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Trastuzumab Deruxtecan (Enhertu) as a New Standard of Care for HER2-low Metastatic Breast Cancer: A summary of the DESTINY-Breast04 clinical trial

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Approximately 150,000 people are diagnosed with metastatic breast cancer annually in the U.S. Half of those cases have pathology that is characterized as having HER2 (Human Epidermal Growth Factor Receptor 2) protein expression in abundant amounts, while the other half has very little HER2 expression. Historically, the population with little to no HER2-expression (also called HER2-low) had fewer treatment options since it was thought that this cancer type had poor response to HER2-targeted therapies. A recent clinical trial that was presented at the American Society of Clinical Oncologists (ASCO) annual meeting in May 2022, has provided convincing new data that disproves the currently accepted treatment paradigms.

The DESTINY-Breast04 trial investigated Trastuzumab Deruxtecan (T-Dxd or Enhertu) in the metastatic HER-2 low population. It was the first open-label, multi-center, randomized, phase 3 clinical trial to do so. Trastuzumab Deruxtecan is a combination drug that works by binding and then entering cells that express HER2 proteins, then releasing the chemotherapy, Deruxtecan, which travels to the nucleus of the cells and damages cellular machinery and DNA, ultimately leading to cell death. The Trastuzumab, which is the HER2-targeting drug, is a monoclonal antibody. Trastruzumab Deruxtecan can be classified as an antibody-drug conjugate.

The study consisted of 557 patients with HER2-low metastatic breast cancer (as defined by standard pathological testing) which were randomized in a 2:1 ratio to receiving Enhertu or “Physician’s choice” chemotherapy which generally meant the standard-of-care treatment. The patients enrolled had received one or two previous treatments for metastatic disease. The median

follow up time was 18.4 months. Impressively, the study found that Trastuzumab Deruxtecan prolonged progression-free survival by 4.8 months and overall survival by 6.6 months. In other words, T-DXd conferred a 50% reduction in risk of disease progression and a 36% reduction in risk of death. There were similar rates of grade 3 or higher adverse events requiring hospitalization (52% in the Enhertu, 67% in the chemotherapy group) which indicates the drug's safety is comparable to standard chemotherapy. However, Enhertu does confer a higher risk of systolic heart dysfunction and interstitial lung disease.

Until this trial, this metastatic patient population had limited treatment options, which mostly consisted of single-agent chemotherapies, and overall poor outcomes. The results of DESTINY-Breast04 mean that this population can now be offered targeted therapy that has proven survival benefit.

When this study was presented at ASCO, it received significant media attention because its survival benefits are impressive. However, it is important to note that its findings do not apply to localized breast cancer or DCIS. Overall, a relatively small population may benefit from this potential change to standard of care, but for them it represents a meaningful advancement. We do not yet know if there may be benefits to those with HER2-negative disease, but other trials like DESTINY-Breast06 are investigating that topic.

In conclusion, the DESTINY-Breast04 trial presented promising new data that has already changed the standard of care for patients with unresectable, metastatic breast cancer that is classified as HER2-low. It paves the way for more research to be done on the use of targeted therapies in metastatic breast cancer and beyond.

References:

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