PD6-08

Early dynamics of tumor microenvironment in triple negative or ER-low breast cancer: updated analyses from window of opportunity (WOO) MEDIOLA trial of olaparib and durvalumab

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Background

- We conducted MEDIOLA WOO trial with olaparib and durvalumab before standard neoadjuvant chemotherapy (NAC) in 54 stage II/III triple negative or ER-low breast cancer (NCT03594396) (Im SA et al., SABCS 2021, PD15-08; Koh J et al., SABCS 2024, PS12-01).
- Pathologic complete response (pCR) was achieved in 38 patients (70.4%) (Koh J et al., SABCS 2024, PS12-01).

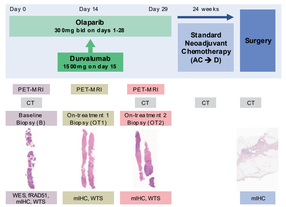


Figure 1. Study scheme

Methods

- Olaparib (300 mg bid) was given continuously for 4 weeks, with a single 1500 mg dose of durvalumab on day 15, followed by standard NAC (4 cycles of doxorubicin/cyclophosphamide, then 4 cycles of docetaxel).
- FDG-PET/MRI scans were performed at baseline, 2 weeks (on-treatment 1; OT1), and 4 weeks (on-treatment 2; OT2); CT scans were performed at baseline and OT2.
- We defined metabolic response (mRes) as a ≥ 30% decrease in FDG standardized uptake value (SUV) by FDG-PET/MRI. We also performed the RECIST version 1.1 assessment based on CT scan at OT2.
- Serial tumor biopsies were collected at baseline, OT1, and OT2. H&E slides from serial biopsies were analyzed using an artificial intelligence (AI)-based tissue segmentation model. RNA-seq was performed on fresh-frozen serial biopsy samples.

Results

Baseline clinicopathological parameters and treatment outcome

- Pathogenic *gBRCA1/2* mutations were present in 17/54 (31.5%). Whole-exome sequencing (WES) revealed somatic mutations, including *TP53* (79.6%), *PIK3CA* (11.1%), *PTEN* (7.4%), and *RB1* (5.6%). Somatic mutations of *BRCA1* (3.7%) and *PALB2* (1.9%) were also found.
- RAD51 foci assays conducted on fresh-frozen baseline biopsies showed functional homologous deficiency (fHRD) in 27/54 (50.0%).
- The pCR rate was significantly associated with metabolic and RECIST responses at OT2 (P < 0.001 and 0.027, respectively).
- No significant associations were observed with PD-L1 (22C3) positivity (combined proportion score ≥ 10 by immunohistochemistry) or fHRD status at baseline.

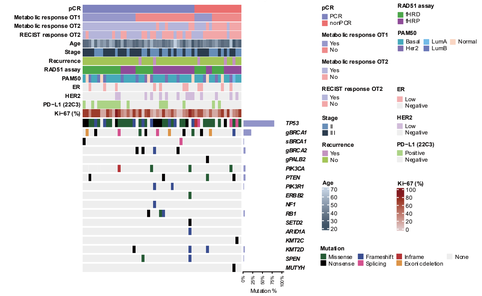


Figure 2. Summary of patient characteristics and mutational profile

Results

Histopathologic transitions in serial biopsies

- AI segmentation demonstrated an early reduction in tumor area and a rise in inflammatory area, which were more pronounced in biopsies from patients who achieved pCR.

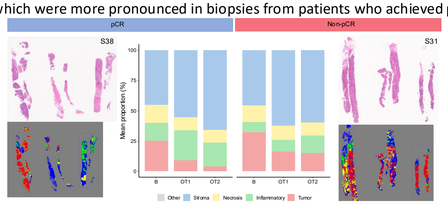


Figure 3. Histopathologic transitions assessed by AI-based tissue segmentation

Dynamic transitions in molecular subtypes occurred during the treatments

- The proportion of basal-like tumors by PAM50 decreased (40.7% at OT1; 14.8% at OT2), while luminal phenotypes expanded, most notably LumA (27.8% at OT1; 53.7% at OT2).
- Among TNBC molecular subtypes, BLIS was the dominant class at baseline (85.2%), shifting toward increased BLIA at OT1 and OT2.
- These transitions were largely confined to patients who achieved pCR, highlighting a plausible association between differential modulation of tumor-intrinsic and microenvironmental features in relation to treatment response.

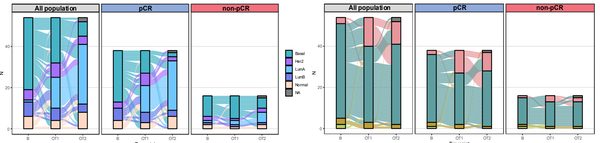


Figure 4. Molecular transitions of tumors throughout the treatment course

Functional pathway analysis highlights the importance of robust PARP inhibition early in the treatment course

- Gene set variation analysis (GSVA) scores of Hallmark gene sets unveiled an overall trend of downregulation in DNA repair, E2F targets, G2M checkpoint, and MYC target gene sets.
- GSVA scores for the DNA repair gene set decreased from baseline to OT1 and from OT1 to OT2 (all adj P < 0.05, except for adj P = 0.14 of OT2 versus OT1 in the non-PCR group), irrespective of pCR outcome, reflecting a consistent treatment effect of olaparib.
- In contrast, downregulation of E2F target and G2M checkpoint gene sets at OT1 compared with baseline was restricted to tumors from patients who achieved pCR (all adj P < 0.05).

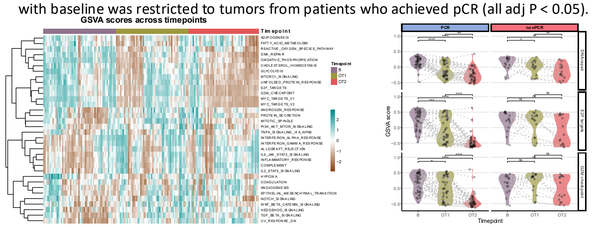


Figure 5. Gene set variation analysis scores throughout treatment course

Results

Transcriptomic profiles at OT1 was more informative for clinical outcome than at baseline

- Interferon-α response was more enriched in pCR tumors at baseline compared with non-pCR tumors at baseline.
- OT1 biopsies from patients with pCR showed a strong enrichment of multiple inflammatory pathways, including the interferon-γ response, interferon-α response, allograft rejection, IL6–JAK–STAT3, and IL2–STAT5 signaling.
- Tumors from patients who developed recurrence (N=4) were already enriched for the epithelial-mesenchymal transition and angiogenesis pathways at OT1.

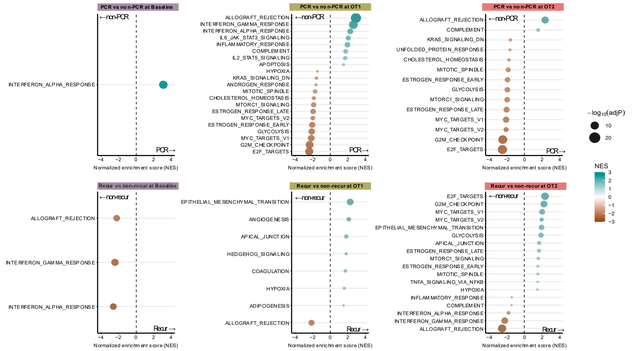


Figure 6. Gene set enrichment analysis within each timepoint

PARP inhibitor-mediated immune modulation during treatment may contribute to treatment response.

- We have shown that olaparib induced significant immune modulation in CD8+ T-cell subsets as early as 2 weeks after treatment initiation (Koh J et al., SABCS 2024, PS12-01).
- Both CD4+ and CD8+/CXCL13+ cells increased at OT1, immediately before durvalumab treatment, only in tumors with pCR.
- The formation of mature TLS was identified in 22.2% (12/54) of cases at OT1.
- TLS presence at OT1 was more frequent in tumors showing metabolic and RECIST response at OT2 after durvalumab treatment (P = 0.024 and 0.035), while no significant association was observed between TLS formation at baseline and pCR (P = 0.547)

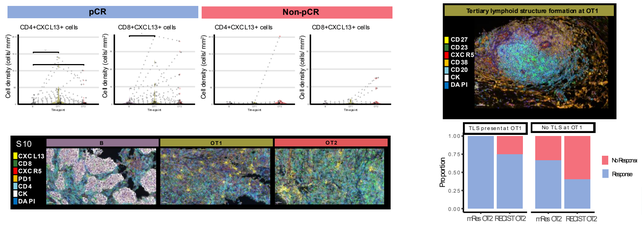


Figure 7. Prognostic impact of CXCL13+ T-cells and tertiary lymphoid structures at OT1

Results

Spatial positioning of immune cells relative to tumor cells was associated with treatment response

- Median distances between cytokeratin (CK)-positive tumor cells and the nearest neighboring immune subsets were analyzed.
- CD8+ T-cells, terminally activated CD8+ T-cells (CD25+/CD45RO+/FOXP3-), activated CD8+ T-cells (CD25+/CD45RO-/FOXP3-), and CD8+CD244+ cells (all P < 0.001) moved significantly closer to tumor cells at OT1 in pCR tumors.

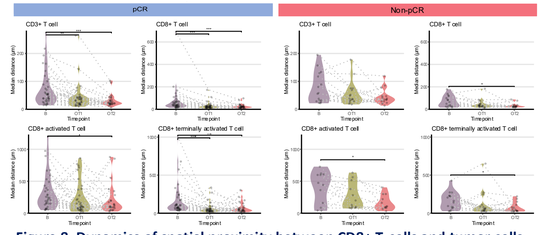


Figure 8. Dynamics of spatial proximity between CD8+ T-cells and tumor cells

- In tumors from patients with recurrence (N=5), CD3+, CD8+, CD8+CD244+, and terminally activated CD8+ T-cells failed to maintain proximity to tumor cells, suggesting that sustained spatial engagement of T-cells may be relevant to durable response.

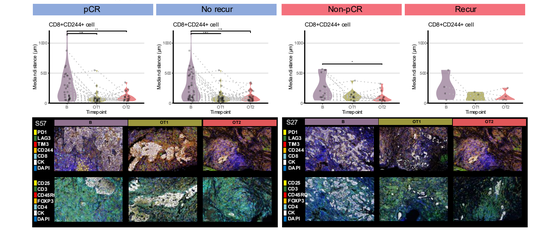


Figure 9. Different spatial positioning of CD8+CD244+ cells according to patient outcome

Conclusions

- Multi-omics serial assessments encompassing digital pathological and transcriptomic analyses showed increased inflammatory infiltrates and a shift toward an immune-activated state after 2 weeks of olaparib, particularly in pCR tumors.
- Multiplex immunohistochemistry confirmed that various CD8+ T-cell subsets drove this change in pCR tumors, not only in numerical density but also in proximity to tumor cells after 2 weeks of olaparib.
- Tertiary lymphoid structure formation and CXCL13+ T-cell infiltration after olaparib were also associated with pCR, suggesting that olaparib reshape the tumor microenvironment into a more favorable condition for immune checkpoint blockade.
- Our study provides a mechanistic rationale for PARP–immunotherapy combinations and supports their optimal treatment sequence.

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