399 **A PHASE II STUDY OF NIVOLUMAB, IPILIMUMAB, PLUS ANDROGEN RECEPTOR BLOCKADE WITH BICALUTAMIDE TO ENHANCE THYMIC T-CELL PRODUCTION AND IMMUNOTHERAPY RESPONSE IN METASTATIC BREAST CANCER**

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Background It has previously been shown that immune checkpoint blockade (ICB) with anti-programmed death 1/ligand 1 (anti-PD-1/L1) improves survival when combined with chemotherapy in PD-L1-positive first-line triple-negative metastatic breast cancer (MBC). Given the lower efficacy of ICB in hormone receptor positive (HR+) or PD-L1-negative disease, and in later lines of therapy, novel combinations are necessary. Dual ICB with nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) has shown success in other solid tumors but has not been extensively studied in MBC. Furthermore, MBCs often express the androgen receptor (AR), which can be targeted to modulate immune response. AR blockade may stimulate thymic production of naïve T-cell clones by modulating the Notch pathway,[1] whereas ICB can amplify the immune activity of recent thymic emigrants by blocking PD-1-mediated peripheral tolerance.[2]

Methods This is an open-label, Simon 2-stage phase II trial investigating the dual ICB (nivolumab 240mg IV q2w; ipilimumab 1mg/kg IV q6w) and AR blockade (bicalutamide, 150mg PO daily) in MBC. Two cohorts will be studied: AR-positive TNBC [> 1% by IHC, constituting ~50% of TNBCs]; and HR+ MBC (of which the great majority are AR-positive). Eligible patients must have RECIST1.1 measurable disease, Eastern Cooperative Oncology Group performance score 0 or 1, adequate hematological/hepatic function, and received no more than 1 prior course of non-curative chemotherapy. Target accrual is n=15 per arm (stage I), with a maximum of 46 patients per cohort. Current cohort accrual n=15 HR+ and n=5 TNBC. The primary endpoint is week 24 clinical benefit by iRECIST criteria, with success defined as >20% improvement over historical control (30% per EMBRACE clinical trial).[3] Safety will be evaluated by CTCAE v4.0. Biomarkers of recent thymic activation will be evaluated via quantitative deep sequencing of T-cell receptors (TcR, ImmunoSEQ assay), TcR excision circles (TRECs), and flow cytometry using markers for recent thymic emigration (CD3+CD45RA +CD45RO-CD31+)

Trial Registration NCT03650894. The trial is open at Providence Cancer Institute (Portland, OR) and Memorial Sloan Kettering Cancer Center (New York, NY).

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Ethics Approval This study was approved by the IRB department and Providence Portland Medical Center, Clinical Trials Department for study NCT03650894.
Consent Written, informed consent is obtained from each participant.

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