TPS629 Poster Session

HERTHENA-Breast03: A phase 2, randomized, open-label study evaluating neoadjuvant patritumab deruxtecan + pembrolizumab before or after pembrolizumab + chemotherapy for early-stage TNBC or HR-low+/HER2− breast cancer.

Joyce O'Shaughnessy, Julie Marie Collins, Lili Yao, Karen L. Smith, Jaime A. Mejia, Michael A. Danso; Baylor University Medical Center, Texas Oncology, Dallas, TX and Sarah Cannon Research Institute, Dallas, TX; Daiichi Sankyo, Inc., Basking Ridge, NJ; Merck & Co., Inc., Rahway, NJ; Virginia Oncology Associates, Norfolk, VA

Background: The standard of care for patients with high-risk, early-stage TNBC is neoadjuvant pembrolizumab (pembro) + chemotherapy followed by adjuvant pembro. Patients with HR-low+/HER2− breast cancer may also be treated per recommendations for TNBC. There is a need for improved neoadjuvant therapy to increase the rate of pCR, as patients who do not achieve pCR have a high risk of recurrence, and to reduce risk of long-term toxicities associated with cyclophosphamide and anthracyclines. HER3 is frequently expressed in breast cancer and implicated in drug resistance. Patritumab deruxtecan (HER3-DXd) is an antibody-drug conjugate comprising a fully human anti-HER3 IgG1 monoclonal antibody linked to a topoisomerase I inhibitor (DXd) via a stable tetrapeptide-based linker that is selectively cleaved within tumor cells. This phase 2 study (NCT06797635) will evaluate neoadjuvant HER3-DXd + pembro before or after carboplatin + paclitaxel + pembro for early-stage TNBC or HR-low+/HER2− breast cancer. **Methods:** Eligible participants (pts) are adults (≥18 y) with untreated, locally advanced nonmetastatic (AJCC stage cT1c, N1–N2 or cT2–cT4, N0–N2) TNBC or HR-low+/HER2− breast cancer. Pts (N ≥10 and ≤30) in part 1 of the study (safety lead-in) will receive neoadjuvant HER3-DXd + pembro followed by carboplatin + paclitaxel + pembro (Table) then surgery. DLT evaluation and dose finding for HER3-DXd (three dose levels of 5.6 mg/kg Q3W, 4.8 mg/kg Q3W and 3.2 mg/kg Q3W) during cycle 1 of neoadjuvant HER3-DXd + pembro will be performed in part 1 to determine an acceptable dose of HER3-DXd for part 2. Pts (N ~342) in part 2 will be randomly assigned 1:1:1 to arm A, B or C (Table) for neoadjuvant treatment. Randomization will be stratified by cancer type (TNBC vs HR-low+/HER2−) and, in the TNBC subgroup, PD-L1 status (combined positive score ≥10 vs <10), overall stage (II vs III) and HER3 expression (low vs high). After neoadjuvant treatment, pts will undergo surgery (with postoperative radiotherapy if clinically indicated) and receive adjuvant pembro 400 mg Q6W for 5 cycles. Pts with residual disease may receive additional adjuvant treatment of physician's choice. Primary endpoints are safety (part 1 and 2) and pCR (ypT0/Tis ypN0) (part 2). Enrollment is ongoing. Clinical trial information: NCT06797635. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). This study is part of a collaboration between MSD and Daiichi Sankyo, Inc.

	Neoadjuvant cycles 1-4	Neoadjuvant cycles 5-8
Part 1 Arm A	HER3-DXd 5.6 or 4.8 or 3.2 mg/kg Q3W + pembro[a]	Carboplatin[b] + paclitaxel[c] + pembro[a]
Part 2 Arm A	HER3-DXd (selected dose from Part 1) + pembro[a]	Carboplatin[b]+ paclitaxel[c] + pembro[a]
Part 2 Arm B	Carboplatin[b] + paclitaxel[c] + pembro[a]	HER3-DXd (selected dose from Part 1) + pembro[a]
Part 2 Arm C	Carboplatin[b] + paclitaxel[c] + pembro[a]	Doxorubicin[d] OR epirubicin[e] + cyclophosphamide[f] + pembro[a]

[a]200 mg Q3W; [b]AUC 1.5 mg/mL/min QW; [c]80 mg/m^2 QW; [d]60 mg/m^2 Q3W; [e]90 mg/m^2 Q3W; [f]600 mg/m^2 Q3W.