SAFETY AND EFFICACY OF DE-ESCALATED NEOADJUVANT CHEMOMMUNOTHERAPY 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 Chemokine-modulating (CKM) regimen, combining rintatolimod (TLR3 agonist), interferon (IFN)-α2b and celecoxib (COX-2 inhibitor), selectively induces CTL-attractants but decreases Treg-attractants2, 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/m² 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)/m² [dose levels (DL) 1,2 respectively] in first 2 patients; 10 MU/m² [DL 3] in 4 patients and 20 MU/m² [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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Trial Registration NCT04081389

REFERENCES

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.