Title

CheckMate-722: The Rise and Fall of Nivolumab with Chemotherapy in TKI-Refractory EGFR-Mutant NSCLC.

Authors

Lee, Alexandria
Nagasaka, Misako

Publication Date

2023

DOI

10.2147/LCTT.S408886

Peer reviewed

Lung Cancer: Targets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

COMMENTARY

CheckMate-722: The Rise and Fall of Nivolumab with Chemotherapy in TKI-Refractory EGFR-Mutant NSCLC

Alexandria TM Lee[1], Misako Nagasaka[1,2]

[1]University of California Irvine School of Medicine, Department of Medicine, Orange, CA, 92868, USA; [2]St. Marianna University School of Medicine, Department of Medicine, Kawasaki, Japan

Correspondence: Misako Nagasaka, Department of Medicine, University of California Irvine School of Medicine, 200 South Manchester, Suite 400, Orange, CA, 92868, USA, Email nagasakm@hs.uci.edu

Abstract: The treatment of non-small cell lung cancer (NSCLC) has increasingly been driven by the presence of targetable driver mutations, including epidermal growth factor receptor (EGFR) mutations. Tyrosine receptor inhibitors (TKIs) have subsequently emerged as the standard-of-care treatment for EGFR-mutant NSCLC. However, there are currently limited treatment options for TKI-refractory EGFR-mutant NSCLC. It is in this context that immunotherapy has arisen as a particularly promising player, especially in the context of favorable results from the ORIENT-31 and IMpower150 trials. Thus, the results of the CheckMate-722 trial were highly anticipated, as it was the first global trial to evaluate the efficacy of immunotherapy in addition to standard platinum-based chemotherapy, specifically in the treatment of EGFR-mutant NSCLC post-progression on TKIs.

Keywords: immunotherapy, epidermal growth factor receptor mutation, osimertinib refractory

Introduction

The ability to classify lung cancers molecularly has been extremely consequential for the management of non-small cell lung cancer (NSCLC). Evolving knowledge about targetable driver mutations in NSCLC has paved the way for the development of targeted therapies, which counteract known cancer-causing mutations. We have currently targeted therapies for nine genes in NSCLC, including alterations in KRAS G12C, EGFR, ALK, ROS1, BRAF, RET, MET, HER2, and NTRK. Perhaps, the most notable driver mutations in NSCLC occur in EGFR, which is harbored in 40–60% of NSCLC cases in South Asian patients, and 10–20% of adenocarcinoma cases in Caucasian patients.[1] EGFR mutation testing is recommended in patients with NSCLC upon initial diagnosis per National Comprehensive Cancer Network guidelines.[2]

Epidermal growth factor receptor (EGFR) mutations occur in several locations along exons 18 through 21. The most commonly encountered mutations, found in about 85% of patient samples, are an in-frame deletion of exon 19 and an L858R point mutation in exon 21.[3] Importantly, these and several other EGFR mutations are sensitive to EGFR tyrosine kinase inhibitors (TKIs), which inhibit the phosphorylation of EGFR, thus halting tumor growth. EGFR TKIs have since become the standard of care (SOC) for treating NSCLC harboring sensitizing EGFR mutations.

The Post TKI Problem

Unfortunately, in spite of excellent initial response with targeted therapies, these treatments have not been found to eradicate disease, and almost all patients with EGFR-mutant NSCLC treated with TKIs eventually develop resistance to treatment. Drug resistance had given rise to the advent of third-generation TKIs, developed in attempts to address the most common mutation conferring resistance to first- or second-generation TKIs, the T790M mutation. In this setting,

Received: 16 February 2023
Accepted: 15 April 2023
Published: 25 April 2023

osimertinib emerged as the SOC treatment for EGFR T790M+ NSCLC after progression on first- or second-generation TKIs, gaining its initial approval in this setting.

Subsequently, the FLAURA trial showed both progression-free survival (PFS) and overall survival (OS) benefit with the use of upfront osimertinib in EGFR-mutant NSCLC when compared to first-generation EGFR TKIs. Osimertinib is now considered the first-line option for advanced metastatic EGFR-mutant NSCLC in many parts of the world.[4,5]

However, there are currently no effective TKI treatments approved for cases of EGFR-mutant NSCLC refractory to third-generation TKIs, which are now mainly used upfront. In this setting, platinum-based doublet chemotherapy has remained the mainstay of treatment, prompting the question of whether other modes of therapy may be of benefit.

Immunotherapy, a Solution to the TKI Problem?

Immunotherapy has become particularly important in the treatment of NSCLC and has been shown to improve survival. Immune checkpoint inhibitors (ICIs), monoclonal antibodies targeting programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1), have demonstrated promise in the treatment of advanced NSCLC over chemotherapy, according to Phase 3 trials. In the KEYNOTE-024 trial, it was shown that patients with advanced NSCLC and tumor cell PD-L1 expression of at least 50% had significant PFS and OS benefit when treated with pembrolizumab compared to platinum-based chemotherapy. Similarly, in the KEYNOTE-042 trial, patients with advanced NSCLC and tumor cell PD-L1 expression of greater than 1% had significant OS benefit when treated with pembrolizumab monotherapy compared to chemotherapy.[6–9]

However, subgroup analyses from multiple studies have demonstrated the limited efficacy of immunotherapy as a single agent in EGFR-mutant NSCLC. In the CheckMate-057 trial, subgroup analyses did not show PFS or OS benefit in patients with EGFR mutations. Similarly, the KEYNOTE-010 and OAK phase 3 trials did not show that patients with NSCLC harboring EGFR mutations had OS benefit from immunotherapy over chemotherapy.[10]

Given the limited efficacy of immunotherapy in EGFR-mutant NSCLC as a single agent, and as the standard of care has shifted to include immunotherapy in combination with chemotherapy in the first-line setting, the question of whether the combination of immunotherapy and standard platinum chemotherapy is of any benefit in the treatment of EGFR-mutant NSCLC post TKI treatment failure has emerged.[11–14]

Indeed, results from studies evaluating chemotherapy and immunotherapy in combination with anti-angiogenic agents were also promising. The IMpower150 trial, in which patients were randomized to atezolizumab plus carboplatin/paclitaxel (ACP), to bevacizumab plus carboplatin/paclitaxel (BCP), or to atezolizumab plus BCP (ABCP), found that the addition of atezolizumab to chemotherapy and bevacizumab conferred significant PFS and OS benefit in patients with NSCLC, regardless of PD-L1 expression or genetic mutation status.[13] However, it is important to note that positive results in patients with EGFR mutations were seen in an unplanned subgroup analysis. Similarly, positive results were reported preliminarily in the ORIENT-31 phase 3 trial, in which patients with EGFR-mutant NSCLC who had progressed on TKI therapy were randomized to sintilimab, an investigational PD1 inhibitor (which has gained certain approvals in China) with IBI305 (bevacizumab biosimilar) plus chemotherapy, to sintilimab plus chemotherapy, or to chemotherapy alone. Initial results have shown that patients with EGFR-mutant NSCLC who had progressed on TKIs experienced significant PFS benefit with the addition of sintilimab and IBI305 compared to chemotherapy alone.[15] Importantly, ORIENT-31 was conducted in China alone, which gave rise to even more anticipation surrounding the results of a global phase 3 trial dedicated to EGFR-mutant NSCLC.

The Highly Anticipated Results of CheckMate-722

In this landscape, characterized by promising findings from the IMpower150 and ORIENT-31 trials, the results from the CheckMate-722 trial were eagerly awaited, as it was the first randomized global phase 3 trial to evaluate the utility of immunotherapy in addition to standard platinum-based chemotherapy specifically in patients with EGFR-mutant NSCLC. CheckMate-722 was a phase 3 randomized control trial that enrolled 294 patients from 109 investigational sites worldwide who had recurrent EGFR-mutant metastatic NSCLC with progressive disease after first-line treatment with first or second-generation TKI without T790M mutations or with progressive disease after first or second-line treatment with osimertinib regardless of T790M mutation status. Patients were then stratified by tumor PD-L1 expression, brain

metastases, smoking history, and prior osimertinib use. The primary endpoint was PFS by blind independent central review (BICR). Secondary endpoints included 9 month and 12 month PFS rates, overall survival, objective response rate, and duration of response. Patients were randomized 1:1 to nivolumab (360 mg) + platinum-based doublet chemotherapy (4 cycles Q3W) or platinum-based doublet chemotherapy alone.[16]

Results from the CheckMate-722 trial were presented at ESMO Asia in December, 2022. Median follow-up was 38.1 months. In all enrolled patients, median PFS by BICR was 5.6 months in the nivolumab and chemotherapy group compared to 5.4 months in the chemotherapy alone group. These findings were not statistically-significant, with a hazard ratio (HR) of 0.75 (95% CI 0.56–1.00). In patients with sensitizing EGFR mutations, median PFS by BICR was 5.6 months in the nivolumab + chemotherapy group and 5.4 months in the chemotherapy alone group, marginally favoring nivolumab + chemotherapy with an HR of 0.72 (95% CI 0.54–0.97). In patients who had received one prior EGFR TKI, median PFS by BICR was 5.6 months in the nivolumab and chemotherapy group and 5.4 months in the chemotherapy alone group, again marginally favoring nivolumab + chemotherapy with an HR of 0.73 (95% CI 0.54–0.97). Further subgroup analysis on patients with PD-L1 expression did not yield significant findings. In patients with tumor PD-L1 <1%, median PFS by BICR was 5.6 months in the nivolumab and chemotherapy group and 5.6 months in the chemotherapy alone group. HR was 0.91 (95% CI 0.58–1.44). In patients with tumor PD-L1 >1%, median PFS by BICR was 5.6 months in the nivolumab and chemotherapy group and 5.3 months in the chemotherapy alone group. HR was 0.76 (95% CI 0.52–1.11). These results were further stratified by PD-L1 expression. In patients with tumor PD-L1 1–49%, the median PFS by BICR was 5.5 months in the nivolumab and chemotherapy group and 4.4 months in the chemotherapy alone group. These results were again not found to be significant, with an HR of 0.88 (95% CI 0.52–1.51). Similarly, in patients with tumor PD-L1 >50%, the median PFS was 6.8 months in the nivolumab and chemotherapy group and 5.6 months in the chemotherapy alone group. The HR was 0.65 (95% CI 0.36–1.15). Finally, overall survival in all randomized patients was 19.4 months in the nivolumab and chemotherapy group compared to 15.9 months in the chemotherapy alone group. These findings were not statistically significant, with an HR of 0.82 (95% CI 0.61–1.10).[16]

Importantly, CheckMate-722 was statistically underpowered to effectively differentiate between treatment arms. Initial plans to study 500 patients would have provided investigators with 90% power to detect an HR of 0.735. However, due to a reduction in sample size in the setting of the COVID-19 pandemic, the resulting sample size of 270 left investigators with 83% power to detect a far stricter HR of 0.692 at an alpha level of 0.05. Final analysis of PFS was then to be completed after 233 PFS events or after 6 months of follow-up. Primary database lock met criteria of minimum 6 months of follow-up, and at the time of final analysis, 212 PFS events had occurred in 294 patients. The lower than planned number of events even further decreased the study's statistical power to 76%, ultimately rendering it difficult to detect differences in treatment benefit between the two arms. Nonetheless, the highly anticipated results of CheckMate-722 did not provide us with the trailblazing results we had hoped for, and treatment options for use in patients with EGFR-mutant NSCLC with or without T790M mutations who have failed prior lines of TKI treatment remain limited.

Discussion

The results of the CheckMate-722 trial prompted us to re-examine the positive results seen in the IMpower150 and ORIENT-31 trials and explore the reasons for the discordance we see between the results of those trials and those of CheckMate-722. To answer this question, we must consider the interplay between EGFR mutation status, the tumor microenvironment, PD-L1 expression in tumor tissue, the impact of TKI exposure on immunogenicity, response to treatment with ICIs, and synergy with VEGF inhibition.

The relationship between PD-L1 expression in lung tumors and response to anti-PD-1 and anti-PD-L1 ICIs has also been researched extensively with exceedingly controversial results in those with mutant EGFR. Several studies have reported higher PD-L1 expression in EGFR-mutant lung tumors when compared to EGFR wildtype tumors.[17–20] Others have found that PD-L1 is expressed less frequently on patients with EGFR-mutant NSCLC. Further studies have failed to definitively confirm correlation between EGFR and PD-L1 expression.[21–23] Interestingly, patients with varying EGFR mutation subtypes have been shown to have varied responses to anti-PD-1 and anti-PD-L1 ICIs. In a multicenter retrospective study delineating EGFR-mutant tumor response to ICI therapy (anti-PD1/L1 agents with or without

CTLA4 blockade), it was shown that patients with EGFR alterations in exon 19 or with L858R mutations conferred less benefit than the EGFR wildtype group.[17]

Tumor mutational burden (TMB) has also been studied for its correlation with NSCLC outcomes. TMB has been found to be lower in EGFR-mutant tumors than in EGFR wildtype tumors. In addition, TMB in patients with EGFR exon 19 deletions has been reported to be lower than in patients with L858R mutations.[24] A retrospective study has also demonstrated that patients with L858R mutations have better responses to ICI therapy when compared to patients with exon 19 deletions, further pointing to the possibility that TMB is related to ICI response.[17] In another retrospective study evaluating driver-mutant NSCLC patients treated with ICI monotherapy, it was shown that EGFR mutation subgroup status was the most strongly related factor in response to therapy. In particular, more favorable outcomes were seen in patients with L858R mutations compared to those with T790M mutations, exon 19 deletions, and others. Importantly, outcomes were not significantly impacted by PD-L1 expression status, smoking status, or previous lines of treatment.[25]

Tumors are complex creatures, known to be comprised of both malignant and normal host cells. The tumor microenvironment (TME) consists of this population of cells, cytokines, chemokines, and growth factors mediating their interactions, and other secreted factors. Tumors can be classified as one of four TME types, based on the presence or absence of tumor-infiltrating lymphocytes (TIL) and PD-L1 expression. Interestingly, tumors that are both TIL+ and PD-L1+ are the only TME subtype that has demonstrated response to ICIs.[26] Furthermore, tumors harboring EGFR mutations have also been shown to be "cold" tumors, with a relatively uninflamed TME. This has been attributed to EGFR signaling, which allows for the creation of an immunosuppressive TME.[27] Consequently, EGFR-mutant NSCLC tends to be associated with immunological tolerance and weak immunogenicity, which may explain the poor response to ICI monotherapy demonstrated by patients with EGFR-mutant NSCLC.[28]

Importantly, treatment with TKIs and the development of resistance may also drive changes in the TME that confer poor response to immunotherapy. During treatment with TKIs, cytotoxic immune cells proliferate, while immunosuppressive cells are inhibited, leading to the formation of an inflammatory TME. However, with long term TKI use and the subsequent acquisition of resistance, this effect is reversed. Tumor cells are able to escape host immune defenses, and immunosuppressive cells become more active, allowing for tumor progression. The uninflamed TME inherent to EGFR-mutant NSCLC, in conjunction with the immunosuppressive environment created as TKI resistance develops, may then explain the poor response to ICIs seen in TKI-resistant EGFR-mutant NSCLC.[29]

The immunosuppressive TME associated with EGFR-mutant NSCLC and its implications for response to immunotherapy may suggest the possibility of clinical benefit from immunotherapy used in combination with treatment modalities with immunomodulatory effects, like those targeting vascular endothelial growth factors (VEGFs). VEGFs are known to mediate the proliferation of tumor microvasculature, allowing for tumor growth and spread. Importantly, VEGFs also function as immunomodulators of the TME, and possess the ability to suppress antigen presentation, stimulate regulatory T cells, and more.[30] Thus, treatments targeting VEGF and VEGF receptors (VEGFRs) may curb the creation of an immunosuppressive TME and could represent a therapy that may be useful when used synergistically with immunotherapy in the treatment of EGFR-mutant NSCLC.

Promising results from the RELAY trial suggest that combination treatment with therapies targeting VEGF pathways may be effective. In this phase 3 randomized control trial, investigators enrolled 449 patients with metastatic EGFR-mutant NSCLC and randomized patients receive oral erlotinib, a TKI, or oral erlotinib and intravenous ramucirumab, a human IgG1 VEGFR2 antagonist. Results showed that the addition of ramucirumab to erlotinib conferred significant PFS benefit in patients with EGFR-mutant metastatic NSCLC.[31]

Moreover, the idea that therapies targeting VEGF pathways may work synergistically with immunotherapy may explain the positive results seen in the IMpower150 and ORIENT-31 trials, in which significant benefit was observed in both groups treated with immunotherapy, chemotherapy, and a VEGF-targeted agent, when compared to groups treated with chemotherapy and immunotherapy only. This may then elucidate the lack of expected benefit seen in the CheckMate-722 trial and suggests that the addition of a VEGF-targeted agent may have altered the TME such that greater benefit may have been seen in the immunotherapy and chemotherapy group when compared to the chemotherapy alone group.

Conclusion

The treatment of TKI-refractory EGFR-mutant NSCLC is tremendously nuanced, as demonstrated by the disappointing results of the CheckMate-722 trial. While it is possible that the reduced statistical power due to the enrollment challenges of CheckMate-722 limit the conclusion of the study and there could still be a subgroup that may benefit from the CheckMate-722 approach, this remains a theoretical interrogation as the study as a whole was statistically underpowered. Treatment efficacy is shaped by TMB, TME, PD-L1 expression, and prior treatments, necessitating that we consider the molecular mechanisms underlying these interactions as we pursue new treatment modalities and regimens. Importantly, the difference seen between the results of the CheckMate-722 trial and the more favorable results from the IMpower 150 and ORIENT-31 trials may suggest that the addition of VEGF-targeted therapies to immunotherapy in the treatment of TKI-refractory EGFR-mutant NSCLC is necessary in order to combat the immunosuppressive effects of prior TKI therapy, as well as the immunosuppressive TME inherent to NSCLC harboring EGFR mutations.

That being said, one must always be cautious on the use of immunotherapy in the treatment of patients with EGFR-mutant NSCLC. A number of fourth-generation EGFR TKIs are currently being evaluated through clinical trials. While the actual risk is uncertain, it is certainly possible that exposure to immunotherapy prior to 4th-generation EGFR TKIs may put one at an increased risk of immune-related adverse events, just as was the case with 3rd-generation EGFR TKIs. At this time, we would prefer to await positive results and tolerable safety profiles demonstrated in a carefully planned and thoughtfully executed global phase 3 study evaluating the synergy of chemoimmunotherapy with VEGF inhibitors in EGFR-mutant NSCLC, to bring this regimen forth in this setting. In addition to the 4th-generation EGFR TKIs, clinical trials evaluating new treatment options for advanced EGFR-mutant NSCLC post progression on osimertinib are ongoing, and these include the HER3 antibody drug conjugate patritumab deruxtecan as well as amivantamab, an EGFR cMET bispecific antibody in combination with lazertinib, a 3rd-generation EGFR TKI. Ultimately, the sequencing question may be in the context of these novel treatment options.

Disclosure

Dr Misako Nagasaka reports personal fees from AstraZeneca, Daiichi Sankyo, Novartis, EMD Serono, Pfizer, Lilly, Genentech, Mirati, Caris Life Sciences, Takeda, Janssen, Blueprint Medicine, personal fees and non-financial support from AnHeart Therapeutics, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Hsu WH, Yang JC, Mok TS, Loong HH. Overview of current systemic management of EGFR-mutant NSCLC. *Ann Oncol*. 2018;29(suppl_1):i3–i9. doi:10.1093/annonc/mdx702
2. National Comprehensive Cancer Network. Non-small cell lung cancer (version 6.2021). Available from: https://www.nccn.org/guidelines/guidelines-process/transparency-process-and-recommendations/GetFileFromFileManagerGuid?FileManagerGuidId=b53b73e4-9354-4bd0-995b-f1089574d01b. Accessed January 10, 2022.
3. Vaclova T, Grazini U, Ward L, et al. Clinical impact of subclonal EGFR T790M mutations in advanced-stage EGFR-mutant non-small-cell lung cancers. *Nat Commun*. 2021;12(1):1780. doi:10.1038/s41467-021-22057-8
4. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378(2):113–125. doi:10.1056/NEJMoa1713137
5. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41–50. doi:10.1056/NEJMoa1913662
6. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123–135. doi:10.1056/NEJMoa1504627
7. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627–1639. doi:10.1056/NEJMoa1507643
8. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823–1833. doi:10.1056/NEJMoa1606774
9. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819–1830. doi:10.1016/S0140-6736(18)32409-7
10. Lee CK, Man J, Lord S, et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4(2):210–216. doi:10.1001/jamaoncol.2017.4427
11. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078–2092. doi:10.1056/NEJMoa1801005

12. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040–2051. doi:10.1056/NEJMoa1810865Impower150
13. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288–2301. doi:10.1056/NEJMoa1716948
14. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):198–211. doi:10.1016/S1470-2045(20)30641-0
15. Lu S, Wu L, Jian H, 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;23(9):1167–1179. doi:10.1016/S1470-2045(22)00382-5
16. Mok T, Nakagawa K, Park K, et al. Nivolumab + chemotherapy versus chemotherapy in patients with EGFR-mutated metastatic non-small cell lung cancer with disease progression after EGFR tyrosine kinase inhibitors in CheckMate 722. Oral presentation at: ESMO Asia; Singapore; 2022.
17. 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;30(8):1311–1320. doi:10.1093/annonc/mdz141
18. Kojima K, Sakamoto T, Kasai T, Kagawa T, Yoon H, Atagi S. PD-L1 expression as a predictor of postoperative recurrence and the association between the PD-L1 expression and EGFR mutations in NSCLC. *Sci Rep*. 2021;11(1):17522. doi:10.1038/s41598-021-96938-9
19. Tang Y, Fang W, Zhang Y, et al. The association between PD-L1 and EGFR status and the prognostic value of PD-L1 in advanced non-small cell lung cancer patients treated with EGFR-TKIs. *Oncotarget*. 2015;6(16):14209–14219. doi:10.18632/oncotarget.3694
20. Azuma K, Ota K, Kawahara A, et al. Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer. *Ann Oncol*. 2014;25(10):1935–1940. doi:10.1093/annonc/mdu242
21. Ji M, Liu Y, Li Q, et al. PD-1/PD-L1 expression in non-small-cell lung cancer and its correlation with EGFR/KRAS mutations. *Cancer Biol Ther*. 2016;17(4):407–413. doi:10.1080/15384047.2016.1156256
22. Dong ZY, Zhang JT, Liu SY, et al. EGFR mutation correlates with uninflamed phenotype and weak immunogenicity, causing impaired response to PD-1 blockade in non-small cell lung cancer. *Oncoimmunology*. 2017;6(11):e1356145. doi:10.1080/2162402X.2017.1356145
23. Koh J, Go H, Keam B, et al. Clinicopathologic analysis of programmed cell death-1 and programmed cell death-ligand 1 and 2 expressions in pulmonary adenocarcinoma: comparison with histology and driver oncogenic alteration status. *Mod Pathol*. 2015;28(9):1154–1166. doi:10.1038/modpathol.2015.63
24. 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;25(3):1063–1069. doi:10.1158/1078-0432.CCR-18-1102
25. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol*. 2019;30(8):1321–1328. doi:10.1093/annonc/mdz167
26. Teng MW, Ngiow SF, Ribas A, Smyth MJ. Classifying cancers based on T-cell infiltration and PD-L1. *Cancer Res*. 2015;75(11):2139–2145. doi:10.1158/0008-5472.CAN-15-0255
27. Madeddu C, Donisi C, Liscia N, Lai E, Scartozzi M, Macciò A. EGFR-mutated non-small cell lung cancer and resistance to immunotherapy: role of the tumor microenvironment. *Int J Mol Sci*. 2022;23(12):6489. doi:10.3390/ijms23126489
28. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature*. 2017;541(7637):321–330. doi:10.1038/nature21349
29. Jiang L, Liu J. Immunological effect of tyrosine kinase inhibitors on the tumor immune environment in non-small cell lung cancer. *Oncol Lett*. 2022;23(5):165. doi:10.3892/ol.2022.13285
30. Zhao Y, Guo S, Deng J, et al. VEGF/VEGFR-targeted therapy and immunotherapy in non-small cell lung cancer: targeting the tumor microenvironment. *Int J Biol Sci*. 2022;18(9):3845–3858. doi:10.7150/ijbs.70958
31. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(12):1655–1669. doi:10.1016/S1470-2045(19)30634-5