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Predictive impact of biomarkers on pCR and survival after de-escalated neoadjuvant T-DM1 with or without endocrine therapy (ET) vs. trastuzumab+ET in HER2+/HR+ early breast cancer: WSG ADAPT TP trial

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Background

HER2+/HR+ EBC is a distinct entity associated with different molecular and clinical features compared to HER2+/HR- EBC. ADAPT TP showed promising pCR rates of 40% after only 4x T-DM1 +/- endocrine therapy (ET) which also corresponded to excellent 5y outcome. Optimal patient selection for de-escalation in HER2+/HR+ EBC is still an unsolved question.

Methods

WSG TP phase II-trial is part of the ADAPT umbrella (NCT 01779206): 375 patients (pts) with HR+/HER2+ EBC were randomized to 12 weeks of T-DM1 with/without ET vs. trastuzumab+ET q3w. Chemotherapy (CT) omission was allowed in all pts with pCR after study treatment. Primary endpoint was pCR (ypT0/is/ypN0). Secondary endpoints include safety, 5y iDFS and OS, translational research. A 3-week biopsy assessed early response defined as Ki67 decrease (vs. baseline) of ≥ 30% or low cellularity (<500 tumor cells). TILs and IHC immune markers (CD8, PD1, PDL1), PI3K mutation status and gene expression (RNA) by a custom 800-gene codeset (nCounter platform; Nanostring Technologies, Inc., Seattle, WA) were assessed on baseline samples.

Results

Baseline IHC expression of CD8 (HR 0.61; 0.36-1.01; p=0.052), of PD-L1ic (HR 0.32; 0.10-1.07; p=0.065) and CD8 expression by mRNA (HR 0.66; 0.47-0.92; p=0.015) but not TILs were associated with a decreased iDFS risk. In T-DM1 arms, $PIK3CA^{mut}$ (HR 3.66; 1.33-10.06; p=0.012) was significantly associated with increased iDFS risk. Those 55% luminal A subtype-patients (vs. others) had improved outcome (5y iDFS 96% vs. 83%; HR 0.50; 0.23-1.08; p=0.079) despite their rather low pCR rate of 25%. In multivariate analysis, clinical nodal burden was significantly associated with poor iDFS, while ESR1 and CD8 gene expression were favorable factors.

Conclusions

In HER2+/HR+ EBC, tumor immunogenicity at baseline is associated with improved survival. Poor outcome associated with $PIK3CA^{mut}$ cannot be overcome by T-DM1. HER2+/HR+ tumors are driven by HER2 and ER; this heterogeneous biology needs to be considered for future de-escalation concepts. Beyond pCR, trials in luminal A tumors should focus on survival as an endpoint.

Clinical trial identification

NCT01779206.

Legal entity responsible for the study

West German Study Group - WSG.

Funding

West German Study Group - WSG, Roche.

Disclosure

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