy) coordinated by GOG-US and MRC-UK. Accrual has been completed on both studies, and results are pending.

Inhibitors of VEGF-associated tryosine kinase (TKI) have also been evaluated in phase II trials, including sorafinib, cediranib, and pazopanib, and phase III studies of maintenance or consolidation have been initiated, with additional plans for front-line trials. Combinations of bevacizumab with TKI appear to have a high response rate, but at the expense of increased serious toxicity, and more studies with newer agents are needed. There are also limited data emerging with regard to other network components involved in tumor angiogenesis, such as angiopoietin-2, protein kinase-cβ, AKT, mTOR, or regulation of HIF1α activity.

Many questions remain with regard to the optimal clinical strategy for incorporation of these agents, including timing (front-line, maintenance, or recurrence), as well as combinations with cytotoxic chemotherapy or other molecular-targeted agents. In addition, there are not yet any comparative data to guide selection of the best agents, or class of agents, for future study.

Finally, the mechanism of action in ovarian cancer remains to be elucidated. Are these agents acting on tumor-associated vessels to normalize blood flow and reduce capillary permeability (as originally proposed), or are they acting directly on tumor cells, or perhaps accelerating the immune response through maturation of dendritic cells? Clearly, more randomized phase II trials with comparative and translational endpoints are needed to guide future investigations.

196 INVITED

Emerging new targets in ovarian cancer

S. Kaye[1]. [1]*Royal Marsden Hospital, Medicine, Sutton, United Kingdom*

In the era of molecular targeted therapy, ovarian cancer provides a particularly exciting opportunity for clinical new drug testing, in which pathway-specific agents are being linked to predictive biomarkers aimed at identifying patients most likely to benefit. The paradigm is the remarkable activity of single agent PARP inhibitor therapy for patients with BRCA 1/2 mutation positive ovarian cancer. This is based on the exquisite sensitivity of cancer cells which are deficient in the ability to repair DNA damage through homologous recombination (HR); the challenge for the future is to assess this new form of treatment in that larger group of ovarian cancer patients, with sporadic disease, who are also likely to have HR deficiency. We already have preliminary evidence to indicate that efficacy in these patients is possible.

Another pathway likely to provide a rich seam of novel agents is the PI3 kinase/AKT/mTOR pathway, since amplifications and mutations are well recognised in ovarian cancer. A number of agents are already in the clinic; here it is likely that a combination strategy will ultimately be employed, aimed at dealing with cytotoxic drug resistance through modulation of this pathway. Similarly, potent inhibitors of other relevant targets such as the SRC oncogene hold particular promise, based on molecular analysis of clinical material indicating the likely relevance of this target in ovarian cancer.

A key aim for the future is the identification of novel targets in so-called 'stem cells', which are increasingly being identified in ovarian cancer patients. These may include novel pathways such as the sonic hedgehog pathway, as well as well-recognised transport proteins (from the ABC transporter family) which may play a particular role in stem cell biology.

197 INVITED

Molecular determinants of acquired resistance

S. De Jong[1]. [1]*Groningen University Hospital, Groningen, The Netherlands*

Resistance to platinum-based chemotherapy is a major problem in the treatment of ovarian cancer. The reduced tendency of ovarian cancer cells to undergo apoptosis contributes to drug resistance. In order to gain more insight in the molecular mechanisms underlying platinum resistance, we profiled 9 paired stage III/IV serous ovarian cancer specimens obtained before and after platinum-based chemotherapy using oligonucleotide microarrays. The prognostic value of differentially expressed genes and deregulated biological pathways was assessed in an independent set of 157 previously profiled late stage serous ovarian cancers. Immunohistochemical staining of MB1 as representative for proteasome pathways confirmed the prognostic value of these pathways at the protein level. Our analyses reveal both well-known as well as novel genes and pathways tentatively involved in platinum resistance, including the insulin-like growth factor (IGF)-axis. High IGF-1 receptor (IGF-1R) and insulin receptor (IR) expression were observed in 51.1% and 19.9% of ovarian cancers, respectively. In univariate analysis for stage III/IV ovarian cancers, high IGF-1R expression was related to improved prognosis. In contrast, high IR expression was independently associated with poor disease specific survival (HR 2.0, 95%CI 1.30−3.09). Almost all cancers expressed IGF-I (100%), IGF-II (100%), IGF-1R (73.3%) and both IR-A and IR-B isoforms (94.4%) but none insulin mRNA. IGF-II levels in cyst fluid were elevated compared to cystadenomas suggesting a possible autocrine/paracrine activation of the IGF-axis. We investigated whether the IR inhibitor hydroxy-2-naphthalenylmethylphosphonic acid (HNMPA) treatment could sensitize the cisplatin-sensitive ovarian cancer cell line A2780 and its cisplatin-resistant subline C30 to cisplatin-induced apoptosis. A2780 and C30 showed membrane expression of IGF-1R and IR. Addition of IGF-I, IGF-II or insulin resulted in activation of the IGF-1R/IR signaling in A2780 and C30. A combination of HNMPA and cisplatin strongly enhanced apoptosis and decreased survival in both cell lines, indicating that inhibition of pro-survival signaling enhances cisplatin-induced apoptosis. Another strategy for targeting ovarian cancer involves shifting cellular balance in favor of cell death via activation of the intrinsic (mitochondrial) and extrinsic apoptotic pathway. In cisplatin resistant ovarian cancer cells we found reduced activation of p53 and reduced apoptosis-induction by recombinant human form of the death ligand TNF related apoptosis inducing ligand (rhTRAIL). Combination of cisplatin and rhTRAIL enhanced apoptosis in A2780 and a cisplatin resistant subline. Both rhTRAIL and rhTRAIL-DR5, a rhTRAIL variant that specifically binds to pro-apoptotic DR5 receptor induced high levels of apoptosis in combination with cisplatin with rhTRAIL-DR5 being most potent. Anti-tumor efficacy of rhTRAIL-DR5 or rhTRAIL in combination with cisplatin was determined in an intraperitoneal growing bioluminescent A2780 xenograft model. Intraperitoneal administration of rhTRAIL or rhTRAIL-DR5 plus cisplatin resulted in 85% ($p = 0.003$) and