560 IMMUNOTHERAPEUTIC AND ANTIMETASTATIC ACTIVITY OF LTX-315 IN PRECLINICAL MODELS OF ICI-RESISTANT BREAST CANCER

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Background Oncolytic peptides are attractive tools for the development of novel anticancer regimens [1]. LTX-315 is a synthetic peptide with a marked capacity to elicit tumor-targeting immunity in preclinical cancer models [2]. Indeed, LTX-315 has been shown to elicit immunogenic cell death (ICD) in malignant cells [3, 4] and to deplete immunosuppressive cells such as CD4+CD25+FOXP3+ TREG cells and myeloid-derived suppressor cells (MDSCs) from the tumor microenvironment (TME) [5]. Accordingly, LTX-315 synergized with immunogenic chemotherapeutics or immune checkpoint inhibitors (ICIs) in preclinical tumor models [5, 6]. Moreover, recent findings from a Phase I clinical trial in patients with advanced solid tumors (NCT01986426) indicate that intratumoral LTX-315 is safe, clinically active, and elicits alterations in the TME that support the initiation of anticancer immunity [7, 8]. However, the dependency of LTX-315 therapeutic effects on the immune system in preclinical models of breast cancer has not been mechanistically investigated.

Methods We harnessed three distinct mouse models of ICI-resistant breast cancer, namely hormone receptor (HR)-positive TS/A established and triple-negative breast cancer (TNBC) 4T1 cells established in immunocompetent syngeneic BALB/c mice, as well as medroxyprogesterone acetate (MPA, M)-initiated, 7,12-dimethylbenz[a]anthracene (DMBA, D)-driven mammary carcinomas evolving in C57BL/6 mice to assess the immunotherapeutic effects of LTX-315 optionally combined with radiation therapy (RT), based on the primary tumor growth, metastatic dissemination and overall survival (depending on model). Multilesion models, rechallenge assays, antibody-mediated depletion experiments as well as experiments in Rag1-/- mice were employed to elucidate the mechanistic involvement of the immune system.

Results In the multilesion TS/A models, intratumoral LTX-315 to one lesion combined with hypofractionated RT to another lesion resulted in superior systemic disease control as manifested by eradication of a 3rd untreated lesion in up to 50% of mice, which were protected from a subsequent rechallenge with living TS/A cells. In the single lesion 4T1 model, LTX-315 mediated enable robust local and metastatic disease control, which could be enhanced (only locally) with RT and dependent on natural killer (NK) cells, but less so on T lymphocytes (as determined with anti-asialo GM1 antibodies and Rag1-/- hosts). In the M/D-driven model, LTX-315 considerably controlled the growth of primary tumors and delayed relapse, an effect that depended on NK cells (as demonstrated with anti-NK1.1 antibodies).

Conclusions LTX-315, alone and combined with RT, mediates robust immunotherapeutic effects in multiple models of ICI-resistant breast cancer. Intriguingly, NK cells appear to be required for such effects, potentially linked to the emergence of immunological memory.

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Ethics Approval This study was approved by Weill Cornell Medical College's Ethics Board; approval number 2015-0028, 2018-0002.

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