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## INVESTIGATING IMMUNE MEDIATED MECHANISMS OF PARPI RESISTANCE IN BRCA1-ASSOCIATED TRIPLE NEGATIVE BREAST CANCER (TNBC)

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**Background** Poly(ADP-ribose) polymerase inhibitors (PARPi) have improved the outcomes of BRCA-associated breast cancer; however, treatment responses are often not durable. Our preclinical studies demonstrated that PARPi activates the cGAS/STING pathway and recruitment of anti-tumor CD8+ T-cells that are required for tumor clearance [1]. These studies contributed to development of clinical trials testing PARPi plus immune checkpoint blockade (ICB). Unfortunately, early phase trials of PARPi + ICB have not yet suggested efficacy will be superior to PARPi monotherapy. Lack of demonstrated clinical synergy between PARPi + ICB underscores the need to study the tumor microenvironment (TME) during PARPi therapy to identify optimal strategies to enhance T-cell activation. We recently showed that PARPi induces CSF-1R+ suppressive tumor associated macrophages (TAMs) that restrict antitumor immune responses, contributing to PARPi resistance [2]. Removing TAMs with anti-CSF-1R therapy in combination with PARPi significantly enhanced overall survival (OS) compared to PARPi monotherapy in preclinical models [2]. Here, we investigate how modulating TAMs can enhance PARPi + ICB.

**Methods** Mice bearing BRCA1-deficient TNBC (K14-Cre; Brca1f/f;p53f/f) tumors were treated for 98 days with PARPi (Talazoparib) ± small molecule inhibitor of CSF-1R (ARRAY-382; CSF-1Ri) ± anti-PD-1 and then followed for survival. Flow cytometry was employed to elucidate changes in the TME after treatment.

**Results** PARPi conferred a significant survival advantage over vehicle treated mice (median OS 33 v. 14 days; p=0.0034) and 2/8 PARPi-treated mice experienced complete tumor clearance at day 98. PARPi + CSF-1Ri treated mice (median OS 140 days) remarkably cleared 7/10 tumors by day 98. The addition of anti-PD-1 to PARPi did not enhance OS compared to PARPi monotherapy. The triple combination of anti-PD-1 + PARPi + CSF-1Ri has not yet significantly enhanced the median OS compared to PARPi + CSF-1Ri (ongoing; 168 v. 140 days); nor did it increase clearance of tumor by day 98 (7/10). However, the triple combination led to superior long term tumor clearance. At day 161 the triple combination exhibited 5/10 tumor free mice compared to 2/10 treated with PARPi + CSF-1Ri. To elucidate how CSF-1Ri enhanced PARPi + ICB responses, flow cytometry was performed and revealed increased expression of the co-stimulatory molecule CD80, reduced tissue resident macrophages (CX3CR1+) and lower CSF-1R expression compared to PARPi + ICB.

**Conclusions** These data suggest that targeting immunosuppressive macrophages may induce a favorable anti-tumor immune response and enhance responses to PARPi plus ICB. We are currently evaluating the adaptive immune response in this context.

### REFERENCES

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