Background: The FDA has approved pembrolizumab in combination with neoadjuvant chemotherapy (doxorubicin, cyclophosphamide, paclitaxel [ACT], and carboplatin) for stage II/III TNBC, on the basis of improved event free survival (EFS) and pathologic complete response (pCR) rate in the Keynote-522 study. Novel combination immunotherapy strategies may further improve outcomes and allow the opportunity to de-escalate the chemotherapy backbone, potentially mitigating grade III/IV toxicities which occurred in 81% of recipients. We have previously reported safety and feasibility of pre-operative IRX-2, a novel cytokine biotherapeutic, that is administered locoregionally in the peri-areolar tissue to enhance the immune microenvironment within the sentinel lymph nodes, the putative site of antigen presentation. In this phase Ib study, pre-operative IRX-2 was safe and was associated with increased tumor infiltrating lymphocytes (sTILs, by H&E and multispectral immunofluorescence [mIF]), PD-L1 expression (Ventana SP142 assay, mIF), and lymphocyte activation (by RNA sequencing). Similar effects were observed in a pre-operative head and neck carcinoma trial. These findings support further study of IRX-2 in combination with anti-PD-1 in early stage TNBC.

Methods: neoIRX is an open-label, phase II trial to evaluate the clinical and immunological activity of induction IRX-2 plus pembrolizumab, followed by de-escalated chemotherapy (ACT) and pembrolizumab as neoadjuvant therapy in TNBC. Patients are randomized to receive pembrolizumab induction (single dose 200mg IV, n=15), versus pembrolizumab + IRX-2 induction (1mL SQ x 2 daily, x 10 days, n=15), followed by research biopsy. All patients will then receive neoadjuvant pembrolizumab plus ACT every three 3 weeks. Eligible subjects will have previously untreated, resectable stage II/III TNBC. The primary endpoint is pCR. The secondary endpoint is safety. On-treatment biopsies will permit a prospective, randomized validation of previously reported immunomodulatory effects of IRX-2 (sTILs, PD-L1, lymphocyte RNA signatures). As of 7/28/2021, n=7/30 subjects are enrolled (Providence Cancer Institute, Portland, OR, Providence St. John’s Cancer Institute, Santa Monica, CA, Baylor Medicine, Houston, TX).

Trial Registration: NCT04373031

REFERENCES:

Ethics Approval: The study protocol was approved by the Providence Portland Medical Center IRB committee and was conducted in accordance with the ethical standards established by the Declaration of Helsinki, PH&S IRB# 2019000486. Written informed consent was obtained for all trial participants.