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Title: Final analysis of WSG-ADAPT HER2+/HR+ phase II trial: Efficacy, safety, and predictive markers for 12-weeks of neoadjuvant TDM1 with or without endocrine therapy versus trastuzumab-endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer

Harbeck N, Gluz O, Christgen M, Braun M, Kuemmel S, Schumacher C, Potenberg J, Kraemer S, Kleine-Tebbe A, Augustin D, Aktas B, Forstbauer H, Tio J, Liedtke C, Kates R, Wuerstlein R, de Haas S, Kiernmaier A, Kreipe H, Nitz U. Westdeutsche Studiengruppe GmbH Moenchengladbach, Germany; Breast Center, University of Munich and CCCLMU; Ev. Hospital Bethesda, Breast Center Niederrhein; Medical School Hannover, Institute of Pathology; Rotkreuz Clinic Munich; Clinics Essen-Mitte, Breast Center; St. Elisabeth Hospital Cologne; Ev. Waldkrankenhaus Berlin; University Clinic Cologne, Breast Center; DRK Clinic Berlin Koepenick, Breast Center; Clinic Deggendorf; University Clinic Essen, Women's Clinic; Practice Network Troisdorf; University Clinic Muenster, Women's Clinic; University Clinics Schleswig-Holstein/Campus Luebeck, Women's Clinic; Palleos Healthcare Services, Statistics; F. Hoffmann - LaRoche

Body: Background: In HER2+ early breast cancer (eBC) pCR rates after standard neoadjuvant chemo- + anti-HER2 therapy differ according to hormone-receptor (HR) status. Molecular analysis reveals HER2+/HR+ BC as a distinct entity within HER2+ BC. The ADAPT HER2+/HR+ phase II trial aims to identify early responders to endocrine + anti-HER2 therapy.

Methods: The trial completed recruitment in January 2015 (n=376). Patients (pts.) were randomized to 12 weeks of neoadjuvant therapy: A:T-DM1 (3.6 mg/kg q3w) vs. B:T-DM1 with endocrine therapy (ET) (pre-: tamoxifen; postmenopausal: aromatase inhibitor) vs C:trastuzumab q3w+ET. After surgery, standard chemotherapy at investigators’ discretion and completion of 1y trastuzumab were recommended. Trial tests pCR (yPN0 and ypT0/is) in after T-DM1 or T-DM1+ET compared to T+ET. Biomarkers are measured at baseline and after 3 weeks.

Results: Pre-planned interim analysis (n=130) aimed to identify an early-response biomarker (e.g. Ki-67 drop) and to validate trial assumptions. Median age was 49 years; 55% were pre-menopausal; 40% had cT1 tumors, 51% cT2; 68% had cN0, 27% cN1; 75% had G3. Median baseline Ki67 was 30%. In all arms, more than 95% received all 4 therapy cycles. 16 SAEs were reported in 13 pts (A:7; B:6; C:3); all CTC grade 1 (1), 2 (11) or 3 (4); all pts completely recovered without sequelae.

Overall pCR rate was 30.8%: T-DM1: 40.5%, T-DM1+ET: 45.8%, T+ET: 6.7%. The difference between either arm T-DM1 arm vs. T+ET was significant (p<0.001). Exploratory analysis suggests benefit of adding ET to T DM1 in pre- (pCR: 27.3% for T-DM1 single agent vs. 45.5% with ET) but not in postmenopausal pts (pCR: 60% vs. 46.2%). Substantial early therapy response did not permit Ki-67 quantification in the 3-week biopsy in 43.1% due to low cellularity (<500 tumor cells). PIK3CA mutation analysis (n=114) revealed a mutation rate of 15.8% (n=18). Overall pCR rate was 35.4% (n=96) for wildtype and 17.6% (n=18) for tumors with PIK3CA mutation. Ongoing biomarker analyses include further mutation analysis and intrinsic subtypes in the total trial collective.

Conclusions: The WSG-ADAPT HER2+/HR+ phase II trial is internationally the first large prospective randomized phase II trial specifically conducted within this distinct subtype. Interim analysis demonstrated for the first time clinically meaningful pCR rates (>40%) after short therapy (12 weeks) of T-DM1 ± ET without systemic chemotherapy in HER2+/HR+ eBC. Final efficacy and safety data will be presented at the meeting together with results of the correlative science program.