Background Although cancer immunotherapy with PD-(L)1 blockade is now routine treatment for patients with lung cancer, remarkably little is known about the molecular and cellular features of acquired resistance. This is partially due to the difficulty in obtaining pre- and post-treatment samples from patients that initially respond to immunotherapy but relapse with time. Studies from smaller cohorts in lung cancer have identified antigen presentation defects, alterations in interferon (IFN) signalling and neoantigen loss as potential mechanisms of immunotherapy resistance.

Methods To address the clinical and molecular landscape of acquired resistance to PD-(L)1 blockade in patients with NSCLCs, we examined the largest clinical cohort (n = 1,201) of acquired resistance to PD-(L)1 blockade in lung cancer to date paired with a systematic genomic and transcriptomic analysis in a subset of patients (n = 29) with pre- and post-treatment tissue samples available. Post-treatment samples were obtained following radiographic progression to PD-1 blockade. We also examined syngeneic lung and colorectal cancer murine model of acquired resistance to PD-1 blockade to validate relationships identified in human samples.

Results Of 1,201 NSCLC patients treated with PD-1 blockade at MSKCC, 243 (20%) achieved initial response. Many responding patients ultimately developed acquired resistance, with an estimated cumulative acquired resistance rate of 61% (95% CI 36% – 85%) at 5 years of follow up using a competing risk model (figure 1a). Post-progression overall survival was significantly longer in acquired resistance compared to primary progression (median 18.9 months vs 4.4 months, Log-rank p< 0.0001, figure 1b), suggestive of persistent, partially effective anti-tumor immune responses that permits prolonged survival even after the initial onset of AR.

In a subset of NSCLC patients (n=29) with available pre- and post-treatment samples (figure 1c), systematic immunogenomic analysis revealed that tumors with acquired resistance generally associated with enriched signals of inflammation (including IFNg signaling and inferred CD8+ T cells) and could be separated into IFNg upregulated and stable subsets. IFNg upregulated tumors had putative routes of resistance with signatures of dysfunctional interferon signaling and mutations in antigen presentation genes (figure 1d).

Transcriptomic profiling of cancer cells from a murine model of acquired resistance to PD-1 blockade showed evidence of dysfunctional IFN signaling and acquired insensitivity to in vitro IFNg treatment (figure 1e,f).

Conclusions We find evidence of ongoing but dysfunctional IFN response associated with acquired resistance to PD1 blockade in preclinical and clinical lung cancer data.

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Ethics Approval All work has been approved by MSKCC regulatory body and study has been performed with approved patient consent.

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