ISSN 2618-1584 Vol. 6, Issue 8: 61-67, DOI: 10.25236/FMSR.2024.060809

# Predictive impact of *EGFR* mutations and tumor mutational burden on immune checkpoint inhibitor efficacy in non-small cell lung cancer

**Yifei Yu[1], Xinan Wang[2]**

[1]*The High School Affiliated to Renmin University of China, Beijing, China*
[2]*Harvard University, Cambridge, Massachusetts, The United States*

***Abstract:*** *Although targeted therapy has improved the clinical prognosis of patients with non-small cell lung cancer (NSCLC) EGFR mutations, these patients eventually will develop resistance to TKIs. Immune checkpoint inhibitors (ICIs) could be the potential subsequent treatment option but there is a great heterogeneity in patients' response to ICIs, which triggers an urgent need for predictive biomarkers to select patients who respond well. Here we displayed the predictive capability of EGFR mutation and tumor mutational burden (TMB) in immunotherapy response prediction using a cohort of 247 patients with advanced NSCLC. The targeted next-generation sequencing panel was used to detect gene expression and mutations from formalin-fixed paraffin-embedded tumor tissue. Progression-free survival was analysed. Patients with EGFR mutations (versus EGFR wild type) demonstrated a worse response to ICIs in patients with advanced NSCLC. Among patients with EGFR mutation, TMB high (versus TMB low) didn't predict an improved response to ICIs whereas, in the EGFRwt group, TMB high showed a beneficial response to ICIs. Our study therefore suggested that EGFR mutations could be a biomarker to predict a poor response to ICIs in patients with NSCLC and TMB could not have predictive value of ICI response although some EGFR mutation subtypes may suggest improved response in patients with NSCLC EGFR mutations.*

***Keywords:*** *EGFR mutations, tumor mutational burden(TMB), immune checkpoint inhibitor(ICI), non-small cell lung cancer(NSCLC)*

## 1. Introduction

### *1.1 Overview and Heterogeneity of Lung Cancer*

Lung cancer is one of the malignant tumors with the highest incidence and mortality all over the world[1]. In 2020, there were an estimated 2.2 million new cases of lung cancer and 1.8 million deaths from lung cancer. Most of the patients showed symptoms only when they reached an advanced condition, resulting in a poor 5-year survival rate of only about 20%. NSCLC including squamous cell carcinoma, adenocarcinoma (LUAD), and others accounting for 85% of the total cases, with LUAD being the most dominant subtype[2] [3].

With the extensive development of gene detection technology, the heterogeneity of lung cancer has been widely studied at the molecular biological level. Over the past two decades, several tumor-driving gene mutations have been identified in NSCLC, including epidermal growth factor receptor (*EGFR*), *KRAS, ALK*,*ROS1*,*BRAF*, *MET*, *NTRK*, and *RET*[4]. Novel targeted therapies have been developed to target these oncogenic driver mutations and significantly extend the survival of patients with lung cancer.

*EGFR* mutation is one of the most common tumor-driver gene mutations in patients with LUAD, and it accounts for about 50% of lung cancer patients in Asian countries[5] whereas only 20% of the patients in Western populations. EGFR tyrosine kinase inhibitor (EGFR-TKI), developed for 3 generations so far, has significantly improved the median progression-free survival (PFS) and overall survival (OS) of *EGFR*-mutated advanced LUAD patients[6] and become the preferred clinical therapeutics for patients with *EGFR*-sensitive mutations[4]. Nevertheless, although around 85-90% of *EGFR* mutations occurring in exon 19 deletion and exon 21 L858R is suitable for the first/second generation EGFR-TKI drug therapy, about 60% of patients with *EGFR* sensitizing mutations have developed $EGFR^{T790M}$ mutation after EGFR-TKI treatment, resulting in EGFR-TKI drug resistance[7]. In addition to some patients with $EGFR^{T790M}$ mutation after drug resistance can receive the third-generation EGFR-TKI targeted therapy,

ISSN 2618-1584 Vol. 6, Issue 8: 61-67, DOI: 10.25236/FMSR.2024.060809

the standard treatment for most EGFR-TKI resistant patients is still chemotherapy and the efficacy is often limited, so there is an urgent need for developing new therapeutics to improve the clinical efficacy.

### *1.2 Immune Checkpoint Inhibitor and Biomarkers*

Immune checkpoint inhibitors, represented by antibodies targeting programmed cell death 1(PD-1) and programmed cell death ligand 1(PD-L1), significantly improved the survival of patients with advanced NSCLC[8], and opened a new era of clinical immunotherapy for lung cancer. Although clinical studies suggested that NSCLC patients with NSCLC *EGFR* mutations obtained limited benefit from immunotherapy[9], EGFR-TKI resistance patients may benefit from two immunosuppressants combination therapy[10] or immunotherapy combined with anti-vascular and chemotherapy agents[11],[12] which seems provide a new immunotherapy option for patients with *EGFR* mutations after TKI treatment failure, but multiple drug combination could also increase risks of toxicities as well. Considering the response to immunotherapy in patients with *EGFR* mutations varied greatly[13],[14], a wise approach could be identifying effective biomarkers to predict the response to ICI treatment and it could improve the sensitivity to ICI monotherapy .

Several factors were suggested to be potential for the prediction of ICI efficacy, including *EGFR* mutations, PD-L1 expression and TMB. Immunotherapy was shown to be more effective in patients with $EGFR^{G719X}$ mutations than in patients with other *EGFR* mutation subtypes. However, it still needed to be verified in large sample clinical trials[13]. Several studies have pointed out that patients with NSCLC high expression of PD-L1 and *EGFR* mutations benefited little from EGFR TKI, but respond well to ICI[15],[16],[17]. However, another study has suggested that patients with *EGFR* mutations respond to ICI, but this relationship was independent of PD-L1 expression. Therefore, PD-L1 expression may not uniformly predict the efficacy of ICI. TMB, representing the total number of somatic/acquired mutations per coding area of a tumor genome, was usually lower in *EGFRm* than *EGFRwt*[18], but increased TMB level in *EGFRm* NSCLC patients could indicate improved response to ICI treatment[19].

Considering the variable response to immunotherapy in patients with *EGFR* mutation and no confirmed indicators to predict ICI efficacy currently, there is an urgent need to identify biomarkers that can predict immunotherapy efficacy. In this study, we aim to explore the interactive associations between *EGFR* mutation/*EGFR* wild type and TMB among 247 patients with stage IV NSCLC who are treated with ICIs.

## 2. Methods

### *2.1 Study Population*

In total, 247 patients with stage IV NSCLC who were treated with PD-(L)1 inhibitors between 2014 and 2019 at MSK were included in this work. Patients who received chemotherapy concurrently with PD-(L)1 inhibitors were not included. PD-L1 expression levels were measured by PD-L1 IHC on tumor specimens and positive PD-L1 IHC staining of the tumor slides was indicated as TPS≥1%. TMB was measured by targeted next-generation sequencing panel MSK IMPACT, a 341–468 gene assay performed on formalin-fixed paraffin-embedded tumor tissue along with matched healthy specimens (blood) from each patient to detect somatic gene alterations.

cBioPortal for Cancer Genomics was used to perform the survival analysis. Briefly, we selected the Lung Adenocarcinoma (MSK Mind, Nature Cancer 2022) database for analysis. A total of 247 patients were classified as patients with *EGFR* mutations (*EGFRm*) and without *EGFR* mutations (*EGFRwt*) for survival analysis. For both *EGFRwt* and *EGFRm* groups, patients were further classified as TMB high , indicated as ≥10 mutations per Mb (mut/Mb) and TMB low (<10 mut/Mb) groups for the comparison of survival after the treatment of ICIs. The Lifelines package was used to compute progression-free survival (PFS) survival curves estimated using the Kaplan–Meier method and the Cox proportional hazard model was used to estimate hazard ratio (HR). All statistical tests were two-sided with a significance level of 2.5% for each tail.

ISSN 2618-1584 Vol. 6, Issue 8: 61-67, DOI: 10.25236/FMSR.2024.060809

## 3. Results

### *3.1 Characteristics of Patients*

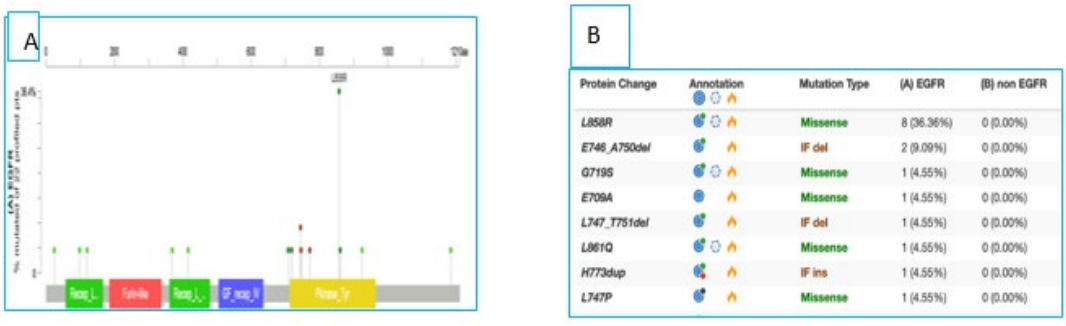
In this study, 247 advanced patients with NSCLC were treated with PD-(L)1 inhibitors monotherapy or PD-(L)1 plus CTLA-4 combination therapy. Among them, 54% of the patients were female with a median age of 68 years (range 38–93 years). A total of 218 (88%) patients had a history of smoking (median 30 pack-years, range 0.25–165). Histological subtypes of NSCLC included 195 (79%) adenocarcinomas, 37 (15%) squamous cell carcinomas, 7 (3%) large cell carcinomas and 8 (3%) NSCLC. Collectively, 169 (68%) patients received one or more lines of therapy before starting PD-(L)1 blockade, and 78 (32%) patients received PD-(L)1 blockade as first-line therapy, of which 14 (6%) received therapy in the context of a clinical trial[20] (**Table.1**).

*Table 1: Characteristics of Patients in This Study*

| Characteristics | | Patients (n=247) n (%) |
|---|---|---|
| Age | median | 68(38-93) |
| Sex | male | 113(46) |
| | female | 134(54) |
| Smoking status | Current/former | 218(88) |
| | Never | 29(12) |
| Line of therapy | 1 | 78(32) |
| | 2 | 136(55) |
| | ≥3 | 33(13) |
| Therapeutic type | Anti-PD-(L)1 monotherapy | 235(95) |
| | Anti-PD-(L)1 + CTLA-4 combination | 12(5) |

### *3.2 Characterization of EGFR Mutation and Subtypes*

Twenty-one patients harbored *EGFR* mutations, involving 16 driver mutations with all located from exons 18 to 21 and 7 variants of uncertain significance (VUS) located on exons 1, 3 (2 VUS), 9,11, 23, and 28 respectively. Among the 16 driver mutations, 12 were missense variants and 4 were inframe mutations. Seven VUS were all missense mutations. Except for driver mutations $EGFR^{L858R}$ (missense) and E746_A750del (in-frame del) were carried by 8 (36.36%) and 2 patients (9.09%) respectively, the other mutations were all carried by only one patient (4.55%) (**Figure1.A-B**).




| Description | Driver (n=16) | VUS*(n=7) |
|---|---|---|
| **Missense** | 12 | 7 |
| **Inframe** | 4 | 0 |
| **Location** | Exon 18-21 | Exons 1, 3, 9,11, 23 and 28 |

*Figure 1: EGFR mutations profiles (n=23) analysis*

ISSN 2618-1584 Vol. 6, Issue 8: 61-67, DOI: 10.25236/FMSR.2024.060809

### *3.3 Survival Analysis of EGFRm vs EGFRwt*

The survival analysis was performed between 21 patients with *EGFRm* and 225 patients with *EGFRwt*. The HR was 0.405 (95% CI: 0.204-0.801) indicating a significantly decreased PFS in *EGFRm* group with P-value of $4.861*10^{-5}$ (Figure 2).

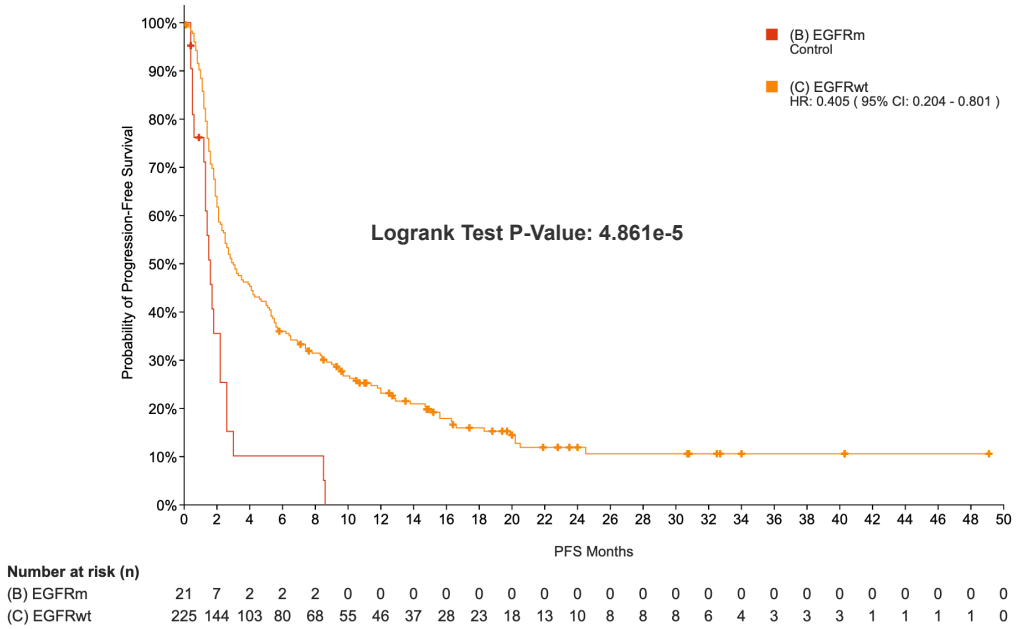



*Figure 2: PFS survival analysis of EGFRm and EGFRwt group*

### *3.4 TMB Distribution and Survival Analysis*

TMB was studied in 247 patients and the median was 7.9 mut/Mb with 133 cases less than or equal to 7.9 mut/Mb and 114 cases more than 7.9 mut/Mb. (**Figure3. A**).We first performed survival analysis in all 247 patients for TMB ≥10 mut/Mb (n=92) vs TMB < 10 (n=154). Patients with TMB ≥ 10 mut/Mb demonstrated a significantly increased survival rate compared to patients with TMB<10 mut/Mb, with an HR of 0.558 (95% CI: 0.425-0.732, P < 0.001)(**Figure3. B**).

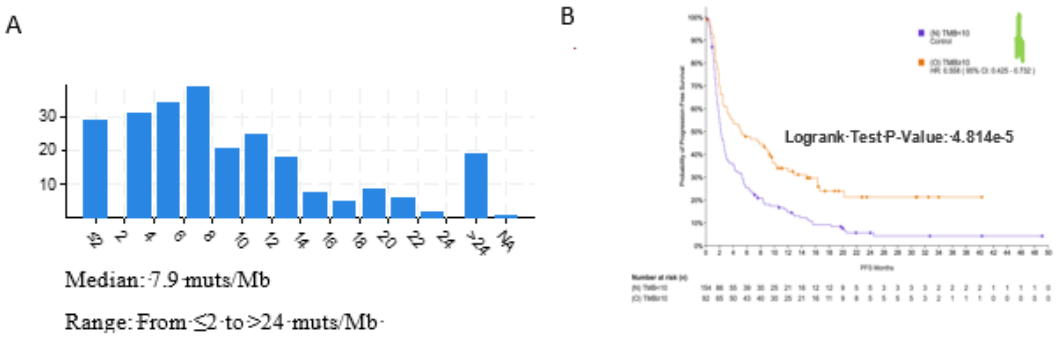



*Figure 3: TMB distribution and survival analysis of PFS based on TMB high and low in all patient group, EGFRm group and EGFRwt group. (A-B)*

Then survival analysis was similarly conducted in *EGFRwt* group for TMB high vs TMB low. Patients with TMB high demonstrated a significantly increased survival rate compared to patients with TMB low (HR=0.547,95%CI:0.411-0.728, P < 0.001) . Survival analysis was also carried out within *EGFRm* group (**Figure4. A** ). No significant differences were observed between the two groups regarding TMB level (P = 0.84). There were 6 and 15 patients in TMB high and TMB low groups respectively (**Figure4. B**).

ISSN 2618-1584 Vol. 6, Issue 8: 61-67, DOI: 10.25236/FMSR.2024.060809

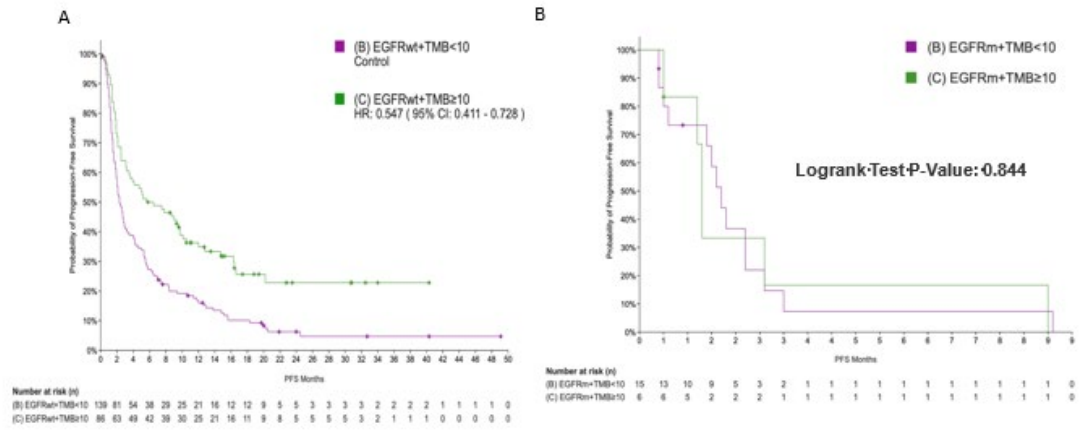



*Figure 4: TMB distribution and survival analysis of PFS based on TMB high and low in all patient group, EGFRm group and EGFRwt group.(A-B)*

## 4. Discussion

To date, two biomarkers have been approved by the FDA to inform treatment decisions of ICIs in patients with NSCLC, including PD-L1 expression(Borghaei, 2021) and TMB. However, PD-L1 expression has a low diagnostic accuracy with a response occurring in 6.5 to 10 percent of patients who do not express PD-L1[21],[22]. TMB, cut-off value is not absolute and may depend on different genomes and molecular techniques used[23],[24], etc. As a result, it is urgent to explore individual or combined biomarkers that better suggest response efficacy to ICIs with high diagnostic accuracy.

In this study, we first explored the predictive value of *EGFRm* for ICI response in 247 patients with NSCLC. A total of 235 (95%) patients have been treated by anti-PD-(L)1 monotherapy and 12 (5%) have accepted anti-PD-(L)1 plus CTLA-4 combination therapy (Table 1). Among them, 214 patients (87%) received ICI monotherapy as the first-line or second-line therapy whereas 33 (13%) patients received it as the third-line or beyond. The survival analysis of PFS was performed between 21 patients with *EGFRm* and 225 patients with *EGFRwt*. *EGFRm* patients demonstrated a significantly shortened PFS compared with patients with *EGFRwt* (P-value < 0.001), which suggested that *EGFRm* had a poor response to ICI. This result has echoed that of some previous studies. Lisberg, *et al* studied the therapeutic effect of pembrolizumab in TKI naïve patients with NSCLC EGFR mutation and PD-L1positive (≥1%, including 8 patients with PD-L1≥50%. In the study, enrollment ceased due to poor efficacy after 11 out of the planned 25 patients were treated. The result indicated that only one patient displayed an objective response, however, the repeated analysis of this patient's tumor confirmed that the previous positive *EGFR* mutation was incorrect[25]. Therefore, pembrolizumab monotherapy didn't bring benefit to TKI naïve patients with NSCLC *EGFR* mutation. A randomized phase 2 trial studied nivolumab and nivolumab plus ipilimumab in EGFR-TKI resistant NSCLC with the primary endpoint of objective response rate (ORR). This study allowed crossover if the disease progressed. Fifteen patients received nivolumab and 16 patients received nivolumab plus ipilimumab. Sixteen (16) patients (51.6%) expressed PD-L1 ≥ 1% and 15 (45.2%) carried *EGFR* T790M. Five patients obtained clinical benefits from ICI but only one objective response (objective response rate 3.2%), and the median PFS was 1.22 months (95% CI: 1.15–1.35) for the overall cohort. Four patients crossed over to nivolumab plus ipilimumab treatment, but none of them achieved salvage response by nivolumab plus ipilimumab[26]. This study indicated that the nivolumab monotherapy or nivolumab plus ipilimumab combination therapy didn't benefit more to advanced patients with NSCLC *EGFR* mutation.

In this study, among the total 247 patients with NSCLC, patients with TMB ≥ 10 (154) demonstrated a significantly increased survival rate vs patients with TMB<10 (92) (P-value $4.814*10^{-5}$). Similarly, patients with TMB ≥ 10 demonstrated a significantly increased survival rate vs patients with TMB<10 among 225 *EGFRwt* patients with NSCLC. Their result indicated that TMB high suggested a beneficial outcome from ICI treatment, which was supported by previous studies. The first study on the efficacy of TMB and NSCLC immunotherapy[23] was published in Science in 2015 and it found that patients with NSCLC with higher than median TMB had longer PFS. After that, many large-scale studies such as Check Mate-026 and Check Mate-227 have confirmed the predictive effect of TMB on the efficacy of immunotherapy for NSCLC. Although FDA has approved pembrolizumab monotherapy for the treatment

ISSN 2618-1584 Vol. 6, Issue 8: 61-67, DOI: 10.25236/FMSR.2024.060809

of patients with high TMB (defined as tissue TMB≥10 muts/Mb tested), there is no unified definition of the cut-off value for distinguishing high and low TMB and different studies have used different methods to determine the cut-off value. Some studies determined the TMB cut-off value through training practice the set[23],[27] and quantile method. Hence, there is still no standard cut-off value for TMB, which makes it incomparable for different studies and the unmet need for future tumor studies.

Compared with the predictive effect of TMB for high ICI response in NSCLC with *EGFRwt*, it is controversial for the predictive effect of TMB in patients with NSCLC *EGFR* mutations. In this study, we also investigated the predictive effect of TMB in *EGFR* mutation patients and we didn't see a significant difference in survival analysis between TMB high (n=6) and TMB low groups (n = 15 ) with a P-value of 0.84. Our results were supported by a phase 2 trial, which carried out nivolumab monotherapy and the combination therapy of nivolumab and ipilimumab in *EGFR*-mutant NSCLC. Among them, 15 received nivolumab, and 16 received of nivolumab and ipilimumab combination. To show the effect of TMB on response to immunotherapy, eight patients were identified as having target lesions that either revealed shrinkage or had a stable tumor size of 6 months or more and underwent tumor biopsy. TMB analyses of the responders and non-responders displayed similar changes regardless of tumor response to ICIs[26]. However, several studies did show some predictive trends of TMB in *EGFRm* NSCLC. A recent study investigated the impact of TMB on clinical outcomes of patients with NSCLC EGFR TKIs treatment. TMB was found to be remarkably lower in *EGFR*-mutated tumors (n =153) than *EGFR* wild-type tumors (n = 1,849) (median 3.77 versus 6.12 mut/Mb; $P < 0.0001$). Furthermore, TMB was also found to have varied expression in different *EGFR* mutations. Among the common sensitizing *EGFR* mutations, TMB was found to be lower in the exon 19 deletion cohort than in the L858R cohort[28]. A study has recently reported that clinical outcomes (OS and ORR) with PD-1 ICIs were worse in patients with exon 19 deletion than in patients carrying $EGFR^{L858R}$ *mutation*[13]. Further TMB analyses of the two patient cohorts suggested that the higher TMB in *EGFR* L858R mutation could contribute to the differential responses to PD-1 ICIs since PD-L1 expression and smoking status were similar in the two patient subpopulations. Reduced TMB may be the mechanism underlying the poor response to ICIs in patients with *EGFR* mutations. Nevertheless, different *EGFR* mutation subgroups could possess varied TMB, which could also influence their response to ICIs. Therefore, it is still not clear whether TMB could be used as a predictive biomarker for ICI efficacy in *EGFRm* NSCLC.

### *4.1 Limitations*

This study has the following limitations. First, given the low prevalence of *EGFRm* in the European population, we have a small sample size (n=21) of patients with *EGFRm* in this study, which limited the statistical power to compare TMB high and low within *EGFRm* group. Moreover, there is no standard cut-off value for TMB yet and we selected the cut-off value of 10 mut/Mb as FDA-approved in this study, which may not accurately reflect the patients who could respond well to ICIs.

### *4.2 Conclusions*

In this study, patients with *EGFR* mutations (versus *EGFRwt*) demonstrated a worse response to ICIs in patients with advanced NSCLC. Among patients with *EGFR* mutation, TMB high (versus TMB low) didn't predict an improved response to ICIs whereas, in the *EGFRwt* group, TMB high showed a beneficial response to ICIs although some *EGFR* mutation subtypes may suggest improved response.

## References

*[1] Hyuna S ,Jacques F ,L. R S , et al.Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries[J].CA: A Cancer Journal for Clinicians,2021,71(3):209-249.*

*[2] Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, Geisinger K, Hirsch FR, Ishikawa Y, Kerr KM, Noguchi M, Pelosi G, Powell CA, Tsao MS, Wistuba I; WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol. 2015 Sep;10(9):1243-1260.*

*[3] Schabath MB, Cote ML. Cancer Progress and Priorities: Lung Cancer. Cancer Epidemiol Biomarkers Prev. 2019 Oct;28(10):1563-1579.*

*[4] Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022 May;20(5):497-530.*

*[5] Shi Y, Au JS, Thongprasert S, Srinivasan S, et al. A prospective, molecular epidemiology study of*

ISSN 2618-1584 Vol. 6, Issue 8: 61-67, DOI: 10.25236/FMSR.2024.060809

*EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol. 2014 Feb;9(2):154-62.*
*[6] Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113-125.*
*[7] Yu HA, Arcila ME, Rekhtman N, Sima CS, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. 2013 Apr 15;19(8):2240-7.*
*[8] Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, et al. Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019 Oct 1;37(28):2518-2527.*
*[9] Lee CK, Man J, Lord S, et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol. 2017 Feb;12(2):403-407.*
*[10] Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017 Jan;18(1):31-41.*
*[11] Lu S, Wu L, Jian H, Chen Y, et al. Sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): first interim results from a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2022 Sep;23(9):1167-1179.*
*[12] Nogami N, Barlesi F, Socinski MA, et al. IMpower150 Final Exploratory Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC Patient Subgroups With EGFR Mutations or Metastases in the Liver or Brain. J Thorac Oncol. 2022 Feb;17(2):309-323.*
*[13] Hastings K, Yu HA, Wei W, et al. EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small-cell lung cancer. Ann Oncol. 2019 Aug 1;30(8):1311-1320.*
*[14] Wiest N, Majeed U, Seegobin K, Zhao Y, et al. Role of Immune Checkpoint Inhibitor Therapy in Advanced EGFR-Mutant Non-Small Cell Lung Cancer. Front Oncol. 2021 Nov 16;11:751209.*
*[15] Chen K, Cheng G, Zhang F, et al. PD-L1 expression and T cells infiltration in patients with uncommon EGFR-mutant non-small cell lung cancer and the response to immunotherapy. Lung Cancer. 2020 Apr;142:98-105.*
*[16] Haratani K, Hayashi H, Tanaka T, et al. Tumor immune microenvironment and nivolumab efficacy in EGFR mutation-positive non-small-cell lung cancer based on T790M status after disease progression during EGFR-TKI treatment. Ann Oncol. 2017 Jul 1;28(7):1532-1539.*
*[17] Yoneshima Y, Ijichi K, Anai S, et al. PD-L1 expression in lung adenocarcinoma harboring EGFR mutations or ALK rearrangements. Lung Cancer. 2018 Apr;118:36-40.*
*[18] Le X, Negrao MV, Reuben A, Federico L, et al. Characterization of the Immune Landscape of EGFR-Mutant NSCLC Identifies CD73/Adenosine Pathway as a Potential Therapeutic Target. J Thorac Oncol. 2021 Apr;16(4):583-600.*
*[19] Lin C, Shi X, Zhao J, et al. Tumor Mutation Burden Correlates With Efficacy of Chemotherapy/Targeted Therapy in Advanced Non-Small Cell Lung Cancer. Front Oncol. 2020 Apr 29;10:480.*
*[20] Vanguri RS, Luo J, Aukerman AT, et al. Multimodal integration of radiology, pathology and genomics for prediction of response to PD-(L)1 blockade in patients with non-small cell lung cancer. Nat Cancer. 2022 Oct;3(10):1151-1164.*
*[21] Brahmer J, Reckamp KL, Baas P, Crinò L, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Jul 9;373(2):123-35.*
*[22] Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016 Apr 9;387(10027):1540-1550.*
*[23] Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015 Apr 3;348(6230):124-8.*
*[24] Yarchoan M, Albacker LA, Hopkins AC, et al. PD-L1 expression and tumor mutational burden are independent biomarkers in most cancers. JCI Insight. 2019 Mar 21;4(6):e126908.*
*[25] Lisberg A, Cummings A, Goldman JW, et al. A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC. J Thorac Oncol. 2018 Aug;13(8):1138-1145.*
*[26] Lai GGY, Yeo JC, Jain A, et al. A Randomized Phase 2 Trial of Nivolumab Versus Nivolumab-Ipilimumab Combination in EGFR-Mutant NSCLC. JTO Clin Res Rep. 2022 Sep 21;3(12):100416.*
*[27] Ready N, Hellmann MD, Awad MM, et al. First-Line Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers. J Clin Oncol. 2019 Apr 20;37(12):992-1000.*
*[28] Offin M, Rizvi H, Tenet M, et al. Tumor Mutation Burden and Efficacy of EGFR-Tyrosine Kinase Inhibitors in Patients with EGFR-Mutant Lung Cancers. Clin Cancer Res. 2019 Feb 1;25(3):1063-1069.*