in patients with aggressive recurrent primary brain tumors. Our preclinical data show that Chemokine modulating (CKM) regimen [rintatolimod, interferon (IFN)-α2b and COX-2 inhibitor] also selectively attracts effector CTLs and Th1 cells (but not suppressive regulatory T-cells or myeloid-derived suppressor cells) into tumors. Importantly, CKM preferentially promotes CTL migration into tumor rather than healthy tissues, providing rationale for its systemic use. We hypothesize that anti-HER2/3 type 1 polarized DC1s in combination with CKM and anti-PD1 will result in improved Th1/CTL response against HER2/3 epitopes, reduce brain recurrence and systemic progression.

Methods This is a phase II single-arm, non-randomized multicenter study (NCT04348747). Eligibility includes patients with triple negative and HER2+ BMBC ≥ 18 years, ECOG PS ≤ 1, normal marrow and organ function with asymptomatic untreated brain metastases who receive αDC1 q2 weeks x 3, with CKM [200 mg IV rintatolimod, IFN-α 20 million units/m2 IV, celecoxib 200 mg oral BID] on days 1-3 with second and third dose of αDC1, followed by pembrolizumab 200 mg IV. Thereafter, pembrolizumab is given every 3 weeks, along with αDC1 and CKM every 3 months as booster dose until disease progression, intolerable side effects or withdrawal from study, or up to 24 months. Baseline and 3-week post-CKM treatment peripheral (non-CNS) biopsies are required for six patients. Primary objective is CNS response rate (RR) using RANO-BM criteria. If no CNS response is observed after 12 patients, study will be terminated. If ≥ 1 response observed, then 9 more patients will be enrolled, for a total of 21 patients. If ≥ 3 CR observed, the proposed therapy will be considered promising for further study. Secondary objectives include non-CNS RR per RECIST v1.1, median CNS, non-CNS and overall progression-free survival, overall survival and safety. Analysis of change in intratumoral biomarkers is an exploratory objective.

Results N/A

Conclusions N/A

Trial Registration NCT04348747

Ethics Approval The study was approved by Roswell Park Comprehensive Cancer Center Institution's Ethics Board, approval number I-19-04120.

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321 PHASE I CLINICAL TRIAL ASSESSING THE COMBINATION OF SYSTEMIC CHEMOKINE MODULATORY REGIMEN TARGETING TLR3 WITH NEOADJUVANT CHEMOTHERAPY IN TRIPLE NEGATIVE BREAST CANCER

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Background Neoadjuvant chemotherapy (NAC) with taxanes is the standard of care in triple negative breast cancer (TNBC). Intratumoral prevalence of CD8+ cytotoxic T-lymphocytes (CTLs) is associated with an improvement in relapse-free survival (RFS) and overall survival (OS), while regulatory T-cells (Treg) and myeloid derived suppressor cells (MDSC) are associated with poor survival. Higher ratio of CTL/Treg is associated with higher probability of obtaining pathological complete response (pCR), a surrogate marker for RFS. Intratumoral production of CCL5, CXCL9, CXCL10 and CXCL11 is critical for local infiltration with CTLs, while CCL22 is responsible for Treg attraction. Previous studies have shown that CXCL9 expression in the pre-treatment breast tissue is associated with a three-fold higher rate of achieving pCR. Our preclinical data show that Chemokine modulating (CKM) regimen, combining rintatolimod (TLR3 agonist), interferon (IFN)-α2b, and celecoxib (COX-2 inhibitor) increases CTL-attracting, and decreases MDSC-, Treg-favoring chemokines, increasing CTL/Treg ratio in tumor microenvironment, with preferential tumor tissue activation than adjacent healthy tissues. We hypothesize that the combination of CKM with paclitaxel will result in infiltration of TNBC with CTLs, and along with doxorubicin/cyclophosphamide (AC), result in higher pCR, translating into improved RFS and OS.

Methods In this phase I study NCT04081389, eligibility includes age ≥18 years, confirmed resectable TNBC, radiographically measurable disease ≥1 cm, ECOG PS ≤ 2, adequate organ and marrow function. Patients with autoimmune disease, serious mood disorders, invasive carcinoma within 3 years, history of peptic ulcers or hypersensitivity to NSAIDs will be excluded. We plan to treat three patients with early stage TNBC with paclitaxel 80 mg/m2 IV weekly for 12 weeks, rintatolimod 200 mg IV, celecoxib 200 mg oral twice daily, and accelerated titration of IFN-α2b at doses 0, 5, or 10 million units (MU)/m2 [Dose Levels (DL) 1, 2 and 3 respectively] on days 1–3 (no intra-patient dose escalation) in weeks 1–3. Dose-limiting toxicity (DLT) is defined as grade 3 or higher toxicities within the first 3 weeks. Any DLT will mandate recruitment per the 3+3 model. If no DLT, three patients will be enrolled at DL 4 at 20 MU/m2 IFN- α2b. This will be followed by standard dose-dense AC, and then surgery. The primary endpoint is safety and tolerability of combination and to identify the appropriate DL of CKM and paclitaxel for extended efficacy study. The secondary endpoints include investigation of efficacy (pCR and breast MRI response), along with RFS and OS. Intratumoral biomarkers will be analyzed in an exploratory manner.

Results N/A

Conclusions N/A

Trial Registration NCT04081389

Ethics Approval The study was approved by Roswell Park Comprehensive Cancer Center Institution's Ethics Board, approval number I-73718.

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322 EFFICACY AND SAFETY OF GX-I7 PLUS PEMBROLIZUMAB FOR HEAVILY PRETREATED PATIENTS WITH METASTATIC TRIPLE NEGATIVE BREAST CANCER: THE PHASE 1B/2 KEYNOTE-899 STUDY

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Background Pembrolizumab monotherapy showed 9.6% ORR and did not significantly improve OS as 2L or 3L treatment for mTNBC compared to standard chemotherapy in phase 3 study (KEYNOTE-119) leading to high unmet needs of a new drug that could enhance the activity of pembrolizumab

when it is combined with. Higher lymphocyte count is an independent factor which correlates with better response to checkpoint blockade in cancer patients. Based on the MoA of GX-I7, which induces increase of T cells in both the tumor microenvironment and peripheral blood, combining GX-I7 with pembrolizumab can potentially enhance the anti-tumor effect.

Methods This is an open-label, phase 1b/2 study in patients with refractory or recurrent TNBC who failed standard chemotherapy from 1st to 3rd line treatment in metastasis setting. Patients pretreated with cyclophosphamide received GX-I7 from 360 μg/kg up to 1,440 μg/kg every 12 weeks and pembrolizumab 200 mg every 3 weeks (n=21). Patients without cyclophosphamide pretreatment received GX-I7 from 720 μg/kg up to 1,440 μg/kg every 9 weeks or 12 weeks and pemrbolizumab 200 mg every 3 weeks (n=24). The objectives were dose limiting toxicities (DLTs), safety, pharmacodynamic markers including lymphocyte increase and ORR.

Results GX-I7 and pembrolizumab were given to 45 patients (pts) (median age 50 years [29–75], ECOG PS 1 [42.2%]). 1 DLT (skin rash, Gr 3) was reported in the 1,440 μg/kg cohort. Treatment-related AEs occurred in 97.8% of pts with Gr 1–2, 15.6% with Gr 3 and 2.2% with Gr 4. Common TEAEs were injection site reaction (75.6%), rash (40.0%), pyrexia (40.0%) which were manageable. GX-I7 treatment induced up to 7-fold increase in absolute lymphocyte counts in all dose levels ranging from 360 μg/kg to 1,440 μg/kg with or without cyclophosphamide. A total of 33 evaluable mTNBC pts showed ORR of 0/3 in 360 μg/kg, 1/9 in 720 μg/kg, 2/9 in 960 μg/kg and, 4/12 in 1,200 μg/kg. Interestingly, 4 out of 6 pts received 1,200 μg/kg of GX-I7 with cyclophosphamide achieved SD and, thus, 1,200 μg/kg of GX-I7 regimens have been selected as candidates for RP2D. The tumor assessment for 1,440 μg/kg with or without cyclophosphamide is ongoing.

Conclusions GX-I7 in combination with pembrolizumab with or without cyclophosphamide was safe and well tolerated in most study participants. GX-I7 significantly increased T cell numbers in combination with pembrolizumab at doses from 360 μg/kg to 1,440 μg/kg. These results suggested GX-I7 in combination with pembrolizumab show promise as a potential treatment option for patients with metastatic TNBC.

Trial Registration ClinicalTrials. gov Identifier: NCT03752723

Ethics Approval The study was approved by the Samsung Medical Center, Gachon University Gil Medical Center, National Cancer Center, Korea University Anam Hospital, Korea University Guro Hospital, Severance Hospital, Ajou University Hospital, Seoul National University Bundang Hospital, Ewha Womans University Mokdong Hospital, Asan Medical center, Catholic Medical Center and Gangnam Severance Hospital Institutional Review Board, protocol number GX-I7-CA-006 (KEYNOTE-899).

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323 SYSTEMIC ADMINISTRATION OF LADIRATUZUMAB VEDOTIN ALONE OR IN COMBINATION WITH PEMBROLIZUMAB RESULTS IN SIGNIFICANT IMMUNE ACTIVATION IN THE TUMOR MICROENVIRONMENT IN METASTATIC BREAST CANCER PATIENTS

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Background Ladiratuzumab vedotin (LV) is an investigational antibody-drug conjugate (ADC) composed of a humanized anti-LIV-1 IgG1 conjugated with monomethyl auristatin E (MMAE), a microtubule-disrupting agent. LV targets LIV-1, a protein expressed by various cancers. Along with a cytotoxic effect, LV has been shown to induce immunogenic cell death (ICD) in preclinical studies. LV is currently being investigated as a monotherapy and in combination with pembrolizumab in patients with metastatic breast cancer and other solid tumors. This correlative biomarker study aims to assess the ability of LV to modulate the tumor microenvironment (TME) in breast cancer patients.

Methods In the SGNLVA-001 trial, metastatic breast cancer patients, predominantly of the triple negative subtype (TNBC), received LV monotherapy (2.0 or 2.5 mg/kg, every 3 weeks [q3w]). In the SGNLVA-002 trial, patients with metastatic TNBC received LV (2.0 or 2.5 mg/kg, q3w) plus pembrolizumab (200 mg, q3w). To investigate the potential effect of LV or LV plus pembrolizumab on the TME, paired pre-treatment and on-treatment tumor biopsies (Cycle [C] 1 Day [D] 5 or C1D15) were collected and analyzed by RNAseq and immunohistochemistry (IHC) staining.

Results Gene expression analysis of paired biopsy TNBC samples (n=59; baseline and C1D5) showed that LV monotherapy treatment significantly induces immune response-related gene expression, MHC, co-stimulatory molecules, and PD-L1. Gene set enrichment analysis (GSEA) demonstrated enrichment of macrophage and tumor inflammation signature genes, supporting the induction of ICD and enhancement of innate immune response. Paired tumor samples from subjects treated with LV plus pembrolizumab (n=16; baseline and C1D15) showed a broader range of gene expression changes on RNAseq compared to LV monotherapy. GSEA evidenced enrichment of genes associated with cytotoxic CD8 T cells, CD4 T helper cells, dendritic cells, and macrophages, further demonstrating the induction of ICD and activation of an innate immune response. Importantly, the combination had a unique adaptive immune response induction signature. IHC analysis confirmed the increased infiltration of macrophages after LV monotherapy. The combination with pembrolizumab resulted in a further increase in macrophages and a prominent influx of CD8 T cells.

Conclusions Systemic administration of LV monotherapy resulted in immune activation in the TME and macrophage infiltration. The combination of LV plus pembrolizumab resulted in a more potent immune activation in the TME and a prominent influx of CD8 T cells in addition to macrophages. Together these results provide a rationale for the continued clinical investigation of LV alone or in combination with pembrolizumab.

Trial Registration NCT01969643 and NCT03310957