and the technology to assess some of them (bone marrow/circulating tumor cells, naked DNAÉ) can be sophisticated and uneasy to disseminate.

(4) Type of trials: in theory non inferiority trials, equivalence or superiority are all possible with the goal to decrease risks and treatment burden, to increase efficacy, to improve benefit/risk ratio. The latter ones should be favored knowing that some non inferiority trials are based on an absolute difference in DFS of 5-7%.

(5) Who should ask for this marketing application. In a number of cases the tested agent(s) will not have a marketing protection at the end of such trials thus not triggering pharmaceutical companies to apply. Some legal opportunities should be defined for Institutions, Learned Societies, Health Authorities to support such variations so as to limit off-label of agents, and to incorporate guidance for the use of an agent or combination in the adjuvant setting.

More than a challenge, AS in fact raise new questions for the Regulatory Agencies to address in the cancer field including approval of multidrug regimens.

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SYMPOSIUM

Primary systemic therapy in operable disease

326 INVITED

Pre- versus postoperative systemic treatment in operable disease

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Pre-operative or neoadjuvant chemotherapy as a therapeutic tool in primary operable breast cancer was introduced in the late seventies. While its role in locally advanced breast cancer has been firmly established, the value of pre-operative chemotherapy in early stage breast cancer is still uncertain. The rationale for the administration of systemic therapy before locoregional therapy was based upon three different premises; first, downstaging of the tumor, second, to improve prognosis by inhibiting surgery-induced tumor cell proliferation, and third, to test chemo-sensitivity of the tumor in situ. To study whether pre-operative chemotherapy results into better overall survival compared to postoperative chemotherapy in early breast cancer patients, the EORTC Breast Cancer Group conducted a randomised phase III trial (EORTC trial 10902) which randomised between four courses of FEC60 given pre-operatively or postoperatively.

In total, 7 randomised phase II / III trials have studied pre-operative chemotherapy versus postoperative chemotherapy in primary operable breast cancer. Tumor response rates ranged from 50% to 85% and patients with a pathological complete response did have an excellent prognosis. Although impressive tumour response rates have been documented, the data concerning the number of breast-conserving therapies vary widely between the respective trials. However, breast-conserving surgery as opposed to mastectomy in this setting appears to be safe, although there is a suggestion of a small increase in local recurrence rate as was demonstrated in the NSABP trial. Most important, data from these trials show that the use of pre-operative chemotherapy neither prolongs nor decreases overall or disease-free survival when compared with the same chemotherapy given postoperatively. However, the ability to assess tumor response may be a significant advantage in that it allows a further option of adjusting systemic treatment in apparently resistant tumours. Especially in combination with highly promising new techniques like microarray technology and high-throughput tissue arrays, pre-operative chemotherapy may prove very useful. Micoroarray technology enables the identification of the entire genomic activity of cells. In cancer, this will also allow the classification of individual tumours by their gene expression profiles and describe and predict therapeutic resistance and sensitivity patterns. Therefore, microarray technology offers a new and unique way to identify tumour characteristics, which may enable physicians to customise anticancer therapy for the individual early breast cancer patient. In addition, high-throughput tissue arrays accelerate studies correlating molecular in situ findings with clinico-pathological information. This technique will lead to a significant acceleration of the transition of basic research findings into clinical applications.

Future pre-operative chemotherapy trials therefore should include predictive factor studies comparing gene expression and protein expression profiles before and after chemotherapy.

327 INVITED

Primary systemic therapy in operable disease - The rationale of chemotherapy - Achievements, predictive and prognostic factors

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Over the last two decades, numerous clinical trials have shown that a significant proportion of patients with large operable tumors requiring mastectomy may benefit from breast conserving treatment after several cycles of neoadjuvant chemotherapy using conventional regimens with demonstrated efficacy (CMF, CAF, AC, FEC, etc). This approach is becoming accepted as safe, although it yields modest results with about 10% absolute increase in breast conservation. Randomized studies did not show any difference in survival over the mere conventional approach using similar postoperative systemic therapy. Objective remission rates differ substantially when they are evaluated according to clinical measurements or with various imaging techniques (mammography, echography, CT-scan, NMR), and do poorly correlate with pathological response. A complete pathology response, defined as the absence of residual invasive tumor at the primary site and in the axilla, is observed in a minority of patients (10 to 30%), and is the sole reliable predictor of improved survival. The optimal duration of neoadjuvant chemotherapy is unknown, but generally lasts for 12 up to 24 weeks, depending on the regimen used. It requires a close monitoring of response, in order to detect early progression (rare within 12 weeks). Locoregional treatment must follow and consists in surgery or surgery plus radiotherapy (mandatory after breast conservation).

The second generation trials currently running investigate newer drugs (taxanes, capecitabine), targeted and potentially synergistic regimens (e.g. trastuzumab plus chemotherapy in case of c-erb/B2 overexpression).

Newer imaging techniques allowing early prediction of response after one or two cycles of treatment like PET-scan (FDG or other tracers) are increasingly used to monitor response. More individualized systemic treatment with modulation of systemic postoperative therapy, according to the response observed during the neoadjuvant induction phase, represents probably the most promising approach, likely to improve survival.

328 INVITED

The role of endocrine therapy in this setting

H.T. Mouridsen. *Righospitalet, Dept. of Oncology, Copenhagen, Denmark*

Tamoxifen as sole therapy in primary operable breast cancer was investigated in the late 1970s and the 1980s in several phase II trials, when the clinicians tried to avoid surgery in elderly or unfit patients. Essentially the studies demonstrated response rates of 30-70% in unselected patients, however long term local disease control was poor.

There have been a series of randomized trials in elderly patients with primary operable breast cancer. Two trials initiated in the early 1980s compared tamoxifen with surgery and another 3 trials compared tamoxifen with surgery followed by tamoxifen. All but one of the trials demonstrated that surgery either as sole initial therapy or followed by adjuvant endocrine therapy provides better local control than initial endocrine therapy alone, but none of the individual trials demonstrated survival differences. However, the power of the studies is small.

These studies have led to the initiation of studies of preoperative endocrine therapy, the major aim being to downstage the tumour and thereby to be able to offer breast conserving surgery to a larger proportion of the patients. These trials have used tamoxifen, fulvestrant and aromatase inhibitors as the endocrine agents. One large randomized trial has been published and demonstrated letrozole to be significantly superior to tamoxifen in clinical response rates (60% vs 41%) and frequency of breast conserving therapy (48% vs 36%).

Preoperative setting provides an optimal model for translational studies. Data from the letrozole versus tamoxifen study suggest that Erb-B1 and Erb-B2 measurements can be used to select the most efficient endocrine therapy in this setting.

The impact upon survival with preoperative endocrine therapy remains to be established.

329 INVITED

Local treatment – Challenges after primary therapy

M. Greco. *Head Breast Unit, National Cancer Institute of Milan, Italy*

The main goals of primary chemotherapy (PC) are: 1) to gain a more effective local and distant control of the disease; 2) to decrease the size of the

primary tumour allowing conservative surgery on the breast. Data analysis, from the many studies performed, shows that this therapeutic approach results in tumour downstaging in 70–90% of cases. Complete clinical remission and no residual palpable disease in the breast, range from 17% to 51% for tumours greater than 3 cm in size, and allows breast - sparing surgery in almost the same number of patients (1–6).

As regards surgical problems related to PC, there are strictly medical issues (i.e., the choice and the way of administration of drugs, the treatment planning), some others of surgical relevance (i.e., surgical techniques or indications, intraoperative planning), and, finally, others of general interest (i.e., the degree of response to PC, the usefulness and the timing of radiotherapy, data analysis). Regarding the surgical questions, these could be summarized on the followings: 1) the possibility of disease progression during the medical treatment; 2) the persistence of microcalcifications at the mammographic examinations at the end of the PC; 3) the bifocality or the multifocality of the tumour, eventually revealed by partial regression induced by medical treatment; 4) the indications to surgery and the surgical techniques; 5) intraoperative planning (i.e., evaluation of surgical margins, surgical approach in case of macroscopic complete regression of the tumour); 6) right and suitable information given to the patients.

One of the less discussed items is the risk of disease progression during chemotherapy: how many cases of operable breast cancer could risk becoming no longer amenable to surgery? In a large series of 536 patients at the National Cancer Institute of Milan, the rate of disease progression during induction chemotherapy was in the range of 3%, but only one patient resulted no longer amenable for any surgical operation. The rate is very low and, moreover, half of these patients were monitored in complete remission after a long follow-up period. A quite similar rate (2–3%) of progressive disease during chemotherapy is presented in the study of Royal Marsden Hosp. in London, and on that of NSABP B-18 carried out by Fisher.

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SYMPOSIUM

Treatment tailoring – translational research

330 INVITED

Can we predict response to therapy in breast cancer?

Abstract not received.

331 INVITED

Development of surrogate endpoints in translational research

Abstract not received.

332 INVITED

Molecular endpoints

M. Dowsett. *Royal Marsden Hospital - NHS Trust, Professor of Biochemical Endocrinology, London, United Kingdom*

The response of breast cancer patients to individual therapies is highly variable. In these circumstances individualised therapy has the potential to maximise the opportunities for response and minimise any associated toxicity and cost in the non-responsive population by avoidance of the unnecessary therapy. The opportunity exists to use molecular markers as intermediate end-points of response early in the presurgical treatment of patients to identify those who are likely to progress to clinical response and derive long-term benefit from the treatment. Changes in proliferation (measured as Ki67) and apoptosis (measured by TUNEL) have been our focus since they are intimately involved in determining changes in tumour growth. Increases in apoptosis after 24 hours of chemotherapy are measurable but these do not appear to predict response, possibly due to temporal variability in the maximal pharmacodynamic response to treatment. In contrast changes in proliferation after 2-3 weeks were significantly associated with response to chemotherapy, endocrine therapy and chemo- endocrine therapy. As such change in Ki67 is an attractive end-point for new drug development and we have applied this to the study of raloxifene, idoxifene and ICI 182780 during the 1-3 week period between diagnosis and surgical excision. Studies in xenografts demonstrate that substantial changes in proliferation and apoptosis can occur which only result in stabilisation of disease. As such these end-points may be more indicative of treatment effects on tumours than response measurements themselves and be particularly useful in the assessment of some of the new biological agents which are expected to have tumouristatic effects.

The search for further, hopefully more sensitive and reliable, indices of response is now being evaluated by modern molecular pathological techniques such as c-DNA arrays and candidate genes have been identified for further assessment in larger cohorts. It is now known that tumour cells can be isolated from the circulation of patients with metastatic breast cancer and assessment of molecular end-points of treatment in these is also an exciting possibility for future study.

333 INVITED

Facilitating translational research: the patient/advocate input

D. O'Connell. *Europa Donna Ireland, Dublin, Ireland*

Translational research utilising developments in biomedical research and medical informatics offers improved prospects for treatment tailoring in the clinic. This has led to debate on issues of concern to scientists and patient/advocates, including the use of biological materials, informed consent, patient confidentiality, and the consequences for patient and family resulting from germline genetic testing. The concerns of patient/advocates reflect an increased awareness of individual rights, balanced by a desire to find better treatments tailored to their disease. Scientists are concerned that exciting new developments leading to improved clinical treatments may be hampered. It is in the interests of both groups to collaborate, with open discussion on such topics as informed consent and privacy. The patient/advocate input includes communicating the concerns of the patient/advocacy community to the scientific community, listening to the concerns of the scientific community, collaborating in addressing those concerns, and disseminating full and accurate information among those she represents. The desired result is to achieve the maximum benefit to present and future breast cancer patients by facilitating translational research resulting in better treatment outcomes, while ensuring that patient concerns in relation to confidentiality, informed consent and other issues are met satisfactorily.

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EUROPA DONNA SYMPOSIUM

The psycho-social implications of breast cancer

334 INVITED

The psycho-social impact

D.K. Wellisch. *UCLA School of Medicine, Department of Psychiatry, Los Angeles, USA*

This talk will address multiple factors related to the psychosocial impact(s) of breast cancer. One set of impacts is related to the individual with breast cancer and another set of impacts is related to the family of the breast cancer patient. For the patient this talk will outline the woman at elevated risk for psychiatric complications in facing breast cancer and its treatments. The talk will then address the etiological factors and prevalence of pathological anxiety, depression, and post-traumatic stress disorder in breast cancer patients. A focus on the psychosexual impacts of breast cancer will also be undertaken. The talk will focus on the impacts of breast cancer for the spouse/significant other and children of the breast cancer patient. The issues of depression, anxiety, and coping for the spouse and children will be addressed. For the daughter of the breast cancer patient, data from the UCLA High Risk Clinic will be presented. Specifically. a profile of the daughter at risk for psychiatric difficulties will be described, as well as levels of depression, anxiety, and post-traumatic stress disorder in such daughters will be presented. The talk will conclude with some suggestions for interventions for the patient and her family.