INTERROGATING ELITE RESPONDER HUMORAL RESPONSES TO IDENTIFY NOVEL TARGETS AND THERAPEUTIC ANTIBODIES FOR THE TREATMENT OF CANCER

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Background The development of checkpoint inhibitors (CPIs) has transformed the treatment landscape for certain cancers. However, the response rates are modest for most cancers and some cancers are not amenable to CPIs and represent a significant unmet medical need.1,2 CPIs promote anti-tumor adaptive responses by lifting the brakes off immune activation, which is known to break tolerance to self-antigens and induce autoantibody formation.3–5 A subset of these autoantibodies may mediate anti-tumor responses and enhance CPI efficacy. B cells and tertiary lymphoid structures have been shown to contribute to CPI efficacy.6–8 We have evaluated serum autoantibody profiles of cancer patients who responded well to CPI therapy and interrogated their memory B cell repertoires to identify novel targets, epitopes, biomarkers, and immunomodulatory anti-cancer antibodies.

Methods Solid tumor patients who remain on CPI therapy for at least 6 months with stable disease, or at least 3 months with a partial or complete response were designated as Elite Responders for this study. Serum samples from healthy donors and matched serum and peripheral blood mononuclear cells from Elite Responders were collected. For novel targets, epitopes, and biomarker discovery, serum samples were tested on proteome microarrays containing >21,000 unique full length human proteins. Serum samples were also probed for binding, by flow cytometry, to a panel of myeloid cells. Elite Responders with seroreactivity specific to suppressive myeloid cells were selected for B cell activations and antibody discovery using the OncoResponse platform. Myeloid-targeting antibodies were subsequently cloned, expressed and evaluated for anti-tumor activity in functional assays.

Results Autoantibody profiling using the microarrays corroborated some targets known to have immunomodulatory activities in the TME across several cancer types, e.g., LILRB2, VSIG1, CD47, Siglec, and identified additional immune-oncolgoy targets of interest. Some autoantigens exhibited broad serological responses across several solid tumor types, while others were specific to a cancer type. The functional importance of the Elite Responder’s humoral response was demonstrated by the discovery of a myeloid-targeting antibody, OR2805, which specifically binds immunosuppressive M2 macrophages and converts them into an immunostimulatory phenotype. In M2 macrophage/T cell coculture assays, OR2805 rescues T cell activation and proliferation and amplifies anti-PD-1 activity. A phase 1–2 dose escalation-expansion study of OR2805 alone or in combination in subjects with advanced solid tumors is ongoing (NCT05094804).

Conclusions Interrogation of humoral responses in cancer Elite Responders is an attractive strategy for discovery of novel targets and therapeutic antibodies for the treatment of cancer.

REFERENCES