Background
Molecular subgroups within early breast cancer (EBC), such as Luminal A, Luminal B, HER2+, Basal-like may help to best to identify patients for specific treatment regimes. Controversy exists as to which methodology is best at identifying these molecular subgroups. Immunohistochemistry (IHC) may be used as a surrogate method to stratify patients. Molecular subtyping, gene expression based tests, such as BluePrint, measure a greater number of genes than pathological criteria. ER, PgR, HER2 and Ki67 protein status are measured individually at the protein level, while BluePrint is designed to capture the functional underlying biologic pathway regulated by these receptors.

Methods
The MINDACT trial is an international, prospective, randomized, phase III trial which has proven the clinical utility of MammaPrint in selecting EBC patients who can safely avoid chemotherapy. Here we present the results of a preplanned MINDACT sub-study to compare outcome based on molecular subtyping to surrogate pathological subtyping as endorsed by 2013 St. Gallen Consensus. Molecular Subtyping (MS) data were obtained by MammaPrint (MP) and BluePrint classifying patients in the following subtypes: Luminal A (MP Low Risk); Luminal B (MP High Risk); HER2-type; and Basal-type. ER, PgR, HER2 and Ki67 protein status were centrally assessed by IHC/FISH. The primary hypothesis was that among Pathological Subtyping (PS) Luminal patients, patients with HER2- or Basal-type tumors by MS would have a decreased DFS compared to MS Luminal patients.

RESULTS

Pathological Luminal A

Pathological Luminal B

Pathological HER2-enriched

Pathological Triple-Negative

Molecular Subtyping (MS) classified 54% as Luminal A among the Luminal B by Pathological Subtyping (PS). MS classified 38% as Luminal A and B and 5% as Basal-type among the HER2+ by PS. MS classified 5% as Luminal A and B among the TN cases by PS.

Molecular Subtyping identifies 63% of patients as Luminal A, while Pathological Subtyping identifies 44% (61.6%). Syr DMRs for both methods was a 96.0%. PS Luminal cancers that were classified as HER-2 or Basal-type by MS had a lower Syr DMRs (88.0% for HER-2+ and 90.2% for Basal), albeit non-significant, than those who were also Luminal by MS (95.9%). HER-2+ 1.40, 95% CI 0.75-2.60.

CONCLUSIONS

1) Molecular Subtyping was able to re-stratify 16% of patients to a low risk Luminal A-type group with an excellent outcome.

2) Centrally assessed Ki67 labeling index of 20% may be better than 14% cut-off for surrogate differentiation between Luminal A and B.

3) Among Triple Negative early breast cancer patients, 5% were classified as Luminal by Molecular Subtyping and had an excellent outcome.

4) The observed subtype discrepancies may have an impact on treatment decision making.

5) Albeit limited by low numbers of patients in each subgroup, this study suggest that Molecular Subtyping is better correlated with outcome than pathological classification.

Acknowledgements
This study received support from the European Commission FP7-2007-2013, the European Commission Framework Programme VI (FP6-LSHC-2006-025740), the Santa Cruz Cancer Institute Foundation (SCCI), the Dutch Cancer Society (KWF), Association Le Cancer du Sein, Mois du Cancer du Sein (2004 award), Susan G. Komen for the Cure (SG05-0922-02), Fondation pour la Recherche Medicale (2005, 2006 JSMF award), Prix Goldhirsch et al, Ann Oncol 2013

Goldhirsch et al, Ann Oncol 2013

BluePrint - measures ER function - mRNA expression of 80 genes

ER protein (IHC)