528 ACQUIRED RESISTANCE TO PD-(L)1 BLOCKADE IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

[1]Biagio Ricciuti*, [1]Giuseppe Lamberti, [1]Joao Victor Alessi, [1]Federica Pecci, [1]Alessandro Di Federico, [2]Xinan Wang, [1]Adriana Barrichello, [1]Victor Vaz, [1]Andy Pangilinan, [1]Danielle Haradon, [1]Lee Elinton, [3]Mizuki Nishino, [3]Scott Rodig, [3]Lynette Sholl, [1]Mark Awad. *[1]Dana-Farber Cancer Institute, Boston, MA, United States; [2]Harvard TH Chan School of Public Health, Boston, MA, United States; [3]Brigham and Women's Hospital, Boston, MA, United States*

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).

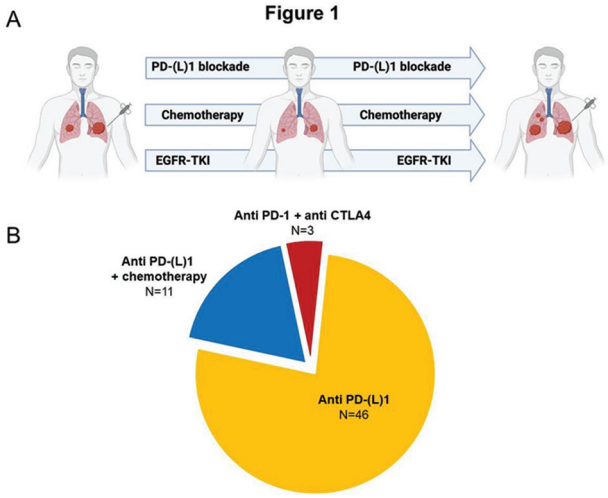
Conclusions Mechanisms of AR to PD-(L)1 blockade are heterogenous, and new therapeutic strategies are required to delay and overcome ICI resistance in patients with NSCLC.

REFERENCES

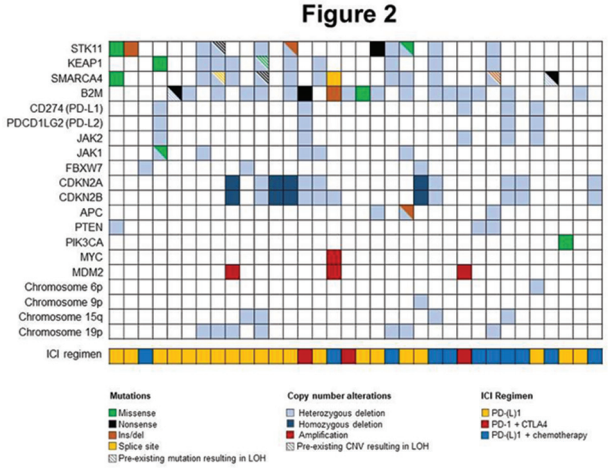
1. Schoenfeld AJ, Antonia SJ, Awad MM, Felip E, Gainor J, Gettinger SN, Hodi FS, Johnson ML, Leighl NB, Lovly CM, Mok T, Perol M, Reck M, Solomon B, Soria JC, Tan DSW, Peters S, Hellmann MD. Clinical definition of acquired resistance to immunotherapy in patients with metastatic non-small-cell lung cancer. *Ann Oncol*. 2021 Dec;**32**(12):1597-1607
2. Passaro A, Brahmer J, Antonia S, Mok T, Peters S. Managing resistance to immune checkpoint inhibitors in lung cancer: treatment and novel strategies. *J Clin Oncol*. 2022 Feb 20;**40**(6):598–610

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 which allowed for conducting translational research and tumor next-generation sequencing, respectively, were included.

Consent Not applicable



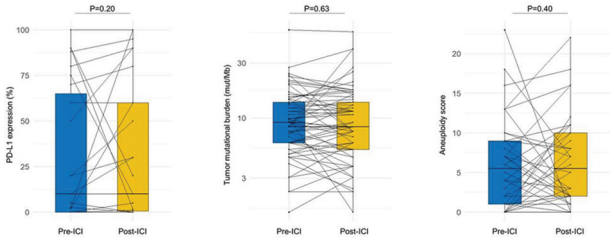
Abstract 528 Figure 1 (A) Study schema. Patients with NSCLC and matched pre and post PD-(L)1 blockade, chemotherapy (control cohort #1) and targeted therapy (EGFR inhibitors, control cohort #2) tumor biopsies were included in this study. (B) Distribution of immunotherapy regimens received by the 60 patients who developed acquired resistance to PD-(L)1 based therapies.



Abstract 528 Figure 2 Summary of the putative mechanisms of acquired resistance to PD-(L)1 blockade identified in this study.

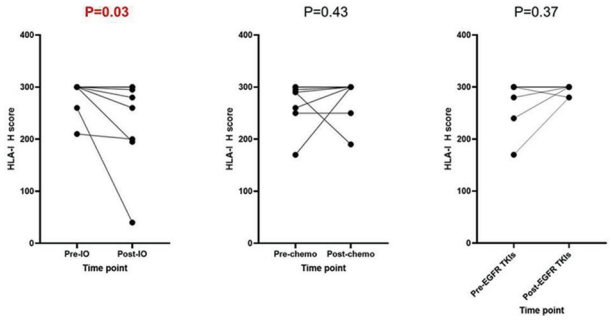
J Immunother Cancer: first published as 10.1136/jitc-2022-SITC2022.0528 on 7 November 2022. Downloaded from http://jitc.bmj.com/ on September 20, 2023 by guest. Protected by copyright.

Figure 3



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



Abstract 528 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.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0528

J Immunother Cancer: first published as 10.1136/jitc-2022-SITC2022.0528 on 7 November 2022. Downloaded from http://jitc.bmj.com/ on September 20, 2023 by guest. Protected by copyright.