337 INTRATUMORAL IMMUNE THERAPY FOR RECURRENT BREAST CANCER WITH POLYICLC, AND TREMELIMUMAB COMBINED WITH SYSTEMIC DURVALUMAB

[1]Craig Slingluff*, [1]Ileana Mauldin, [1]Elizabeth Gaughan, [1]Patrick Dillon, [2]Mateusz Opyrchal, [2]Igor Puzanov, [3]Megan Kruse, [3]Brian Gastman, [4]Philip Friedlander, [4]Thomas Marron, [5]Kristen Aufiero, [5]Mary Macri, [5]Paul Schwarzenberger, [6]Toni Ricciardi, [5]Aileen Ryan, [5]Ralph Venhaus, [4]Mansi Saxena, [1]Nicole Edmonds, [4]Nina Bhardwaj. *[1]University of Virginia, Charlottesville, VA, USA; [2]Roswell Park Cancer Institute, Buffalo, NY, USA; [3]Cleveland Clinic, Cleveland, OH, USA; [4]Mount Sinai School of Medicine, New York, NY, USA; [5]Ludwig Institute for Cancer Research, New York, NY, USA; [6]Ludwig Institution for Cancer Research, New York, NY, USA*

Background Intratumoral (IT) cancer therapies may enhance T cell activation and tumor infiltration when combined with systemic checkpoint blockade. This approach may improve treatment of advanced breast cancer, which is commonly resistant to immune therapy.

Methods A multicenter basket-style trial (NCT02643303) was performed in patients with advanced solid tumors, who received polyICLC IT 1mg x 6, then intramuscular (IM) x 3, combined with intravenous (IV) durvalumab 1500 mg q4W. Most were assigned to cohorts also receiving tremelimumab: 10 mg IT or 75 mg IV. Goals were to assess tolerability and clinical activity. Treated tumors were evaluated for immune infiltrates on days (d) 0, 15, and 29 by multiparameter immunofluorescence histology. A strong signal for clinical response was in breast cancer patients; thus, an expansion cohort was enrolled. We report analysis of that breast cancer subgroup.

Results Nineteen participants with treatment-refractory recurrent breast cancer with median 4 prior lines of therapy were enrolled and treated with IV durvalumab and IT/IM polyICLC. Seventeen also received tremelimumab (15 IT, 2 IV). Common treatment-related AEs were fatigue, injection site pain, and chills. There was one dose-limiting toxicity in a participant who received tremelimumab IV, and died with severe hyponatremia (DLT) and progressive disease. Objective clinical responses (1 complete; 4 partial (1 unconfirmed)) were observed in 5 (26%), including 2/9 patients with triple-negative breast cancer (TNBC) and 3/10 with non-TNBC. Median OS was longer for those with CR, PR, or SD (not reached) vs. those with PD or not evaluable (5 months): two responders remain alive at 34+ and 40+ months. In injected tumors, there were significant increases from d0 to d29 in numbers/mm2 of CD8+ T cells, CD20+ B cells, mature dendritic cells (DC), macrophages, and CD56+ NK cells, and in CD8+ cells with antigen-experience (CD45RO), cytotoxic function (granzyme B), activation (ICOS1), or proliferation (Ki67). CD8+ cells expressing LAG3 and TIM3 increased, as did PDL1+ tumor cells and stromal cells. There were no differences in cells expressing IDO, ARG1, CD39, or CD73. Among patients with objective response, vs. all others, proportions of intratumoral CD8+ cells expressing Ki67 increased ($p < 0.04$).

Conclusions IT tremelimumab and polyICLC plus systemic durvalumab is safe and has clinical activity in patients with advanced TNBC and non-TNBC. The therapy enhances intratumoral immune effectors and markers of T cell function in hypothesis-generating data that warrant confirmatory studies. Clinical response was associated with longer survival and increased CD8 T cell proliferation.

Trial Registration NCT02643303

Ethics Approval The study has been performed with approval of the institutional review boards of each participating institution (Roswell Park Cancer Institute: STUDY 00000121/I291016; Mount Sinai School of Medicine: IRB-17-01692; University of Virginia: IRB # 19276; Cleveland Clinic: 18-694; Toledo: 300176; Dartmouth: STUDY00031630; Emory: IRB00099445). All participants give informed consent before enrolling and participating. The study was also performed with approval from the FDA

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