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Appendix S1. Supplemental Methods.

Collection of Data

BMI: Body mass index (BMI) was computed using the largest weight record at a single visit (given the mean height) for each individual (less any potential error readings due to incorrect height or weight) in attempt to capture the normal BMI for each individual rather than BMI deflated by disease or treatment. Height and weight measures that were too far from the mean or nearest other measure, respectively, were excluded (>7cm height, >5kg weight).

Comorbidities: ICD9/10 codes were used to determine if a patient had records for asthma, chronic obstructive pulmonary disease (COPD), or emphysema (a form of COPD). Those with codes for 'chronic airway obstruction not elsewhere classified' were designated as likely having COPD and categorized with COPD. Those with no records for these conditions were placed in the 'None Reported' category.

Total follow time: Total follow time is the total length of time that a patient has records for and was computed as the time of the first recorded visit to the hospital to the patients end time. For censored individuals, we assigned end time as the last visit date. For individuals who died before the study end date, we set end time as the study end date.

Patient: A individual who had at least 5 years total follow time was considered a regular hospital patient. 95 individuals met these criteria.

Complete Follow Up: 1) For OS: Patients who died within 120 days of their last visit or whose last visit was within 120 days of the study end date were considered to have complete follow up. 2) For TTD: Patients who reached TTD, died within 120 days of their last anti PD1/PD-L1 treatment, or whose last treatment was within 120 days of the study end date were considered to have complete follow up.

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Statistical Methods

Survival Analysis:

Survival times, KM curves, and HRs were produced in the R survival (v2.44) package. P-values for median times and group comparisons were computed from the overall model using the score (logrank) test from the Cox proportional hazards regression model. For single and multivariable Cox regression models, Wald test p-values were reported for individual variables and categories. Hazard ratios and median times were not computed for cell counts less than 7.

Propensity Matching:

The balance of a covariate between two groups (such as the White and African American cohort) was assessed using the R package tableone (v 0.10.0). This package performs the groupwise fisher test and t-test for categorical and continuous variables, respectively. P-values were reported along with the standardized mean difference (SMD). In this package, the SMD is generalized to multilevel categorical variable by computing the Mahalanobis distance between the two samples based on the categorical variable. Variables with an SMD > 0.1 are considered not to be well matched between any two test groups.

Propensity matching uses the predicted value (based on potential confounders) of an individual belonging to one of two groups, to match individuals between the two groups. The predicted values were computed using logistic regression with LOT (first versus second or higher), anti PD1/PD-L1 initiation year (coded as numeric to preserve ordinality), total follow time, and concurrent chemotherapy with anti PD1/PD-L treatment. The total follow time can be viewed an indicator of whether the patient was already a hospital patient prior to diagnosis versus patients who came to the hospital for cancer treatment after diagnosis (see definition in Data Collection). Matching on treatment variables can reduce treatment bias between groups, a bias which could potentially drive differential outcomes such as TTD or OS. Here we use 1:1 nearest neighbor matching to select a group of treatment matched individuals.

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Appendix S2. ADDITIONAL RESULTS:

Descriptive Statistics for cohort follow up:

The median total follow time for patients was 44.1months. 77.1% of the patients either were followed to the end of study or had treatment discontinuation. Additional descriptive statistics for censoring and drop-out rates are presented in Supplementary Table 1.

Correlation Between TTD and OS:

The R package SurvCorr (v1.0) computes the correlation between two outcomes with censored data using the iterative multiple imputation approach to account for censoring. In this study, the correlation between TTD and OS was 0.78 (95% CI 0.65-0.87), concordant with the results of 0.78 for Spearman's rank correlation in the main text. The high correlation implies that TTD may potentially be used as a proxy for OS. However, we observed that some variables associated with OS are not associated with TTD, such as gender (see Figures 3A and 3B).

Single Variable Analysis (median times reported in Table 1 of main text)

Hazard ratios for single variable analysis are reported in Supplemental Table 2 for both TTD and OS. As in Figures 1-3, Race/ethnicity is associated with both TTD and OS. Never smoking is associated with shorter TTD (HR=1.84, p=0.012), while being male is associated with shorter OS (HR=1.50, p=0.033). PDL1 status is not significantly associated with OS, but PDL1 positive individuals have longer survival times (HR=0.61, p=0.14). No association of age or BMI with either TTD or OS was observed. While there was no association between COPD and OS, COPD was associated with longer TTD (HR=0.67, p=0.44). A recent article looked at the response of COPD patients to immunotherapy in lung cancer and found that those with COPD had better progression free survival (PFS) but no difference in OS was observed. Additionally, they found better PFS in smokers and former smokers[1]. In our cohort, the frequency of COPD was also elevated among those with response (44.6% in responders 22.7% in those with progression or stable disease).

For the top 5% of responders (n=13), those with continuous treatment (TTD) > 694 days we see evidence of the trends reported for longer TTD and OS. Within these 13 individuals, 9 had response and 4 had stable disease, 7 were African American while only 4 were White, 5 had records for squamous cell carcinoma, 8 were female, and 12 patients were smokers. 7 were not tested for PDL1 status and 5 were positive, while 7 were not tested for EGFR/ALK mutations and none were positive.

Race and Cohort Matching

A previous study on NSCLC with anti-PD1/PD-L1 inhibitors reported similar race/ethnicity trends as in Figure 2B and Table 1 for OS[2]. Although their results for race were not statistically significant, they report a median OS (95% CI) in Blacks and Asians of 9.0 months (4.8-12.7) and 9.7 months (6.8-13.2) versus a slightly shorter OS in White and Other of 8.0 months (7.3-9.2) and 7.8 months (5.1-12.3), respectively. Their 'Other' group includes Hispanic/Latino, and no between group comparisons were reported. While their study is overall much larger, this study has similar absolute numbers of African Americans, Asians, and Others (including Hispanics).

Propensity Matching and Multivariable analysis:

To further investigate the observed trend of longer TTD and OS (Figures 1C and 2C of the main text) in African American versus White individuals, any potential treatment bias was first controlled for via propensity matching, and then clinical variables potentially associated with both race and outcome were examined within the matched groups. The results for variable comparisons in the full set of individuals are presented in Supplemental Table 3. In general, the African American group appears to have higher censoring (lower death rate) but similar dropout and follow up rates, although with slightly lower total follow times and follow up times after anti PD1/PD-L1 treatment was initiated. Additionally, African Americans were more likely to be treated recently and on first line.

Reviewing differences in clinical and demographic variables, the African American group has a younger mean age of PD1/PD-L1 initiation than the White group: 65.0 versus 70.5 years of age. This is consistent with the US military NSCLC study, where the mean age of diagnosis was 62 for African Americans and 67

for White individuals[3]. Potential causes of earlier onset of lung cancer are heavier smoking or earlier age of smoking onset. African Americans were more likely to be current smokers, have squamous cell carcinoma and have asthma, but were less likely to have COPD or an EGFR/ALK mutation.

Propensity matching was performed to determine if results remained consistent when African American and White individuals were matched on treatment variables. Supplemental Figure 1 plots the propensity scores before and after nearest neighbor 1:1 matching (which retains all African American individuals).

Supplemental Table 4 examines covariate differences after matching and Supplemental Figure 2 presents the Kaplan Meier curves for the propensity matched groups for both TTD and OS. Within the matched cohort, the median TTD for White is 3.5 (95% CI 2.1-8.6) months and for African American is 7.8 (95% CI 5.4-NE) months, and the median OS for White is 13.2 (95% CI 7.2-NE) months and for African American is not reached (95% CI 18.4-NR). The trends are similar to the full cohort and remain statistically significant with HRs of 0.61 (p=0.026) and 0.56 (p=0.033) for TTD and OS, respectively. A robust score test that assumes non-independence of the samples within a pair produces similar p-values, 0.022 for TTD and 0.026 for OS. In a multivariable model of the propensity matched pairs adjusted for the clinical variables above, the HRs for TTD and OS between the African American and White cohorts remain statistically significant after adjustment (supplemental Table 5). Key unmeasured variables that could explain some of the difference in outcomes may still be missing, such as smoking pack years.

Subgroup analysis:

For subgroup analysis, we repeated single variable Cox regression for OS in the specific subgroup.

Subtype: Smokers & Non-EGFR/ALK

Cancer in smokers versus non-smokers and in those with EGFR or ALK mutations may be different subtypes of cancer and may respond differently to anti PD1/PD-L1 treatment. Analysis was restricted to

smokers without EGFR/ALK mutations and clinical variables are reanalyzed (Supplementary Table 6). African Americans have significantly longer OS than White individuals (HR=0.55, p=0.039). Similar trends are observed for better OS in females, Asians, and PDL1 positive individuals (not statistically significant). EGFR/ALK mutations are more likely to occur in never smokers (of the 25 individuals reported to have EGFR/ALK mutations, 13 are never smokers). These groups were not large enough to analyze covariates within them.

By LOT

Figures 2D and 3D in the main text compare those taking immunotherapy drugs for their first LOT versus those who started treatment as the second or higher LOT. In Figure 2D, we see LOT seems to have no effect on TTD, but we see a small difference in OS in Figure 3D. However, although this difference is not statistically significant it may be expected as those taking on their second LOT or higher will be further from their metastatic diagnosis date. Those on first LOT are more likely to be treated in conjunction with chemotherapy (31.0% versus 9.6% for second line or higher). Single variable survival analysis for OS was repeated by first versus second or higher LOT in supplemental Table 7. For both groups, we again see a trend for longer OS in females and African Americans.

Within Race

Survival analysis for OS was then performed within the White population and within the African American population to mitigate interactions of race with other covariates. Results are presented in Supplemental Table 8. Other populations had too few individuals to perform meaningful analysis. Again, trends for longer OS in females were observed in both groups, and a trend for shorter OS in EGFR/ALK mutations was seen in the White group.

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