To date, it has not been widely addressed whether treatment with neoadjuvant therapy significantly alters index signatures between pre- and post NAT breast tumors for patients who do not achieve a complete response (pCR) as the endpoint (Whitworth et al. 2014). The Neoadjuvant Breast Symposia Trial (NBRST) has shown that MammaPrint and BluePrint reclassify 22% of tumors by intrinsic subtype, and better predicts response to neoadjuvant chemotherapy (NCT) than clinicopathological factors, using pathologic complete response (pCR) as the endpoint (Whitworth et al. 2014). To date, it has not been widely addressed whether treatment with neoadjuvant therapy (NAT) leads to molecular changes in a tumor or eliminates susceptible clones leaving resistant subtypes.

The purpose of this study was to determine if there is a meaningful change in gene expression profiles between pre- and post NAT breast tumors for patients who do not achieve a pathologic complete response.

BluePrint Indices: significantly altered by subtype following NAT, sometimes resulting in a different dominant subtype in the residual disease

Mean differences in MP and BP indices (post-NAT minus pre-NAT), by pre-NAT molecular subtype, show index-subtype dependent changes.

Comparison of MammaPrint and BluePrint Genetic Signatures in Pre- and Post-Neoadjuvant Chemotherapy Treated Breast Cancer

Peter Beitsch1, Pat Whitworth2, Paul Baron3, James PeliCANe, Pond Kelemen4, Andrew Ashkari5, Beth Ann Lesnikoski6, Cristina Lopez-Penalver7, Arnold Baskes8, Michael Rotkis9, David T. Rock10, Heidi Memmel11, Hanadi Bu-Al12, David Carlson13, Laura Lee13, Robert Reilly14, William Dooley17, Angela Misloskva18, Tina Teree19, Jia-Peng Jennifer Wei20, Mark Gittleman20.

Background

• Breast cancer is not a singular disease, rather a spectrum of cancers with different intrinsic molecular subtypes (Perou, Parker et al. 2010, Perou and Borresen-Dale 2011, von Minckwitz, Uchit 2012).

• MammaPrint® (MP) and BluePrint™ (BP) are two assays that use gene expression profiles to classify breast tumors into these intrinsic subtypes and can be used clinically to predict patient relapse, overall survival, and response to endocrine and chemotherapies (Kriigman, Roagman et al. 2012, de Snoo et al. 2013, Whitworth, Stock-Scouts et al. 2014).

• The Neoadjuvant Breast Symposia Trial (NBRST) has shown that MammaPrint and BluePrint reclassify 22% of tumors by intrinsic subtype, and better predicts response to neoadjuvant chemotherapy (NCT) than clinicopathological factors, using pathologic complete response (pCR) as the endpoint (Whitworth, Stock-Scouts et al. 2014).

• To date, it has not been widely addressed whether treatment with neoadjuvant therapy (NAT) leads to molecular changes in a tumor or eliminates susceptible clones leaving resistant subtypes.

• The purpose of this study was to determine if there is a meaningful change in gene signatures between pre- and post NAT breast tumors for patients who do not achieve a pathologic complete response.

• All patients with shifting indices may benefit from extended treatment

• Luminal A: minimal change in MP and BP indices indicates no response to NAT

• Luminal B: largest group with residual disease shows shift toward lower risk profile after NAT

• HER2: MP and BP indices significantly change following NAT, residual disease exhibits different genetic characteristics compared to the untreated tumor

• Basal: Post NAT residual tumors exhibit either minimal or substantial change in MP and BP Basal indices

Discussion

• Subtyping suggests that treatment may have 1) eliminated the most susceptible tumor subclone, or 2) that under therapeutic pressure, the original cell population illustrated an evolutionary genomic change. Either mechanism could suggest that treatment may have 1) eliminated the most susceptible subclone, or 2) that under therapeutic pressure, the original cell population illustrated an evolutionary genomic change. Either mechanism could warrant an adjustment in further disease management.

• Future clinical utility: More research is needed to assess whether index changes detected after completing NAT can also be detected during treatment, and whether those changes correlate with residual tumor burden and long-term breast cancer specific survival.