Combining Intra-Tumoral Treg Depletion with Androgen Deprivation Therapy (ADT): Pre-Clinical Activity in the Myc-CaP Model of Prostate Cancer

Ying-Chun Shen[1,2,11], Ali Ghasemzadeh[1,3,4,5], Christina M. Kochel[1, 12], Thomas R. Nirschl[2,3], Brian J. Francica[1,6], Zoila A. Lopez-Bujanda[1,3,5,7], Maria A. Carrera Haro[1,3,5], Ada Tam[1,3], Robert A. Anders[7], Mark J. Selby[8], Alan J. Korman[8], Charles G. Drake[1,5,9,10]

[1]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[2]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan
[3]Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[4]Medical Scientist Training Program, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[5]Columbia Center for Translational Immunology, Columbia University Medical Center, New York, NY, USA
[6]Current Address: Aduro Biotech, Berkeley, CA
[7]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[8]Bristol-Myers Squibb, Redwood City, CA, USA
[9]The Brady Urological Institute, Johns Hopkins University, Baltimore, MD
[10]Current address: Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, USA
[11] Graduate Institute of Oncology, School of Medicine, National Taiwan University, Taipei, Taiwan
[12]Current Address: Tizona Therapeutics, South San Francisco, CA

Introduction: Immune checkpoint blockade has anti-tumor activity in variety of tumor types. Responses in castration-resistant prostate cancer remain relatively rare - possibly due to low baseline levels of baseline immune infiltration. Using an immunocompetent cMyc-driven model (Myc-CaP), we studied the immune infiltrate induced by androgen deprivation therapy (ADT) and attempted to leverage that infiltration toward therapeutic benefit.

Methods: We quantified ADT-induced immune infiltration in terms of cell type and function using flow cytometry, qPCR and IHC. Preclinical studies tested the combinatorial effects of ADT and immune checkpoint blockade with tumor outgrowth and overall survival as endpoints.

Results: Androgen deprivation therapy induces a cellularly mixed pro-inflammatory infiltrate. This pro-inflammatory infiltrate was apparent in the early post-castration period but diminished as castration resistance emerged. Combining androgen deprivation therapy with tumor-infiltrating regulatory T cell (Treg) depletion using a depleting anti-CTLA-4 antibody significantly delayed the development of castration resistance and prolonged survival of a fraction of tumor-bearing mice. Immunotherapy as a monotherapy failed to provide a survival benefit, and was ineffective if not administered closely prior to ADT.

Conclusions: The immune infiltrate induced by ADT is cellularly complex and evolves over time. Therapeutic strategies focusing on depleting Treg in the peri-castration period have potential clinical utility.

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