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-