Single cell discrimination of immunotherapy-induced changes in the prostate tumor microenvironment

David Y. Oh[1,2], Anthony Wong[3], Katsuto Shinohara[4], Hao Nguyen[4], Rahul R. Aggarwal[1], Terence W. Friedlander[1], Eric J. Small[1], Felix Y. Feng[3], Lawrence Fong[1,2]

1. Division of Hematology/Oncology and Genitourinary Medical Oncology, 2. Parker Institute for Cancer Immunotherapy, 3. Department of Radiation Oncology, 4. Department of Urology, University of California, San Francisco.

Background: The therapeutic benefit of immunotherapy in earlier stages of prostate cancer, in particular the metastatic hormone-sensitive state, remains unclear. Also, the phenotype and specificities of T cells that may confer benefit, and whether these represent enhancement of existing responses versus de novo responses only found in prostate tumors, are unknown.

Methods: To address these questions, we have continued single-cell analysis combining whole-transcriptome RNA sequencing and paired T cell receptor (TCR) analysis. This characterizes known or unanticipated T cell populations modulated by immunotherapy in an ongoing phase II trial testing combinations of immunotherapy (anti-PD-1 +/- the Toll-like receptor 9 agonist SD-101) with radiation (SBRT to prostate tumor) and combined androgen deprivation therapy (GnRH-directed therapy + abiraterone/prednisone) for newly diagnosed oligometastatic hormone-sensitive prostate cancer. By interrogating serial biopsies from prostate tumors and paired normal prostate taken before and after immunotherapy, we are determining which T cell populations are enriched in tumor, and which are pre-existing versus newly induced by immunotherapy.

Results: In this ongoing phase II trial, we have treated 10 patients, including multiple veterans, without additional safety signals. We have successfully obtained prostate tumor biopsies from 7 treated patients, most which include collections of paired tumor and adjacent normal tissue as well as paired pre- and on-treatment tissues. Preliminary analyses identify non-cytotoxic T cells and macrophages which are enriched in tumor across multiple patients, as well as cytotoxic T cells which express a highly polyclonal repertoire. Further progress in pooled analyses of T cell phenotypes and repertoire, and how these are modulated by immunotherapy, will be presented.

Conclusions: Using unbiased analytic approaches for identifying known and novel cell populations, we identify conserved, tumor-enriched non-cytotoxic T cells and macrophages. Further analysis of this high-dimensional data set will allow us to determine which immune responses are enhanced by immunotherapy.

Conflict of interest: D.Y.O. and L.F. have received research support from Merck.

Funding: D.Y. Oh is supported by NIH 4T32 CA177555, 1K08 AI139375, the Harry F. Bisel, MD Endowed Young Investigator Award from the Conquer Cancer Foundation of the American Society of Clinical Oncology, the Bladder Cancer Advocacy Network Palm Beach New Discoveries Young Investigator Award, and the Prostate Cancer Foundation Young Investigator Award. L. Fong is supported by NIH 5R01 CA194511 and the Prostate Cancer Foundation.