

# Updates on treatment for HER2-positive breast cancer

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In this morning's session, two updated results were presented on HER2-positive breast cancer.

The first one was a trial that compared the HER2 kinase inhibitor, Tykerb, alone or in combination with Herceptin in patients who had already progressed on Herceptin therapy. This strategy of "dual" blockade of the same target (HER2) is based on the notion that resistance to Herceptin might be overcome with Tykerb since it acts on a different part of the HER2 protein. This appears to be the case in the laboratory, and this study was reported earlier, showing an increase in the time to progression with both drugs compared to Tykerb alone.

This follow-up study was to look at survival, which was confounded by the fact that three-quarters of the patients who progressed on Tykerb had Herceptin added to their treatment, possibly diluting any survival difference. Still, this study showed an improvement in survival with dual blockade, about five months longer--this was statistically significant. Serious cardiac side effects were uncommon, 2 percent in the combination arm. This is the only study that has shown a survival advantage in patients who have progressed on Herceptin or with combination targeted therapy; therefore, the presenter, Dr. Kimberly Blackwell, felt that this all-biological regimen was a reasonable choice for patients in this setting, in addition to the approved Xeloda plus Tykerb regimen.

This study was followed by a presentation of the BCIRG 006 trial that examined Herceptin added to chemotherapy in the adjuvant setting. This study was unique among the four major adjuvant trials in that it tested a regimen (known as TCH, for Taxotere, carboplatin, and Herceptin) that did not include Adriamycin, a standard chemotherapy drug that can cause heart failure when used alone and can accentuate this side effect that is also caused by Herceptin.

The question that has not been fully answered is whether this regimen is equally as effective as the more standard combination of Adriamycin plus Cytoxan followed by a taxane plus Herceptin (AC/TH). The TCH regimen has already been adopted widely as it causes less heart side effects, and the final results of the update did indeed confirm that TCH was as good as AC/TH, with both these regimens being superior to the non-Herceptin comparator regimen of AC/T. While there were slightly more recurrences with TCH compared to AC/TH, this was not statistically significant. In addition, the small risk of leukemia that is known to occur with Adriamycin was not seen with TCH (except in one patient diagnosed with lymphoma after breast cancer and was treated with Adriamycin prior to developing leukemia).

According to the presenter, Dr. Dennis Slamon, who has spearheaded the scientific and clinical development of HER2-targeted therapy, TCH can now be considered

as effective even for high-risk HER2-positive early stage breast cancer. The subgroup of higher risk patients with four or more nodes showed similar outcomes with either Herceptin-containing regimen. He also showed some controversial information about patients who exhibit gene amplification of topoisomerase II, a cell cycle-dependent gene that is also a target of Adriamycin, and is seen in about one third of HER2-positive cases. These patients appear to be sensitive to Adriamycin such that they do not even appear to benefit from adding Herceptin, with all three regimens being equivalent in this patient subset. He still favors TCH for this group given the absence of leukemia risk seen with the two other regimens (AC/T and AC/TH).

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