Background: Although immune checkpoint inhibition (ICI) has improved survival in patients with non-small cell lung cancer (NSCLC), the majority of patients develop acquired resistance (AR) to ICI after an initial benefit.1-2 However, the mechanisms underlying AR to ICI in NSCLC are largely unknown.

Methods: Comprehensive genomic profiling and HLA-I immunohistochemistry (IHC) by blinded pathology assessment were performed on samples from patients with NSCLC treated with PD-(L)1 blockade at the Dana-Farber Cancer Institute and matched pre and post ICI tumor biopsies (figure 1). Acquired resistance was defined as the development of disease progression after an initial objective response, or stable disease ≥3 months with PD-(L)1 blockade.

Results: Among 1823 patients with advanced NSCLC who received ICI, 60 developed acquired resistance to treatment and had matched pre- and post-ICI tissue samples. Putative mechanisms of AR to PD-(L)1 blockade were identified in 56.7% (34/60) of cases (figure 2). Acquired mutations in STK11 were identified in 8.3% of cases (N=5) resulting in homozygous loss in 2, due to acquired copy deletion. Acquired mutations in KEAP1 and SMARCA4 were noted in one (1.7%) and 3 patients (5%), respectively. Four patients (6.7%) developed acquired deleterious mutations in the beta 2-microglobulin (B2M) gene. Of these, one exhibited bi-allelic loss due to concurrent B2M copy deletion. Other acquired alterations implicated in resistance to ICI included homozygous loss in JAK1 (N=1, 1.7%) and APC (N=1, 1.7%), and acquired activating PI3KCA mutation (N=1, 1.7%). In examining acquired copy number variations (CNVs), we found bi-allelic deletions in CDKN2A/CDKN2B in four cases (6.7%), and acquired heterozygous deletion in CD274 (PD-L1) and PDCD1LG2 (PD-L2) genes in four cases (6.7%), while high level MDM2 and MYC amplifications were identified in 3 (5%) and 1 (1.7%) case, respectively. PD-L1 expression, tumor mutational burden, and total aneuploidy levels were not impacted by intervening ICI (figure 3). Among patients with tissue available for HLA-I IHC, we found a significant decrease in HLA-I expression by H-score at the moment of acquired resistance to ICI (median H-score decrease -10 [range: 0 to -220], P=0.03, figure 4).

In 2 independent control cohorts of patients with pre- and post-chemotherapy (N=41) or EGFR inhibitors (N=90) tumor genomic profiling, no acquired mutations in STK11 or B2M were detected. Intervening chemotherapy and EGFR inhibition had no impact on HLA-I expression (figure 4).

Conclusions: Mechanisms of AR to PD-(L)1 blockade are heterogeneous, and new therapeutic strategies are required to delay and overcome ICI resistance in patients with NSCLC.

REFERENCES


Ethics Approval: Patients at the Dana-Farber Cancer Institute who consented to institutional review board-approved protocols DF/HCC 02-180, 11-104, 13-364, and/or 17-000 allowed for conducting translational research and tumor next-generation sequencing, respectively, were included. Consent Not applicable
Abstract 528  

**Figure 3**  PD-L1 expression on tumor cells, tumor mutational burden, and aneuploidy levels are not impacted by intervening PD-(L)1 blockade in NSCLC.

**Figure 4**  HLA-I expression by immunohistochemistry (IHC) significantly decreased in PD-(L)1 blockade resistant samples compared to baseline samples. In independent control cohorts of patients with pre- and post-chemotherapy or targeted therapy (EGFR inhibition) tumor biopsies, HLA-I expression did not change between baseline and resistant samples.