

HR⁺BREAST CANCER: DEFINING INNATE AND ACQUIRED RESISTANCE TO IMMUNE CHECKPOINT INHIBITORS

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Background Hormone receptor (HR)⁺breast cancer (BC) is responsible for the majority of BCs and -related deaths in the US.¹ Standard treatment for local disease involves surgery, followed by adjuvant endocrine therapy (ET) ± radiation therapy (RT) and/or chemotherapy (CT), depending on risk for relapse. However, many women receive CT and experience its severe side effect to benefit only a few. Immune checkpoint inhibitors (ICIs) have successfully been implemented in the management of other solid tumors like melanoma.² Conversely, the clinical experience with single-agent ICIs has been disappointing in patients with HR⁺ BC³, at least in part reflecting a limited immune infiltration at baseline and calling for the development of combinatorial regimens unlocking ICI efficacy in this patient population. In this setting, progress has also been hampered by the lack of a preclinical model that would faithfully recapitulated key immunobiological features of human HR⁺ BC. We have recently demonstrated that endogenous mammary carcinomas driven in immunocompetent mice by medroxyprogesterone acetate (M) plus 7,12-dimethylbenz[a]anthracene (D) represent a superior preclinical model to study HR⁺BC resistance to ICI and identify strategies to overcome it.⁴

Methods We established M/D-driven mammary carcinomas in immunocompetent, female C57BL/6 mice and randomized them to: (1) no treatment; (2) PD1 clockers (on d0/d3/d6 or d3/d6/d9); (3) RT (3x10 Gy on d0/d1/d2); (4) recombinant FLT3L (from d0-d9 or d3-d12), or all the 2- and 3-agent combinations thereof. Besides monitoring local and systemic tumor control, we collected tumors for RNAseq, and spleens for immunoprofiling by flow cytometry.

Results RT controls primary ICI-resistant M/D-driven carcinomas and extends the overall survival (OS) of the hosts, with marginal benefits from the addition of a PD-1 blocker. Recombinant FLT3L improves local tumor control by RT, but fails to ameliorate OS, mainly due to compromised control of distant, unirradiated lesions. RT followed by PD-1 blockage plus recombinant FLT3L is superior to all other approaches at primary tumor control and exhibits a trend for improved OS over RT alone, reflecting partial control of distant lesions.

Conclusions RT is highly effective in ICI-resistant HR⁺ BC tumors. Combination of RT with different immunotherapeutics alters the pattern of local vs systemic disease progression. This may define immunological signatures potentially linked to resistance/sensitivity and identify novel target to break through the resistance of HR⁺ BC to immunotherapy.

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Ethics Approval This study was approved by Weill Cornell Medical College Institutional Animal Care and Use Committee; Protocol Number 2018-0053

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