Background PARP inhibitors (PARPi) have shown significant improvement in PFS compared to chemotherapy in patients with BRCA1/2m advanced breast cancer (ABC). However, response durability remains a challenge. PARPi activates the cGAS-STING pathway, leading to increased PD-L1 expression and cytotoxic T-cell recruitment, potentially rendering tumors more susceptible to immunotherapy.

Methods The TALAVE trial (NCT03964532) enrolled two cohorts: cohort 1 included BRCA1/2m, HER2-negative ABC, and cohort 2 included BRCA1/2 wildtype TNBC. Patients received a 4-week induction of talazoparib (1mg daily D1-D28), followed by combined daily talazoparib and avelumab (800mg D1, D15). Serial biopsies were collected for comprehensive molecular analysis, including RNA profiling using Nanostring PanCancer IO360TM Panel, GeoMx® Digital Spatial Profiler (DSP) Whole Transcriptome Atlas (WTA), and protein spatial analysis using NanoString GeoMx® DSP Protein Assays, multiplex tissue Cyclic Immunofluorescence (CyCIF), and AKOYA Biosciences Vectra®.

Results Cohort 1 exhibited significantly prolonged median PFS compared to cohort 2 (9.3 vs. 2.9 months). Protein and RNA assays of pre- and post-treatment biopsies demonstrated distinct differences between the cohorts. Talazoparib monotherapy led to increased PD-L1 protein expression in tumor cells and macrophages. RNA profiling demonstrated disrupted microhomology-mediated end-joining, antiproliferative effects, upregulation of cGAS-STING pathway genes, and enhanced response to interferon signaling after talazoparib monotherapy in cohort 1, whereas these effects were absent in cohort 2. Protein spatial analysis revealed tumor shrinkage and increased T-cell and macrophage infiltration in BRCA1/2m tumors following combination therapy in cohort 1, while cohort 2 showed no significant changes. Importantly, CD8+/PD1+ T cells increased in cohort 1 but decreased in cohort 2 after combination treatment. Two macrophage lineage markers, CD68 and CD163, identified distinct macrophage populations. CD68+ macrophages showed higher expression of cell state markers (PD-L1, pERK, pTBK1, MCL, BCL-xL) compared to CD163+ macrophages in both cohorts. CD68+ macrophages were present within and outside tumor beds, while CD163+ macrophages were predominantly in the stromal region. Notably, CD68+/CD163+/PD1+/MCL1+/pERK+ macrophages in baseline biopsies correlated with longer PFS when two cohorts are combined.

Conclusions In TALAVE, responses to PARPi combined with immunotherapy were limited to patients with BRCA1/2m. RNA and protein analyses demonstrated changes in the TME including cGAS-STING activation and immune cell infiltration in BRCA1/2m tumors, consistent with preclinical models. Deep phenotyping of tumor and immune cells, along with spatial analysis, provided valuable insights into the distinct responses, such as the presence of CD68+ macrophage populations associated with longer PFS, potentially contributing to a more immunostimulatory TME favorable for T cells.