Response **I**n a**D**vanced br**E**ast cancer) is a global randomized double-blind placebo-controlled phase III study assessing the efficacy and safety of L-BLP25 in combination with hormonal treatment as first-line therapy for postmenopausal women with hormone receptor-positive, advanced BC. Here we present the design of the STRIDE study.

Methods: Eligible pts are postmenopausal women aged ⩾18 years with estrogen and/or progesterone receptor-positive, inoperable (by RECIST criteria) locally advanced, recurrent, or metastatic BC. They have HER2-negative disease and express ⩾1 of the following five HLA haplotypes: HLA-A2, -A3, -A11, -B7, or -B35. Accrual into the study is ongoing with a target of 909 pts to be recruited by approximately 180 sites in around 30 countries worldwide. In addition to receiving standard hormonal treatment (tamoxifen, anastrozole or letrozole), pts are randomized 2:1 to receive either 1000 μg L-BLP25 or placebo. Pts receive weekly subcutaneous vaccinations for 8 weeks, followed by maintenance vaccinations every 6 weeks until disease progression. Patients are stratified by disease stage, concomitant use of tamoxifen vs aromatase inhibitors, and exposure to prior adjuvant hormonal treatment. The primary endpoint is progression-free survival (PFS) time; secondary endpoints include overall survival time, objective tumor response, safety/tolerability, and quality of life. Exploratory biologic analyses are planned.

Results: The final analyses of PFS time and secondary efficacy endpoints will be conducted using data obtained when more than 586 progression-defining events have occurred in the study population.

Conclusions: The STRIDE study will investigate whether vaccination with L-BLP25 can extend PFS time in pts treated with hormonal therapy as first line therapy, who have inoperable, locally advanced, recurrent or metastatic BC.

Wednesday, 24 March 2010 18:15–19:15

POSTER SESSION

Targeting and profiling predictive and prognostic factors

102 Poster discussion

How the 70-gene tumour expression profile "MammaPrint" can assist in St Gallen 2009 treatment recommendations in 12 Italian hospitals

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Background: A microarray-based 70-gene tumor expression profile "MammaPrint" was established as a powerful predictor of disease outcome in breast cancer. The St Gallen 2009 recommendations include gene-expression signatures as an indicator for adjuvant therapy. Here we determined in a prospectively assessed Italian cohort how the 70-gene profile can assist in patient management.

Methods: MammaPrint was determined on 524 samples submitted in 2008 and 2009, from breast cancer patients (clinical T1−4N0−3M0) aged 26 to 98 years (median age 62 years). Fresh tumor samples were prospectively collected in 12 Italian hospitals by core needle biopsy or from a surgical specimen (study protocol MP 090). We assessed agreement between the treatment advice as recommended by the 2009 St Gallen Highlights and classification according to the 70-gene MammaPrint profile.

Results: According to the St Gallen 2009 treatment recommendations, 17 patients could forego any adjuvant treatment (<1cm, LN0, PVI 0). Of these patients, 9 (53%) were classified to be poor prognosis signature by MammaPrint. The 84 Her2+ patients would be recommended anti-HER2 treatment as well as adjuvant chemotherapy according to the 2009 recommendations. Of these patients, 11 (13%) were classified as good prognosis signature by MammaPrint. All 43 (ER−) patients who are recommended chemotherapy alone are classified as poor prognosis by MammaPrint. For the 380 ER+, HER2− patients, 9 would be recommended no adjuvant chemotherapy (Grade I and LN0 and 2 cm and ER >50%) and 199 would be recommended adjuvant chemotherapy being either Grade III, or ?4LN, or >5 cm, or ER < 50%. Of these 199 patients, 60 (30%) are classified as low risk by MammaPrint. The remaining 172 ER+, HER2− patients fall in the subgroup for which St Gallen 2009 states that they have characteristics that are not useful for decision making; MammaPrint classified 102 (59%) as poor prognosis and 70 (41%) as good prognosis. Clinical data collection for an additional 364 patients is pending.

Conclusion: Widespread use of the MammaPrint prognosis signature has been accomplished in Italian community hospitals. For the majority of patients (90%) the St Gallen Highlights 2009 either recommend or suggest considering treatment with cytotoxic adjuvant therapy for whom MammaPrint indicates a low risk of recurrence in 31% of cases, potentially sparing patients from adverse effects.

103 Poster discussion

Socioeconomic differences in breast cancer tumour size and relative survival in the Netherlands

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Background: Breast cancer is the most commonly diagnosed cancer among females in developed countries. Despite improvement in survival over the last years, socially deprived females with breast cancer seem to have a decreased survival; usually due to a higher stage of disease at diagnosis. Aim of this study was to assess differences in T-stage and survival according to socioeconomic status (SES) for females with breast cancer in the Netherlands.

Methods: All females diagnosed with breast cancer between 1995 and 2005 in the Netherlands were selected from the Netherlands Cancer Registry. Patients were linked to the database of the Netherlands Institute for Social Research which keeps record of the SES according to postal code. A multivariable logistic regression was used to assess factors associated with SES. Overall Survival (OS) and Relative Survival (RS) were calculated where RS was calculated as the ratio between the survival observed and the survival that would have been expected based on the corresponding general population.

Results: Overall, 127599 patients were included. There was an association between SES and T-stage at diagnosis ($p < 0.0001$) after adjusting for histology, grade, N-stage and M-stage. Both OS and RS were associated with SES, with a decreased survival for the patients with a lower SES. Overall, 5-year OS was 80% for the high SES group and 75% for the low SES group (HR 1.4 (95% CI 1.3−1.5; $p < 0.001$) and RS was 87% versus 83% (RER 1.3 (1.2−1.4; $p < 0.001$). The socioeconomic differences remained statistically significant ($p < 0.001$) after adjustment for age, years, grade, TNM stage and surgical treatment.

Conclusion: Socioeconomic differences in T-stage and survival were observed in the Netherlands. The higher T-stage at diagnosis of patients with a lower SES only partly explains the decreased survival for females with breast cancer. To improve the decreased survival further research is needed to identify reasons for these socioeconomic disparities.

104 Poster discussion

Molecular biomarkers to predict neoadjuvant chemotherapy response in breast cancer patients treated with weekly paclitaxel plus carboplatin

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Background: Previously, we have reported the weekly PCb (Paclitaxel + Carboplatin) regimen in neoadjuvant chemotherapy (NCT) for breast cancer had a pCR rate of 19.4% (SABCS 2009, abstract 1099). However, there is lack of reliable marker to predict the efficacy of PCb. To identify molecular biomarkers and built different models including various markers to predict the efficacy and to evaluate whether including candidate molecular markers can improve the predictive accuracy of model for predicting response of weekly PCb NCT.

Materials and Methods: Retrospectively analyzed patients treated with weekly PCb (Paclitaxel 80 mg/m^2 and Carboplatin AUC=2, given day1, day8 and day15 out of every 4 weeks) NCT, routine clinical and pathological markers as well as pCR status were collected. Hormonal Receptor (HR)

positive was defined as ER/PR positivity. Breast cancer were calssified into different molecular subtypes as follows: Luminal A (HR+/HER2−), Luminal B (HR+/HER2+), Triple-negative (HR−/HER2−) and HER2 positive (HR−/HER2+) subtype. 11 candidate molecular biomarkers including Tau, β-Tubulin III, PTEN, MAP4, Thioredoxin, MDR1, Ki67, p53, Bcl-2, BAX and ERCC1 were detected by IHC in pre-NCT core needle biopsy specimens and analyzed the relationship between these markers and pCR. Logistic Regression Models including routine clinical, pathological markers and candidate molecular markers in various combinations were built to compare different predictive accuracy of models for predicting pCR.

Results: 91 patients had available core needle biopsy specimens for evaluation, and 18 patients achieved pCR with pCR rate 19.8%. Univariate analysis showed that ER, PR, molecular classification (clinicopathological markers) and Tauβ-Tubulin III?p53?Bcl-2?ERCC1 (candidate molecular markers) were associated with pCR; Multivariable analyze revealed that β-Tubulin III, Bcl-2 and ERCC1 were independent pCR predictive markers, β-Tubulin III-negative, Bcl-2-negative or ERCC1-negative was associated with higher pCR rate, with OR 6.03 (95% CI, 1.44–25.24, $P = 0.014$), 7.54 (95% CI, 1.52–37.40, $P = 0.013$) and 4.09 (95% CI, 1.17–14.30, $P = 0.028$), respectively. To compare different Logistic Regression Models built with different combination of these variables, we found the model including routine clinical, pathological and β-Tubulin III, Bcl-2, ERCC1 these three candidate molecular markers had highest predictive power, area under ROC (Receiver Operating Characteristic, ROC) curve was 0.900 (95% CI, 0.831–0.968).

Conclusion: β-Tubulin III, Bcl-2 and ERCC1 were independent pCR predictive factors among breast cancer patients treated with weekly PCb regimen as NCT. Patients with β-Tubulin III-negative, Bcl-2-negative or ERCC1-negative tumors had a higher pCR rate. Model integrating routine clinical, pathological and β-Tubulin III, Bcl-2, ERCC1 candidate molecular markers had highest predictive power of predicting the pCR rate of this weekly PCb regimen.

105 Poster discussion

Association of the germline MDM2 SNP309 and TP53 R72P variants with breast cancer survival in specific tumour subgroups

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Germline and somatic mutations in genes such as those of the "DNA damage response pathways" are associated with development of specific tumor subtypes and influence breast cancer outcome. One of those pathways includes the tumor suppressor gene *TP53* and its regulator *MDM2*. Interaction between *TP53* germline mutation status and *MDM2* SNP309 carriership is known to accelerate tumor development. Moreover, somatic inactivation of the *TP53* gene in breast tumors is related to a poor prognosis. Here we inverstigated wether common germline polymorphisms in genes of the 'TP53 response pathway' might affect breast cancer outcome. In particular we evaluated their contribution to the prognosis of tumors that harbor specific additional somatic changes. We determined the effect of the germline *TP53* R72P and *MDM2* SNP309 polymorphisms on breast cancer survival in distinct tumor subgroups in a consecutive cohort of breast cancer patients (age at diagnosis <53 years, n = 295). Tumors were classified in subgroups according to *TP53* somatic mutation status (n = 209) (wild type (including silent mutations) versus missense and non-missense mutations) or the 70-gene prognostic (good versus poor prognosis) profile (n = 295). Analyses were performed using Cox regression models adjusting for clinico-pathological characteristics and treatment. A decreased breast cancer-specific survival was found for carriers of the germline *MDM2* SNP309 GG genotype compared to those carrying the common TT genotype, only within those patients having *TP53* mutated tumors (HR 3.35 (95% CI: 1.02–11.0) compared to *TP53* wild type tumors: HR 1.01 (0.31–3.29)). Additionally the same effect was seen within those patients with a poor prognosis profile tumors (HR 2.39 (1.21–4.73) compared to the good prognosis profile tumors: HR 0.55 (0.10–3.22)).

A similar trend was seen for carriers of the germline *TP53* R72P GC genotype versus those carrying the common GG genotype (*TP53* mutated tumors compared to *TP53* wildtype tumors: HR 2.01 (0.87–4.64) and HR 1.16 (0.53–2.54); poor compared to good prognosis profile tumors: HR 1.57 (0.98–2.51) and HR 0.33 (0.08–1.37)). These results support our hypothesis and are in line with the available biological evidence. Common polymorphisms in specific pathways in combination with somatic changes (in the same pathway) in the tumor may become of importance in predicting prognosis of breast cancer patients.

106 Poster discussion

Locoregional recurrence after breast conserving therapy remains an independent prognostic factor even after an event free interval of ten years in early stage breast cancer

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Background: Locoregional recurrence after breast-conserving therapy is a well-known independent risk factor associated with unfavourable long-term outcome. Controversy exists however of the prognostic impact of a locoregional recurrence after a very long event free interval.

Materials and Methods: Data were pooled from 4 EORTC Breast Group trials, which accrued patients with early stage breast cancer. Only locoregional recurrences as first event were taken into account. Univariate and multivariate Cox regression analyses were conducted using locoregional recurrence as a time-dependent variable in a landmark analysis to study the independent prognostic impact of locoregional recurrence on long-term outcome after different event-free time intervals. Long-term outcome was defined as distant disease-free survival and overall survival. Three different landmark analyses were undertaken. One analysis including all breast conserved patients, one analysis that included only patients with an event-free interval of at least 5 years, and one analysis including patients who were event-free for at least 10 years after primary diagnosis.

Results: In total, 7749 early stage breast cancer patients who underwent breast-conserving therapy were included. At time of the analysis, the median follow up was 10.9 years. In the multivariate analysis, including all patients, locoregional recurrence, tumour size, nodal status, young age, oestrogen receptor status and chemotherapy remained independent prognostic factors with a significant impact on long-term outcome. Locoregional recurrence was the strongest prognostic factor for overall survival (HR 5.07 95% CI 4.37–5.88, P < 0.01) and distant disease-free survival (HR 5.24, 95% CI 4.50–6.10, P < 0.01). In the multivariate analysis including patients that had an event-free interval of at least 5 years, locoregional recurrence remained the strongest independent prognostic factor for overall survival (HR 3.69, 95% CI 2.64–5.19, P < 0.01) and distant disease-free survival (HR 3.87, 95% CI 2.84–5.27, P < 0.01). In patient that were event free f more than over ten years after primary treatment, locoregional recurrence remained the only independent prognostic factor with a significant impact on both distant-disease free survival (HR 4.08, 95% CI 1.25–13.27, P 0.02) and overall survival (HR 8.38, 95% CI 2.54–27.63, P < 0.01).

Conclusions: Locoregional recurrence after breast-conserving therapy is a very strong time dependent independent factor for long term outcome even after a very long event-free interval in early stage breast cancer patients. These findings suggest that even after a long event free interval, locoregional recurrence seems to be associated with distant disease rather than a cause of subsequent distant disease.

107 Poster discussion

Comparison of Adjuvant! Online prediction with 10-year follow-up results according to the uPA and PAI-1 levels in Slovenian early breast cancer patients

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Background: Adjuvant! Online is very useful tool for prognosis assessment of early breast cancer (EBC) patients. It is very consistent for the low risk patient according to the classical clinicopathological criteria (eg. small tumors, node negative, grade 1−2), as it was presented in our previous work. uPA and PAI-1 are level 1 prognostic markers in EBC and when high they characterize poor prognosis.

Methods: 753 EBC patients diagnosed and treated in the Institute of Oncology from 1996–1999 and with 10-year follow-up were included into the study. The basic clinical-pathological characteristic were assessed for each patient and entered into the Adjuvant! Online (Version 8.0) to calculate estimated 10-year OS. uPA and PAI-1 levels were measured routinely using ELISAs (American Diagnostica Inc.; CT) in tumor tissue extracts