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## Survival disparities in Black patients with *EGFR*-mutated non-small cell lung cancer

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### Abstract

**Background:** Little is known about the difference between black and non-black patients with *EGFR*-mutated NSCLC particularly regarding survival. We thus characterized the *EGFR* expression profile, clinical characteristics, and survival outcome in these patients.

**Patient and Methods:** We reviewed the cancer registry and patient charts at a New York-Bronx network (n=2773) treating a large population of minority patients, for non-squamous NSCLC (n=1986) diagnosed between 2009 and 2015. Survival was adjusted for smoking, gender, age, weight, and stage.

**Results:** The *EGFR* mutation rate was 15% (98/652) in tested patients (Black: 14%; non-black: 16%). There was no significant difference between two cohorts with respect to age at diagnosis, gender, presenting stages and socioeconomic status. On the other hand, weight was noted to be heavier in Black patients with *EGFR*-mutated NSCLC than their non-black counterparts (p=0.012). After adjusting for gender, age, smoking status, weight and stage, the multivariate analysis revealed no racial disparity in survival among patients with wild-type *EGFR* (p=0.774); However, among patients with *EGFR*-mutated NSCLC, black patients had shorter survival in

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comparison to non-black patients ( $p=0.001$ ), with two-year survival rates being 33% vs. 61% respectively. Such shorter survival was also observed among EGFR-inhibitor treated patients with common *EGFR*-mutations ( $P=0.040$ ).

**Conclusions:** To our knowledge, this is the first report of inferior survival among Black NSCLC patients with *EGFR* mutations, relative to non-black patients. The survival disparities suggest the need of more tailored management for this patient population.

### MicroAbstract

Non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (*EGFR*) mutation is a distinct molecular subgroup with effective targeted therapy. In our study of 2773 patients, the survival was similar between races among *EGFR* wild-type NSCLC; however, black patients with *EGFR*-mutant NSCLC had inferior survival compared to non-black counterparts. More tailored management for this population is warranted.

### Keywords

EGFR; black patients; survival; lung cancer; uncommon *EGFR* mutations

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### Introduction

Lung cancer is the most common cause of cancer death, with only 18% of patients surviving 5 years or longer<sup>1</sup>. It has been reported that Black patients diagnosed with lung cancer may experience worse overall survival relative to their Caucasian counterparts<sup>2</sup>. Hypotheses have been put forth that this disparity may be attributed to socioeconomic status, access to care, or possible variations in tumor characteristics<sup>3</sup>.

Advances in lung cancer diagnosis and treatment have led to improved clinical outcome in certain molecular subgroups of lung cancer patients, including those with activating *EGFR* mutations<sup>4</sup>. The prevalence of these *EGFR* mutations in non-small cell lung cancer (NSCLC) is approximately 10%–15% in Caucasian patients and up to 50% in Asian patients<sup>5</sup>. Among them, deletions in exon 19 (Del 19) and L858R in exon 21 are the two most common *EGFR* mutations, representing ~85–90% of all *EGFR* mutations in NSCLC and convey sensitivity to *EGFR* tyrosine kinase inhibitors (TKI)<sup>6</sup>. About 10–15% of patients with *EGFR* mutated NSCLC have uncommon mutations, such as exon 20 insertions<sup>6</sup>. A recent pooled analysis of 260 Black patients with NSCLC found that only 5% harbored an *EGFR* mutation, which deviates from the mutational spectrum observed in Caucasians<sup>7</sup>.

Little is known, however, if the variations in mutational frequencies explain the ethnic disparity in overall survival experienced by Black patients. In particular, scarcity of data exists about the lung cancer survival among Black patients harboring *EGFR* mutations, relative to the non-black patients. Thus, in the current study, we determined the *EGFR* mutational profile in a large cohort of Black patients with NSCLC correlating mutational status with clinical, socioeconomic correlates and survival in these patients.

## Patients and Methods

In order to further elucidate lung cancer survival associated with *EGFR* mutations among Black patients, we retrospectively reviewed a New York-Bronx (Montefiore) network cancer registry database and individual patient charts for non-squamous NSCLC patients diagnosed from 1/1/2009 to 12/31/2015. In total, 2,773 lung cancers were diagnosed at the network during this period, of whom 787 patients were diagnosed with squamous cell carcinoma, small cell carcinoma, or other. Out of the remaining 1,986 non-squamous NSCLC patients, 636 were excluded due to lack of pathology reports in the network. Of the remaining 1,350 eligible patients, 698 were excluded due to lack of *EGFR* mutation status. As such, our final analytic dataset consisted of only non-squamous NSCLC patients with available pathology and *EGFR* mutational data (n = 652) (Figure 1A). *EGFR* testing was performed by Integrated Oncology (Labcorp) via PCR-based technology. This assay analyzes exons 18–21 of the *EGFR* tyrosine kinase domain, and has been increasingly used as part of routine care in the network (14% of non-squamous NSCLC patients were tested in 2009, 25% in 2010, 46% in 2011, 62% in 2012, 79% in 2013, 75% in 2014, and 76% in 2015) (Figure 1B).

### Statistical Analysis

Socioeconomic status was represented by annual household income based on home ZIP code. Differences in patient characteristic were compared by chi-squared and Mann-Whitney tests, when appropriate. Response was evaluated according to RECIST v1.1. Survival rates were compared by Kaplan-Meier curves and Cox proportional Hazard Models, adjusted for smoking status (never/ever), gender, age, weight and stage (using the 7<sup>th</sup> edition of AJCC criteria). P-values < 0.05 were considered significant.

## Results

### *EGFR* mutation profiles

The overall *EGFR* mutation rate was 15% (98/652) in all patients, with 14% (35/258) of Black patients and 16% (63/394) of non-black patients harboring mutations. The mutational spectrum with Del 19, L858R and uncommon mutations was found to be 46%, 23% and 31% in Black patients, compared to 43%, 35% and 22% in non-black patients. No significant difference was observed (p=0.39) (Table 1A).

Different from the common mutations (Del 19 or L858R), uncommon *EGFR* mutations are a heterogeneous group with diverse genetic composition and various responses to *EGFR* TKIs. In non-black patients with uncommon *EGFR* mutations, 6 (43%) had likely sensitive mutations to FDA-approved *EGFR* TKIs, including G719A in Exon 18 (n=3), E709K and G719A in Exon 18 (n=1), Q701L and G719A in Exon 18 (n=1), G719S in Exon 18 and S768I in Exon 20 (n=1); Eight (57%) had likely resistant mutations, including H773\_V774insHPH mutation in Exon 20 (n=1), H773dup mutation in Exon 20 (n=1), N771\_P772insH mutation in Exon 20 (n=1), S768\_D770dupSVD mutation in Exon 20 (n=3), N771, H773 dupNPH mutation in Exon 20 (n=1), D770\_N771insG mutation in Exon 20 (n=1).

In Black patients with uncommon *EGFR* mutations, 4 (36%) had likely sensitive mutations, including G719A in Exon 18 and L861Q in Exon 21 (n=1), L858R in Exon 21 and S768I in Exon 20 (n=1), G719A in Exon 18 and S768I in Exon 20 (n=1), L747\_P753del7insS in Exon 19 and L833V in Exon 21 (n=1); Three (27%) had likely resistant mutations, including N771\_H773dupNPH mutation in Exon 20 (n=1), P772\_H773insGHP mutation in Exon 20 (n=1), A763\_Y764ins4 mutation in Exon 20 (n=1); Four (36%) had undetermined or controversial sensitivity of mutations, including L833F in Exon 21 (n=1), H773L and V774M in Exon 20 (n=1), S768I and V769L in Exon 20 (n=2).

### Patient demographics, clinical characteristics and use of EGFR TKIs.

Black patients were similar to non-black patients with respect to age at diagnosis, gender, presenting stages and socioeconomic status (SES, represented by annual household income) (Table 1A and 1B). On the other hand, there was a significant weight difference between Black and non-black lung cancer patients harboring *EGFR* mutations (uncommon plus common), (75.1kg vs. 65.6 kg,  $p=0.012$ , Table 1A). On the other hand, such weight difference was not observed in *EGFR* wild-type patients (Table 1B). There was no significant difference in terms of exposure to EGFR TKIs (51% vs. 49%,  $p=0.42$ ). Similarly, among patients harboring common *EGFR* mutations, there was a significant weight difference (black: 78.4kg vs. non-black: 65.1 kg,  $p=0.0051$ ), whereas no significant difference in terms of the uses of EGFR TKI ( $p=0.40$ ); Between Black and non-black patients with metastatic NSCLC harboring common *EGFR* mutations, neither was there a significant difference among the types of first-line TKI use (either erlotinib or afatinib) ( $p=0.57$ ) (Table 1C).

Among those with metastatic or recurrent disease, 21 patients did not receive EGFR TKIs due to death before *EGFR* results coming back or patients' wish to pursue hospice (non-black 38.5% vs. black 50.0%), loss to follow-up (23.1% vs. 50.0%), insensitive *EGFR* mutations (23.1% vs. 0.0%), and lack of oncology visit due to frequent hospitalizations (15.4% vs. 0.0%). No statistical significance was observed ( $p=0.230$ ). Among 35 patients who progressed after first or second generation of TKI, the subsequent treatment was not significantly different ( $p=0.413$ ) -osimertinib (non-black 28.6% vs. 14.3%), chemotherapy (33.3% vs. 14.3%), continuation of first/second generation of TKI (4.8% vs. 7.1%), other treatment (4.8% vs. 14.3%), and no treatment (28.6% vs. 50.0%). None of the patients received immunotherapy. Of 13 patients who did not receive treatment after TKI progression, all but one patient (patient refusal) were due to poor functional status or death following progression.

### Survival analysis

The objective response rate was 63.6% in black and 76.0% in non-black patients ( $p=0.454$ ). The two-year survival rate among *EGFR* wild-type patients was similar by race [Black = 38.2% (52/136); non-black = 39% (75/192), Figure 2A and supplementary for full Cox models]. In contrast, the two-year survival rates varied dramatically by race among patients harboring *EGFR* mutations [Black = 33.3% (9/27); non-black = 61.3% (27/44), Figure 2B]. Multivariate regression models, adjusting for gender, age, smoking status, weight and stage,

showed similar racial differences in survival (*EGFR* wild-type Black vs. non-black,  $p=0.774$ ; *EGFR* mutated Black vs. non-black,  $p=0.001$ .)

Interestingly, even with limited sample size, the survival difference was significant for patients with uncommon *EGFR* mutations (Black vs. non-black,  $p=0.008$ ) (Figure 3B). There was also a trend for shorter survival in Black patients with common *EGFR* mutations (Black vs. non-black,  $p=0.074$ ) (Figure 3A). Moreover, the survival disparity was particularly evident for earlier stages (I-III) ( $p=0.001$ ) (Figure 3C), and was also observed amongst the group with metastatic disease (stage IV,  $p=0.044$ ) (Figure 3D). The recurrence rate was similar by race (Black = 40%; non-black = 47%). For patients with metastatic disease harboring common *EGFR* mutation who were treated with EGFR TKIs as per standard practice at that time, Black patients had significantly inferior survival compared to non-black ( $p = 0.040$ , Figure 4A). Among those patients, the 2-year survival rate of Black patients was 44.4% compared to 77.3% of non-black patients.

When patients with *EGFR* mutation were further stratified by gender, non-black female patients had significantly favorable survival ( $p=0.049$ ), but black women did not appear to survive longer compared to black men (Figure 4B).

## Discussion

Studies addressing racial disparities among lung cancer patients with *EGFR* mutation are limited. The survival comparison between different races is particularly lacking. We hereby determined the clinical attributes, socioeconomic characteristics and survival differences between Black vs. non-black lung cancer patients. Surprisingly, despite similar survival outcomes among wild-type patients in our cohort, Black patients with *EGFR* mutated NSCLC experienced significantly shorter survival than their non-Black counterparts. These results suggest that even in the era of molecularly targeted therapy, black patients face disparate survival outcomes and more tailored care is needed. To the best of our knowledge, this study is the first reporting racial differences in outcome for *EGFR* mutated non-squamous NSCLC.

The underlying cause of such disparity among patients harbouring *EGFR* mutation is not entirely clear. The fact that such disparity was not found among *EGFR* wild-type patients in the same study period suggests that differential access to cancer care may have not played a major role, although the access and compliance to oral medications may be different. Consistent with this observation, recent studies also showed that after controlling for stage, treatment, and comorbidities, racial disparity in overall lung cancer survival may disappear<sup>8-10</sup>. It should also be noted that we found no significant difference in terms of gender, socioeconomic status, smoking status, stage distribution, and use of EGFR TKI between black and non-black patients irrespective of *EGFR* mutation status. Although we cannot entirely exclude the possibility that small difference in TKI use may have impact on survival outcomes. In addition, among TKI-treated patients with metastatic disease and common *EGFR* mutations, a group that should derive clear and consistent clinical benefits, black patients still suffer poorer survival compared to non-black patients. However, we noted that although not statistically significant, there was a trend that black patients who

progressed after front-line TKI were more likely to receive no treatment (50.0% vs. 28.6%). This might contribute to the inferior survival observed in blacks.

Racial difference of pharmacogenetic factors may contribute to such racial disparity. Erlotinib is known to be inactivated through CYP3A metabolism<sup>11, 12</sup>, the activity of which has been described higher in black patients<sup>13</sup>. Indeed, a recent phase II randomized study of African American patients with NSCLC (n = 55) found that erlotinib exposures were lower than those observed in previous studies, consistent with CYP3A pharmacogenetics implying higher metabolic activity and suboptimal dosing in African American patients<sup>14</sup>.

On the other hand, larger weight in black patients with *EGFR*-mutated lung cancer and set dosing for *EGFR* TKIs might lead to under-dosing issue of the cohort of black patients, but in our cohort, even after adjustment of weight, the survival difference still exists suggestive of other contributing factors. Another possible cause is medication adherence, which has been shown to be lower among black patients<sup>15</sup>. Unlike intravenous chemotherapy that can be easily tracked for adherence, the nature of being an oral medication makes assessing TKI adherence more difficult, which is now a subject to be further explored.

We also noted that black women do not gain similar survival benefits as non-black women (Figure 4B). Consistent with other studies reporting that women with lung cancer have favorable survival compared to men, our study showed that non-black women with *EGFR* mutation had the best survival compared to non-black men, black women, and black men. However, the survival between black men and women are quite similar in our population (Figure 4B), suggesting the need of further research on gender disparity.

Previous studies have reported the frequency of *EGFR* mutations greatly varying from 2 to 40% dependent on smoking history, histology and patient population (Summarized in Table 2), but none of the studies reported survival outcomes and comparisons to contemporaneous non-black patients. Although some studies reported lower frequency of *EGFR* mutation in black patients compared to white, this is not the case for a majority of studies.

Prior studies identified factors contributing to survival disparities. A study of a national cancer database showed that death from competing causes, including cardiovascular and other cancers can largely explain the notable racial disparities in early stage lung cancer patients<sup>10</sup>. Another study reported lower utilization of appropriate lung cancer screening among black patients<sup>16</sup>, but this is not the case in our community based on our prior report<sup>17</sup>. Older age, squamous histology, gender, larger tumor, and tendency to forgo treatment have also been reported<sup>18</sup>. However, a recent study from Vanderbilt showed that after controlling stage and treatment, racial disparities may disappear, although *EGFR* mutational status was not addressed in this particular study<sup>8</sup>. Stage and treatment were considered more important to predict survival.

#### Limitations:

Despite our efforts to control for common prognostic factors – gender, smoking status, stage, socioeconomic status, and weight, the nature of this retrospective study cannot eliminate all the potential biases. We were not able to assess the potential impact of pharmacokinetics,

comorbidities and medication adherence that may affect survival disparity and these will be the focus of upcoming studies. The study is also limited in data retrieved from just one cancer registry with a relatively small sample size of EGFR mutated patients.

## Conclusions

To our knowledge, this is the first report of inferior survival among black NSCLC patients with *EGFR* mutations, relative to non-black patients despite similar survival in wild-type patients. Black patients are heavier, but even after correcting weight, the survival disparity still exists. More studies on racial disparity specific to patients with targetable genetic alterations are needed, and subsequently more tailored management plans for this patient population are warranted.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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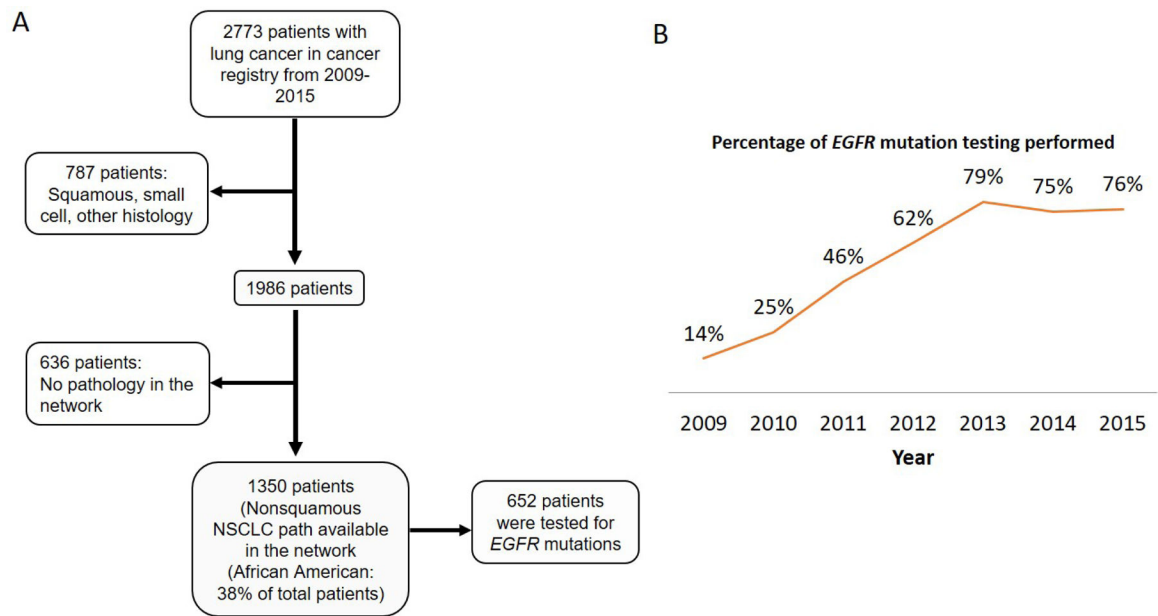
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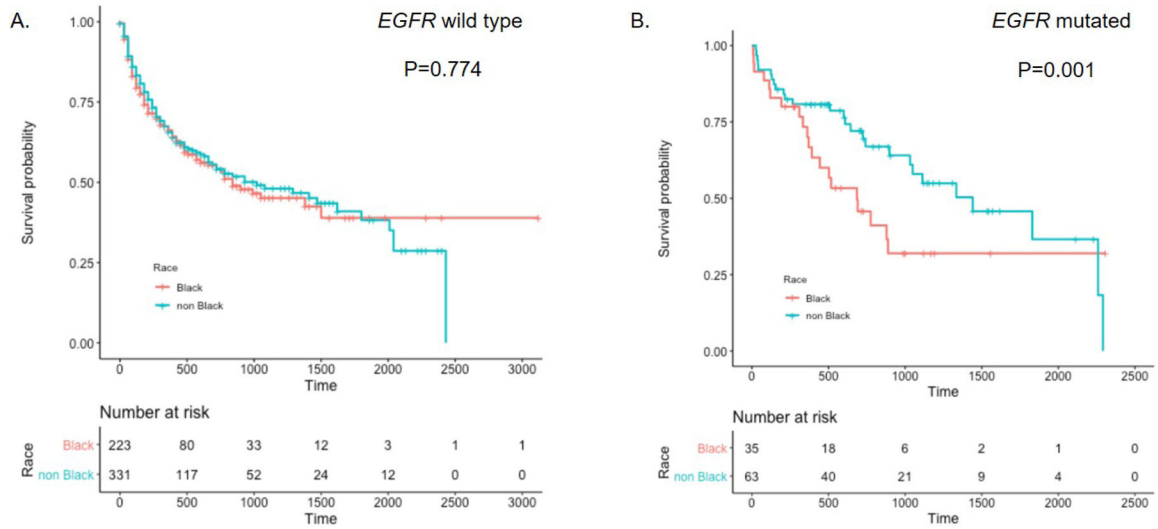
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### Clinical Practice Points

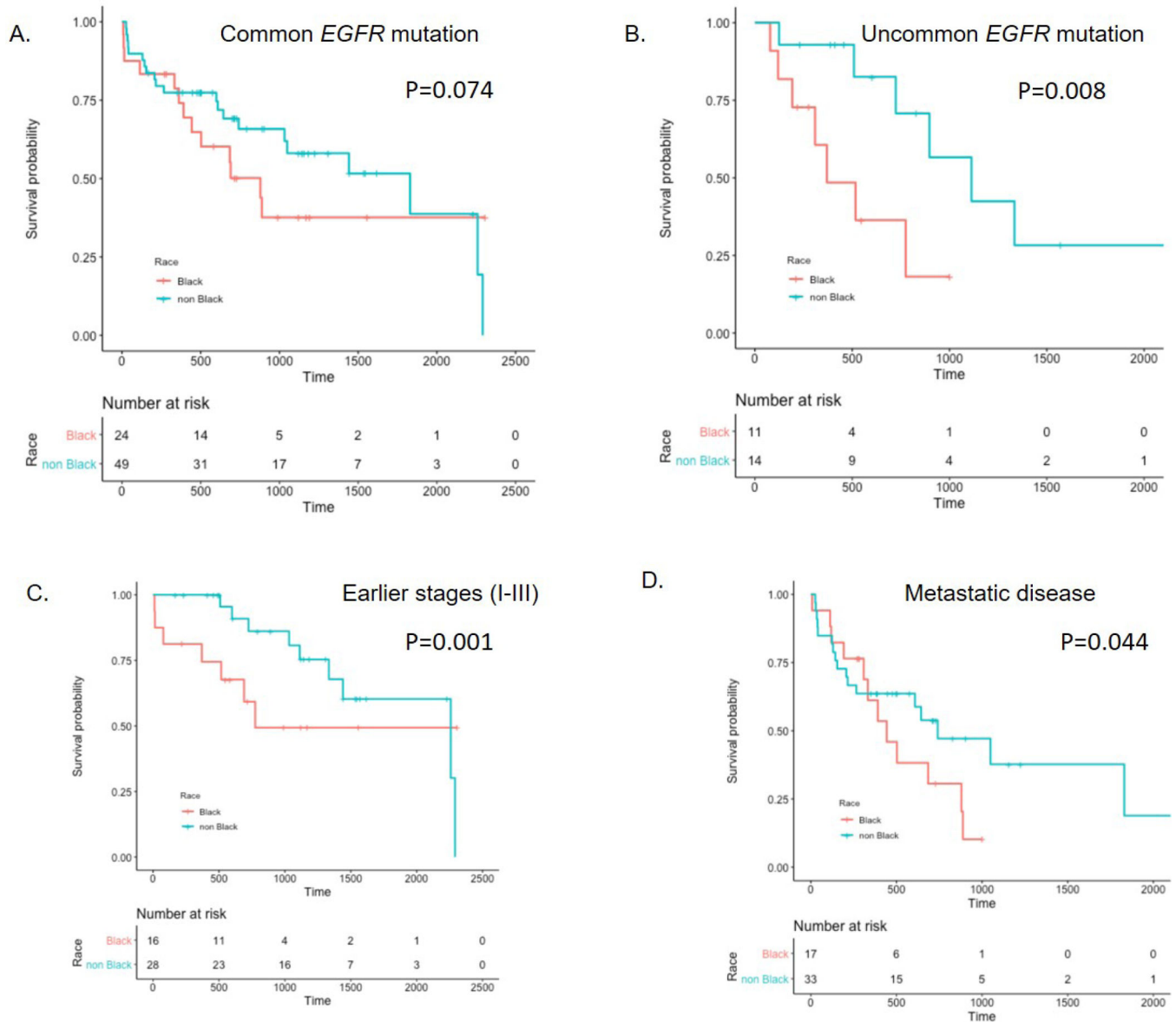
- Racial disparity is known to exist among lung cancer patients, but its existence in patients harbouring *EGFR* mutation remains elusive.
- This is the first study reporting that *EGFR*-mutated black patients had worse survival compared to non-black patients, after adjustment for smoking, gender, age, weight, and stage. Black women may not derive similar magnitude of survival benefit compared to non-black counterparts.
- A more tailored care and further research is needed for black patients with *EGFR* mutations.



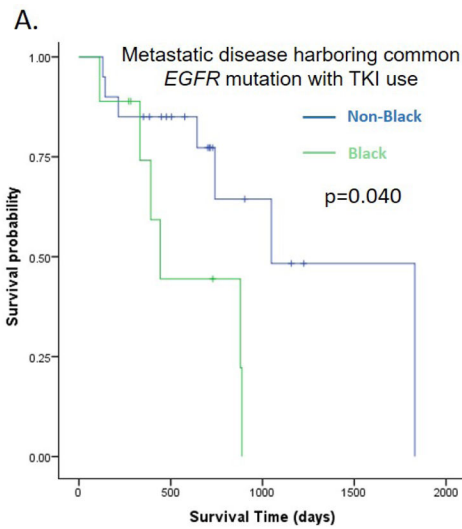
**Figure 1.**  
 A. Flowchart of study design and number of patients. B. Percentage of *EGFR* mutation testing by year among patients diagnosed with non-squamous non-small cell lung cancer



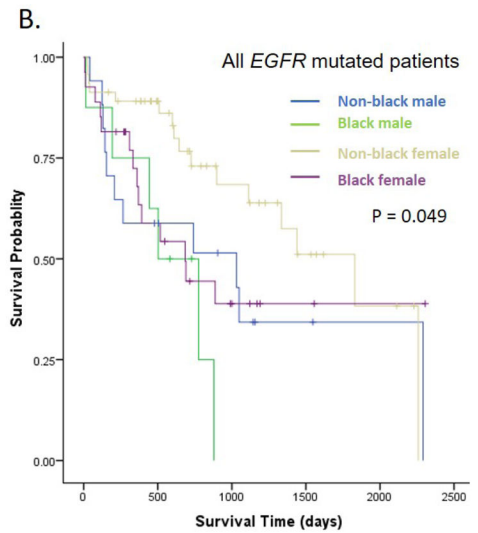
**Figure 2.** Survival time associated with non-squamous NSCLC by ethnicity A. *EGFR* wild-type patients; B. *EGFR* mutated patients. \*P-values from Cox proportional Hazard Models adjusting for smoking status, gender, age, weight and stage.



**Figure 3.** Survival of patients with *EGFR* mutation stratified by race. A. Patients with common *EGFR* mutations; B. Patients with uncommon *EGFR* mutations. C. Patients with early stages (I+II +III) disease. D. Patients with metastatic disease. \*P-values from Cox proportional Hazard Models adjusting for smoking status, gender, age, weight and stage.



	Number at risk					
Time	0	500	1000	1500	2000	2500
Black	9	3	0	0	0	0
non-black	20	13	4	1	0	0



	Number at risk					
Time	0	500	1000	1500	2000	2500
Non-black Male	17	9	6	2	1	0
Black Male	8	5	0	0	0	0
Non-black Female	46	31	15	7	3	0
Black Female	27	13	6	2	1	0

**Figure 4.** Survival of patients with *EGFR* mutation A. EGFR-TKI treated patients with metastatic disease and common *EGFR* mutation stratified by race (p value from Cox proportional Hazard Model adjusting for smoking status, gender, age, weight and stage); B. Patients with *EGFR* mutation stratified by race and gender (P value from log-rank test). TKI: tyrosine kinase inhibitor

**Table 1:**  
**Patient demographics and clinical characteristics**

<b>Table 1A Patients with <i>EGFR</i> mutation</b>			
	<b>Non-Black (n=63) N (%)</b>	<b>Black (n=35) N (%)</b>	<b>P-Value</b>
Mean age at diagnosis	68.2	63.2	0.06
Gender			0.84
Male	17(27%)	8 (23%)	
Female	46 (73%)	27 (77%)	
Stage at diagnosis <sup>a</sup>			0.85
I+II	19 (30%)	11 (31%)	
III	9 (14%)	6 (17%)	
IV	35 (54%)	17 (49%)	
Smoking status			1.00
Never	34 (54%)	19 (54%)	
Ever	29 (46%)	16 (46%)	
Weight (kg)	65.6	75.1	0.01
Socioeconomic status (income, \$)	23853	21208	0.47
Types of <i>EGFR</i> mutations			0.39
Del 19	27 (43%)	16(46%)	
L858R	22 (35%)	8 (23%)	
Uncommon <sup>b</sup>	14 (22%) <sup>b</sup>	11(31%) <sup>c</sup>	
Use of EGFR TKI	32(51%)	17(49%)	0.42
<b>Table 1B Patients without <i>EGFR</i> mutation (<i>EGFR</i> wildtype)</b>			
	<b>Non-Black (n=331) N (%)</b>	<b>Black (n=223) N (%)</b>	<b>P-Value</b>
Mean age at Diagnosis	67.4	64.7	0.83
Gender			0.62
Male	157(47%)	122(55%)	
Female	174 (53%)	101 (45%)	
Stage at diagnosis			0.40
I+II	94 (28%)	54 (24%)	
III	55 (17%)	45 (20%)	
IV	163 (49%)	112(50%)	
Smoking status			0.91
Never	42(13%)	29(13%)	
Ever	289 (87%)	194 (87%)	
Weight (kg)	69.3	70.6	0.40
<b>Table 1C: First line tyrosine kinase inhibitors used in <i>EGFR</i> mutated patients with metastatic disease.</b>			
	<b>non-Black N (%)</b>	<b>Black N (%)</b>	<b>P-value</b>
Total	20	9	
Erlotinib	18(90.0)	7 (77.8)	0.57
Afatinib	2 (10.0)	2 (22.2)	

<sup>a</sup>The stage at diagnosis for one *EGFR*-mutated black patient is not available.

<sup>b</sup>Mutation types: Likely sensitive mutations to FDA-approved EGFR TKIs (SM): G719A in Exon 18 (n=3), E709K and G719A in Exon 18, Q701L and G719A in Exon 18, G719S in Exon 18 and S768I in Exon 20. Likely resistant mutations (RM): H773\_V774insHPH mutation in Exon 20, H773dup mutation in Exon 20, N771\_P772insH mutation in Exon 20, S768\_D770dupSVD mutation in Exon 20 (n=3), N771, H773 dupNPH mutation in Exon 20, D770\_N771insG mutation in Exon 20.

<sup>c</sup>Mutation types: SM: G719A mutation in Exon 18 and L861Q mutation in Exon 21, L747\_P753del7insS in Exon 19 and L833V mutation in Exon 21. S768I mutation in Exon 20 and L858R mutation in Exon 21, G719S mutation in Exon 18 and S768I mutation in Exon 20. RM: N771\_H773dupNPH mutation in Exon 20, H773L and V774M mutations in Exon 20, P772\_H773insGHP mutation in Exon 20, A763\_Y764ins4 mutation in Exon 20. Undetermined or controversial sensitivity of mutations (UM): L833F mutation in Exon 21, S768I and V769L mutations in Exon 20 (n=2).

Abbreviations: SM, sensitive *EGFR* mutations to FDA approved EGFR TKIs. RM, resistant *EGFR* mutations. UM: undetermined or controversial sensitivity of *EGFR* mutations. TKI, tyrosine kinase inhibitor

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**Table 2:** Summarized studies reporting *EGFR* mutation in Black patients with non-small cell lung cancer

Study	Year of Publication	Number of Blacks	% Female	% Ever Smoker	% Adenocarcinoma	% <i>EGFR</i> Mutation in Blacks	% Uncommon of <i>EGFR</i> Mutation in Blacks	% <i>EGFR</i> Mutation in Whites	Location
Leduc <sup>19</sup>	2017	169	Not Reported	37	100	40	Not Reported	19	Martinique and Guadeloupe
Campbell <sup>20</sup>	2017	245	53	88	61	12	Not Reported	15	Tennessee, USA
Steuer <sup>21</sup>	2016	66	58	23	100	22		25	14 US sites
Legius <sup>22</sup>	2016	6	67	0	100	50	33	Not Reported	Sub-Saharan Africa
Bollig-Fischer <sup>23</sup>	2015	137	58	90	67	15	67	7	Wisconsin, USA
Araujo <sup>7</sup>	2015	260	37	90	53	5	8	6	Tennessee, Michigan, and Ohio, USA
Phelps <sup>14</sup>	2014	45	Not Reported	Not Reported	Not Reported	4	2	N/A	Ohio and North Carolina, USA
Yamaguchi <sup>24</sup>	2013	22	Not Reported	27	Not Reported	18	Not Reported	N/A	Massachusetts, USA
Errihani <sup>25</sup>	2013	137	44	58	100	21	10	N/A	Morocco
Baum <sup>26</sup>	2013	67	63	84	Not Reported	4.8	Not Reported	14	Pennsylvania, USA
Reinersman <sup>27</sup>	2011	121	Not Reported	Not Reported	100	19	Not Reported	13	New York and Michigan, USA
Harada <sup>28</sup>	2011	16	56	50	75	31	40	Not Reported	Maryland, USA
Cote <sup>29</sup>	2011	67	66	84	72	40	12	16	Michigan, USA
Leidner <sup>30</sup>	2009	53	43	86	44	2	Not Reported	Not Reported	Ohio, USA
Krishnaswamy <sup>31</sup>	2009	66	52	88	38	2	50	50	Illinois, USA
Yang <sup>32</sup>	2005	41	Not Reported	Not Reported	Not Reported	2	Not Reported	Not Reported	Maryland, USA