# Medicine®

# The association of efficacy with PD-1/PD-L1 inhibition and tumor mutational burden in advanced nonsmall cell lung cancer
## A PRISMA-guided literature review and meta-analysis

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**Abstract**

**Background:** Tumor mutation burden (TMB) has been reported to emerge as an independent biomarker of response to identify patients who would achieve benefit from immune checkpoint inhibitors. However, it still remains controversy that whether TMB can be a robust biomarker of response to programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibition. We performed this meta-analysis to assess the relationship between TMB and the efficacy with PD-1/PD-L1 inhibition in advanced nonsmall cell lung cancer (NSCLC).

**Methods:** Following the recommendations of the PRISMA statement, electronic databases literature search was done on the published articles till March 2021, including Pubmed, Embase, and Cochrane library databases. Studies were selected that focused on comparing the efficacy of TMB-high group and TMB-low group in NSCLC patients received with immune checkpoint inhibitors. Meta-analysis Revman 5.3 software was utilized to calculate the pooled outcomes.

**Results:** A systematic literature search was conducted 8 articles, including 11 comparative articles. Findings of our studies shown that patients with TMB-high group was associated with better clinical outcomes than TMB-low group, including progression-free survival (odds ratio [OR], 0.38; 95% confidence interval [CI], 0.29–0.49; $P < .00001$), complete response (OR, 4.71; 95% CI, 2.32–9.57; $P < .0001$), durable clinical benefit (OR, 3.76; 95% CI, 2.38–5.96; $P < .00001$) and the objective response rate (OR, 3.14; 95% CI, 1.83–5.37; $P < .0001$). While, it failed to predict overall survival benefits (OR, 0.74; 95% CI, 0.45–1.20; $P = .22$).

**Conclusions:** Our study found that NSCLC with high TMB who benefit from immunotherapy. The findings suggest that TMB could associated with a greater predictive power of response. Possibly a more TMB-oriented prediction model might gain more benefits from PD-1/PD-L1 inhibitors.

**Abbreviations:** CI = confidence interval, CR = complete response, DCB = durable clinical benefit, ICIs = immune checkpoint inhibitors, NSCLC = nonsmall cell lung cancer, OR = odds ratio, ORR = objective response rate, OS = overall survival, PD-1 = programmed death-1, PD-L1 = programmed death-ligand 1, PFS = progression-free survival, TMB = tumor mutation burden.

**Keywords:** efficacy, immune checkpoint inhibitors, meta-analysis, prognoses, tumor mutation burden

## 1. Introduction

The advent of immune checkpoint inhibitors (ICI) has revolutionized the treatment for a multitude of malignancies, including nonsmall cell lung cancer (NSCLC).[1–3] Nevertheless, a plenty of NSCLC patients experience primary resistance, and just a small subset of patients demonstrated remarkable clinical activity.[4] This experience highlights identification of predictive biomarkers to identify patients who achieve a greater clinical benefit from this treatment approach.

Tumor expression of programmed death-ligand 1 and DNA mismatch repair deficiency/microsatellite instability-high cancer have been accepted as the predictive biomarker for immunotherapy.[3,5] While, none of these biomarkers can fully defined as the determinants of response to ICIs,[6] which has prompted the search for more sensitivity and specificity predictive tools.

Tumor mutation burden (TMB) has been reported to be with a promising predict value in prediction of ICIs therapy in NSCLC.[7,8] Several studies have reported that patients with high TMB achieve better clinical outcomes, suggesting TMB is an emerging predictive biomarker for immunotherapies in NSCLC.[9,10] However, similar to existing biomarker, TMB is not perfectly associated with immunotherapy response. According to the findings of retrospective analyses, patients with high TMB are prone to derive a poor survival, resulting in a conflict.[11,12]

The contradictory results have attracted clinicians' attention, and whether TMB can be primed to respond to immunotherapy as a predictive biomarker to distinguish responders and nonresponders of ICIs therapy remains to be explored.

Therefore, it is necessary to conduct a systematic review with meta-analysis to provide more powerful evidence to confirm the association between TMB and the efficacy with ICIs therapy in advanced NSCLC.

## 2. Materials and Methods

### 2.1. Search strategy

This meta-analysis was based on the Cochrane Manual of Intervention System Assessments and systematic review and meta-analysis guidelines. Since the meta-analysis is base on the existing data, the ethical approval was not necessary.

Two reviewers independently conducted a systematic search through the Pubmed, EMBASE and Cochrane Database of Systematic Reviews up to March, 2021. The MeSH terms and free key words were "immune checkpoint inhibitors", "tumor mutation burden", "efficacy", "prognoses". The reference lists also hand-searched to identify any potentially relevant publications.

### 2.2. Inclusion criteria

Articles were included should relate to the following criteria: articles that enrolled NSCLC who treated with immunotherapy; trails focused on the efficacy of high TMB group compared with low TMB group; the outcomes of interest were tumor responses (complete response [CR], objective response rate [ORR], durable clinical benefit [DCB]) and survival outcomes (overall survival [OS], progression-free survival [PFS]); and the full-text with the latest data.

### 2.3. Risk-of-bias assessments

Two authors separately assess the risk of bias based on Cochrane handbook version 5.1.0 for Systematic Reviews by Cochrane Collaboration. Newcastle–Ottawa Quality Assessment Scale was used to assess the quality of the included studies.

### 2.4. Data selection and extraction

Two researchers separately extract data including first author, year of publication, treatment measures, immune checkpoint inhibitor, stage, the cutoff value of TMB No. of patients, median age, and outcomes. Disagreement was revolved by consensus.

### 2.5. Statistical analysis

All statistical analysis were carried out by Rev Man 5.3. The chi-square was used to assess significance of heterogeneity, and $I^2$ statistic was used to analysis the degree of heterogeneity.[13] When there was low heterogeneity among articles, the fixed-effects model was used ($I^2 \leq 50\%$). Otherwise, the random-effect effects model was conducted ($I^2 > 50\%$). A $P$ value <.05 was identified as statistically significant difference.[14]

## 3. Results

### 3.1. Study selection

There were 280 studies involving potentially relevant published data. Two hundred sixty-six irrelevant studies were excluded due to missing the inclusion criteria. After intensive reading of the 12 included citations, 4 studies were further eliminated. Hence, a total of 8 researches including 11 comparative studies.[7,15–21] were assessed for eligibility in our study (Fig. 1). Table 1 describes a brief description of these 11 comparative studies, also presented the summary of the quality assessment process.

### 3.2. Meta-analyses results

**3.2.1. Pooled analysis of OS between TMB-high and TMB-low.** As shown in Figure 2, heterogeneity among those 5 studies was high ($I^2 = 60\%$, $P = .06$). The pooled result showed that there is no statistically significant between 2 groups in terms of the difference of OS (odds ratio [OR], 0.74; 95% confidence interval [CI], 0.45–1.20; $P = .22$). In other words, patients with high TMB did not achieve OS advantage.

**3.2.2. Pooled analysis of PFS between TMB-high and TMB-low.** Low heterogeneity was found in PFS comparisons ($I^2 = 0\%$, $P = .67$) (Fig. 3). The pooled OR was 0.38 (95% CI, 0.29–0.49; $P < .00001$), representing that TMB-high group patients was associated with longer PFS compared to TMB-low group.

**3.2.3. Pooled analysis of CR between TMB-high and TMB-low.** Heterogeneity among those 3 studies was low ($I^2 = 0\%$, $P = .59$). With regard to CR, differences was found in the TMB-high group than those with TMB-low (OR, 4.71; 95% CI, 2.32–9.57; $P < .0001$), as shown in Figure 4.

**3.2.4. Pooled analysis of DCB between TMB-high and TMB-low.** DCB was defined as CR/PR or SD that lasted >6 months. Heterogeneity among those 7 studies was low ($I^2 = 0\%$, $P = .54$). The pooled analysis of DCB was also significantly higher in the TMB-high group (OR, 3.76; 95% CI, 2.38–5.96; $P < .00001$) than the TMB-low group, as shown in Figure 5.

**3.2.5. Pooled analysis of ORR between TMB-high and TMB-low.** Heterogeneity among those 6 studies was low ($I^2 = 0\%$, $P = .66$). As displayed in Figure 6, the result shown that ORR in the TMB-high group is higher than controls (OR, 3.14; 95% CI, 1.83–5.37; $P < .0001$).

## 4. Discussion

TMB is defined as somatic mutations within a tumor.[22] Given that some mutations can lead to neoantigen production, which have effect on the immune system to recognize and attack tumor cells.

TMB has been reported to be an emerging predictive biomarker that correlates with the response of immune checkpoint blockade treatments in various cancer types, including lung cancers.[16,23] However, the Keynote-189 and Keynote-021
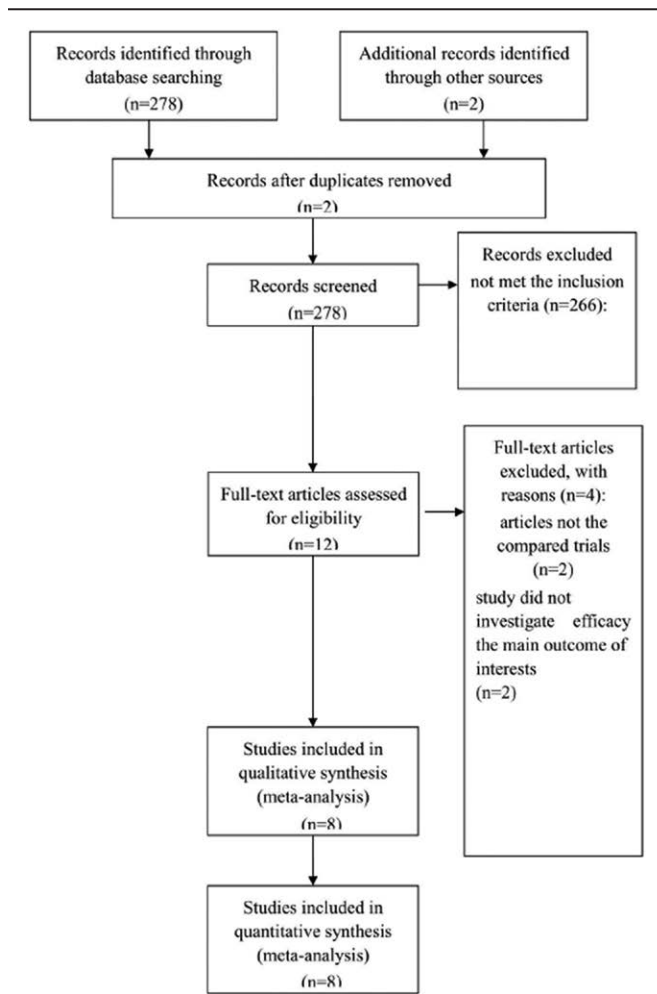
**Figure 1.** PRISMA flow chart of selection process to identify studies eligible for pooling.

articles have reported that TMB was assessed to be negatively associated with the efficacy of pembrolizumab combined with chemotherapy.[11,12]

A recent retrospective study reported that a high bTMB status is instead related to the poor clinical efficacy following immunotherapy. Our results observed superiority response for immunotherapy in patients with TMB-high. High TMB patients experienced better tumor responses and longer PFS.

The underlying mechanism(s) between TMB and superior effectiveness with ICIs therapies is not entirely clear. A leading hypothesis shown that neoantigens, tumor-specific nonself peptides relate to somatic nonsynonymous mutations, represent the mechanistic link. Some previous studies have reported neoantigen-specific T cell responses that elucidate antitumor responses.[24–26]

Neoantigen-specific T cell responses appear to be few in numbers for any given patient, such that increased TMB may relate to benefit by an increased effective neoantigen generated and presented.

The OS prediction with TMB in our study yielded unsatisfactory result, which has increased concerns over the clinical use of TMB to guide ICIs therapy in future.

Consistent results were observed from Wang study. They found that TMB was related to the poor OS, indicating the it is unable to predict who may achieve OS benefit of immunotherapy due to the interference of the MSAF.[21] Given the complex interactions among the immune system and tumors, it is imaginable that multiple biomarkers are warranted to distinguish responders and nonresponders.

## Table 1

**The primary characteristics of the eligible studies in more detail.**

| Study (yr) | Study | Immune checkpoint inhibitor | Stage | The cutoff value of TMB | No. of patients TMB high group | No. of patients TMB low group | Median age TMB high group | Median age TMB low group | NOS |
|---|---|---|---|---|---|---|---|---|---|
| Huang et al (2020) | / | Nivolumab; pembrolizumab; atezolizumab | IIIB–IV | 10 mutations/Mb | 14 | 20 | 64 | 59 | 8 |
| Hellmann et al (2018) | / | PD-1 blockade monotherapy | IIIB–IV | Above versus below median | 37 | 38 | 65 | 66 | 6 |
| Ready et al (2019) | Nes | Nivolumab | Recurrent IIIB–IV | 10 mutations/Mb | 48 | 27 | / | / | 6 |
| Fang et al (2019)[1] | Panel | PD-(L)1 blockade monotherapy | III–IV | Above versus below median | 25 | 48 | / | / | 6 |
| Fang et al (2019)[2] | | PD-(L)1 blockade monotherapy | III–IV | | 26 | 49 | / | / | 6 |
| Jiao et al (2019) | / | PD-(L)1 blockade monotherapy | III–IV | 3.77 mutations/Mb | 178 | 111 | / | / | 6 |
| Wang et al (2019) | | PD-(L)1 blockade monotherapy | IIIB–IV | 6 mutations/Mb | 28 | 22 | / | / | 6 |
| Wang et al (2020)[1] | NCL cohort | PD-(L)1 blockade monotherapy | IIIB–IV | 6 mutations/Mb | 28 | 36 | / | / | 7 |
| Wang et al (2020)[2] | POPLAR/OAK | | IIIB–IV | 6 mutations/Mb | 103 | 326 | / | / | 7 |
| Rizvi et al (2015)[1] | Discovery | PD-1 blockade monotherapy | III–IV | Above versus below median | 8 | 8 | / | / | 6 |
| Rizvi et al (2015)[2] | Validation | | III–IV | | 9 | 9 | / | / | 6 |
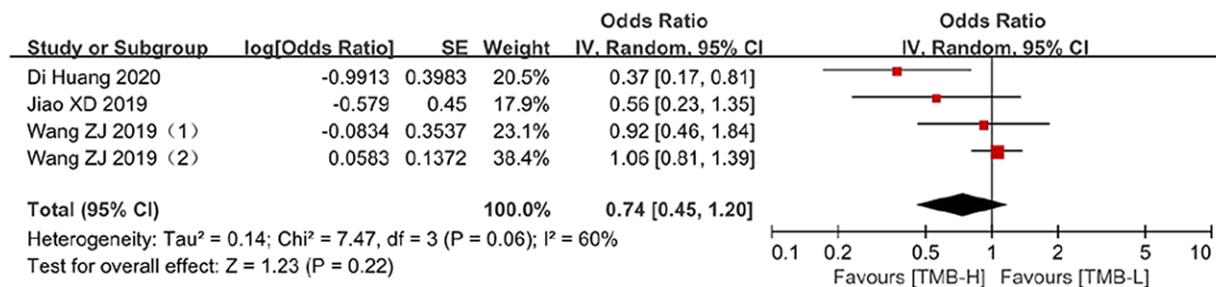
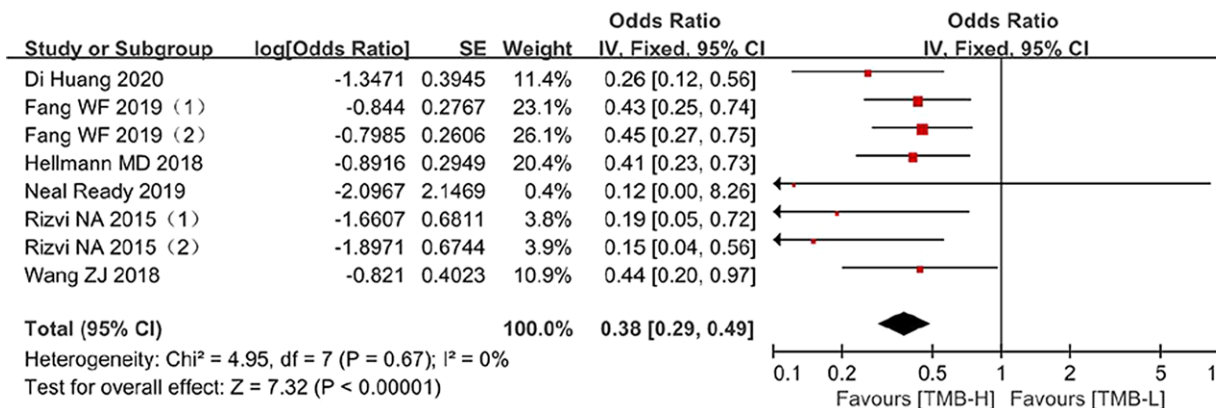**Figure 2.** Pooled analysis of OS between TMB-high and TMB-low.



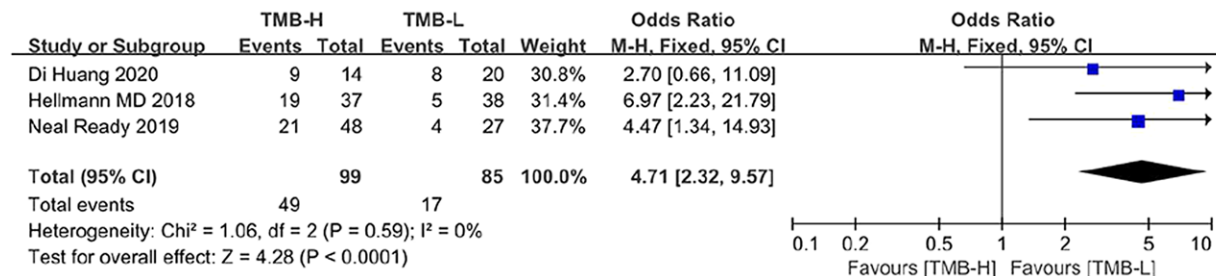**Figure 3.** Pooled analysis of PFS between TMB-high and TMB-low.



**Figure 4.** Pooled analysis of CR between TMB-high and TMB-low.
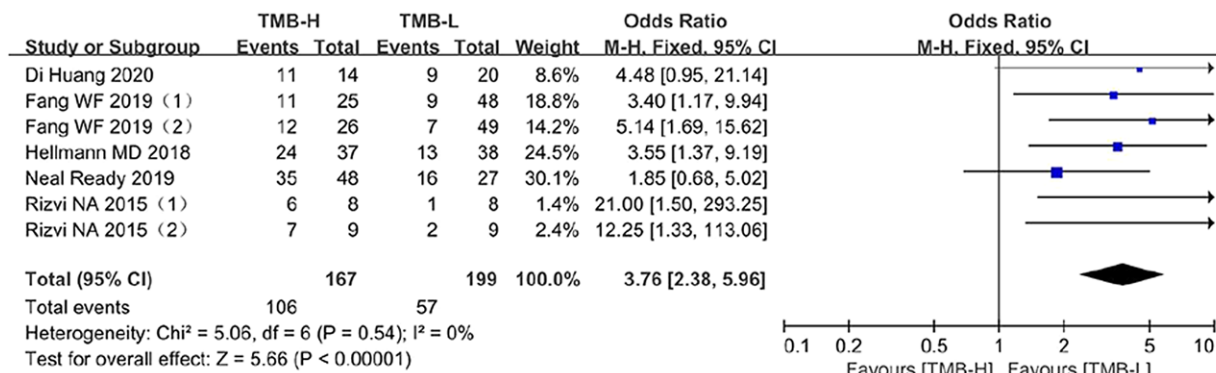


**Figure 5.** Pooled analysis of DCB between TMB-high and TMB-low. DCB = durable clinical benefit.
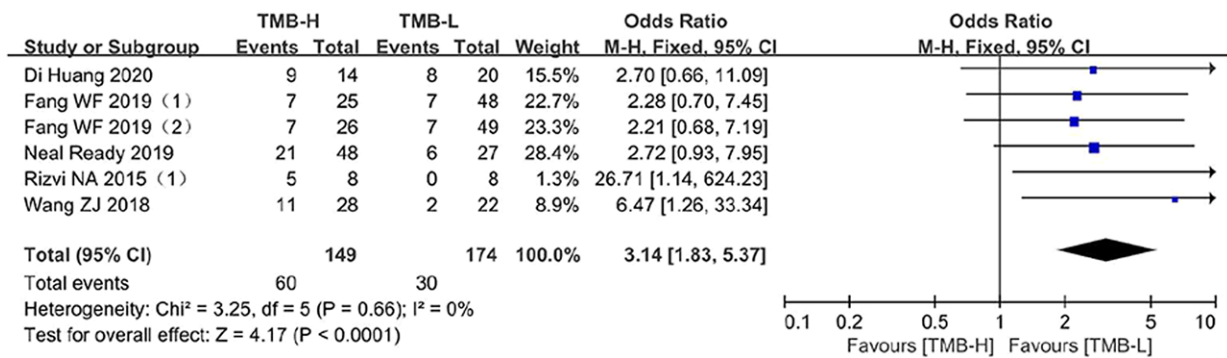
**Figure 6.** Pooled analysis of ORR between TMB-high and TMB-low.

Even recognizing the TMB as a predictive biomarker is growing in popularity, which is associated with ICI therapy responses, categorization of patients estimated by TMB status alone does not accurate enough to predict the survival outcome and some patients might be mis-classified with receiving an ineffective therapy or missing the best therapy opportunity. Therefore, raised concerns over understanding of underlying mechanisms associated with ICI efficacy and exploration of extratumor characteristics are warranted to increase the predictive power of this biomarker.[18]

There are some limitations should not be ignored. First, selection bias exists due to the retrospective nature and various investigator's TMB reporting level of all included studies. In fact, there is no unified standard for TMB testing. The different criteria/cutoff points of TMB-high and TMB-low may have a potential confounding effect on the validity of analyses. Second, our study could not include potential confounding factors, such as response duration, different grades of TMB and different ICIs, due to the limited data of covariates available to analysis. Further researches are needed to clarify this issue.

TMB-high was related to a superior result in NSCLC patients who treated with immunotherapy. Our results suggest that TMB was significantly have association with greater predictive power of response. While, large gaps remain in the understanding of the molecular determinants associate with ICI efficacy. Thus, raised concerns over exploration of additional tumor characteristics and understanding of underlying mechanisms are warranted to increase the predictive power of TMB or programmed death-ligand 1 expression.

## Author contributions

DHY is responsible for the guarantor of integrity of the entire study, study concepts & design, definition of intellectual content, literature research, clinical studies, experimental studies, manuscript preparation; CY and HDZ are responsible for the data acquisition & analysis, statistical analysis; WYC is responsible for the manuscript editing & review. All authors read and approved the final manuscript.
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Investigation: Dahui Yu.
Methodology: Dahui Yu.
Project administration: Dahui Yu.
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Writing – review & editing: Wenyan Chu.

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