HER2 positive breast cancer is 1 of 4 main subtypes of breast cancer. It is defined by the over expression of HER 2, a protein that promotes the growth of cancer cells. It occurs in about 20 – 25% of all breast cancer. HER2 breast cancers tend to be more aggressive than other types of breast cancer. They typically carry a bad prognosis. Trastuzumab and Lapatinib are two recently developed therapies that target HER2 and have made a significant difference in the outcome of the disease. More recently genomic analysis has made it possible to look more closely at the composition of tumors with the hope of determining specific biomarkers that can be targets for treatment. In particular, focus on HER2 positive disease has found that these 4 subtypes, can also be found in HER2 positive disease.

CALGB 40601, the Alliance Trial consisted of three arms: Taxol (T) + Trastuzumab (H) + Lapatinib (L). Taxol + Trastuzumab, and Taxol + Lapatinib. Drugs were given weekly for 16 weeks, followed by surgery and then dose dense Adriamycin and Cytoxan followed by Trastuzumab for 34 weeks. The primary endpoint of the trial was pathological complete response (pCR). The Taxol/Lapatinib arm was closed early due to this arm being clearly inferior in terms of efficacy and more toxicity. This presentation looked at the most common gene mutations in the tumor to see if there was any correlation between mutation and response to treatment.

According to Dr. Carey, the motivation for this analysis was the increasing recognition that clinical subtypes of breast cancer have substantial variability in biology, which may dictate response to therapy, and particularly, that response to chemotherapy can vary depending on the subtype of disease.

The team obtained research biopsies from all women participating in CALGB 40601, and examined the molecular subtypes contained within HER2-positive disease. They found
that even within this clinically defined subset, there was marked molecular heterogeneity. About 1/3 of the tumors were biologically defined by HER2 signaling, called the “HER2-Enriched” subtype, which had the highest responsiveness. A significant number were actually luminal tumors, which are more biologically driven by hormone receptors and had lower responsiveness. The remainder included subtypes such as the basal-like that is typically associated with triple negative disease. TP53 was the most frequently mutated gene found in 56%, of the tumors, but in the HER2 enriched subtype it was found in 88% of the tumors. It was found to predict pCR to chemotherapy and HER2 targeting. PIK3CA mutation was the second most common mutation found. There was no correlation between this mutation and pCR.

NSABP – B31 was one of the adjuvant clinical trials that showed the benefit of adding Trastuzumab to the tradition treatment of Adriamycin + Cytoxan followed by Taxol that was the standard of care for treating early stage breast cancer. Together with NCCTG-N9831, these trials resulted in changing the standard of care for HER2 positive breast cancer.

Dr. Paik analyzed tissue from the NSABP – B31 trial in an effort to determine in PIK3CA and PAM 50 intrinsic subtype of a tumor was markers of response to ani-HER2 therapies. Expression data for 49 genes were used to generate PAM50 intrinsic subtypes for 1578 tumor blocks. He examined the heterogeneity of Trastuzumab treatment across different subsets and used disease free survival as an endpoint. 47% of the tumors (741) were classified as HER2 enriched subtype and 24.7% (166) of these had PIK3CA mutations. He found that PIK3CA and PAM50 intrinsic subtypes were not markers for particular additional benefit from Trastuzumab. Disease free survival improvements due to trastuzumab were similar for both HER2 enriched, non HER2 enriched tumors and tumors with PIK3Ca mutations.

This is an analysis of presentations S3-5 given by Dr. Soonmyung Paik and S3-6 given by Dr. Lisa Carey.
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