Similar Efficacy Observed for First-Line Immunotherapy in Racial/Ethnic Minority Patients With Metastatic NSCLC

Matthew Lee, MD, MPH[1]; Jianyou Liu, MS[2]; Emily Miao, PharmD[1]; Shuai Wang, MD[1]; Frank Zhang, MD[3]; John Wei, MD[3]; Julie Chung, CTR, BA[4]; Xiaonan Xue, PhD[2]; Balazs Halmos, MD[1]; H. Dean Hosgood, PhD[2,*]; and Haiying Cheng, MD, PhD[1,*]

ABSTRACT

Background: Limited data exist on the impact of immunotherapy use in ethnic minority patients with non–small cell lung cancer (NSCLC), because they have been underrepresented in immunotherapy trials. This study aims to evaluate race/ethnicity and other demographic, socioeconomic, and clinical factors of patients with metastatic NSCLC treated with first-line immunotherapy. **Methods:** A retrospective cohort study of 5,920 patients diagnosed with lung cancer treated at Montefiore Einstein Cancer Center from January 1, 2013, to June 1, 2022, was used to identify patients with metastatic NSCLC without *EGFR*, *ALK*, or *ROS1* alterations who underwent first-line immunotherapy (n=248). The primary endpoint was overall survival (OS), with secondary endpoints of progression-free survival (PFS) and time to discontinuation (TTD) from the start of immunotherapy. **Results:** Among the 248 patients, median follow-up time was 12.0 months, median age at start of treatment was 66 years, and 39.1% were non-Hispanic Black, 30.2% were Hispanic, and 30.7% were non-Hispanic White. OS ($P=.39$), PFS ($P=.29$), and TTD ($P=.98$) were similar among racial/ethnic groups. Patients with an ECOG performance status (PS) of <2 at the start of immunotherapy had longer OS compared with those with ECOG PS of ≥2 ($P<.0001$). PD-L1 expression (<50% vs ≥50%; $P=.03$) and body mass index (BMI) ($P=.01$) were also found to be associated with PFS, and ECOG PS ($P<.0001$) and BMI ($P=.02$) were associated with TTD. In a multivariate analysis of OS and PFS, ECOG PS was the only variable found to be significant. **Conclusions:** Our study observed similar benefits of immunotherapy in patients with metastatic NSCLC in different racial and ethnic groups. Furthermore, ECOG PS was associated with OS, and PD-L1 expression and BMI were associated with PFS and TTD. These findings help identify potential factors associated with outcomes and care while patients are undergoing immunotherapy.

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[1]Department of Medical Oncology, Montefiore Medical Center, Montefiore Einstein Cancer Center, Albert Einstein College of Medicine, Bronx, New York; [2]Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, New York; [3]Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York; and [4]Department of Health Information Management, Montefiore Medical Center, Bronx, New York.

*These authors are co–last authors.

Background

Lung cancer is the leading cause of cancer-related mortality in the United States, but survival has improved over the last decade, largely driven by increased screening, identification of actionable driver alterations, use of targeted therapies, and the paradigm-shifting incorporation of immunotherapy. Because more than half of patients with advanced non–small cell lung cancer (NSCLC) do not harbor a targetable alteration, they are treated instead with standard first-line therapy consisting of immunotherapy with or without chemotherapy.[1–11]

Despite the advances from immunotherapy clinical trials, questions remain on whether various socioeconomic and demographic characteristics influence clinical outcomes. Immunotherapy trials typically include patients that tend to be younger and healthier and have a more homogenous racial/ethnicity composition compared with clinical practice. Most patients with advanced NSCLC enrolled in these immunotherapy trials were White or Asian, with Black and Hispanic patients composing only 1% to 10% of trial participants, even though they represent 13% to 20% of the US general population.[10–14]

The phase III PACIFIC trial found that White patients with unresectable stage III NSCLC who received durvalumab after chemoradiotherapy had improved survival compared with the White patients in the placebo arm[10]; however, because only 2.5% of the patients who received durvalumab were Black, no analysis was able to determine whether there was also a survival advantage in Black patients. Similarly, the phase III IMpower132 trial, consisting of patients with advanced NSCLC who received first-line atezolizumab with chemotherapy or chemotherapy alone, demonstrated improved progression-free survival (PFS) among the White and Asian patients in the immunotherapy arm; however, only 0.7% of the patients were Black, and thus no further analysis was possible for that racial group.[11] Therefore,

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generalizability of trial data in clinical practice can pose a problem in the real-world clinical setting, and it is unknown whether other racial and ethnic groups would benefit from immunotherapy in these trials or previous immunotherapy trials.

Studies prior to the immunotherapy era examined the impact of race/ethnicity on patients with NSCLC and found that non-Hispanic Black (NHB) patients with NSCLC had worse survival outcomes compared with non-Hispanic White (NHW) patients.[15,16] Interestingly, Hispanic patients have been shown to have improved survival outcomes with significant prognostic factors, including female sex and treatment type (chemotherapy, surgery, radiotherapy), but an increased risk of mortality if they are unmarried, are active or former smokers, and have comorbidities.[17,18]

Even after immunotherapy was approved for patients with NSCLC, disparities among different racial groups persisted, with Black patients less likely to receive immunotherapy than White patients.[19] Previous studies examining race/ethnicity in patients with NSCLC treated with immunotherapy have shown mixed results regarding whether there is an association with clinical outcomes.[20–25] Nonetheless, of these limited studies, none addressed other demographic or socioeconomic factors, such as insurance or income, that may also play a role in immunotherapy clinical outcomes and enrollment onto trials.

The Montefiore Einstein Comprehensive Cancer Center (MECCC) is uniquely situated to address these questions because it serves a diverse ethnic minority patient population. This real-world study provides updated information on the use of immunotherapy in the first-line setting in patients with advanced NSCLC, examining multiple clinical and sociodemographic factors that can play a role in treatment efficacy among these patients in order to help identify and predict those who may benefit and address any potential barriers.

Methods

Patients and Clinical Information

We used a retrospective cohort study of 5,920 patients diagnosed with lung cancer based on ICD-10 site codes C34.0 to C34.9 from January 1, 2013, to June 1, 2022, at MECCC. Electronic medical records (EMRs) were reviewed to identify patients who met the inclusion criteria: confirmed metastatic NSCLC, at least 2 clinical visits completed, age ≥18 years, receipt of at least 1 cycle of first-line immunotherapy and at least a follow-up of 2 weeks after the last dose of immunotherapy, and no known driver alterations in *EGFR*, *ALK*, or *ROS1*. This study was approved by the Institutional Review Board at Albert Einstein College of Medicine.

The clinical and demographic information was extracted from the EMRs, with self-reported race and ethnicity combined into NHB, Hispanic, and NHW groups. Other demographic variables collected were age at start of treatment, self-reported biological sex, histology based on pathology reports and registry ICD-10 coding, smoking status (former/active or never smoker), body mass index (BMI) at the start of immunotherapy, and insurance (commercial, Medicare, Medicaid, or a combination of Medicare and Medicaid). Annual household income was determined by the zip code of the patient's address listed in the EMR, US Census Bureau data from the American Community Survey's 2021 estimates in USD amounts, and census-based geographic data.[26] The clinical status was determined by clinicians based on the patient's ECOG performance status (PS) at the start of immunotherapy. PD-L1 expression was evaluated using immunohistochemistry staining with the Dako 22C3 antibody.

Endpoints

The primary clinical endpoint was overall survival (OS), defined as the time from first date of immunotherapy administration to the date of death or last recorded visit. Secondary outcomes included PFS and time to treatment discontinuation (TTD). PFS was defined as the time from first date of immunotherapy adminstration to the date of documented progression by imaging based on RECIST v1.1. Patients with no real-world progression were censored at their last known visit or start of a new therapy. TTD was determined from the first date of immunotherapy administration to the last date that immunotherapy was administered and discontinued. Treatment-related adverse events (TRAEs) were graded based on CTCAE v5.0.

Statistical Analysis

Demographic and clinical characteristics and TTD were compared between race/ethnicity groups using the Wilcoxon rank-sum or Kruskal-Wallis test for continuous variables, and the chi-square or Fisher exact test for categorical variables. PFS and OS were first compared using Kaplan-Meier survival curves along with the log-rank tests. A full comprehensive multivariate analysis with a Cox proportional hazards model was used to examine OS and PFS differences between NHW, NHB, and Hispanic patients while adjusting for clinically relevant covariates of age, sex, smoking status, histology, ECOG PS at start of immunotherapy, PD-L1 score, immunotherapy given with or without chemotherapy, and presence of brain metastasis. A proportional hazards assumption was tested using Schoenfeld residuals. In addition, reduced models were conducted for OS and PFS on significant covariates from the full models along with age, PD-L1 score, and ECOG PS among the different race/ethnicity groups. Log-transformed TTD was analyzed using a linear regression model to examine the ratios in TTD among the 3 race/ethnicity groups. All

statistical analyses were conducted via SAS 9.4 (SAS Institute Inc.), and the significance level was set at $P<.05$ using 2-sided tests.

Results

Clinical and Socioeconomic Characteristics

Among the 248 patients with metastatic NSCLC treated with first-line immunotherapy who met the inclusion criteria (Figure 1), the median age at the start of treatment was 66 years (range, 37–91 years) (Table 1). More than half the patients were male (58.5%), and a vast majority were former or active smokers (91.9%). There was diverse mix of patients, with 39.1% self-reporting as NHB, 30.2% as Hispanic, and 30.7% as NHW. The most common NSCLC histology was adenocarcinoma (81.1%) followed by squamous cell carcinoma (18.9%). Brain metastases at the start of immunotherapy were noted in 27% of the patients, with 64.9% of patients having ECOG PS <2 at the start of immunotherapy. Most patients were positive for PD-L1 expression, with 71.8% of patients having a PD-L1 tumor proportion score (TPS) ≥1% and 39.9% having a TPS ≥50%. Age, smoking status, biological sex, histology, BMI, ECOG PS, brain metastases, immunotherapy regimens, and PD-L1 TPS were similar by racial and ethnic group (Table 1). Most patients (94.5%) were treated with a pembrolizumab-based regimen, with more than half the immunotherapy regimens combined with chemotherapy (56.1%) and the remainder being immuno-monotherapy (43.9%). In our cohort, the median duration of immunotherapy received by patients was 4.8 months. Further analysis that examined the duration of immunotherapy in mutually exclusive groups revealed that 12.1% of the study's cohort completed only 1 cycle of immunotherapy, 10.9% were treated for 6 months, 8.9% were treated for 1 year, and 11.3% were treated for ≥2 years. Notably, there was no significant difference in the duration of immunotherapy treatment among the different racial/ethnic groups ($P=.85$) (Table 1).

There were significant differences in socioeconomic characteristics among the different race/ethnicity groups by insurance ($P=.02$), median household income ($P<.0001$), and income groupings ($P<.0001$). Overall, 20.2% of patients had commercial insurance, 48.4% had Medicare, 23.8% had Medicaid, 6.8% had a combination of dual Medicare/

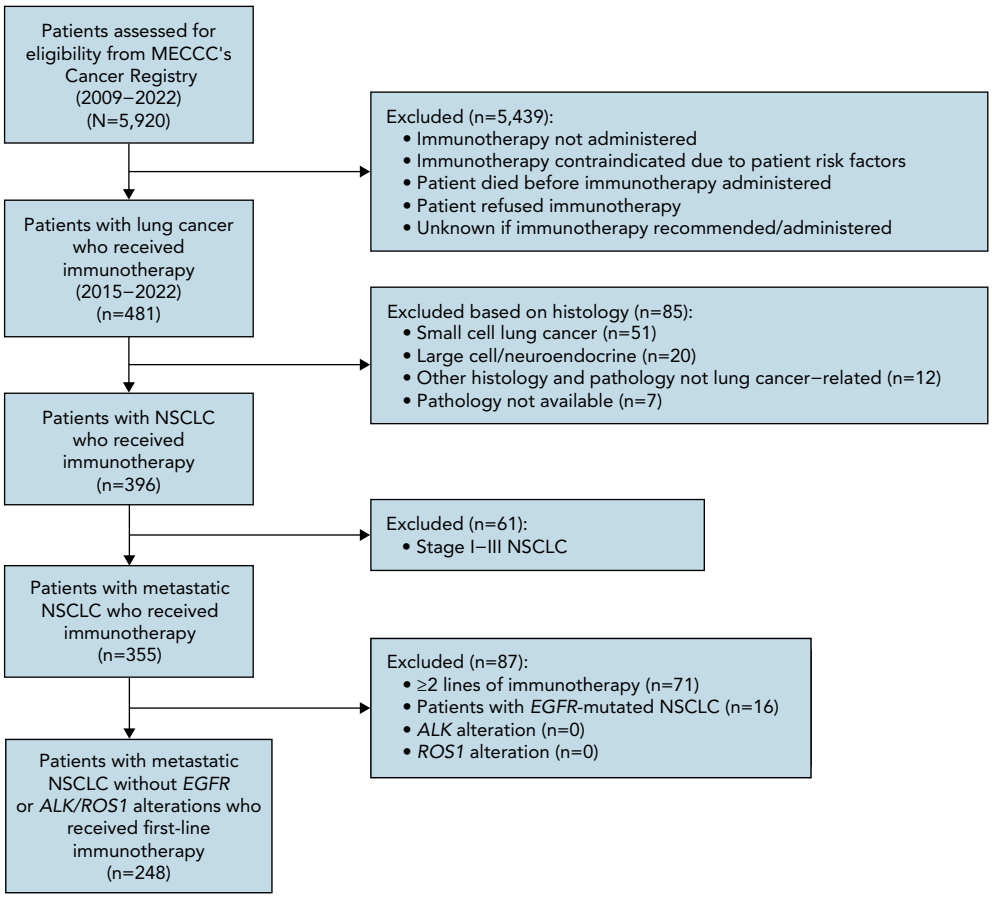

Figure 1. CONSORT diagram of inclusion criteria and cohort selection.
Abbreviations: MECCC, Montefiore Einstein Comprehensive Cancer Center; NSCLC, non–small cell lung cancer.

Table 1. Patient Demographics and Clinical Factors

	All Patients n (%)	Non-Hispanic White n (%)	Non-Hispanic Black n (%)	Hispanic n (%)	*P* Value
Total	248 (100)	76 (30.7)	97 (39.1)	75 (30.2)	
Age, median (range), y	66 (37–91)	68 (46–91)	65 (44–86)	67 (37–89)	.71
Biological sex					.21
Male	145 (58.5)	49 (64.5)	58 (59.8)	38 (50.7)	
Female	103 (41.5)	27 (35.5)	39 (40.2)	37 (49.3)	
Smoking status					.6
Former/Active	228 (91.9)	71 (93.4)	90 (92.8)	67 (89.3)	
Never	20 (8.1)	5 (6.6)	7 (7.2)	8 (10.7)	
Median BMI, kg/m^2	23.3	24.2	23.2	22.7	.46
BMI					.58
Underweight (<18.5 kg/m^2)	32 (12.9)	7 (9.2)	14 (14.7)	11 (12.9)	
Healthy (18.5–24.9 kg/m^2)	116 (46.8)	33 (43.4)	46 (49.3)	37 (46.8)	
Overweight/Obese (≥25 kg/m^2)	100 (40.3)	36 (47.4)	37 (36.0)	27 (40.3)	
Insurance					.02*
Commercial	50 (20.2)	21 (27.6)	22 (22.7)	7 (9.3)	
Medicare	120 (48.4)	35 (46.1)	49 (50.5)	36 (48.0)	
Medicaid	59 (23.8)	16 (21.1)	18 (18.5)	25 (33.4)	
Dual Medicare/Medicaid	17 (6.8)	2 (2.6)	8 (8.3)	7 (9.3)	
None	2 (0.8)	2 (2.6)	0 (0)	0 (0)	
Median annual household income (range), USD	$53,819 ($23,337–$193,085)	$60,802 ($28,831–$193,085)	$53,819 ($23,337–$145,667)	$37,777 ($23,337–$74,889)	<.0001*
Annual household income[a]					<.0001*
<$35,000	51 (20.6)	4 (5.3)	20 (20.6)	27 (36.0)	
$35,000–$49,999	59 (23.8)	11 (14.5)	24 (24.7)	24 (32.0)	
$50,000–$99,999	121 (48.8)	45 (59.2)	52 (53.7)	24 (32.0)	
≥$100,000	17 (6.8)	16 (21.0)	1 (1.0)	0 (0)	
ECOG PS					.96
<2	161 (64.9)	49 (64.5)	64 (66.0)	48 (64.0)	
≥2	87 (35.1)	27 (35.5)	33 (34.0)	27 (36.0)	
Histology					.1
Adenocarcinoma	201 (81.1)	58 (76.3)	85 (87.6)	58 (77.3)	
Squamous	47 (18.9)	18 (23.7)	12 (12.4)	17 (22.7)	
PD-L1 TPS, 1% cutoff					.76
<1%	57 (23.0)	16 (21.1)	25 (25.8)	16 (21.3)	
≥1%	178 (71.8)	54 (71.1)	68 (70.1)	56 (74.7)	
Missing	13 (5.2)	6 (7.9)	4 (4.1)	3 (4.0)	
PD-L1 TPS, 50% cutoff					.12
<50%	136 (54.9)	41 (54.0)	60 (61.9)	35 (46.7)	
≥50%	99 (39.9)	29 (38.1)	33 (34.0)	37 (49.3)	
Missing	13 (5.2)	6 (7.9)	4 (4.1)	3 (4.0)	
Immunotherapy with chemotherapy					.57
No	109 (43.9)	30 (39.5)	43 (44.3)	36 (48.0)	
Yes	139 (56.1)	46 (60.5)	54 (55.7)	39 (52.0)	

(*continued on next page*)

Table 1. Patient Demographics and Clinical Factors (cont.)

	All Patients n (%)	Non-Hispanic White n (%)	Non-Hispanic Black n (%)	Hispanic n (%)	*P* Value
TRAEs					.48
Yes	90 (36.3)	31 (40.8)	31 (32.0)	28 (37.3)	
No	158 (63.7)	45 (59.2)	66 (68.0)	47 (62.7)	
TRAE grade					.41
<3	52 (57.8)	15 (48.4)	20 (64.5)	17 (60.7)	
≥3	38 (42.2)	16 (51.6)	11 (35.5)	11 (39.3)	
Brain metastasis					.39
Yes	67 (27)	21 (27.6)	22 (22.7)	24 (32.0)	
No	181 (73)	55 (72.4)	75 (77.3)	51 (68.0)	
Median duration of immunotherapy (range)	4.8 (0.1–52.0)	4.9 (0.1–52.0)	4.5 (0.1–47.1)	4.9 (0.1–41.5)	.98
Duration of immunotherapy[b]					.85
1 cycle	30 (12.1)	8 (10.5)	13 (13.4)	9 (12.0)	
6 months	27 (10.9)	11 (14.5)	7 (7.2)	9 (12.0)	
1 year	22 (8.9)	6 (7.9)	8 (8.3)	8 (10.7)	
≥2 years	28 (11.3)	7 (9.2)	14 (14.4)	7 (9.3)	

Abbreviations: BMI, body mass index; NA, not available; NSCLC, non–small cell lung cancer; PS, performance status; TPS, tumor proportion score; TRAE, treatment-related adverse event.
[a]Determined by the ZIP code of the patient's address listed in the electronic medical record, US Census Bureau data from the American Community Survey's 2021 estimates in USD amounts, and census-based geographic data.
[b]Exclusively defined durations of patients completing only 1 cycle, 6 months, 1 year, or ≥2 years of treatment, respectively defining the number of patients in each group. The n (%) is the number of patients in these exclusive groups and percentage of the total within each race/ethnicity group.
*$P<.05$.

Medicaid, and only 0.8% had no insurance reported. Within the race/ethnicity groups, the largest difference was between NHW and Hispanic patients, with Hispanic patients having the highest reported Medicaid enrollment (33.4%); the NHW patients had the highest commercial insurance enrollment (27.6%). Moreover, there was an income gap between NHW patients who had a median annual household income of $60,802 (range, $28,831–$193,085), with most (80.2%) earning ≥$50,000, compared with Hispanic patients, who had a median household income of $37,777 (range, $23,337–$74,889) with most (68.0%) earning <$50,000.

Clinical Outcomes

At a median follow-up of 12.0 months (range, 0.5–66.2 months), the primary OS (26.3 vs 23.5 vs 16.8 months; $P=.39$), PFS (8.7 vs 6.7 vs 7.6 months; $P=.29$), and TTD (4.5 vs 4.9 vs 4.9 months; $P=.98$) were similar between NHB, Hispanic, and NHW patients, respectively (supplemental eTable 1, available with this article at JNCCN.org). Kaplan-Meier estimates for OS revealed similar results by race/ethnicity ($P=.39$) (Figure 2A) and PFS ($P=.29$) (Figure 2B). Age, biological sex, smoking status, BMI, insurance, household income, histology, PD-L1 score, immunotherapy regimen, and presence of brain metastasis were not associated with OS. In terms of PFS, patients with a lower BMI of ≤24.9 kg/m^2 had shorter median PFS compared with those with a BMI of ≥25 kg/m^2 ($P=.01$). Patients with Medicare insurance had longer PFS compared with those who had commercial or Medicaid insurance ($P=.008$). Those with a higher PD-L1 TPS of either ≥1% or ≥50% had a longer PFS ($P=.01$ and $P=.03$, respectively). Regarding TTD, similar trends were noted for BMI: those with a lower BMI of ≤24.9 kg/m^2 had a significantly shorter TTD compared with those who had a BMI of ≥25 kg/m^2 ($P=.02$). Conversely, ECOG PS ≥2 was associated with worse OS, PFS, and TTD compared with ECOG PS <2 ($P<.0001$).

After accounting for potential confounding factors with a comprehensive multivariate model adjusting for race/ethnicity, age, sex, smoking status, histology, ECOG PS, PD-L1 score, chemotherapy, and brain metastasis, ECOG PS was confirmed to be associated with OS (Figure 3) and PFS (supplemental eFigure 1) ($P<.0001$), and PD-L1 expression was confirmed to be associated with PFS ($P=.0152$). A reduced multivariate model that specifically evaluated factors such as age, PD-L1 score, ECOG PS, and NHB, NHW, or Hispanic race/ethnicity again confirmed that ECOG PS was associated with OS ($P<.0001$) (supplemental eTable 2). When PFS was evaluated using the same covariates in the same reduced multivariate model, PD-L1 and ECOG PS were found to be associated with PFS,

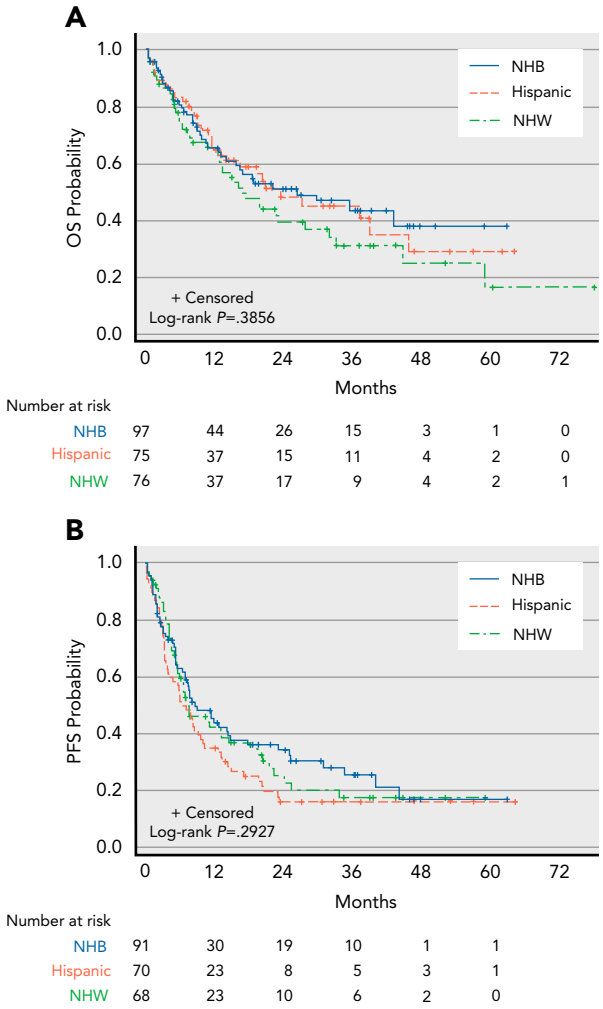

Figure 2. **(A)** OS and **(B)** PFS rates of patients with metastatic non–small cell lung cancer receiving first-line immunotherapy by race/ethnicity.
Abbreviations: NHB, non-Hispanic Black; NHW, non-Hispanic White; OS, overall survival; PFS, progression-free survival.

and Hispanic patients were found to have shorter PFS compared with NHB patients (hazard ratio [HR], 1.458; 95% CI, 1.038–2.047; P=.0296) (supplemental eTable 3). Furthermore, exploratory race/ethnicity-specific analyses revealed again that ECOG PS ≥2 was associated with worse OS among Black patients compared with non-Black patients (P<.0001) (supplemental eTable 4), and among Hispanic patients compared with non-Hispanic patients (P<.0001) (supplemental eTable 5).

Safety Outcomes

Regarding safety, overall TRAEs were reported in 36.3% of patients, with the majority being grade <3 (57.8%). There were no significant differences in incidence of TRAEs among the different racial/ethnic groups (P=.48), or in the occurrence of grade 3 TRAEs (P=.41) (Table 1). An analysis of the subset of patients who experienced TRAEs revealed a significantly longer OS (P=.02) and PFS (P=.003) compared with those without reported TRAEs (supplemental eTable 6). However, when stratified by grade <3 or ≥3 TRAEs, the association with OS (P=.72) or PFS (P=.65) was no longer significant (supplemental eTable 6).

Discussion

Our racially and ethnically diverse cohort of patients with metastatic NSCLC treated with first-line immunotherapy regimens had similar clinical efficacy with respect to OS, PFS, and TTD. Comparably, this study revealed a range of 16.8 to 26.3 months for median OS, similar to the long-term outcomes of clinical trials with patients who had advanced NSCLC and who were treated with monotherapy pembrolizumab with a median OS ranging from 10.5 to 26.3 months.[27–30] Trials with pembrolizumab and chemotherapy regimens had a median OS that ranged from 17.2 to 34.5 months, with similar incidences of TRAEs.[31–33] Previous research on the efficacy of immunotherapy in NHB patients have had mixed results, with some studies showing similar efficacy and tolerability in NHB patients with advanced NSCLC versus NHW patients, with no difference in OS or PFS,[20–22] whereas other studies have shown that NHB patients had a longer OS, PFS, and TTD.[23,24]

In regard to Hispanic patients, our analysis revealed no significant difference in OS between Hispanic and non-Hispanic patients in all 3 models, including a univariate model (supplemental eTable 1), a comprehensive multivariate model (Figure 3), and a reduced exploratory multivariate model (supplemental eTable 2 and eTable 5). However, a discrepancy emerged when examining PFS in these 3 models. Whereas both the univariate (supplemental eTable 1) and comprehensive multivariate analysis (supplemental eFigure 1) showed concurrence, indicating no significant difference in PFS among the different race/ethnicity groups, the reduced exploratory multivariate model revealed instead that Hispanic patients had a significantly worse PFS compared with NHB patients (supplemental eTable 3). Notably, a prior study that included patients with lung cancer and those with head and neck cancer found that Hispanic and NHB patients had a lower objective response rate (ORR) compared with NHW patients.[25] Our study did not analyze ORR, but it is possible that a lower response to immunotherapy could lead to a lower PFS as more patients demonstrate disease progression. Nevertheless, similar in both our study and the previous report,[25] OS was not significantly different. These intriguing findings require further validation in future studies.

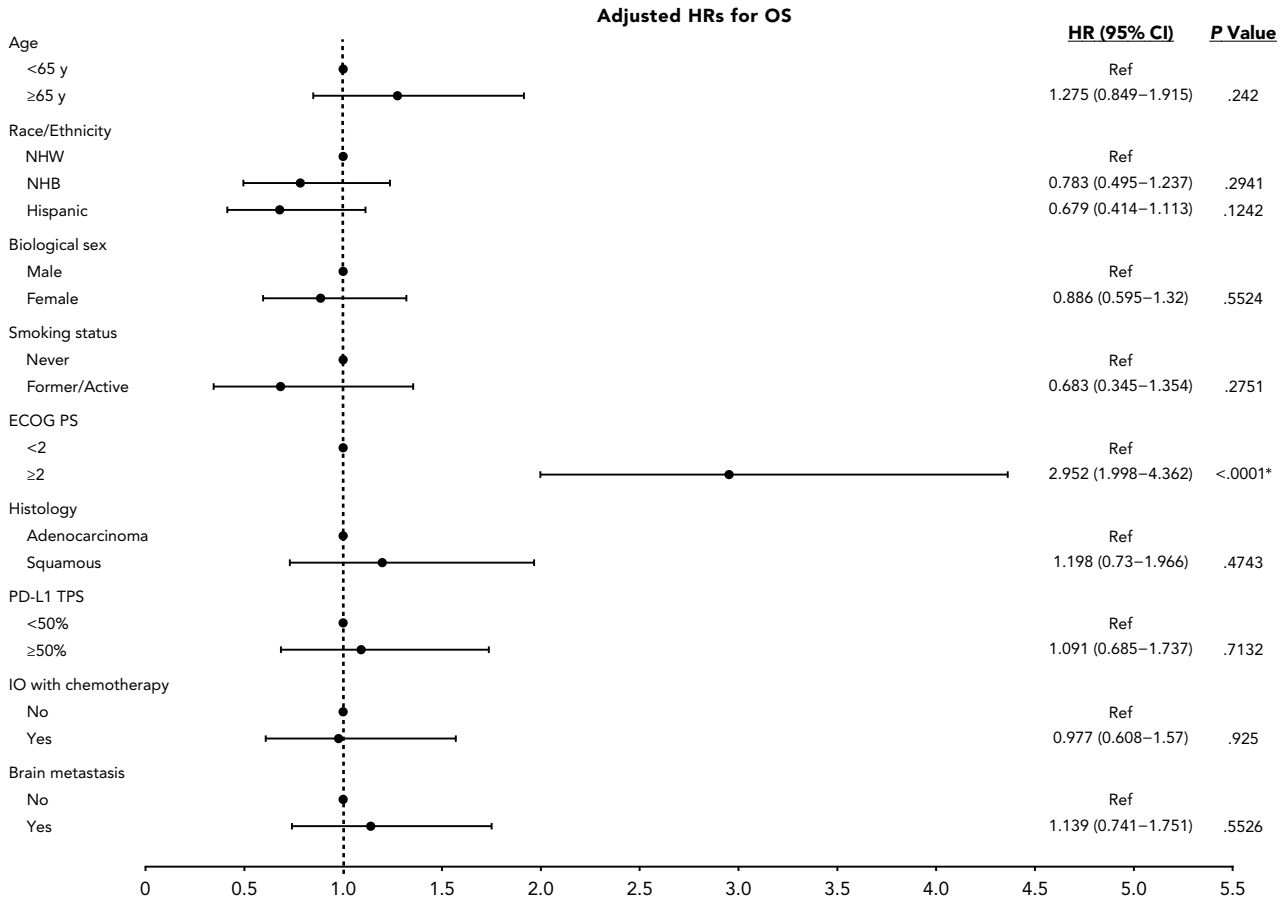

Figure 3. Risk of death among patients with metastatic non–small cell lung cancer receiving first-line IO, adjusted for age, race/ethnicity, biological sex, smoking status, ECOG PS, histology, PD-L1 TPS, IO regimen, and presence of brain metastasis.
Abbreviations: HR, hazard ratio; IO, immunotherapy; NHB, non-Hispanic Black; NHW, non-Hispanic White; OS, overall survival; PS, performance status; TPS, tumor proportion score.
*$P < .05$.

Our research not only adds to the growing literature surrounding the use of immunotherapy in ethnic minority groups but also expands on other potentially significant predictors of immunotherapy efficacy, particularly BMI, ECOG PS, PD-L1 status, and the socioeconomic factors of insurance and annual household income.

Clinical factors such as weight changes, BMI, and the presence of cachexia have been shown in the past to be associated with outcomes in patients with NSCLC who are treated with immunotherapy.[34–45] With the production of inflammatory cytokines by the immune system resulting in the multifactorial syndrome of anorexia, weight and muscle loss, and functional impairment, those with cachexia experience worse survival.[42–45] This is a key understudied and poorly understood factor that is faced clinically in the real-world setting for patients with advanced NSCLC.[46] Specifically, the association of BMI with clinical outcomes in immunotherapy has been studied previously, and results have shown that patients with higher BMI (ranging from ≥22 to 25 kg/m^2) and obesity have been associated with improved clinical outcomes of significantly higher OS, PFS, and TTD compared with patients who are not overweight.[34–41] Similarly, in this study, patients who had a higher BMI of ≥25 kg/m^2 were also found to have a significantly improved PFS ($P = .01$) and TTD ($P = .02$) but not OS compared with those who had a BMI of <25 kg/m^2. In preclinical studies, obesity was associated with a proinflammatory status and upregulation of PD-1 and PD-L1 expression[47] and was clinically shown to increase the risk of immune-related adverse events.[48–50] The presence of lower BMI and cachexia are clinical factors that need to be taken into consideration when administrating immunotherapy, as highlighted by our results and by prior studies, and that should be further investigated in future studies.

Lung cancer is predominantly diagnosed in elderly patients; the data in this study reconfirmed this, given that 58% of the patients with metastatic NSCLC started immunotherapy at age ≥65 years and additionally 35% had an ECOG PS ≥2. Although this aligns with previous reported

estimates of up to 35% to 50% of patients with lung cancer having an ECOG PS ≥2 and aged ≥65 years, clinical trials often exclude this population, thus resulting in no specific guidelines for this older and frailer population.[51–53] Reviews of the limited number of immunotherapy trials that included patients with advanced/metastatic NSCLC aged ≥65 years have shown no difference in OS compared with younger patients.[54,55] A meta-analysis examined the association of a patient's ECOG PS and their clinical outcomes of 18 trials that involved various malignancies, including lung cancer, that were treated with immunotherapy. Findings showed that patients with an ECOG PS of 0 had similar OS as those with an ECOG PS 1–2.[56] However, only 54 of the 11,354 patients examined in the analysis had an ECOG PS of ≥2 and no definitive conclusions could be drawn for those with higher ECOG PS. Prospective studies such as ELDERS[57] and PePS2[58] and have attempted to address this group of older patients with advanced NSCLC and ECOG PS ≥2 and have found no significant difference in response, OS, and toxicities compared with patients aged <70 years or who had an ECOG PS of 0 to 1, respectively.[57,58] In contrast, retrospective studies and reviews revealed that patients with a ECOG PS ≥2 have significantly worse survival and response rates than those with a PS <2.[34,35,59,60] Another retrospective study that examined patients with NSCLC and ECOG PS ≥2 treated with immunotherapy with or without chemotherapy showed a survival benefit compared with no treatment,[61] indicating that there could still be a clinical benefit of treatment. Thus, chronological age should not be the main selection for treatment, and it should be noted that elderly patients are a heterogeneous group. The clinical approach for how to choose management may depend more on functional status, such as ECOG PS, in the real-world setting, which is highlighted in the results of this study with ECOG PS being significant in both univariate and multivariate analysis of OS, PFS, and TTD.

Another group of patients who are often underrepresented and excluded from clinical trials are those diagnosed with brain metastases.[62] To reflect the real-world clinical setting, the inclusion criteria in this analysis encompassed patients with either symptomatic or asymptomatic brain metastasis. Examination of the study cohort revealed that 27% of the patients were diagnosed with brain metastasis at the onset of immunotherapy, which aligns with prior studies that report brain metastases occurring in up to 10% to 40% of patients with metastatic lung cancer either at diagnosis or during their clinical course.[63–66] Moreover, prognosis for patients with NSCLC who have brain metastasis has been shown to be poor in previous studies.[66–69] To our knowledge, this study is one of the first real-world investigations reporting similar incidences of brain metastases among racial/ethnic groups, with no significant difference in OS or PFS (Figure 3; supplemental eTable 1 and eFigure 1). Furthermore, 2 pooled analyses of the KEYNOTE-001, -010, -024, and -042[70] and KEYNOTE-021, -189, and -407 clinical trials,[71] which included patients with metastatic NSCLC with baseline stable and previously treated brain metastasis treated subsequently with pembrolizumab with or without chemotherapy, yielded comparable results to our study. Median OS was 19.7 months in the pooled analysis of KEYNOTE-001, -010, -024, and -042,[70] and 18.8 months in the pooled analysis of KEYNOTE-024, -189, and -407,[71] similar to our study's reported OS of 18.7 months in the overall patient subset (supplemental eTable 1). These findings may be attributed to improvements in earlier detection and more effective management of central nervous system metastases through advances in neurosurgery and radiotherapy with stereotactic radiosurgery and whole-brain radiation therapy.[65,72–74] Therefore, these results highlight the continued importance of proper staging and imaging in this patient population and emphasize the need for further research.

Although there are limitations to PD-L1 expression as a predictive biomarker, it currently remains the primary biomarker used to determine immunotherapy regimen selection for patients with NSCLC.[75] Our study revealed longer PFS in patients with PD-L1 TPS ≥1%, but with no difference in OS or TTD. Notably, most patients (71.8%) in our cohort exhibited PD-L1 TPS ≥1%, and 39.9% demonstrated PD-L1 TPS ≥50%, with no significant difference observed among the different racial/ethnic groups. Consistent with prior studies, NHB patients were found to have PD-L1 expression similar to that of NHW patients.[76–78] Interestingly, Hispanic patients have been shown to have less PD-L1 positivity compared with non-Hispanic patients (P=.016).[78] However, it is worth noting that these previous studies were conducted between 2014 and 2017, which was before the widespread adoption of immunotherapy in the first-line setting, and they were limited to only 92 patients with PD-L1 test results. Consequently, further research is warranted to explore the role of PD-L1 expression as a prognostic and predictive factor in patients with NSCLC treated in the real-world setting, with careful consideration of race/ethnicity.

The association of clinical efficacy of immunotherapy and TRAEs has previously been reported, with patients who experience TRAEs demonstrating significantly higher OS and PFS.[79–83] Our study showed similar results in terms of OS and PFS, but this association was not significant when patients with TRAEs were stratified by either grade <3 or ≥3 based on CTCAE v5.0 (supplemental eTable 6). These findings suggest that the presence of TRAEs may be associated with clinical outcomes, but the grading of the TRAE itself may not be the main determining factor.

Studies from the era before immunotherapy that examined socioeconomic characteristics in patients with NSCLC have shown an association of insurance and income with low-dose CT screening,[84,85] staging,[86,87] chemotherapy access,[88] and survival.[89] However, studies that examined the socioeconomic factors of patients treated with immunotherapy are scarce, and only one study has specifically examined income.[19] That study revealed that after FDA approval of immunotherapy, lower median household income (<$63,000) was associated with lower receipt of immunotherapy compared with a median household income of ≥$63,000.[19] Our study is one of the first to incorporate insurance, income, and clinical outcomes. We observed that annual household income was not associated with OS, PFS, or TTD, although there was a trend toward higher OS, PFS, and TTD in patients with a household income of ≥$100,000 compared with those earning <$100,000. Another finding was that although on average it takes Medicare 17 months after FDA approval to cover novel treatments with requirements for prior authorization,[90,91] patients with Medicare had a higher PFS compared with those who had commercial insurance or Medicaid. Further studies evaluating income and insurance are needed as financial toxicity and burden grows with increasing costs, and to confirm the findings in this study.

Despite the important findings in this study, there are several limitations. This study is a retrospective analysis of data from a healthcare system comprising multiple hospitals. Despite efforts to control confounding factors, the inability to capture all variables limits the provision of more specific patient data. In particular, socioeconomic details such as individual income data were unavailable, and estimations were based on annual household income from US census data derived from the patient's zip code. In addition, 13 patients (5.2%) with missing PD-L1 scores were excluded from the analyses involving PD-L1 scores as covariates. Another aspect not accounted for in this cohort was the examination of comorbidity scores; instead, ECOG PS at the start of immunotherapy, as determined by clinical providers, was analyzed. At the same time, most of the patients in this cohort received all of their therapy at our institution, and with extensive records available, the overall extent of missing data was not substantial. Furthermore, no discernible trends related to missing data were observed, indicating that no major bias was associated with missing data.

Another important limitation in this real-world study pertains to the evaluation of TRAEs. The TRAEs were extracted from medical record reviews based on detailed documentation by providers. The analysis and interpretation were then determined by CTCAE v5.0 as accurately as possible. However, the study did not differentiate between TRAEs resulting from immunotherapy and those occurring in conjunction with chemotherapy. In addition, the presence of immortal time bias and survivor bias could introduce confounding effects, because the occurrence of TRAEs during a patient's clinical course may not only indicate clinical efficacy but may also suggest that the patient survived long enough for an AE to manifest itself.[83,92] Moreover, previous research has demonstrated that the timing of TRAEs, whether early- or late-onset, can influence OS. Thus, in future studies examining TRAEs in patients treated with immunotherapy, considering specific time points for evaluation may prove crucial in assessing clinical efficacy.[83,92] Although this study lacks a landmark timepoint, and the reported TRAEs encompass any events occurring during the course of immunotherapy, it indicates the need for further analysis to better understand the implications of TRAEs on treatment outcomes.

Similar to the limitations in the pooled analyses of the KEYNOTE trials, in our study, prior local therapy was not analyzed, and no distinction was made regarding whether the brain metastases were symptomatic or not and if patients required possible steroids. Additionally, this study did not address other metastatic sites that can also potentially contribute to differential treatment responses and clinical outcomes and the number of additional sites.[93] Thus, further studies are warranted given the increasing amount of data on the efficacy and safety of immunotherapy and radiotherapy and on the optimal sequencing of treatments,[94–96] as well as to investigate expanding the inclusion criteria to include patients with either active or asymptomatic brain metastases.

Nonetheless, the limitations of this study are also its strengths, because this study provides valuable insights into an unmet need for detailing the clinical efficacy of immunotherapy in a real-world setting comprising a diverse patient population that is rarely reported in either clinical trials or in retrospective studies. Although these patients were included in this analysis to emulate the real world, results from this study are similar to those from the 5-year updates of the KEYNOTE trials. Thus, the results from our study can help determine patient selection factors for future treatment, and illustrate the need for larger studies to examine clinical and socioeconomic factors that can influence patient care and lead to inclusion of a more diverse group of patients in future trials. Our data add to the growing body of literature on the impact of race/ethnicity on first-line immunotherapy in patients with NSCLC.

Conclusions

Despite the advances in immunotherapy for patients with NSCLC, the lack of inclusion of a more diverse group of patients in clinical trials has created a gap in knowledge about the impact of healthcare disparities and race/ethnicity. This study is one of the first that incorporates ethnic minorities as the majority of the patient population and demonstrates that despite significant differences

in socioeconomic factors such as income and insurance, race/ethnicity may not impact the benefits of immunotherapy. However, factors such as ECOG PS do significantly impact OS, and BMI and PD-L1 expression are significantly associated with PFS and TTD. These findings help identify potential factors that can be addressed to optimize outcomes and care while patients are undergoing immunotherapy, and they highlight the need for randomized trials evaluating the efficacy of immunotherapy in high-risk patients such as those with poor ECOG PS. This real-world study provides insightful analysis of these understudied factors that warrant further study to improve clinical care and create more inclusive trials.

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Correspondence: Matthew Lee, MD, MPH, Montefiore Medical Center, Department of Medical Oncology, 1695 Eastchester Road, Bronx, NY 10461. Email: mlee7@montefiore.org; and
Haiying Cheng, MD, PhD, Montefiore Medical Center, Department of Medical Oncology, 1695 Eastchester Road, Bronx, NY 10461. Email: hcheng@montefiore.org

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Similar Efficacy Observed for First-Line Immunotherapy in Racial/Ethnic Minority Patients With Metastatic NSCLC

Matthew Lee, MD, MPH; Jianyou Liu, MS; Emily Miao, PharmD; Shuai Wang, MD; Frank Zhang, MD; John Wei, MD; Julie Chung, CTR, BA; Xiaonan Xue, PhD; Balazs Halmos, MD; H. Dean Hosgood, PhD; and Haiying Cheng, MD, PhD

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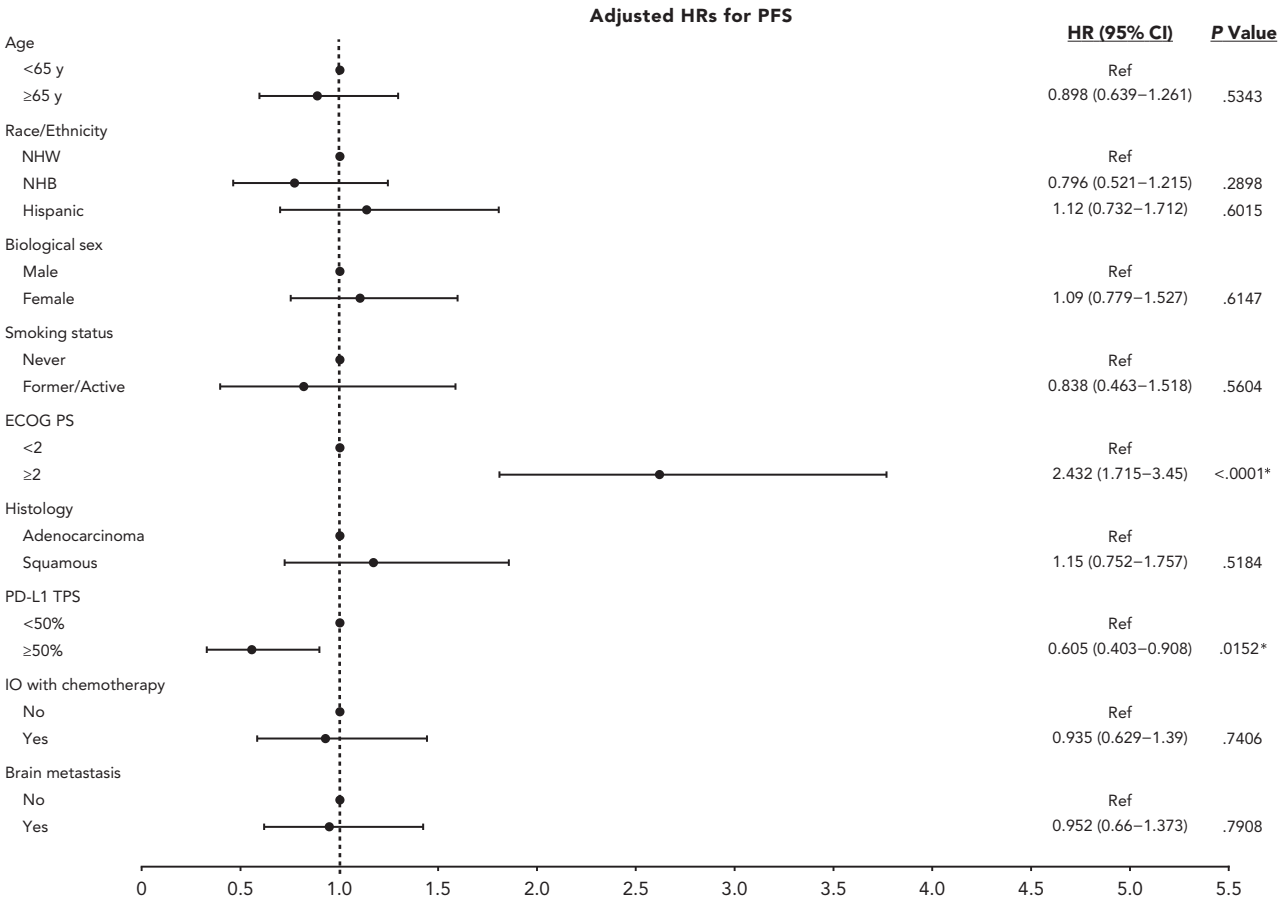

eFigure 1. Risk of disease progression among patients with metastatic non–small cell lung cancer receiving first-line IO, adjusted for age, race/ethnicity, biological sex, smoking status, ECOG PS, histology, PD-L1 TPS, IO regimen, and presence of brain metastasis.
Abbreviations: HR, hazard ratio; IO, immunotherapy; NHB, non-Hispanic Black; NHW, non-Hispanic White; PFS, progression-free survival; PS, performance status; TPS, tumor proportion score.
*$P < .05$.

eTable 1. OS, PFS, and TTD of Patients With Metastatic NSCLC Receiving First-Line Immunotherapy

		OS, mo		PFS, mo		TTD, mo	
	n (%)	Median (95% CI)	*P* Value	Median (95% CI)	*P* Value	Median (IQR)	*P* Value
Age at start of treatment			.3		.74		.29
<65 y	104 (41.9)	22.7 (16.7–43)		7.6 (5.6–12.7)		5 (2.1–12)	
≥65 y	144 (58.1)	20.7 (12.6–31.8)		7.9 (6.5–11.9)		4.3 (1.4–11)	
Biological sex			.75		.32		.91
Male	145 (58.5)	19.7 (14–31.8)		7.8 (6.5–12.8)		4.9 (1.9–10.5)	
Female	103 (41.5)	22.7 (15.4–43)		8.2 (5.3–11.3)		4.4 (1.4–13)	
Race/Ethnicity			.39		.29		.98
Non-Hispanic Black	97 (39.1)	26.3 (14–NA)		8.7 (7–14.8)		4.5 (1.4–12.5)	
Hispanic	75 (30.2)	23.5 (13.9–45.7)		6.7 (4.1–9.7)		4.9 (2.1–11.9)	
Non-Hispanic White	76 (30.7)	16.8 (12.8–27.7)		7.6 (5.6–14.6)		4.9 (1.7–9.5)	
Smoking status			.26		.25		.68
Former/Active	228 (91.9)	22.1 (16.7–33.1)		7.9 (6.7–11.3)		4.8 (1.7–11.7)	
Never	20 (8.1)	13.9 (4–NA)		6.3 (3.1–14.3)		4.3 (1.1–12.2)	
Median BMI (range), kg/m^2	23.3 (14.1–41.4)						
BMI			.4		.01*		.02*
Underweight (<18.5 kg/m^2)	32 (12.9)	12.1 (8.4–NA)		6.9 (3.2–23)		3.8 (1.8–8.5)	
Healthy (18.5–24.9 kg/m^2)	116 (46.8)	20.2 (13.9–31.8)		6 (5–7.8)		3.7 (1.3–8)	
Overweight/Obese (≥25 kg/m^2)	100 (40.3)	23.5 (16.4–44.7)		11.9 (8.2–18.3)		7 (2.6–13.6)	
Insurance			.15		.008*		.08
Commercial	50 (20.2)	18.5 (13–31.8)		7.6 (5.5–11.3)		4.9 (2.3–9.3)	
Medicare	120 (48.4)	35.4 (19.7–NA)		13.2 (7.6–20.4)		5.6 (2.1–14)	
Medicaid	59 (23.8)	16.4 (10.7–29.6)		6 (4–7.9)		3.7 (1.4–8.5)	
Dual Medicare/Medicaid	17 (6.8)	—[a]	—	—	—	—	—
None	2 (0.8)	—	—	—	—	—	—
Median annual household income[b] (range), USD	$53,819 ($23,337–$193,085)						
Annual household income[b]			.73		.48		.19
<$35,000	51 (20.6)	27.1 (16.7–59)		9.7 (5–20.3)		5.4 (2.1–13.1)	
$35,000–$49,999	59 (23.8)	19.8 (14–31.8)		6.9 (5.3–9.3)		3.7 (1.1–9)	
$50,000–$99,999	121 (48.8)	16.8 (12.6–45.7)		7.8 (6.5–12.8)		4.7 (1.5–10.6)	
≥$100,000	17 (6.8)	27.7 (15.4–NA)		20.4 (6–NA)		7 (4.3–20.4)	
ECOG PS			<.0001*		<.0001*		<.0001*
<2	161 (64.9)	37.2 (20.7–NA)		12.8 (8.2–17.1)		5.9 (2.8–13.9)	
≥2	87 (35.1)	9 (6.3–15.7)		4.6 (3.4–7.6)		2.6 (0.7–7.3)	
Histology			.36		.27		.09
Adenocarcinoma	201 (81.1)	22.7 (16.7–35.4)		8.5 (7.3–12.8)		5.2 (1.9–11.9)	
Squamous	47 (18.9)	14.8 (7.8–59)		5.6 (3.4–8.2)		3.5 (1.4–7.9)	
PD-L1 TPS, 1% cutoff			.75		.01*		.82
<1%	57 (23.0)	19.4 (10.7–45.7)		6.5 (5.3–7.3)		4.3 (1.4–11.9)	
≥1%	178 (71.8)	23 (15.7–38.9)		8.7 (7.6–14.3)		5.1 (1.4–9)	
Missing	13 (5.2)						
PD-L1 TPS, 50% cutoff			.51		.03*		.67
<50%	136 (54.9)	20.7 (14.8–NA)		6.7 (5.4–8.2)		4.2 (1.5–10.1)	
≥50%	99 (39.9)	20.2 (12.8–37.2)		11.3 (7.8–20.4)		5.2 (1.4–12.2)	
Missing	13 (5.2)						

(*continued on next page*)

eTable 1. OS, PFS, and TTD of Patients With Metastatic NSCLC Receiving First-Line Immunotherapy (cont.)

		OS, mo		PFS, mo		TTD, mo	
	n (%)	Median (95% CI)	*P* Value	Median (95% CI)	*P* Value	Median (IQR)	*P* Value
Immunotherapy with chemotherapy			.66		.6		.18
No	109 (43.9)	23 (12.1–43)		8.2 (5.2–14.4)		4 (1.4–12.2)	
Yes	139 (56.1)	19.8 (16.1–33.1)		7.6 (6.5–11.4)		5.6 (2.1–10.6)	
Brain metastasis			.62		.7		.25
Yes	67 (27)	18.7 (11.5–27.7)		6.3 (5.3–12.8)		5.2 (2.6–13.5)	
No	181 (73)	23.5 (16.4–37.2)		7.9 (6.9–11.4)		4.5 (1.4–10.1)	

Abbreviations: BMI, body mass index; NA, not available; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; TPS, tumor proportion score; TTD, time to discontinuation.
[a]Could not be calculated due to small sample size.
[b]Determined by the zip code of the patient's address listed in the electronic medical record, US Census Bureau data from the American Community Survey's 2021 estimates in USD amounts, and census-based geographic data.
*$P < .05$.

eTable 2. HRs for Overall Survival in Multivariable Cox Proportional Hazards Models

	HR (95% CI)	*P* Value
Age		
<65 y	Ref	
≥65 y	1.191 (0.840–1.688)	.3274
PD-L1 TPS		
<1	Ref	
≥1	0.884 (0.605–1.292)	.5250
Race/Ethnicity		
NHB	Ref	
Hispanic	0.947 (0.629–1.427)	.7944
NHW	1.226 (0.817–1.842)	.3256
ECOG PS		
<2	Ref	
≥2	2.580 (1.831–3.637)	<.0001*

Abbreviations: HR, hazard ratio; NHB, non-Hispanic Black; NHW, non-Hispanic White; PS, performance status; TPS, tumor proportion score.
*P<.05.

eTable 3. HRs for Progression-Free Survival in Multivariable Cox Proportional Hazards Models

	HR (95% CI)	*P* Value
Age		
<65 y	Ref	
≥65 y	0.890 (0.662–1.196)	.4404
PD-L1 TPS		
<1	Ref	
≥1	0.641 (0.464–0.885)	.0070*
Race/Ethnicity		
NHB	Ref	
Hispanic	1.458 (1.038–2.047)	.0296*
NHW	1.313 (0.901–1.913)	.1563
ECOG PS		
<2	Ref	
≥2	2.390 (1.755–3.255)	<.0001*

Abbreviations: HR, hazard ratio; NHB, non-Hispanic Black; NHW, non-Hispanic White; PS, performance status; TPS, tumor proportion score.
*P<.05.

eTable 4. HRs for Overall Survival in Race-Specific Multivariable Cox Proportional Hazards Models

	HR (95% CI)	*P* Value
Age		
<65 y	Ref	
≥65 y	1.181 (0.834–1.673)	.3481
PD-L1 TPS		
<1	Ref	
≥1	0.864 (0.593–1.259)	.4461
Race/Ethnicity		
Non-Black	Ref	
Black	0.940 (0.667–1.326)	.7264
ECOG PS		
<2	Ref	
≥2	2.530 (1.799–3.559)	<.0001*

Abbreviations: HR, hazard ratio; PS, performance status; TPS, tumor proportion score.
*P<.05.

eTable 5. HRs for Overall Survival in Ethnicity-Specific Multivariable Cox Proportional Hazards Models

	HR (95% CI)	*P* Value
Age		
<65 y	Ref	
≥65 y	1.213 (0.857–1.715)	.2758
PD-L1 TPS		
<1	Ref	
≥1	0.885 (0.606–1.292)	.5269
Race/Ethnicity		
Non-Hispanic	Ref	
Hispanic	0.865 (0.602–1.243)	.4321
ECOG PS		
<2	Ref	
≥2	2.574 (1.827–3.626)	<.0001*

Abbreviations: HR, hazard ratio; PS, performance status; TPS, tumor proportion score.
*P<.05.

eTable 6. Evaluation of TRAEs in Association With OS and PFS

	n (%)	Median OS (95% CI)	*P* Value	Median PFS (95% CI)	*P* Value
TRAE					.003*
Yes	90 (36.3)	38.9 (22.7–NA)	.02*	14.3 (8.2–22.4)	
No	158 (63.7)	16.3 (12.6–23.5)		6.7 (5.3–7.9)	
TRAE grade					.65
<3	52 (57.8)	26.3 (19.4–NA)	.72	14.4 (8.2–23.1)	
≥3	38 (42.2)	38.9 (19.7–59.0)		9.7 (6.0–24.1)	

Abbreviations: NA, not applicable; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.
*$P < .05$.