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Real-world Outcomes of Immune Checkpoint Inhibitors (ICI) in Lung Cancer Patients

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B.S.
University of California, Davis
2017

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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By Jiapeng Shuang

Background: Lung cancer is the most-common cancer attributing to incidence and mortality. There were 2.09 million new cases of lung cancer around the world in 2018. Different treatment methods including chemotherapy, surgery and radiation therapy have been applied to defeat the disease. Immunotherapy is one of those treatment and it can let patient's immune system can detect and eliminate cancer tumors. Scientists have developed several immune checkpoint inhibitors (ICI) for immunotherapy to regulate our immune system's response. In this study, we want to compare the overall survival (OS) and progression free survival (PFS) of lung cancer patients between different races, sex and social status. We also compare the rate of response among patients with different races.

Methods: Our data is collected from a retrospective review of clinical outcome of patients who received immunotherapy at Emory Winship Cancer Institute since 2013. There are 101 patients included in this study. We use Kaplan-Meier Method, Stratified Log-rank Test and Cox proportional hazards model to compare OS and PFS among patients who have NSCLC stratified by race, sex and PD-L1. Logistic regression model and Wald Chi-squared test are applied to check if there is any difference on partial response between different races.

Results: There is no significant difference on OS and PFS between SCLC or NSCLC patients with different race, sex and PD_L1 status. Even though histology, ECOG and TP53 show significant effect on OS and PFS in univariate model, all those effects are removed from multivariate model by backward selection. Furthermore, we find out that race also have no significant effect on response situation. The only significant factor that will influence response is smoking status.

Conclusion: Both stratified log-rank test and Cox proportional hazard model shows no significant impact of race/ethnicity, sex and PD-L1 status on efficacy of immunotherapy for lung cancer. The logistic regression model indicates that there is no difference on response between patients with different races.

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Contents

1. Introduction

Lung disease, which was a rare disease in the past 100 years, has transformed to the most-common cancer attributing to incidence and mortality.[1] In 2018, there were 2.09 million new cases of lung cancer all over the world and 1.76 million deaths due to lung cancer. Lung cancer is classified into two major categories which are small cell lung cancer (SCLC) and Non-small cell lung cancer (NSCLC). [2] Different treatment methods are applied depending on patients' cancer categories and disease stages. Chemotherapy is considered as one effective treatment for SCLC patients to prolong their life and improve their living quality. [2] Even though this treatment shows efficacy on SCLC patients of any stage at the beginning, a large number of patients still cannot survive for a long time. Treatments for NSCLC patients includes surgery, chemotherapy, radiation therapy, or the combination of those approaches. Unfortunately, these therapies still cannot ensure disease control and improve survival rates obviously. Therefore, it is urgent for researchers to develop effective therapies to cure lung cancer. In this study, we investigate the effectiveness of immunotherapy on the treatment of patients with lung cancer on advanced stages.

As we known, our immune system can defeat bacteria and viruses to keep our body healthy. Immunotherapy is applied to eliminate cancer by let patients' immune system help our body detect and attack lung cancer tumors in the same way that it defeats bacteria and viruses. [3] Even though our immune system may detect malignant cancer cells at the atomic level, the cancer tumors may develop multiple resistance mechanisms

to avoid our immune system's detection and elimination. These resistances include local immune evasion, induction of tolerance and systemic disruption of T cell signaling.[4] In the last few years, scientists developed several immune checkpoint inhibitors (ICI) such as programmed cell death 1 (PD-1), program death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4). ICI play the role of a regulator to adjust our immune system's response. [5] It can help our immune system distinguish the difference between normal cells and cancer cells to achieve the destruction of cancer tumors.

Pervious study has shown that racial disparity exists in early-stage surgical treatment for lung cancer and indicated that the refusal rate for African American patients is greater than Caucasian patients.[6] However, there are few studies about the racial disparity in ICI efficacy for lung cancer because of the under-representation of Africa American patients participated in immunotherapy. Immunotherapy is a newly established effective treatment for lung cancer based on results of trials conducted in a predominantly Caucasian patient population and less than 2% of patients enrolled in the trials are African American. More studies need to be conducted to explore the real-world differences on immunotherapy performance between multiracial patient populations.

For this study, our goal is to explore real-world outcomes for all lung cancer patients treated with immunotherapy. The target for this study is all adult NSCLC and SCLC patients who received immunotherapy at Emory Winship Cancer Institute since 2013. The first objective is to compare the overall survival (OS) and progression free survival (PFS) of lung cancer patients between different race, sex and PD-L1 status. The second objective is to compare the response situation among patients with different categories.

2. Materials and Methods

Our data is collected from a retrospective review of clinical outcome of patients provided by Amber Draper Pharm D from 2013 to July 2018. The inclusion criteria for patients is all adult NSCLC and SCLC patients who received immunotherapy (at least 1 dose of ICI or one dose of ICI with CTLA4 inhibitors) for advanced or metastatic disease at Emory Winship Cancer Institute since 2013, for all lines of therapy. Patients who have another or prior malignancy if they are not receiving another form of systemic therapy for the second malignancy are also included in our study. The Emory University Institutional Review Board approved this study.

2.1. Patients Selection and Parameters Calculation

Among the 389 individual patients, 101 patients are included in our study following the including criteria mentioned above. Patients' demographic and physical indicators (race, sex age, ZIP code, smoking status, BMI, brain imaging, PD-L1 and other biomarkers) are reviewed. Status at the end of immunotherapy treatment cessation, date of immunotherapy initiation, progression date, last contact date, date of death and hospice enrollment date are recorded for survival analysis and progression free analysis. Response status and date of best response are used to calculate the response rate and the median duration of response. Co-morbid conditions are recorded to calculate the Charlson Comorbidity Index.

2.2. Statistical Analysis

2.2.1. Descriptive Analysis

Patients' characteristics are summarized in descriptive statistics. For continuous variables, median and range are calculated; for categorical variables, frequency is measured in the form of percentage.

2.2.2. Survival Analysis

To compare OS and PFS, we first define OS as the time (in month) from date of starting therapy to death from any cause or loss to follow up and define PFS as the time from treatment initiation to first imaging evidence of disease progression, death, or lose to follow up.

2.2.2.1. Kaplan-Meier Method and Stratified Log-rank Test

We use Kaplan-Meier method and stratified log-rank test to estimate PFS and OS for patients with all kinds of lung cancer and analyze the difference between patients who have NSCLC stratified by race, sex and PD-L1.

The Kaplan-Meier Method provides us with a survival curve which shows the probability of surviving in a given length of time in the form of many small intervals. [7] Kaplan-Meier estimator is given by:

$$\hat{S}_{KM}(t) = \prod_{k:\, t_{(k)} \le t} \left(1 - \frac{d_k}{n_k}\right),$$

$$where\ n_k = size\ of\ the\ risk\ set\ R_k\ at\ time\ t_{(k)},$$

$$d_k = size\ of\ failures\ at\ time\ t_{(k)}.$$

By checking the Kaplan-Meier estimator result, we can have a generation understanding of patients with different race, sex and PD-L1 status. Also, we can compare the median survival of patients in different groups.

Furthermore, if we want to adjust for a categorical covariate when checking two groups of time-to-event observations, we can use stratified log-rank test to do the comparison. First, we separate data into N groups where N is the number of levels of categorical covariates. Let us suppose that:

$$H_0: S_1^{(I)}(\,) = S_2^{(I)}(\,), I = 1,2, \dots, L.$$

Under H_0, test statistic is:

$$Z = \frac{\sum_{I=1}^{L}\left(O^{(I)} - E^{(I)}\right)}{\sqrt{\sum_{I=1}^{L}(V^{(I)})}} \sim N(0,1),$$

$$where\ O^{(I)} = observed\ number\ of\ failure\ for\ the\ I_{th}\ stratum,$$

$$E^{(I)} = Expected\ number\ of\ failure\ for\ the\ I_{th}\ stratum,$$

$$V^{(I)} = conditional\ variance\ under\ H_0.$$

By using stratified log-rank test, we can find the difference of ICI effectiveness between different race, sex and PD-L1 status by adjusting for black and white patients with NSCLC.

2.2.2.2. Cox Proportional Hazards Model Formulation

To compare the survival difference between patients in different categories, we can construct a Cox proportional hazard model. Suppose we have a hazard function:

$$h(t|Z) = h_0(t) * e^{\beta^T Z}.$$

When Z = 0, the hazard function $h_0(t)$ is the baseline hazard. The hazard ratio between Z_1 and Z is:

$$\frac{h(t|Z_1) = h_0(t) * e^{\beta^T Z_1}}{h(t|Z) = h_0(t) * e^{\beta^T Z}} = e^{\beta^T Z_1}, which\ is\ independent\ of\ t.$$

This hazard ratio describes the relative risk between baseline covariates and other covariates. Wald test, score test and likelihood ratio test will be conducted to check the survival difference between different levels of covariates. All analysis was coded by SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) and the significant level is set at < 0.05.

2.2.3. Response Analysis

We use the logistic regression model to compare the response situation of people from different categories such as black and white. A multiple linear regression function is presented as:

$$logit(p) = \log\left(\frac{p(y=1)}{1-(p(y=1)}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n,$$

where y is the indicator of response situation, x is the indicator of dependent variables and β_i are the parameters of the model, i=1, ..., n.

First, we fit each dependent variable in a univariate logistic regression model and use Wald chi-square test to check if there is any significant variable which has p-value < 0.05. Furthermore, we pick all significant variables and fit them into a multivariate logistic regression model and use backward model selection process to select the best model to present the relationship. The removing criteria for the backward model selection is p-value > 0.05.

3. Results

3.1. Result for Descriptive Analysis

The descriptive statistics for patients' characteristics was shown in Table 1. According to the table, we see that the median age at diagnosis of lung cancer patients received immunotherapy was 68 years old with the range from 46 to 86. 50.5% of the patients are male and 49.5% of the patients are female. Only 10.9% of the patients have SCLC and the rest of the patients have adenocarcinoma NSCLC (60.4%), adenosquanmous NSCLC (1.0%), large cell NSCLC (1.0%), NOS NSCLC or poorly differentiated carcinoma (7.9%) and squamous NSCLC (18.8%). The race of patients consists of Asian (5.0%), Black/African American (30.7%), White/Caucasian (62.4%) and other (2.0%). Only 38 patients have recorded PD_L1 status and 39.5% of them have PD_L1 ≥ 50%. 36.5% patients have brain metastasis at the time of ICI initiation. The percentage of ICI line 1, 2, 3, 4, 6 are 15%, 68%, 13%, 3% and 1% respectively. Nivolumab (41.6%) is the mostly used ICI agent. There are only 12.3% patients have ECOG functional status > 2. Most patients (84.9%) have smoking habit. 87.9% AND 66.7% patients have negative EGFR

and negative TP53. For CCI value, all patients get +6 for metastatic malignancy. All screened patients do not have HIV, leukemia, lymphoma, localized solid tumor that they are receiving therapy for. The median of CCI is 9 with the range from 6 to 14.

3.2. Result for Survival Analysis

3.2.1. Result for Kaplan-Meier Method and Stratified Log-rank Test

3.2.1.1. Analysis for both NSCLC and SCLC patients

First, we analyze both NSCLC and SCLC patients for OS. According to Table 5a, there are total number of 75 subjects and 41% of them are censored. The median survival is 10.2 months with 95% CI (5.7, 23.3). The survival probability for 12 months is 46.1% with 95% CI (34.2%, 57.2%). The survival probability for 24 months is 31.3% with 95% CI (18.5%, 44.9%). Then, we analyze the OS for all patients stratified by race. According to Table 5b, there are only one Asian and one person of other race included in the analysis, so the median survival for the two patients is not available and the 12-month survival and 24-month survival for the two patients are 100%. 20 Black/African American are included in the analysis and 30.0% of them are censored. The median survival time for Black/African American is 3.5 months with 95% CI (1.3, 23.3). The survival probability of Black/African American for 12 months is 35.0% with 95% CI (15.7%, 55.2%). The survival probability of Black/African American for 24 months is 26.3% with 95% CI (8.4%, 48.5%). 53 White/Caucasian are included in the analysis and 43.0% of them are censored. The median survival time for White/Caucasian is 10.5 months with 95% CI (8.2%, 23.7%). The survival probability of White/Caucasian for 12 months is 48.1% with 95% CI (33.5%, 61.2%). The survival probability of White/Caucasian for 24 months is 30.7% with 95% CI (15.4%, 47.5%). Table 2 indicates

that p-value of the log-rank test for OS is 0.2671. Therefore, there is no significant difference in OS among different races.

Furthermore, we analyze both NSCLC and SCLC patients for PFS. According to Table 5c, there are total number of 93 subjects and 22% of them are censored. The median survival is 2.9 months with 95% CI (2.8, 5.4). The survival probability for 12 months is 30.5% with 95% CI (21.3%, 40.2%). The survival probability for 24 months is 14.4% with 95% CI (6.7%, 24.8%). Then, we analyze the PFS for all patients stratified by race. According to Table 5d, there are only three Asian and one person of other race included in the analysis, the median survival for Asian is 12.7 months with 95%CI (3.6, 18.4). The survival probability of Asian patients for 12 months is 66.7% with 95% CI (5.4%, 94.5%). The survival probability of Asian patients for 24 months is 0.0%. There is only one person from other race with 2.1 months survival. 27 Black/African American are included in the analysis and 7.0% of them are censored. The median survival time for Black/African American is 2.6 months with 95% CI (1.3, 4.5). The survival probability of Black/African American for 12 months is 17.8% with 95% CI (6.1%, 34.4%). The survival probability of Black/African American for 24 months is 8.9% with 95% CI (1.6%, 24.1%). 61 White/Caucasian are included in the analysis and 30.0% of them are censored. The median survival time for White/Caucasian is 5.4 months with 95% CI (3.0%, 10.0%). The survival probability of White/Caucasian for 12 months is 34.8% with 95% CI (23.0%, 46.8%). The survival probability of White/Caucasian for 24 months is 20.0% with 95% CI (8.6%, 35.9%). According to Table 3, the p-value of the log-rank test for PFS is 0.0820 > 0.05. Therefore, there is no significant difference in PFS among different races.

3.2.1.2. Analysis only for Black/African American and White /Caucasian patients with NSCLC stratified by race, sex and PD_L1.

In this case, we focus on black and white patients with NSCLS. In Table 6a, we notice that there are 18 Black/African American with NSCLC and 33% of them are censored. The median survival time for them is 4.2 months with 95% CI (1.6, NA). The 12-month survival probability and 24-month survival probability are 38.9% (17.5%, 60.0%) and 29.2% (9.3%, 52.8%) respectively. There are 47 White/Caucasian with NSCLC and 47% of them are censored. The median survival time for them is 15.3 months with 95% CI (NA, NA). The 12-month survival probability and 24-month survival probability are 53.2% (37.5%, 66.7%) and 34.0% (17.0%, 51.9%) respectively. Table 6d indicates that the p-value of log-rank test is 0.1778 > 0.05. Thus, we can conclude that there is no significant difference in OS between Black/African American and White/Caucasian.

When we analyze the OS difference between Black/African American and White /Caucasian patients with NSCLC stratified by sex, Table 6b shows that there are 33 females and 55% of them are censored. The median survival time for them is 23.7 months with 95% CI (5.1, NA). The 12-month survival probability and 24-month survival probability are 60.1% (41.3%, 74.6%) and 42.9% (19.9%, 64.2%) respectively. There are 34 male and 35% of them are censored. The median survival time for them is 10.2 months with 95% CI (4.5, 15.5). The 12-month survival probability and 24-month survival probability are 41.8% (24.7%, 58.1%) and 25.1% (9.7%, 44.0%) respectively. From Table 6d, we notice that the p-value of log-rank test is 0.2870 > 0.05. Thus, we can conclude that there is no significant difference in OS between male and female.

When we analyze the OS difference between Black/African American and White /Caucasian patients with NSCLC stratified by PD_L1. Table 6c shows that there are 20 patients with PD_L1 < 50% and 35% of them are censored. The median survival time for them is 9.8 months with 95% CI (3.2, NA). The 12-month survival probability is 31.7% (12.5%, 53.1%). There are 12 patients with PD_L1 ≥ 50% and 58% of them are censored. The 12-month survival probability is 57.1% (25.4%, 79.6%). From Table 6d, we notice that the p-value of log-rank test is 0.2049 > 0.05. Thus, we can conclude that there is no significant difference in OS between PD_L1 statuses.

3.2.2. Result for Cox Proportional Hazard Model

Cox proportional hazard model can show us the difference of ICI efficacy between Black/African American and White /Caucasian patients with NSCLC with different race, sex and PD_L1 status.

When we set White/Caucasian as the reference group, we get the hazard ratio = 1.604 (0.802, 3.210), shown in Table 6d. It means that the risk of death for Black/African American is 1.604 times of that for White/Caucasian. However, Since HR p-value is 0.1817 > 0.05, there is no significant difference in OS among white and black.

When we set male as the reference group, we get the hazard ratio = 0.700 (0.362, 1.354), shown in Table 6d. It means that the risk of death for female is 0.700 times of that for male. However, Since HR p-value is 0.2894 > 0.05, there is no significant difference in OS among male and female.

As we set PD_L1 >= 50% as the reference group, we get the hazard ratio = 1.932 (0.685, 5.448), shown in Table 6d. It means that the risk of death for patients with PD-L1 < 50% is 1.932 times of that for patients with PD_L1 >= 50%. However, Since HR p-value is 0.2129 > 0.05, there is no significant difference in OS between different PD_L1 statuses.

3.3. Analysis for Response

To compare the response situation, a partial response is treated as a good response and other response options is treated as no response.

According to Table 4, 19.23% Black/African American patients have partial response and 8.62% White/Caucasian patients have partial response. The crude odds ratio of response between White/Caucasian and Black/Africa American is 0.448 (0.119, 1.683). Since the p-value for race is 0.2274 < 0.05, there is no significant difference in response situation between different races. As Table 4 indicated, smoking status (p-value = 0.0492) is the only variable shows significant effect on response status.

4. Conclusion and Discussion

In this study, we find out that there is no significant difference on OS between races for patients who have SCLC or NSCLC and received immunotherapy. Also, racial disparity has no impact on PFS for both SCLC and NSCLC patients. For NSCLC White/Caucasian and Black/African American patients in Emory Winship Cancer Institute, our analysis based on both stratified log-rank test and Cox proportional hazard model shows no

significant impact of race/ethnicity, sex and PD-L1 status on efficacy of immunotherapy for lung cancer. Race does not influence the result of response situation. The only significant variable which will affect response situation is smoking status.

Our study only has 101 patients' uncompleted data from a retrospective study. This may cause the insignificance on the test of equality over race, sex and PD-L1 status. Also, since this is a retrospective study, we cannot make an evidence-based conclusion and all results are based on predictions. Lung cancer rates show a trend of decline in many western countries, but Asian countries have substantially increasing incidence of lung cancer. [8] In our data, there are only 5 Asian patients, which could not correctly reflect the true situation of lung cancer among Asian society. Since 89.1% patients in Emory Winship Cancer Institute are NSCLC, our study is mainly targeted at NSCLC patients. However, SCLC is an extremely serious disease and our society has little development on the treatment of SCLC in the past 30 years. [9] We may collect more SCLC patients' data and analyze NSCLC and SCLC patients separately to improve the study. As we known, the proportionality of hazard assumption is an important prerequisite to perform Cox proportional hazard model. However, there are few scientific reports properly check this assumption. [10] We can test whether there is a violation of this assumption before performing the model.

To sum up, we need collect more data containing more minority, SCLC patients from different institutes to make our analysis more generalizable. Also, the confirmation of proportionality can be performed to ensure validity. Other models should also be established if applicable.

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6. Tables

Table 1: Descriptive Statistics of Patients' Characteristics Variables

Variable	Level	N(%)=101
Sex	Male	51 (50.5)
	Female	50 (49.5)
Histology	Adenocarcinoma NSCLC	61 (60.4)
	Adenosquanmous NSCLC	1 (1.0)
	Large cell NSCLC	1 (1.0)
	NOS NSCLC or poorly differentiated carcinoma	8 (7.9)
	SCLC	11 (10.9)
	Squamous NSCLC	19 (18.8)
Race	Asian	5 (5.0)
	Black/African American	31 (30.7)
	Other	2 (2.0)
	White/Caucasian	63 (62.4)
Insurance	Medicaid	4 (4.0)
	Medicare	62 (61.4)
	Not Listed	3 (3.0)
	Private	27 (26.7)
	Uninsured	5 (5.0)
Stage at initial diagnosis of lung cancer	I	1 (1.0)
	II	3 (3.0)
	IIIA	7 (6.9)
	IIIB	10 (9.9)

Variable	Level	N(%)=101
	IV	80 (79.2)
PD_L1	<1%	14 (36.8)
	1-49%	9 (23.7)
	>=50%	15 (39.5)
	Missing	63
ECOG	0	8 (12.3)
	1	27 (41.5)
	2	22 (33.9)
	3	8 (12.3)
	Missing	36
Smoking Status	Current or former	84 (84.9)
	Never	15 (15.2)
	Missing	2
EGFR	Negative	51 (87.9)
	Positive	7 (12.1)
	Missing	43
ALK	Negative	55 (55.0)
	Unknown	45 (45.0)
	Missing	1
TP53	Negative	23 (66.7)
	Positive	6 (33.3)
	Missing	83
Brain Mets	No	54 (63.5)

Variable	Level	N(%)=101
	Yes	31 (36.5)
	Missing	16
ICI line	1	15 (15.0)
	2	68 (68.0)
	3	13 (13.0)
	4	3 (3.0)
	6	1 (1.0)
	Missing	1
ICI agent	Atezolizumab	29 (28.7)
	Nivo+Ipi	5 (5.0)
	Nivolumab	42 (41.6)
	Pembrolizumab	25 (24.8)
Age at diagnosis	Median	68
	Minimum	46
	Maximum	86
CCI	Median	9
	Minimum	6
	Maximum	14

Table 2: Univariate Analysis of OS for Cox Proportional Hazards Model

Variable	**Level**	**N**	**OS (months)**		
			HR (95% CI)	**HR P-value**	**Log-rank P-value**
Sex	Male	41	-	-	0.0406
	Female	34	0.526 (0.281, 0.984)	0.0443	
Histology	Adenocarcinoma NSCLC	43	-	-	0.0015
	Adenosquanmous NSCLC	1	0	0.9905	
	Large cell NSCLC	1	0	0.9905	
	NOS NSCLC or poorly differentiated carcinoma	7	1.154 (0.394, 3.385)	0.7938	
	SCLC	8	5.313 (2.170, 13.007)	0.0003	
	Squamous NSCLC	15	1.924 (0.939, 3.942)	0.0736	
Race	White/Caucasian	53	-	-	0.2671
	Black/African American	20	1.607 (0.848, 3.045)	0.9913	
	Other	1	0	0.1459	
	Asian	1	0	0.9908	
Insurance	Medicaid	3	-	-	0.2471
	Medicare	48	2.247	0.4264	

Variable	Level	N	OS (months)		
			HR (95% CI)	HR P-value	Log-rank P-value
			(0.306, 16.515)		
	Not Listed	1	15.224 (0.898, 258.170)	0.0594	
	Private	21	2.224 (0.286, 17.300)	0.4451	
	Uninsured	2	2.877 (0.260, 31.864)	0.3890	
Stage at initial diagnosis of lung cancer	IV	56	-	-	0.1214
	II	3	0.331 (0.045, 2.425)	0.2765	
	IIIA	6	1.828 (0.712, 4.694)	0.2103	
	IIIB	8	0.655 (0.232, 1.847)	0.4234	
	I	1	0	0.9867	
PD_L1	>=50%	12	-	-	0.1230
	1-49%	7	0.912 (0.218,3.819)	0.8993	
	<1%	13	2.500 (0.844, 7.404)	0.0981	
ECOG	0	7	-	-	0.0016
	1	21	6.264 (0.813,48.261)	0.0782	

Variable	Level	N	OS (months)		
			HR (95% CI)	**HR P-value**	**Log-rank P-value**
	2	16	5.577 (0.705,44.141)	0.1034	
	3	5	26.824 (2.946,244.229)	0.0035	
Smoking Status	Never	11	-	-	0.8528
	Current or former	62	0.926 (0.411, 2.085)	0.8529	
EGFR	Negative	38	-	-	0.3802
	Positive	4	1.737 (0.498,6.051)	0.3862	
ALK	Negative	40	-	-	0.0328
	Unknown	34	1.912 (1.043,3.505)	0.036	
TP53	Negative	8	-	-	0.0151
	Positive	5	0	0.9961	
Brain Mets	No	43	-	-	0.7794
	Yes	21	1.100 (0.565,2.143)	0.7797	
ICI line	1	10	-	-	0.8087
	2	53	1.520 (0.538,4.294)	0.4296	

Variable	Level	N	OS (months)		
			HR (95% CI)	**HR P-value**	**Log-rank P-value**
	3	8	1.377 (0.369,5.140)	0.6339	
	4	3	0.819 (0.091,7.372)	0.8589	
ICI agent	Atezolizumab	23	-	-	0.6027
	Nivo+Ipi	4	2.143 (0.600,7.659)	0.2409	
	Nivolumab	30	1.139 (0.550,2.357)	0.7263	
	Pembrolizumab	18	0.907 (0.382,2.153)	0.8245	
Age at diagnosis	-	75	1.016 (0.983,1.050)	0.3454	0.3448
CCI	-	75	1.052 (0.869, 1.274)	0.6046	0.6047

Table 3: Univariate Analysis of PFS for Cox Proportional Hazards Model

Variable	Level	N	PFS (months)		
			HR (95% CI)	**HR P-value**	**Log-rank P-value**
Sex	Male	48	-	-	0.3404
	Female	44	0.798 (0.501,1.273)	0.3436	
Histology	Adenocarcinoma NSCLC	54	-	-	<0.0001
	Adenosquanmous NSCLC	1	0	0.9908	
	Large cell NSCLC	1	0	0.9908	
	NOS NSCLC or poorly differentiated carcinoma	7	0.883 (0.346, 2.253)	0.7951	
	SCLC	10	5.915 (2.689, 13.013)	<0.001	
	Squamous NSCLC	19	1.406 (0.792, 2.497)	0.2444	
Race	White/Caucasian	61	-	-	0.0820
	Black/African American	27	1.800 (1.094, 2.960)	0.0206	
	Other	1	3.438 (0.462,25.561)	0.2276	
	Asian	3	1.079 (0.334,3.486)	0.8994	

Variable	Level	N	PFS (months)		
			HR (95% CI)	HR P-value	Log-rank P-value
Insurance	Medicaid	4	-	-	0.6022
	Medicare	56	1.743 (0.421,2.206)	0.4431	
	Not Listed	3	2.669 (0.442,16.101)	0.2845	
	Private	25	2.194 (0.507, 9.495)	0.2933	
	Uninsured	4	3.007 (0.547,16.527)	0.2054	
Stage at initial diagnosis of lung cancer	IV	72	-	-	0.1993
	II	2	0.343 (0.047, 2.521)	0.2932	
	IIIA	7	1.167 (0.502, 2.713)	0.7206	
	IIIB	10	0.439 (0.175, 1.101)	0.0792	
	I	1	0	0.9886	
PD_L1	>=50%	14	-	-	0.5529
	1-49%	8	1.383 (0.491,3.890)	0.5492	
	<1%	14	1.615 (0.667, 3.909)	0.2876	
ECOG	0	8	-	-	0.0031
	1	24	2.833	0.0634	

Variable	Level	N	PFS (months)		
			HR (95% CI)	HR P-value	Log-rank P-value
			(0.944,8.503)		
	2	20	1.730 (0.566,5.286)	0.3364	
	3	7	7.342 (2.035,26.482)	0.0023	
Smoking Status	Never	12	-	-	0.6153
	Current or former	78	0.847 (0.443,1.620)	0.6165	
EGFR	Negative	45	-	-	0.0535
	Positive	6	2.364 (0.957,5.840)	0.0622	
ALK	Negative	49	-	-	0.1854
	Unknown	42	1.368 (0.857,2.183)	0.1885	
TP53	Negative	11	-	-	0.0077
	Positive	6	0.095 (0.012,0.774)	0.0279	
Brain Mets	No	51	-	-	0.6924
	Yes	27	1.112 (0.665,1.890)	0.6935	
ICI line	1	14	-	-	0.6180

Variable	Level	N	PFS (months)		
			HR (95% CI)	**HR P-value**	**Log-rank P-value**
	2	61	1.108 (0.543,2.261)	0.7787	
	3	12	1.502 (0.631,3.577)	0.3577	
	4	3	0.373 (0.047,2.968)	0.3511	
	6	1	0.787 (0.099,6.247)	0.8209	
ICI agent	Atezolizumab	27	-	-	0.0746
	Nivo+Ipi	4	3.897 (1.107,13.718)	0.0341	
	Nivolumab	37	0.923 (0.519,1.641)	0.7857	
	Pembrolizumab	24	0.819 (0.429,1.567)	0.5470	
Age at diagnosis	-	92	0.996 (0.971,1.021)	0.7517	0.7523
CCI	-	75	0.960 (0.822,1.121)	0.6053	0.6054

Table 4: Univariate Analysis of Response for Logistic Regression Model

Variable	**Level**	**Responder**		**Crude Odds Ratio (95% CI)**	**P-value**
		Yes (N=12)	No (N=89)		
Sex	Male	6	44	-	0.9709
	Female	6	45	1.023 (0.306,3.414)	
Histology	Adenocarcinoma	8	53	-	0.9624
	NSCLC Adenosquanmous NSCLC	0	1	<0.001 (<0.001, >999.999)	
	Large cell NSCLC	0	1	<0.001 (<0.001, >999.999)	
	NOS NSCLC or poorly differentiated carcinoma	2	6	2.208 (0.378,12.894)	
	SCLC	0	11	<0.001 (<0.001, >999.999)	
	Squamous NSCLC	2	17	0.779 (0.151,4.030)	
Race	Black/African American	5	26	-	0.2274
	Asian	2	3	3.467 (0.456,26.372) (0.456,26.372)	
	Other	0	2	<0.001	

Variable	Level	Responder		Crude Odds Ratio (95% CI)	P-value
		Yes (N=12)	No (N=89)		
				(<0.001, >999.999)	
	White/Caucasian	5	58	0.448 (0.119,1.683)	
Insurance	Medicaid	0	4	-	0.9958
	Medicare	9	53	>999.999 (<0.001, >999.999)	
	Not Listed	0	3	1 (<0.001, >999.999)	
	Private	3	24	>999.999 (<0.001, >999.999)	
	Uninsured	0	5	1 (<0.001, >999.999)	
Stage at initial diagnosis of lung cancer	IV	10	70	-	0.9115
	II	1	2	3.500 (0.290,42.224)	
	IIIA	1	6	1.167 (0.127,10.723)	
	IIIB	0	10	<0.001 (<0.001, >999.999)	
	I	0	1	<0.001 (<0.001, >999.999)	
PD_L1	>=50%	4	11	-	0.6764
	1-49%	0	14	0.344	

Variable	Level	Responder		Crude Odds Ratio (95% CI)	P-value
		Yes (N=12)	No (N=89)		
				(0.032,3.688)	
	<1%	1	8	<0.001 (<0.001, >999.999)	
	Missing	63			
ECOG	3	0	8	-	0.6984
	1	3	24	>999.999 (<0.001, >999.999)	
	2	5	17	>999.999 (<0.001, >999.999)	
	0	2	6	>999.999 (<0.001, >999.999)	
	Missing	36			
Smoking Status	Never	4	11	-	0.0492
	Current or former	7	77	0.250 (0.063,0.995)	
	Missing	2			
EGFR	Positive	0	7	-	0.9631
	Negative	9	42	>999.999 (<0.001, >999.999)	
	Missing	43			
ALK	Unknown	4	41	-	0.3908
	Negative	8	47	1.745	

Variable	Level	Responder		Crude Odds Ratio (95% CI)	P-value
		Yes (N=12)	No (N=89)		
				(0.489,6.220)	
	Missing	1			
TP53	Positive	3	3	-	0.0705
	Negative	1	11	0.091 (0.007,1.222)	
	Missing	83			
Brain Mets	Yes	5	26	-	0.5090
	No	6	48	0.650 (0.181,2.335)	
	Missing	16			
ICI line	6	1	0	-	0.9451
	2	8	60	<0.001 (<0.001, >999.999)	
	3	0	13	<0.001 (<0.001, >999.999)	
	4	0	3	<0.001 (<0.001, >999.999)	
	1	3	12	<0.001 (<0.001, >999.999)	
	Missing	1			
ICI agent	Pembrolizumab	4	21	-	0.9371
	Nivo+Ipi	0	5	<0.001	

Variable	Level	Responder		Crude Odds Ratio (95% CI)	P-value
		Yes (N=12)	No (N=89)		
				(<0.001, >999.999)	
	Nivolumab	5	37	0.709 (0.172,2.934)	
	Atezolizumab	3	26	0.606 (0.122,3.011)	

Table 5a: OS at 12-months and 24-months for both NSCLC and SCLC

No. of Subject	Event	Censored	Median Survival (95% CI)	12 month Survival	24 month Survival
75	44 (59%)	31 (41%)	10.2 (5.7, 23.3)	46.1% (34.2%, 57.2%)	31.3% (18.5%, 44.9%)

Table 5b: OS at 12-months and 24-months for both NSCLC and SCLC stratified by race

Race	No. of Subject	Event	Censored	Median Survival (95% CI)	12 month Survival	24 month Survival
Asian	1	0 (0%)	1 (100%)	NA (NA, NA)	100.0% (NA, NA)	100.0% (NA, NA)
Black/African American	20	14 (70%)	6 (30%)	3.5 (1.3, 23.3)	35.0% (15.7%, 55.2%)	26.3% (8.4%, 48.5%)
Other	1	0 (0%)	1 (100%)	NA (NA, NA)	100.0% (NA, NA)	100.0% (NA, NA)
White/Caucasian	53	30 (57%)	23 (43%)	10.5 (8.2, 23.7)	48.1% (33.5%, 61.2%)	30.7% (15.4%, 47.5%)

Table 5c: PFS at 12-months and 24-months for both NSCLC and SCLC

No. of Subject	Event	Censored	Median Survival (95% CI)	12 month Survival	24 month Survival
93	72 (78%)	20 (22%)	3.9 (2.8, 5.4)	30.5% (21.3%, 40.2%)	14.4% (6.7%, 24.8%)

Table 5d: PFS at 12-months and 24-months for both NSCLC and SCLC stratified by race

Race	No. of Subject	Event	Censored	Median Survival (95% CI)	12 month Survival	24 month Survival
Asian	3	3 (100%)	0 (0%)	12/7 (3.6, 18.4)	66.7% (5.4%, 94.5%)	0.0% (0.0%, 0.0%)
Black/African American	27	25 (93%)	2 (7%)	2.7 (1.3, 4.5)	17.8% (6.1%, 34.4%)	8.9% (1.6%, 24.1%)
Other	1	1 (100%)	0 (0%)	2.1 (NA, NA)	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)
White/Caucasian	61	43 (70%)	18 (30%)	5.4 (3.0, 10.0)	34.8% (23.0%, 46.8%)	20.0% (8.6%, 35.9%)

Table 6a: OS at 12-months and 24-months for Black/African American and White/Caucasian patients with NSCLC stratified by race

Race	No. of Subject	Event	Censored	Median Survival (95% CI)	12 month Survival	24 month Survival
Black/African American	18	12 (67%)	6 (33%)	4.2 (1.6, NA)	38.9% (17.5%, 60.0%)	29.2% (9.3%, 52.8%)
White/Caucasian	47	25 (53%)	22 (47%)	15.3 (NA, NA)	53.2% (37.5%, 66.7%)	34.0% (17.0%, 51.9%)

Table 6b: OS at 12-months and 24-months for Black/African American and White/Caucasian patients with NSCLC stratified by sex

Sex	No. of Subject	Event	Censored	Median Survival (95% CI)	12 month Survival	24 month Survival
Female	33	15 (45%)	18 (55%)	23.7 (5.1, NA)	60.1% (41.3%, 74.6%)	42.9% (19.9%, 64.2%)
Male	34	22 (65%)	12 (35%)	10.2 (4.5, 15.5)	41.8% (24.7%, 58.1%)	25.1% (9.7%, 44.0%)

Table 6c: OS at 12-months and 24-months for Black/African American and White /Caucasian patients with NSCLC stratified by PD_L1

PD-L1	No. of Subject	Event	Censored	Median Survival (95% CI)	12 month Survival	24 month Survival
<50%	20	13 (65%)	7 (35%)	9.8 (3.2, NA)	31.7% (12.5%, 53.1%)	NA (NA, NA)
>=50%	12	5 (42%)	7 (58%)	NA (2.9, NA)	57.1% (25.4%, 79.6%)	NA (NA, NA)

Table 6d: Univariate analysis of OS of black and white patients with only NSCLC stratified by sex, race and PD_L1 in Cox Proportional Hazards Model

Variable	Level	N	PFS (months)		
			HR (95% CI)	HR P-value	Log-rank P-value
Sex	Male	34	-	-	0.2870
	Female	31	0.700 (0.362,1.354)	0.2894	
Race	White/Caucasian	47	-	-	0.1778
	Black/African American	18	1.604 (0.802,3.210)	0.1817	
PD_L1	>=50%	12	-	-	0.2049
	<50%	19	1.932 (0.685,5.448)	0.2129	

7. Appendix

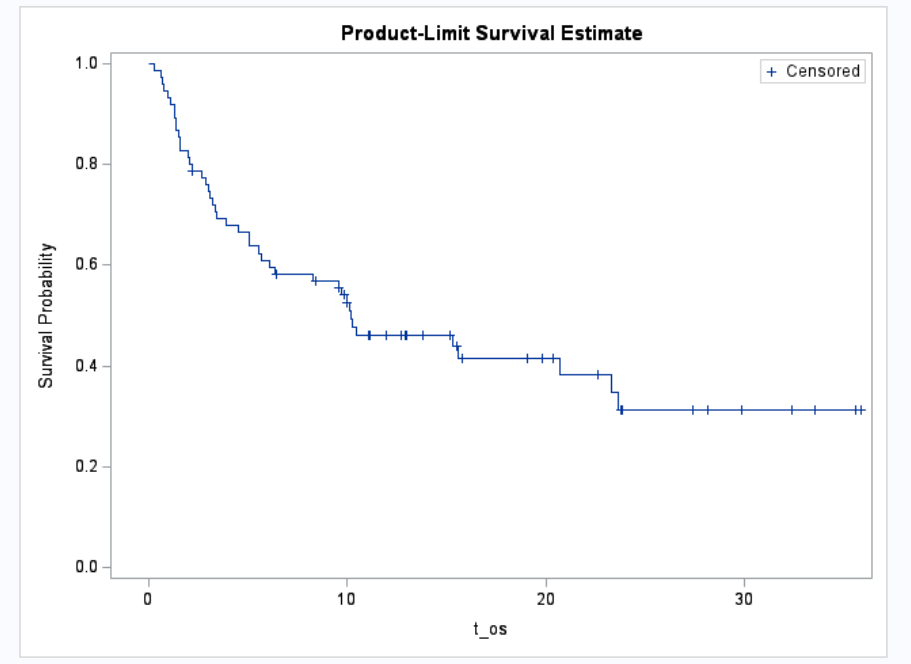

Figure 1a: Kaplan-Meier Plot of OS (in months) for both NSCLC and SCLC

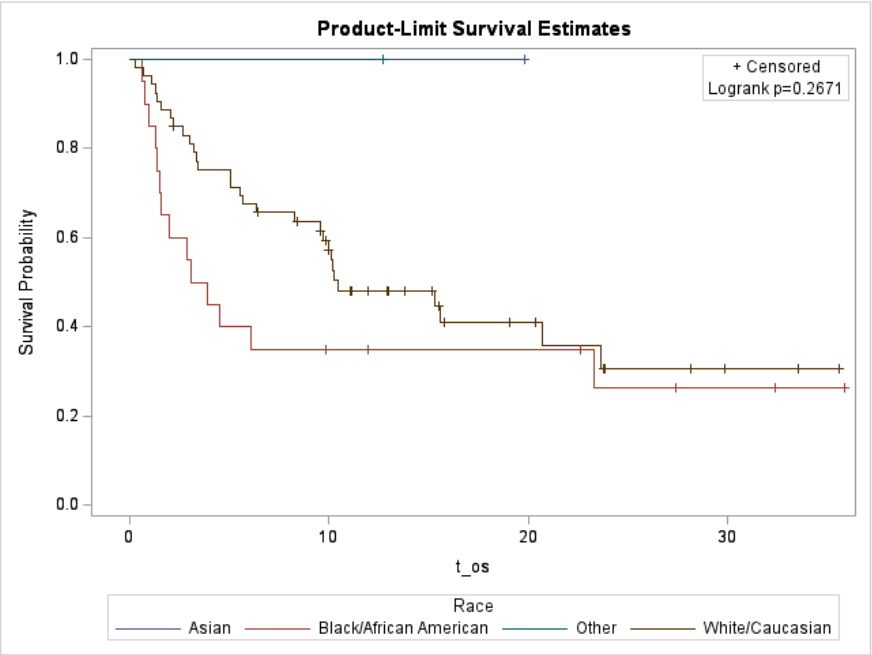

Figure 1b: Kaplan-Meier Plot of OS (in months) for both NSCLC and SCLC stratified by race

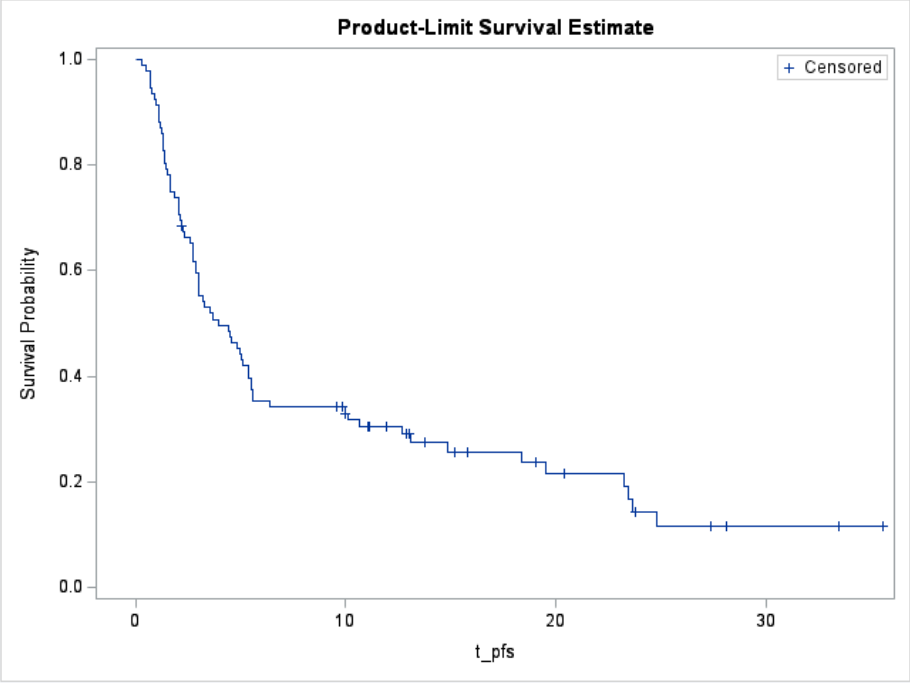

Figure 1c: Kaplan-Meier Plot of PFS (in months) for both NSCLC and SCLC

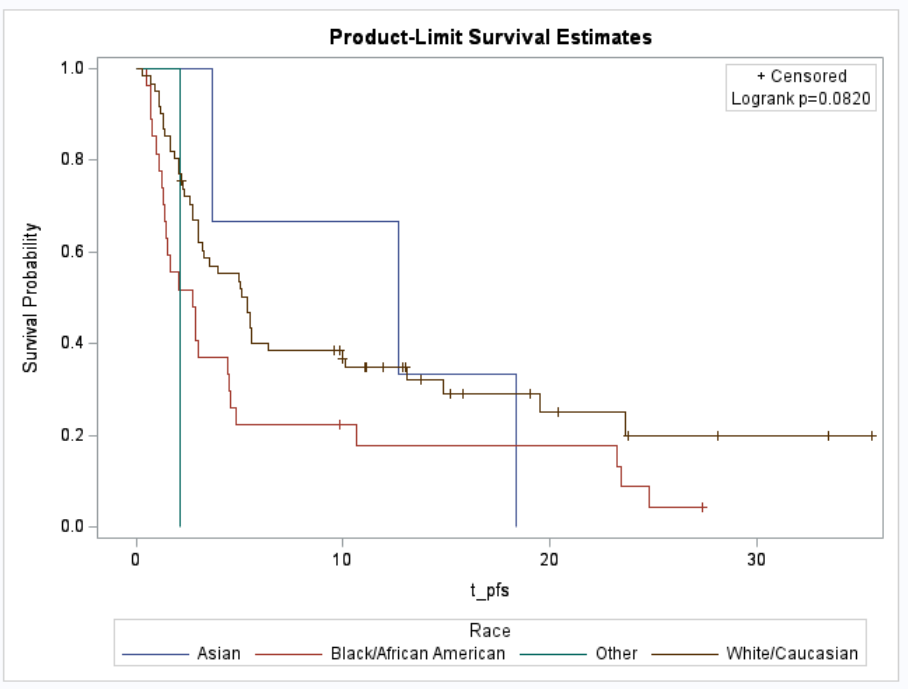

Figure 1d: Kaplan-Meier Plot of PFS (in months) for both NSCLC and SCLC stratified by race

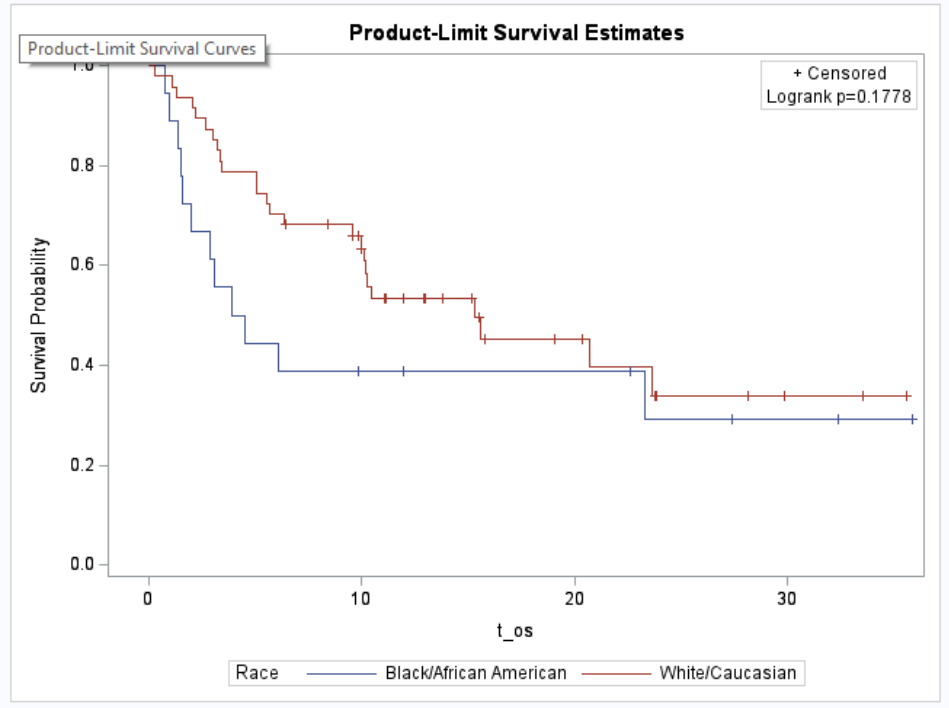

Figure 2a: Kaplan-Meier Plot of OS for Black/African American and White /Caucasian patients with NSCLC stratified by race

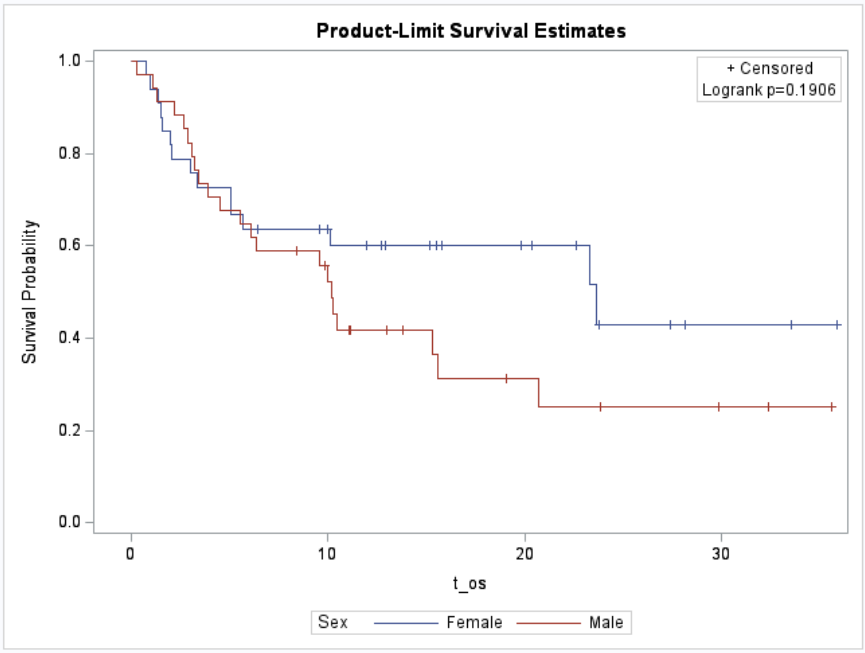

Figure 2b: Kaplan-Meier Plot of OS for Black/African American and White /Caucasian patients with NSCLC stratified by sex

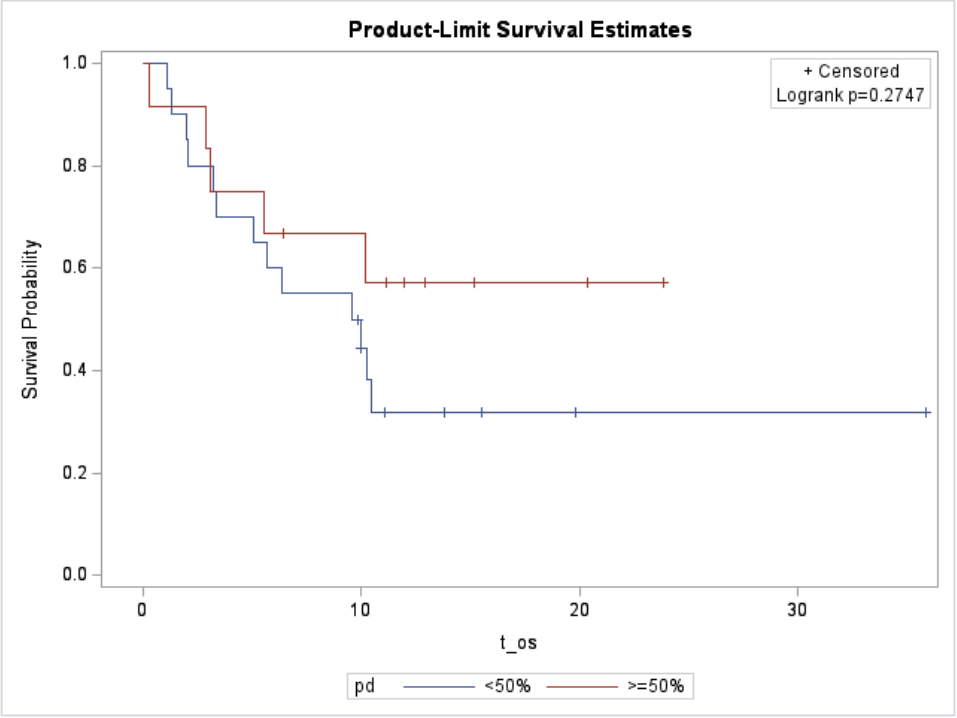

Figure 2c: Kaplan-Meier Plot of OS for Black/African American and White /Caucasian patients with NSCLC stratified by PD_L1