547 SAFETY AND EFFICACY OF DE-ESCALATED NEOADJUVANT CHEMOIMMUNOTHERAPY OF TRIPLE NEGATIVE BREAST CANCER (TNBC) USING CHEMOKINE-MODULATING REGIMEN (RINTATOLIMOD, IFN-α2B, CELECOXIB)

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Background Pathologic complete response (pCR) or microinvasive residual disease (ypTmic), following neoadjuvant chemotherapy (NAC) of triple negative breast cancer (TNBC) predicts improved relapse-free and overall survival. Combination of NAC with pembrolizumab, the new standard of care, increases pCR rate from 40% to 65% but is associated with significant immune-related permanent toxicities. Production of chemokines CCL5, CXCL9, CXCL10 and CXCL11 in the tumor microenvironment (TME) is critical for the infiltration with $CD8^+$ cytotoxic T-lymphocytes (CTLs), predicting higher probability of pCR.[1] Guided by our preclinical data that **C**hemo**k**ine-**m**odulating (**CKM**) regimen, combining rintatolimod (TLR3 agonist), interferon (IFN)-α2b and celecoxib (COX-2 inhibitor), selectively induces CTL-attractants but decreases Treg-attractants[2], we hypothesized that the combination of CKM with chemotherapy will promote CTL infiltration and result in higher pCR.

Methods In phase I study NCT04081389, 9 patients with stage I-III TNBC, median age 47 (37-55) years were treated with paclitaxel 80 mg/m^2 IV weekly for 12 weeks; CKM for first 3 weeks, days 1-3 (IV rintatolimod 200 mg daily and oral celecoxib 200 mg twice daily). IFN-α2b was administered in an accelerated dose-escalation at 0 or 5 million units (MU)/m^2 [dose levels (DL) 1,2 respectively] in first 2 patients; 10 MU/m^2 [DL 3] in 4 patients and 20 MU/ m^2 [DL 4] in 3 patients. CKM/Paclitaxel was followed by standard dose-dense doxorubicin and cyclophosphamide (AC) and surgery. Dose-limiting toxicity (DLT) was defined as grade 3 or higher toxicities within the first 3 weeks. Primary endpoint was safety and tolerability. Secondary endpoints included pCR rate. Tumor and blood biomarkers were analyzed in exploratory studies.

Results Treatment was well-tolerated with mostly grade 1 or 2 treatment-related adverse events (TRAEs) without DLTs or delayed or immune-related toxicities. Grade 3 TRAEs included neutropenia (3/9) attributed to CKM (1/9) or paclitaxel (3/9), pneumonia (1/9) and anemia (1/9) attributed to AC. Additional pneumonia and skin squamous cell carcinoma in situ were observed, unrelated to study treatment. Paclitaxel- or AC-related toxicities were not higher than expected. 5/9 (56%) patients attained pCR and 1 more patient attained ypTmic. CTL marker CD8α was selectively elevated in post-CKM tumor biopsies (5 patients at DL3 and 4) but decreased in the post-CKM blood.

Conclusions The treatment was well tolerated, with promising clinical activity of pCR + ypTmic at 66%, comparable to pembrolizumab/NAC. Upcoming phase II study in early stage TNBC is planned to determine if CKM can be used as an alternative to pembrolizumab or to overcome pembrolizumab/NAC resistance.

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Ethics Approval The study obtained ethics approval through Roswell Park institutional review board, and is registered under NCT04081389. The participants signed an informed consent before participating in this study.

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