Thursday, 21 March 2002 **9:00–9:45**

EUROPA DONNA TEACHING LECTURE

Epidemiology and statistics

178 INVITED

Epidemiology and statistics

Abstract not received.

Thursday, 21 March 2002 **11:00-13:00**

KEYNOTE SYMPOSIUM

Breast cancer incidence and mortality trends are changing. Why?

179 INVITED

Is it life style and environment?

Abstract not received.

180 INVITED

Is it early diagnosis?

S. Moss. *The Institute of Cancer Research, Cancer Screening Evaluation Unit, Sutton, United Kingdom*

The introduction of population screening for breast cancer will inevitably result in an increase in recorded incidence rates due to advancement of date of diagnosis, and such increases have been observed in a number of countries. Incidence rates of invasive disease should eventually return to the background level, other than in areas or age-groups in which women are being screened for the first time. Incidence rates of ductal carcinoma in situ will also increase as a result of screening; the long-term impact of the detection of DCIS on invasive breast cancer rates will depend on the natural history, which is not precisely known.

Any attempt to assess the impact of screening or earlier diagnosis on trends in both breast cancer incidence and mortality needs to take account of birth cohort effects, which are likely to be due to changes in risk factor patterns. These effects had already resulted in changes in mortality trends in a number of countries before any effect of screening would be anticipated.

The expected impact of screening on population breast cancer mortality rates will depend on the timing and duration of the introduction of screening and on the proportion of deaths due to cancers diagnosed before the start of screening, as well as the intensity of screening (for example coverage and frequency). It can be misleading to study mortality rates too soon after the start of screening, and improvements in treatment are likely to be affecting rates over a similar period. However in several countries where population screening programmes have now been in place for a number of years the effect on breast cancer mortality can be investigated.

181 INVITED

Is it treatment?

Abstract not received.

Thursday, 21 March 2002 **14:45–16:15**

SYMPOSIUM

Novel targets for therapy

182 INVITED

Tyrosine kinase inhibitors

Abstract not received.

183 INVITED

Farnesyl transferase inhibitors and proteasome inhibitors

S.R.D. Johnston. *The Royal Marsden NHS Trust, Dept of Medicine, London, United Kingdom*

Novel drugs have been developed to inhibit key enzymes in breast cancer biology which are involved in signal transduction and cell cycle progression. The 21kD ras protein is a central link between activated transmembrane growth factors (EGFR, HER-2) and downstream intra-cellular kinases (MAPK, ERK) which trigger growth. The rate-limiting step in processing ras involves attachment to the inner membrane by addition of a lipid moiety through the enzyme farnesyl protein transferase (FTPase). Specific inhibitors of FPTase prevent the post-translational processing of ras, thereby inhibiting cell growth. Breast carcinomas contain a low frequency of oncogenic Ras mutations (<2%), although aberrant function of the ras pathway is common due to upstream growth factor-mediated activity. We have shown that breast cancer xenografts are growth inhibited by R115777, an orally active non-peptidomimetic FPTase inhibitor. In a phase II clinical study in 41 women with advanced breast cancer we demonstrated efficacy for R115777 as a single agent following prior endocrine/chemotherapy, with 4 partial responses and prolonged stable disease (>24 weeks) in an additional 6 patients. In view of pre-clinical data suggesting synergy with conventional agents used to treat breast cancer, it is appropriate to examine how inhibitors of FPTase may be combined with either cytotoxic or endocrine therapies. Another key enzyme in cancer cell biology is the 26S proteosome which modulates regulatory proteins involved in the cell cycle. Cancer cells which show uncontrolled replication require proteosome-dependent turnover of many cell-cycle proteins to successfully complete mitosis. Proteosome inhibitors prevent degradation of ubiquitinated-protein complexes and have pro-apoptotic effects on tumour cells. The proteosome inhibitor PS-341 has shown potent anti-tumour activity in-vitro and in animal models. Furthermore, resistance to chemotherapy may relate to enhanced expression of anti-apoptotic proteins, and additive/synergistic effects occur when PS-341 was combined with several cytotoxic drugs. Clinical trials of PS-341 in breast cancer are now proposed. In conclusion, FPTase inhibitors and proteosome inhibitors represent new anti-cancer drugs rationally developed to target key enzymes involved in breast cancer biology. Both therapies may best be utilised in combination with conventional chemotherapy/endocrine drugs, and further clinical trials in breast cancer are in progress.

184 INVITED

Tumour vessels and vessel formation as therapeutic target

L. Gianni, G. Grasselli. *Istituto Nazionale Tumori, Milan, Italy*

Tumor angiogenesis is a tightly regulated multi-step process requiring endothelial cell activation, degradation of extracellular matrix, migration and proliferation of activated endothelial cells and their organization into newly formed blood vessels. Markers of angiogenic activity may have prognostic importance in different tumor types. The prognostic significance of angiogenesis in breast cancer has been thoroughly investigated. The most commonly used method has been the assessment of intratumor vascularization by immunohistochemical assays. Microvessel density significantly and independently correlated with long-term disease-free survival in early*stage invasive breast cancer. Another method is to measure soluble angiogenic (VEGF, bFGF, PD-ECGF) and antiangiogenic factors (thrombospondins) in plasma and urine. Recent data indicate that high levels of VEGF are a powerful prognostic indicator. Based on this evidence, breast cancer represents an obvious choice for application of drugs targeting tumor-vasculature. The two main types of drugs are either aimed at preventing new ves-

sel formation (anti-angiogenic drugs), or directed against existing tumor-vasculature (anti-vascular drugs). Among anti-angiogenic drugs the monoclonal antibody bevacizumab blocking VEGF has completed Phase II evaluation showing preliminary antitumor activity (10%) at the cost of some unpredicted toxicity (hypertension). Studies are now ongoing with bevacizumab in combination with chemotherapy in breast cancer. Other anti-angiogenic molecules include inhibitors of tyrosine-kinase receptors for angiogenic peptides, selective metalloproteinase-inhibitors, and endogenous angiogenesis-inhibitors (angiostatin, endostatin). All are at an earlier stage of development, and no evidence of antitumor activity was reported yet. Antivascular drugs contribute to the rapid destruction of existing blood vessels in tumors containing activated endothelial cells. Among these, combretastatins and immunotoxins selectively targeting tumor endothelial cells appear of special promise, although vascular toxicity to the myocardium has been reported and may limit their development. In this wealth of pharmacologic opportunities, the main challenges are those of defining the appropriate way of evaluating the therapeutic benefit of anti-angiogenic/antivascular drugs (long-term control of micrometastases?), and defining the optimal modality of combining them with existing drugs to fully exploit their therapeutic potential.

185 INVITED

Anti receptor antibodies: Update of their current role in the treatment of breast cancer

M.J. Piccart, M. Mano, S. Dolci, A. Di Leo. *Jules Bordet Institute, Brussels, Belgium*

The only anti receptor antibody with a current role in the treatment of breast cancer (B.C.) is Herceptin® (trastuzumab), a humanized monoclocal antibody (Mab), produced against the extra cellular domain of HER_2, a type I tyrosine kinase receptor of the HER family.

In the last 16 years the following sequence of critical events has taken place: 1) the cloning of the human HER_2 gene in 1985; 2) the identification of its corresponding protein HER_2; 3) the correlation between HER_2 gene amplification and HER_2 receptor overexpression with an aggressive form of B.C.; 4) the demonstration that the murine Mab 4D5 markedly inhibits the proliferation of human tumor cells overexpressing HER_2; 5) the humanization of 4D5 to produce the drug Herceptin®; 6) the start of Herceptin® clinical trials in 1992; 7) the registration of the drug worldwide for use as monotherapy in patients with HER_2 overexpressing B.C. who have failed anthracyclines and taxanes, as well as upfront use in combination with paclitaxel (1998–2000); and 8) the initiation of large adjuvant randomized clinical trials of Herceptin® (2000–2001).

There is still room for further progress with the use of Herceptin® in the management of B.C.

In advanced disease priorities include: 1) the optimization and standardization of HER_2 testing; 2) the refinement of the Herceptin® administration schedule; 3) the comparison of single agent Herceptin® to Herceptin® plus chemotherapy; 4) understanding the mechanisms of resistance to Herceptin®; 5) the identification of predictive factors linked to Herceptin's cardiotoxicity; 6) and the exploration of combinations of Herceptin® with other targeted therapies. Among these, combinations of Herceptin® with endocrine therapy, with Zarnestra® (a farnesyltransferase inhibitor) or with a preteasome inhibitor will be briefly discussed.

In early disease, close to 12 000 women with HER_2 overexpressing B.C. will be enrolled in four large adjuvant trials investigating the role of Herceptin® given together with or following adjuvant chemotherapy. These trials, with their complimentary designs, should provide a clear answer as to the benefit/risk ratio of adjuvant Herceptin® by 2006–2007.

Thursday, 21 March 2002 14:45–16:15

SYMPOSIUM

Clinical implications of lymphatic mapping by sentinel node biopsy

186 INVITED

Micrometastases: Detection and clinical significance

H.S. Cody. *The Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, Associate Professor of Clinical Surgery, The Weill Medical College of Cornell University New York, NY, USA*

About 30% of axillary lymph node (ALN) negative breast cancer patients die of distant metastases despite adequate local therapy. Might more intensive surveillance for subclinical regional or systemic disease uncover this metastatic potential? In breast cancer the search has focused on three sites: 1) the ALN, 2) the bone marrow, and 3) the peripheral blood, and all three have produced exciting developments over the past decade. This presentation addresses the clinical significance of *occult metastases in the ALN*, and topic made particularly relevant by the advent of sentinel lymph node (SLN) biopsy.

Two types of study encompass the literature on micrometastases in breast cancer, 1) those in which patients *classified initially as ALN-positive* are stratified by size of ALN metastasis, and 2) those in which patients *classified initially as ALN-negative* are found on further study to be ALN-positive. Both, given adequate study size and length of follow-up, suggest that micrometastases are prognostically significant. SLN biopsy, a *targeted* examination of an average of 2 ALNs (those most likely to contain metastases), for the first time makes enhanced pathologic analysis by serial sectioning (SS) and immunohistochemistry (IHC) logistically feasible and allows the identification of a group of patients whose risk of systemic relapse might otherwise go unrecognized.

Enhanced pathologic techniques have played at least four undisputed roles in the evolution of SLN biopsy for breast cancer: 1) improved staging of the axilla, 2) validation of the SLN hypothesis, 3) reduction in the rate of false-negative SLN, and 4) the prediction of non-SLN metastases in patients with positive SLN. The prognostic significance of SLN micrometastases remains a subject of controversy. Critics suggest that "micrometastases" 1) are displacement artifact and not biologic metastases, 2) require prospective trials to establish prognostic significance, and 3) should not alter treatment, especially if detected only by IHC.

Breast cancer is a disease characterized by heterogeneity and nowhere is this heterogeneity more apparent than at the level of nodal metastases. "Micrometastases" are not a single entity but comprise a spectrum of pathologic findings, and probably a spectrum of risk. The weight of current evidence is that occult nodal metastases are prognostically significant, but this may in fact only prove true for those patients with a larger volume or number of micrometastases and not single cells detected by IHC. Even with the maturity of prospective trials now in progress, the prognostic significance of occult SLN metastases will remain a matter of debate.

187 INVITED

Sentinel node biopsy or axillary clearance: equal staging and less morbidity? The ALMANAC trial

R.E. Mansel. *Univ. Hospital Wales, Department of Surgery, Cardiff, UK*

The promise of sentinel node biopsy is that it will deliver axillary staging equivalent to axillary node clearance without the well-documented but underestimated morbidity of that procedure. The first part of this promise seems to be deliverable as detection rates for sentinel nodes are greater than 95% in experienced hands with false negative rates of less than 5%,especially with the combined isotope/blue dye method. However, the best results have been reported from high-caseload, experienced centres and the learning curve problem has begun to emerge in some series of low caseload surgeons who have undertaken the technique with a minimum of prior training. The literature suggests that around 30 to 40 audit cases are needed to be sure of producing a high standard. In the multicentre UK study (ALMANAC trial)each surgeon performed an audit set of 40 cases after prior in the unit training supervised by the principal investigator of the trial. The data shows that this approach produced high success rates of around 96% detection of sentinel nodes and a false negative rate of 4.5%, but with an abbreviated learning curve.