

RELATIONSHIPS BETWEEN IRAES AND CHECKPOINT INHIBITOR RESPONSE IN RADIOHEAD: A LARGE PROSPECTIVE PAN-TUMOR COHORT OF STANDARD-OF-CARE PATIENTS WITH CLINICAL ANNOTATION, MOLECULAR AND IMMUNE PROFILING

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Background Checkpoint immunotherapies (CPI) have resulted in long lasting responses in subsets of cancer patients. Despite this, responses come with the risk of immune-related adverse events (irAEs) which can limit the overall benefit of CPI. Associations with response, such as the correlation between development of irAE and better overall survival (OS), are well characterized in clinical trials but less understood in standard of care settings with wide varieties of patient profiles. Thus, real-world evidence cohorts are integral to bridging the gap between clinical trials reports and clinical practice. The RADIOHEAD study is a pan-tumor, prospective cohort study of 1,200 individuals on standard of care first-line CPI treatment regimens aiming to identify drivers of irAEs and clinical response.

Methods To capture a comprehensive profile of each patient, we prospectively collected blood samples and clinical features at pretreatment, early on treatment, and 6 and 12 month timepoints via case report forms and electronic medical records from 52 community oncology clinics across the United States. Patients who experienced irAEs had additional samples and clinical data collected at analogous time intervals from the irAE onset. Clinical data were structured and harmonized and unbiased statistical analysis was performed to identify clinical predictors of OS.

Results A total of 3951 samples and associated clinical data points were collected over the course of participants' treatment. Patients with any irAE (25%) had significantly longer OS in the pan-tumor cohort (n=1061, HR=0.4, 95% CI=[0.3, 0.6]). The association between irAE and survival held in the largest tumor sub cohorts, non-small cell lung cancer (NSCLC) (N = 397) and melanoma (N = 128), when adjusting for age, and in multivariable analysis. Patients who reported already taking steroids at the time of their pretreatment blood draw had significantly shorter survival than those who did not (HR=1.5 [1.2, 2]); this association appeared more pronounced in patients taking systemic steroids. Comparing NSCLC and melanoma to all other tumor types in this standard of care dataset, patients with melanoma had significantly longer (HR=0.4 [0.3,0.6]) OS.

Conclusions Results from this cohort study of standard of care patients support previously identified variables associated with CPI response. In the future, the potential for molecular profiling of samples collected in the RADIOHEAD cohort provides an opportunity to elucidate the potential mechanistic link between irAE and clinical response to CPI, as well as identify clinically actionable mechanisms for immunotherapy resistance via integrated analyses of multi-omic datasets to be generated from longitudinal patient samples.

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