Interleukin-6 blockade abrogates immunotherapy toxicity and promotes tumor immunity

Noha Abdel-Wahab, MD, PhD; Daniel H. Johnson, MD; Yared Hailemichael, PhD; Wai Chin Foo, MD; Salah-Eddine Bentebibel, PhD; Gregory A Lizee, PhD; Suhendan Ekmekcioglu, PhD; Adi Diab, MD
The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
Correspondence: adiab@mdanderson.org

INTRODUCTION
• To mitigate immune checkpoint inhibitors (ICIs) induced immune-related adverse events (irAEs), we need a comprehensive understanding of their pathogenesis

METHODS
• We profiled gene expression in intestinal, colitis (n=23), and tumor tissue (n=22) from ICI treated cancer patients, with parallel studies in preclinical models, and validated our findings in a review of clinical cohort (n=31) treated with IL-6 receptor (IL-6R) blockade at MD Anderson Cancer Center

RESULTS
Nanostring gene expression analysis tumor versus irEC
• Th17 differentiating cytokines significantly higher upregulated in irEC compared to responding tumor
• Th1 differentiating cytokine significantly higher upregulated in responding tumor

IL-6 blockade increases anti-CTLA-4 efficacy in murine models
• Adding IL-6 blockade to anti-CTLA-4 significantly enhanced antitumor immunity and prolonged survival

IL-6 blockade improves anti-CTLA-4 therapeutic activity while not exacerbating autoimmunity in EAE model
• In tumor bearing EAE mice, anti-CTLA-4 alone accelerated clinical signs of EAE compared with anti-CTLA-4 + IL-6 blockade
• Anti-CTLA-4 + IL-6 blockade resulted in better tumor control

CONCLUSION
• IL-6R blockade could be effective therapy for irAEs without dampening ICI efficacy
• A phase II trial (NCT04940299) with longitudinal blood, tumor, and inflamed tissue biopsies is ongoing to evaluate the upfront use of tocilizumab with ICI combination in melanoma, lung, and urothelial cancer and to better study immunobiology of irAEs