Certainly! But it too will have to evolve. In this presentation the new multigene expression signatures will be reviewed. There are certainly signatures based on both protein and nucleic acid technologies that can refine estimates of patient prognosis beyond the estimates that can be made by classic pathologic information. Some of these signatures have also shown promise in making estimates of treatment efficacy. Adjuvant! was specifically designed so that estimates for prognosis and efficacy from other sources and can be entered either to be combined with or to override estimates based on newer technologies.

No tool can ever be claimed to be perfect. This is because many factors evolve with time. Screening, exogenous exposures, general medicine and salvage therapy all in a state of change. Much of what we "know" in terms or treatment efficacy is based on short term follow-up. We are inevitably developing new models for 10 year outcome based on population of patients from at least 10 years ago, and making projections of outcome for 10 years from now. Given the rapid evolution of technology these will always be approximations. Nonetheless prognostic and treatment efficacy tools that produce numerical estimates have moved us beyond the era of vague non-numerical statements to an era of shared decision making where patients and their health care team can discuss options in a more complete way.

443 Proffered paper oral

PARP is expressed in all subtypes of early breast cancer and is a predictive factor for response to neoadjuvant chemotherapy

G. von Minckwitz[1], B. Müller[2], S. Loibl[3], J.U. Blohmer[4], A. duBois[5], J. Huober[6], R. Kandolf[7], J. Budczies[2], C. Denkert[2]. *[1]GBG Forschungs GmbH, Managing Director, Neu-Isenburg, Germany; [2]Charité Universitätsmedizin Berlin, Institut für Pathologie, Berlin, Germany; [3]German Breast Group, Medicine & Research, Neu-Isenburg, Germany; [4]St. Gertrauden Krankenhaus, Gynecology, Berlin, Germany; [5]HSK Wiesbaden, Gynecology, Wiesbaden, Germany; [6]UFK Tübingen, Internal Medicine, Tübingen, Germany; [7]University of Tübingen, Institut für molekulare Pathologie, Tübingen, Germany*

Background: The polyadenosine diphosphate [ADP]-ribose polymerases (PARPs) are a large family of multifunctional enzymes. PARP-1 plays a key role in the genomic stability. Increased expression is considered to be associated with resistance to DNA damage-inducing therapeutic agents. Combining these cytotoxic agents with a PARP inhibitor showed improved activity in patients with triple negative metastatic breast cancer.

We investigated PARP expression in various hormone (HR)/HER2 receptor subtypes of early breast cancer and evaluated its predictive value for pathological complete response (pCR; defined as no invasive residuals in breast and nodes).

Methods: Tissue microarrays from core biopsies of 582 patients recruited to the phase III GeparTrio trial, who received neoadjuvant 6−8 cycles TAC/NX chemotherapy, were centrally stained immunohistochemically for PARP, ER, PgR and HER2 expression. Cytoplasmatic and nuclear staining of PARP was assessed with regard to intensity and percentage of positive cells and scored as low, medium or high expression.

Results: Overall, cytoplasmatic PARP expression was high in 24.4%, medium in 52.4% and low in 23.2% of patients. High expression was found in 19.9% of 286 HR+/HER2−, 20.2% of 129 HR+/HER2+, 36.0% of 50 HR−/HER2+ and 35.6% of 101 HR−/HER2− tumours ($p = 0.001$). High PARP expression was significantly correlated with undifferentiated tumour pattern ($p < 0.001$), non-lobular cancers ($p < 0.001$), negative HR ($p < 0.001$). Correlation was only of borderline significance for tumour size and nodal status, no correlations were found for HER2 status and age. Patients with high PARP expression showed a pCR rate of 25.7% compared to 18.8% and 6.1% in patients with medium or low expression ($p < 0.001$). In univariate logistic regression, pCR rate was different between PARP high and low expressing tumours with OR = 5.3 (95% CI 2.4–12.0). This result remained significant when corrected for tumour stage, nodal status, histological type, tumour grade, molecular subtype and age, OR = 2.6 (1.1−6.4). No such correlations were found regarding nuclear PARP staining.

Conclusions: Cytoplasmatic PARP expression can be detected by immunohistochemistry in all subtypes of early breast cancers and is correlated with an aggressive biological tumour pattern. Cytoplasmatic PARP expression predicts pCR to neoadjuvant taxane-anthracycline-based chemotherapy. Clinical investigation of PARP inhibitors should not be limited to triple negative tumours alone.

444 Proffered paper oral

The EORTC 10041/BIG 03−04 MINDACT trial is feasible: first results of the pilot phase

E. Rutgers[1], M. Piccart[2], S. Delaloge[3], L. Van 't Veer[4], I. Rubio[5], G. Viale[6], J. Bogaerts[7], F. Cardoso[2]. *[1]The Netherlands Cancer Institute, Department of Surgery, Amsterdam, The Netherlands; [2]Institut Jules Bordet, Department of Medical Oncology, Brussels, Belgium; [3]Institut Goustave Roussy, Department of Surgery, Villejuif, France; [4]Netherlands cancer institute, Department of Molec. pathology, Villejuif, The Netherlands; [5]Hospital Vall d'Hebrón, Department of Breast Pathology, Barcelona, Spain; [6]European Institute of Oncology, Department of Pathology, Milano, Italy; [7]EORTC, EORTC Breast Cancer Group, Brussels, Belgium*

The MINDACT trial (Micro array In Node negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy) investigates whether the 70-gene profile (Mammaprint™) selects the right pts for adjuvant chemotherapy (CT) as compared to standard clinicopathological criteria. All pts have the 70-gene test (genomic high vs low risk) and clinical-pathological prognostic risk, the latter assessed through a modified version of Adjuvant! Online (low risk defined as >88% 10-years breast cancer specific survival for ER-positive and >92% for ER-negative disease). Genomic (G) and clinical (C) high risk pts are proposed adjuvant CT and may be randomized between an anthracycline-based regimen and the combination docetaxel-capecitabine. G-low and C-low risk patients do not receive CT. All ER-positive pts are offered an endocrine therapy randomization between 7 years of letrozole and 2 years of tamoxifen followed by 5 years of letrozole. Discordant patients (G-low/C-high or G-high/C-low) are randomized between decision of adjuvant CT based on G or C risk assessment. The study aims to enroll 6000 pts and has a predefined "pilot phase" of 800 pts to ensure its feasibility. The first pt was enrolled in March 2007, and in November 2008 accrual passed the 800 enrolled pts (i.e. pts with treatment assigned); these first pts are all node negative. The IDMC reviewed data from this pilot phase and endorsed communication of these results:

- The accrual is currently around 140 enrolled pts/month.
- 46% of screened pts were enrolled; 73% of screened pts had their sample shipped; of the shipped samples, 67% went through successful hybridization and testing by the 70-gene array.
- Reasons for non-eligibility: 28% of cases node positivity (before amendment), 29% for sample quality problems, 43% for failure to enrol within timelines or other reasons.
- C/G risk allocation: C/G low risk: 386 pts (48%); C/G high risk 198 pts (24.8%); C low risk/G high risk: 75 pts (9.4%); C high risk/G low risk 141 pts (17.6%). Total proportion of discordant cases: 27%.
- A statistically significant difference of 8.25% (C. I 4.7–11.8) is observed between pts that have a high C risk (42%) and those with a high G risk (34%) showing that, in the accrued population, more pts are assigned low risk by the G test than the C one.
- Compliance to randomization: within the key group of 69 pts with high C risk/low G risk assigned to no CT, 3 pts still received CT. In the 39 pts C low/G high risk assigned to CT, 5 pts did not receive it. Overall compliance >92%.

Conclusions: (1) The logistically complex MINDACT trial is feasible in an multinational setting. (2) The proportion of discordant pts, the expected reduction in CT in the 70-gene low risk group, and the compliance to treatment assignment in the discordant groups are according to plan. (3) The trial continues to accrue with new centers joining, and it was amended to include node positive disease, decreased tumor cellularity needed and increased timelines; these measures have already substantially decreased the number of ineligible pts.

445 Proffered paper oral

Beta-blocker treatment is associated with a reduction in tumour metastasis and an improvement in specific survival in patients with breast cancer

D.G. Powe[1], M.J. Voss[2], H.O. Habashy[3], K.S. Zänker[2], A.R. Green[3], I.O. Ellis[1], F. Entschladen[2]. *[1]Nottingham University Hospitals Trust, Cellular Pathology, Nottingham, United Kingdom; [2]University of Witten/Herdecke, Institute of Immunology, Witten, Germany; [3]University of Nottingham, Molecular Medical Sciences, Nottingham, United Kingdom*

Background: Breast cancer (BC) is the most common cause of cancer death in women and usually results from metastatic events. Recent studies suggest that neurotransmitters induce cancer cell migration mediated by beta2-adrenergic receptors (β_2AR). Therapeutic treatment with beta-blockers could protect against metastasis development giving improved clinical outcome in BC.

Materials and Methods: An epidemiologic study of beta-blocker treatment and its associations with metastasis and BC-specific survival

were undertaken in patients with primary operable BC (n = 466). Secondly, protein levels of one of the target receptors for beta-blockers, β_2AR, was assessed as a candidate biomarker of clinical outcome using tissue microarray and immunohistochemistry (n = 689 cases).

Results: 92/466 patients received antihypertensive treatment and 43/92 (46.7%) BC patients were on beta-blocker treatment at the time of BC diagnosis and they showed a significant reduction in formation of distant metastases ($p = 0.03$) and local recurrence ($p = 0.003$). Moreover, they showed increased survival and 71% reduced risk of BC specific mortality, indicated by a hazard ratio of 0.288 ($p = 0.007$).

β_2AR protein expression was significantly increased in small tumours ($p = 0.006$) of low grade ($p < 0.001$) and lymph node stage ($p = 0.027$), characterized by positive association with luminal markers (CK18, ER, PgR: all $p < 0.001$). β_2AR expression did not significantly predict clinical outcome.

Conclusions: Beta-blocker treatment appears to significantly reduce metastasis and mortality in BC patients. Measurement of one of the beta-blocker target receptors, β_2AR, was not shown to be predictive for determining clinical outcome and other beta-blocker targets need investigating. Further studies are needed to validate the use of beta-blockers as a possible adjuvant therapy in BC.

Friday, 26 March 2010 15:30–17:00

EUROPA DONNA SESSION

Implementation of the European Union Guidelines for quality assurance in breast cancer screening and diagnosis

446 Invited

Breast specialist perspective

M. Rosselli del Turco[1]. [1]*EUSOMA, President, Florence, Italy*

Since 1990, in USA and many European countries, breast cancer mortality is decreasing by 1−2% per year, thanks to early detection and improved treatment. Breast cancer care is complex, onerous and expensive; therefore quality assurance is essential to monitor effectiveness and to guide improvements in healthcare.

In Europe there are wide differences in breast cancer care in terms of quality and offer of screening and treatment (mastectomy and radiotherapy rates, use of adjuvant chemotherapy and hormone therapy). It has also been shown that high quality screening programs and specialized breast cancer care are associated with a significant reduction in mortality.

The European Guidelines for Quality Assurance in Breast cancer screening and diagnosis (EG) were published in the first edition in 1993 under the scientific co-ordination of EUREF and were periodically updated: the current edition is the fourth, published in 2006. The first task of the EG was to improve the quality of the screening test (mammography): the protocol for physico-technical quality control of conventional mammography is a worldwide reference document, such as the protocol for quality assurance of digital mammography, included in the last edition. Then guidelines for epidemiology, pathology, radiology, training and communication have been developed within the European Cancer Network and, in co-operation with EUSOMA, different aspects of quality in breast cancer care as multidisciplinarity, surgical treatment and requirements of a breast unit, have been defined. All these documents are included in the fourth edition and represent a comprehensive document that all European breast-dedicated services should strictly follow.

The major tasks now are:

– to assure a periodic update of the EG according to new technologies and clinical evidence
– to expand quality assurance to other aspects of breast cancer care as medical treatment, radiotherapy, follow-up and patient support.
– to verify that the EG are effectively implemented in all Europeans countries.

It has to be noticed, anyhow, that the great success of the EG was due to the recognised professional skill of the AA, fully dedicated to breast cancer care, who have been able to demonstrate that quality can be reached by following standardised procedure and protocols.

447 Invited

Mammography screening − what is going on in Europe

L. Von Karsa[1]. [1]*IARC, Quality Assurance Group, Lyon, France*

Introduction: Europe leads the way world-wide in implementation of population-based screening. Breast cancer claims the lives of more women than any other cancer. According to 2006 estimates of the International Agency for Research on Cancer, 330,000 women in the EU are diagnosed with breast cancer and 90,000 women die from the disease every year [1]. In 2003, the Council of the European Union invited the EU member states to implement mammography screening programmes for women 50−69 years of age according to European Guidelines for quality assurance in mammography [2]. A Citizens' Guide to the EU Guidelines [5] has been published by Europa Donna, the European Breast Cancer Coalition. The ECN has also examined the extent to which population-based breast screening programmes recommended by the Council of the EU have been implemented in Europe.

Methodology: In 2007 a questionnaire was sent to the 27 EU member states by DG SANCO. Data from two pan-European projects in the EU Health programme were used to check plausibility and to supplement the data base: ECN and EUNICE (European Network for Information on Cancer). Population statistics were obtained from EUROSTAT or from national sources, if more recent data were available. The final report was based on information provided by official sources in all EU 27 member states.

Results: In 2007, publically mandated breast screening programmes were running or being established in 26 of the 27 EU member states. Population-based programmes were running or being established in 22 member states. In the member states which have adopted a population-based approach for breast cancer screening, the smallest target age range was 50−59 years and the largest age range was 40−74 years.

The greatest uniformity is reflected in the recommended screening interval which only exceeded a two-year period for women in the age group 50−69 years in two of the 26 member states.

Development and piloting of an EU-wide accreditation/certification scheme mandated by the member states and based on EU quality assurance guidelines would encourage programmes throughout the EU to take the initiative to continuously improve perfor-mance and would help consumers to recognize which services achieve the EU standards.

Conclusions: Despite the broad consensus among the EU member states in the expanded EU on the importance of population-based screening as a tool of cancer control, considerable effort will be required over the coming years to successfully implement current policies and to overcome existing barriers to successful programme implementation.

Astrid Scharpantgen, RN, MPH, Europa Donna Luxembourg, Ministry of Health, Luxembourg
Dr. Lawrence von Karsa, Quality Assurance Group, International Agency for Research on Cancer, Lyon, France

References

[1] Karsa L v, Anttila A, Ronco G, et al. (2008) Cancer screening in the European Union, Report on the implementation of the Council Recommendation on cancer screening − First Report. European Communities (publ.), Luxembourg
[2] Council of the European Union (2003) Council of the European Union. Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC). Off J Eur Union; L 327/34−38.
[3] European Commission. European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. Fourth edition (2006) Perry N, Broeders M, de Wolf C, et al. (eds). Office for Official Publications of the European Communities, Luxembourg.
[4] Perry N, Broeders M, de Wolf C, et al. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition-summary document. Ann Oncol 2008 19(4): 614−22.
[5] Short guide to the European Guidelines for quality assurance in breast cancer screening and diagnosis, 1st edition, October 2007, EUROPA DONNA, The European Breast Cancer Coalition.

448 Invited

Advocacy perspective

S. Knox[1]. [1]*European Breast Cancer Coalition (EUROPA DONNA), Executive Director, Milan, Italy*

The overriding mission of European breast cancer advocacy is to ensure that all European women have information on and access to state-of-the-art early detection, screening, and treatment of breast cancer. A main objective of Europa Donna-The European Breast Cancer Coalition (ED), has been to establish advocacy groups in all the countries of Europe in order to advocate for guidelines for best practice, i.e. implementation of the 2006 "European Guidelines for quality assurance in breast cancer screening and diagnosis" published by the European Commission. This has been our priority for the last few years and continues to be so for the foreseeable future until all women have access to these essential services for their breast health. ED uses this document as the basis for all its information, advocacy and lobbying programmes today. It is highlighted at all our conferences, at our advocacy training course, on our website and has even