

## ARTICLE

# A model-based meta-analysis of immune-related adverse events during immune checkpoint inhibitors treatment for NSCLC

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**Abstract**

Immune checkpoint inhibitors (ICIs) have become a vital part of the therapeutic landscape for non-small cell lung cancer (NSCLC) in recent years benefiting from their remarkable efficacy. However, ICIs are associated with potentially life-threatening immune-related adverse events (irAEs). This study aims to quantify dose dependence and additional influencing factors of both any grade and grade greater than or equal to 3 irAEs in patients with NSCLC treated by ICIs. The trial-level irAE data was collected and pooled from 129 cohorts in 81 clinical studies. A logit-transformed meta-regression model was applied to derive the quantitative relationship of irAE rate and ICI exposure. Programmed cell death-1 (PD-1) or programmed cell death ligand-1 (PD-L1) inhibitors showed no dose dependence in patients with NSCLC, whereas cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors exhibited a statistically significant dose dependence when used alone or combined with PD-1 or PD-L1 inhibitors. Besides, therapy line and combination of ICIs with chemotherapy or target therapy were significant covariates. Hopefully, the results of this study can improve clinicians' awareness of irAEs and be helpful for clinical decisions during ICI treatment for NSCLC.

**Study Highlights****WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

Conventional clinical trials and meta-analysis have pooled and compared the incidence of immune-related adverse events (irAEs) induced by diverse immune checkpoint inhibitors (ICIs) in several cancer types.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

A latest comprehensive model-based meta-analysis based on multiple types of clinical studies was conducted to quantify dose dependence and additional influencing factors of both any grade and grade greater than or equal to 3 irAEs during ICI treatment for non-small cell lung cancer (NSCLC) up to April 30, 2021.

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### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

In patients with NSCLC, PD-(L)1 inhibitors showed no dose dependence of any grade or grade greater than or equal to 3 irAE rates, whereas CTLA-4 inhibitors exhibited a statistically significant normalized exposure dependence when used alone or combined with PD-(L)1 inhibitors. Besides, patients receiving ICIs as second-line or later therapy had a lower irAE rate compared with those receiving ICIs as first-line therapy. In addition, combination of ICIs with chemo or target therapy would increase the incidence of irAEs.

### HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The results in this study can improve clinicians' awareness and provide quantitative evidence and reference for the reasonable clinical application of ICI in patients with NSCLC from the perspective of irAEs.

## INTRODUCTION

According to the Global Cancer Statistics in 2020, lung cancer remained the leading cause of cancer death in the world.<sup>1</sup> Non-small cell lung cancer (NSCLC) is the main histological subtype accounting for about 80–85% of lung cancer.<sup>2</sup> Because more than two-thirds of patients with NSCLC are diagnosed at an advanced stage when they miss the best time to accept surgical resection, medical therapy is still the major method for the treatment of NSCLC currently.<sup>3</sup> In addition, immune checkpoint inhibitors (ICIs) including programmed cell death-1 (PD-1) inhibitors, programmed cell death ligand-1 (PD-L1) inhibitors, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors, have received increasing attention and consideration over recent years benefitting from their remarkable clinical efficacy in NSCLC therapy.<sup>4</sup> Under the circumstances, ICIs become a vital part of the therapeutic landscape for NSCLC treatment.

However, the inhibition of immune checkpoints can cause nonspecific activation of the normal immune system, resulting immune-related adverse events (irAEs) that may lead to treatment discontinuation and even life threat.<sup>5</sup> Consequently, the evaluation of irAEs induced by ICIs is an essential consideration for treatment options, early recognition, and management of patient safety.

Conventional meta-analysis mainly based on randomized clinical trials (RCTs) has pooled and compared the incidence of irAEs across different ICI targets, drugs, and dosing regimens.<sup>6–8</sup> But modeling approaches are rarely used in these meta-analyses to comprehensively investigate the dose dependence and additional influencing factors of irAEs induced by diverse ICIs. Besides, pooled results from RCTs may differ from other types of clinical trials as well as real-world settings.

A model-based meta-analysis (MBMA) of PD-1 and CTLA-4 inhibitors has developed a methodology to quantify

the relationship between ICI dose and irAE rates.<sup>9</sup> However, PD-L1 inhibitors were not included in this analysis for the lack of irAE data. In addition, the results were pooled from several cancer types. But it has been shown that the type, incidence, and severity of irAEs vary across different cancer types.<sup>10,11</sup>

What's more, in the last few years, ICIs have shown great promise in clinical trials and were rapidly incorporated into the standard treatment of NSCLC.<sup>12</sup> But a latest model-based meta-analysis of irAEs has not been conducted for NSCLC. Therefore, this study aims to evaluate the dose dependence and additional influencing factors of both any grade and grade greater than or equal to 3 irAEs during ICI treatment for NSCLC based on multiple types of clinical studies. Hopefully, it can improve clinicians' awareness and provide help for the management of irAEs in patients with NSCLC.

## METHODS

### Literature search

A systematic literature search was conducted on PubMed, Embase, and Cochrane library up to April 30, 2021. The following keywords were used: “carcinoma, non-small-cell lung” (MeSH terms) AND “programmed death 1” (all fields) OR “programmed death ligand 1” (all fields) OR “anti-cytotoxic T-lymphocyte antigen 4” (all fields) AND “clinical trial” (publication type). The detailed search syntax is presented in Table S1. Additional information on published trials was further searched from [clinicaltrials.gov](https://clinicaltrials.gov) websites. We have conducted the literature search and screening following the Cochrane recommendations for the preferred reporting items for systematic reviews and meta-analyses (PRISMA).<sup>13</sup>

Studies were included if they met all of the following criteria: (1) treatment for patients with NSCLC; (2) containing the information about at least one of the seven ICIs

(nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, ipilimumab, and tremelimumab); (3) clinical trials and real-world studies (RWSs) with safety data. Nivolumab and pembrolizumab are PD-1 inhibitors. Atezolizumab, durvalumab and avelumab are PD-L1 inhibitors. Ipilimumab and tremelimumab are CTLA-4 inhibitors. This analysis extracted clinical studies from not only RCTs but also dose escalation trials, single-arm trials (SATs), trials with nonrandomized design, and RWSs to get closer to the clinical practice.

However, the studies were excluded if they were: (1) review articles, meta-analysis, case reports, or comments; (2) not treated by the defined drugs; and (3) in vitro or nonclinical studies.

## Outcome measures

A data extract template was firstly established including the potential irAEs during ICI treatment for NSCLC, which is provided in Table S2. Trial-level irAE rates were obtained across all included trials if an adverse event (AE) was reported in any trial as “irAE,” “selected treatment-related AE,” or “AE of special interest.” Once the information of overall incidence of any grade or grade greater than or equal to 3 irAEs was not given in the included trials, the highest incidence of a potential irAE was used instead.<sup>14</sup>

## ICI exposure normalization

The mean values of published population pharmacokinetic (PopPK) parameters were used to simulate the average steady-state plasma concentrations ( $C_{av}$ ) at different dosing regimens based on a two-compartment linear pharmacokinetic (PK) model for each drug.<sup>15–21</sup> In order to combine irAE data from different ICIs acting on the same target receptor, the simulated  $C_{av}$  was then normalized by dividing the  $C_{av}$  by drug concentrations at 50% inhibition ( $IC_{50}$ ) which was obtained from published studies of in vitro experiments.<sup>22–26</sup> This methodology took into account differences both in PKs and potencies of these ICIs.<sup>9</sup> The detailed values of PopPK parameters and  $IC_{50}$  are summarized in Table S3. Simulations were performed using NONMEM version 7.4.

## Statistical analysis

Trial-level irAE rates were meta-analytic pooled using a random-effects model. The Cochran Q test was used to assess the between-study heterogeneity. The funnel plot and Egger’s test were used to evaluate publication bias.<sup>27</sup>

A logit transformation of irAE rate was used to meet the normal distribution assumption for variance and a generalized linear mixed model approach was used to stabilize the overestimation bias that might be introduced by continuity of zero events.<sup>28,29</sup>

A multiple meta-regression model was applied to derive the quantitative relationship of irAE rate and the normalized exposure of ICIs.<sup>27</sup> Additive forms of normalized exposure of PD-(L)1 and CTLA-4 inhibitors and interaction terms characterizing synergistic effect of PD-(L)1 plus CTLA-4 inhibitor were included in the model.

$$\text{Logit}(\text{Pr}_{\text{irAE}}) = \beta_0 + \beta_1 C_{\text{PD-1}} + \beta_2 C_{\text{PD-L1}} + \beta_3 C_{\text{CTLA-4}} + \beta_4 C_{\text{PD-1}} C_{\text{CTLA-4}} + \beta_5 C_{\text{PD-L1}} C_{\text{CTLA-4}} \quad (1)$$

where  $\text{logit}(\text{Pr}_{\text{irAE}})$  is the logit-transformed rate of any grade or grade greater than or equal to 3 irAEs, and  $\beta_0$  is the intercept.  $\beta_{1-5}$  are the coefficients.  $C_{\text{PD-1}}$ ,  $C_{\text{PD-L1}}$ , and  $C_{\text{CTLA-4}}$  refer to the normalized exposure of PD-1, PD-L1, and CTLA-4 inhibitors, respectively.

However, because normalized exposure of the PD-(L)1 inhibitor had no significant association with neither any grade nor grade greater than or equal to 3 irAE rate in any multiple meta-regression model, the effect of PD-(L)1 inhibitor was translated into binominal form. Thus, the base models for any grade and grade greater than or equal to 3 irAE were finally simplified as follows:

$$\text{Logit}(\text{Pr}_{\text{Any grade irAE}}) = \beta_0 + \beta_1 \text{Factor}_{\text{PD-L1}} + \beta_2 C_{\text{CTLA-4}} \quad (2)$$

$$\text{Logit}(\text{Pr}_{\text{Grade} \geq 3 \text{ irAE}}) = \beta_0 + \beta_1 \text{Factor}_{\text{PD-L1}} + \beta_2 C_{\text{CTLA-4}} + \beta_3 \text{Factor}_{\text{PD-1}} C_{\text{CTLA-4}} + \beta_4 \text{Factor}_{\text{PD-L1}} \text{Factor}_{\text{CTLA-4}} \quad (3)$$

where  $\beta_0$  represents the irAE rates of PD-1 inhibitor monotherapy.  $\text{Factor}_{\text{PD-L1}}$  is set to 1 if a PD-L1 inhibitor was given as monotherapy or in combination with a CTLA-4 inhibitor, and to 0 when not given.  $\text{Factor}_{\text{PD-1}}$  was similar with  $\text{Factor}_{\text{PD-L1}}$ , and  $\text{factor}_{\text{CTLA-4}}$  is set to 1 only if a CTLA-4 inhibitor was given with a PD-L1 inhibitor, and to 0 otherwise. Due to data characteristics, base model for any grade irAEs did not capture the interactions between PD-(L)1 and CTLA-4 inhibitors whereas base model for grade greater than or equal to 3 irAEs did.

After the base model for normalized exposure dependence of irAE rates was established, trial-level patient baseline characteristics were included in additive or interactive form to explore the potential significant covariates. The following covariates were screened and selected in a step-wise method: (1) categorical covariates: therapy line (second-line or later therapy vs. first-line therapy), ICI therapy combination (ICIs plus chemotherapy or target

therapy vs. ICIs), drugs (nivolumab vs. pembrolizumab; atezolizumab vs. avelumab vs. durvalumab; ipilimumab vs. tremelimumab); (2) continuous covariates: age (median age), sex (percentage of men vs. women), smoking status (percentage of current/former smokers vs. never smokers), PD-L1 status (percentage of PD-L1 positive), tumor stage (stage III vs. stage IV), and histology (percentage of squamous vs. nonsquamous) of the patients in the study or cohort.

At last, an additive form of binominal effect of therapy line and combination with chemo or target therapy was chosen for the final model in the same way for both any grade and grade greater than or equal to 3 irAEs.

$$\text{Logit}(\text{Pr}_{\text{Any grade irAE}}) = \beta_0 + \beta_1 \text{Factor}_{\text{PD-L1}} + \beta_2 C_{\text{CTLA-4}} + \beta_3 (\text{line2+}) + \beta_4 \text{chemo/target} \quad (4)$$

$$\text{Logit}(\text{Pr}_{\text{Grade} \geq 3 \text{ irAE}}) = \beta_0 + \beta_1 \text{Factor}_{\text{PD-L1}} + \beta_2 C_{\text{CTLA-4}} + \beta_3 \text{Factor}_{\text{PD-1}} C_{\text{CTLA-4}} + \beta_4 \text{Factor}_{\text{PD-L1}} \text{Factor}_{\text{CTLA-4}} + \beta_5 (\text{line2+}) + \beta_6 \text{chemo/target} \quad (5)$$

If fewer than 20% of the covariate values were missing, missing covariates were imputed first based on the most similar study with a non-missing value and as the median for continuous variables or the mode for categorical variables across the remaining studies.<sup>30</sup>

The fit of the meta-regression model was required to meet the following criteria. First, the regression coefficients of the exposure and covariates should be statistically significant ( $p < 0.05$ ) and the confidence interval of the coefficients cannot range across 0. Second, change in model structure and inclusion of covariates are required to reduce the Akaike information criterion (AIC) and residual heterogeneity of the model. Third, model prediction curves should fit the trend of observations as closely as possible.

## Model simulation

A model simulation based on the final model was performed in order to predict the incidence of irAEs in patients with NSCLC treated by ICIs under different covariate combinations or dosing regimens. Because PD-(L)1 inhibitor has no dose dependence, diverse treatment scenarios were simulated with different covariate combinations (first line vs. second or later line therapy, monotherapy vs. combination with chemo/

target therapy). In addition, the only CTLA-4 inhibitor currently approved for NSCLC in clinical practice is ipilimumab, which is mostly used for first-line therapy. Hence, the irAE rates of first-line ipilimumab treatment for NSCLC were simulated under some most common clinical dosing regimens (1 mg/kg Q6W or Q3W with nivolumab/pembrolizumab, 1 or 10 mg/kg Q3W with chemo/target therapy).

Meta-regression model development, evaluation, and simulation were performed using R software version 4.0.4 (“meta” and “metafor” package).<sup>29</sup>

## RESULTS

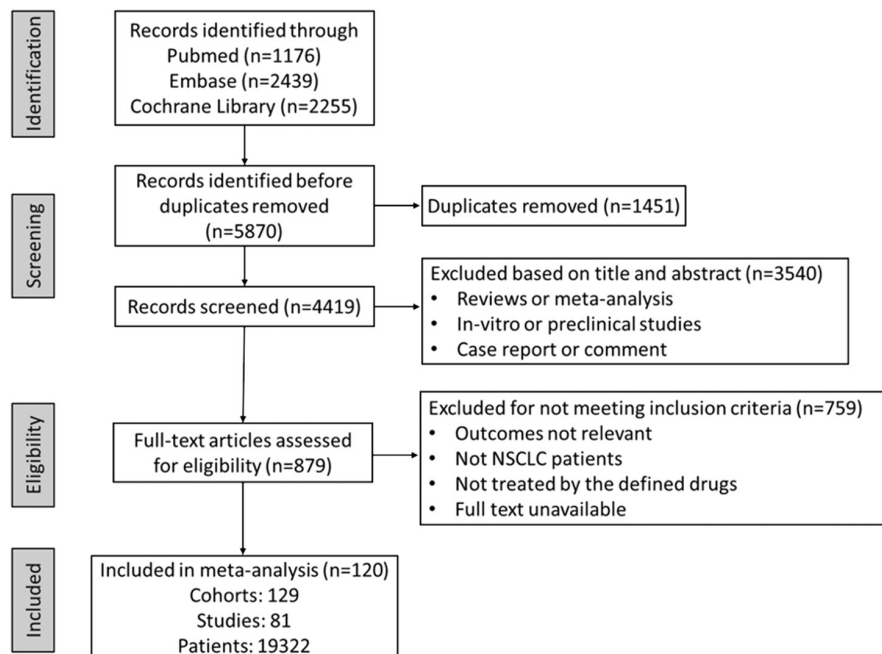
### Literature data

The initial literature research identified a total of 5870 publications. After duplicate and ineligible articles were removed, 120 publications including 81 clinical studies with 19,322 patients were finally enrolled in the meta-analysis. The flow chart of the study selection process and reasons for study exclusion are displayed in [Figure 1](#). The included studies consisted of 53 RCTs, 18 dose escalation trials, 21 single arm trials, 20 trials with nonrandomized design, and 17 RWSs. A detailed description of the included studies is provided in [Table S4](#).

Results of pooled irAE rates using the random-effects model were displayed by the forest plots ([Figure S1](#)). Although there were several points outside the funnel which might be caused by large heterogeneity between studies, the funnel plots showed no significant asymmetry. In addition, results of the funnel plot and Egger’s test indicted no obvious publication bias with regard to both any grade and grade greater than or equal to 3 irAEs ([Figure S2](#)).

In the current study, irAEs have been evaluated, including pulmonary (pneumonitis), gastrointestinal (diarrhea and colitis), endocrine (hypothyroidism), and skin (pruritus and rash), etc. with total irAEs (any grade irAEs) and sever irAEs (grade  $\geq 3$  irAEs), and irAEs are graded according to Common Terminology Criteria for Adverse Events (CTCAE) guidance shown in [Table S5](#). The overall incidence of any grade and grade greater than or equal to 3 irAEs induced by ICIs in patients with NSCLC, including the cohorts and 95% confidence intervals (CIs) is summarized in [Table 1](#). For ICI monotherapy, CTLA-4 inhibitors had the highest incidence of any grade and grade greater than or equal to 3 irAEs (43.96% and 12.56%, respectively), followed by PD-1 inhibitor (21.15% and 3.68%, respectively), and PD-L1 inhibitor had the lowest (16.62% and 2.23%, respectively). The irAE rates of PD-(L)1 plus

**FIGURE 1** Flow chart describing the study selection procedure for the analysis. NSCLC, non-small cell lung cancer.



**TABLE 1** Overview of irAE rates

|                     |        | PD-1           | PD-L1          | CTLA-4         | CTLA-4 + PD-1  | CTLA-4 + PD-L1 |
|---------------------|--------|----------------|----------------|----------------|----------------|----------------|
| Any grade irAE      | Rate % | 21.15          | 16.62          | 43.96          | 36.53          | 27.30          |
|                     | 95% CI | [17.56, 25.24] | [12.69, 21.49] | [28.38, 60.82] | [31.13, 42.28] | [17.69, 39.61] |
|                     | Cohort | 73             | 33             | 5              | 10             | 5              |
| Grade $\geq 3$ irAE | Rate % | 3.68           | 2.23           | 12.56          | 7.02           | 9.36           |
|                     | 95% CI | [2.87, 4.71]   | [1.54, 3.23]   | [7.99, 19.19]  | [5.48, 8.96]   | [5.06, 16.68]  |
|                     | Cohort | 71             | 29             | 5              | 10             | 5              |

Abbreviations: CI, confidence interval; irAE, immune-related adverse event.

CTLA-4 inhibitor combination were higher than those of PD-(L)1 inhibitor monotherapy but lower than those of CTLA-4 inhibitor monotherapy, probably due to the reduced dose of CTLA-4 inhibitor in combination with PD-(L)1 inhibitor compared to CTLA-4 inhibitor monotherapy. For example, ipilimumab was administered 1 mg/kg Q6W in combination with nivolumab but 10 mg/kg Q3W during monotherapy.<sup>31,32</sup>

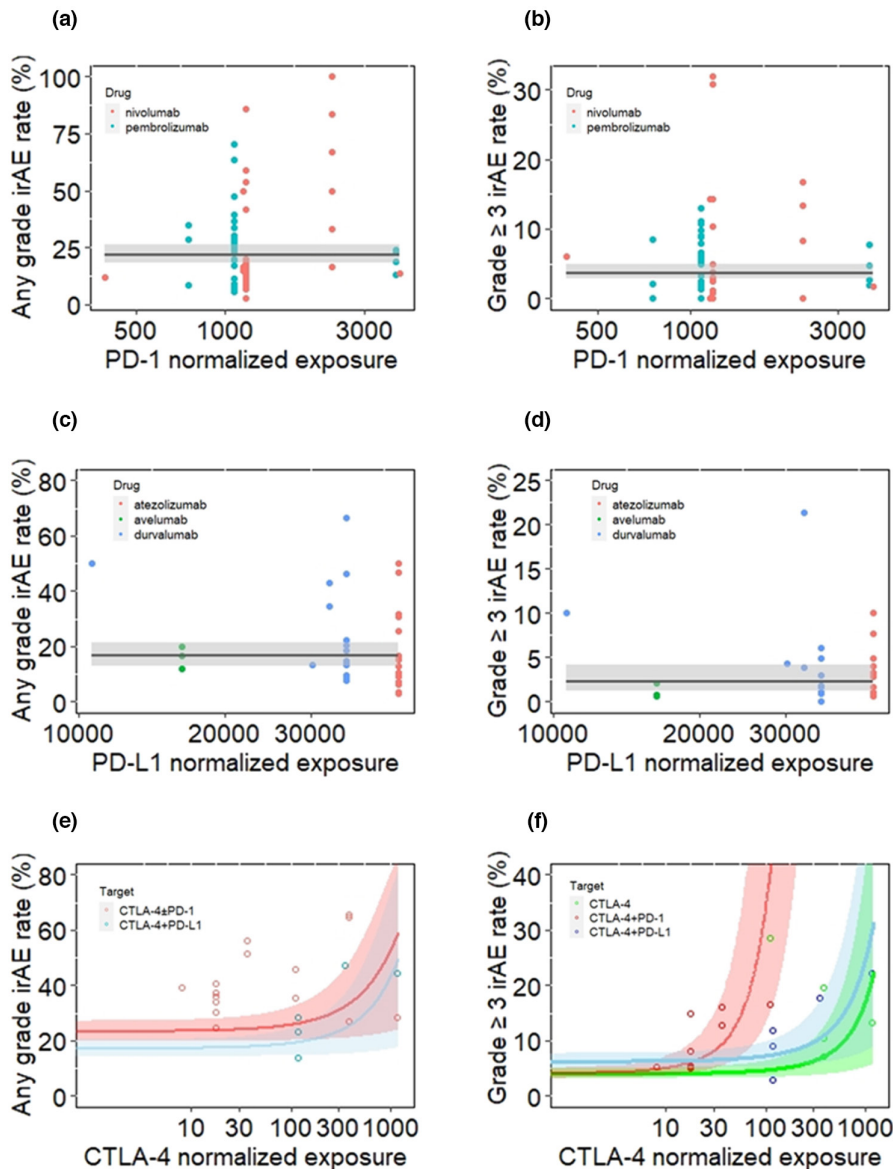
### Meta-regression for normalized exposure

In the initial meta-regression model (Equation 1), the quantitative relationship of irAE rates and the normalized exposure was explained by an additive effect of PD-(L)1 and CTLA-4 inhibitors as well as synergistic effect of PD-(L)1 plus CTLA-4 inhibitors. However, normalized exposure of PD-(L)1 inhibitor had no significant correlation with neither any grade nor grade greater than or equal to 3 irAE rate no matter in univariate or any forms of multiple

meta-regression model ( $p > 0.1$ ), indicating no dose dependence of PD-(L)1 inhibitor (Figure 2a-d). Therefore, the effect of PD-(L)1 inhibitor on irAE rates were characterized by a binomial factor (Equations 2 and 3).

In contrast to PD-(L)1 inhibitor, CTLA-4 inhibitor exhibited a statistically significant normalized exposure dependence of both any grade and grade greater than or equal to 3 irAE rates when used alone or combined with PD-(L)1 inhibitor ( $p < 0.05$ ; Figure 2e,f). It is worth noting that the combination of CTLA-4 and PD-1 inhibitors strengthen the dependence of grade greater than or equal to 3 irAE rate on normalized exposure of CTLA-4 inhibitor, whereas combination of CTLA-4 and PD-L1 inhibitors only increase the baseline value of grade greater than or equal to 3 irAE rate. The parameters of base model for any grade and grade greater than or equal to 3 irAEs are provided in Table 2. According to the base model, the intercept represented the baseline rates of PD-1 inhibitor monotherapy. The other terms referred to the difference from PD-1 inhibitor monotherapy to the other ICI regimens, respectively.





**FIGURE 2** Dependencies of irAE rates upon ICI normalized exposure. (a) Any grade and (b) grade greater than or equal to 3 irAEs for PD-1 inhibitor; (c) any grade, and (d) grade greater than or equal to 3 irAEs for PD-L1 inhibitor and (e) any grade and (f) grade greater than or equal to 3 irAEs for CTLA-4 inhibitor. The dots and circles are observed values. The lines and shadow represent the prediction line and 95% confidence interval, respectively. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

**TABLE 2** Parameter estimates of the base model

| Parameter  | Estimate | 95% CI             | Standard error | p value |
|--|----------|--------------------|----------------|---------|
| Any grade irAE   |          |                    |                |         |
| $\beta_0$ (intercept)  | -1.1889  | [-1.3938, -0.9840] | 0.1045         | <0.0001 |
| $\beta_1$ (on $\text{factor}_{\text{PD-L1}}$ )                               | -0.3862  | [-1.0287, -0.1825] | 0.1837         | 0.0356  |
| $\beta_2$ (on $C_{\text{CTLA-4}}$ )  | 0.0013   | [0.0002, 0.0024]   | 0.0006         | 0.0213  |
| Grade $\geq 3$ irAE  |          |                    |                |         |
| $\beta_0$ (intercept)  | -3.1666  | [-3.3898, -2.9434] | 0.1139         | <0.0001 |
| $\beta_1$ (on $\text{factor}_{\text{PD-L1}}$ )                               | -0.6056  | [-1.0287, -0.1825] | 0.2159         | 0.0050  |
| $\beta_2$ (on $C_{\text{CTLA-4}}$ )  | 0.0016   | [0.0005, 0.0026]   | 0.0006         | 0.0048  |
| $\beta_3$ (on $\text{factor}_{\text{PD-1}} C_{\text{CTLA-4}}$ )              | 0.0176   | [0.0032, 0.0319]   | 0.0073         | 0.0163  |
| $\beta_4$ (on $\text{factor}_{\text{PD-L1}} \text{Factor}_{\text{CTLA-4}}$ ) | 1.0711   | [0.1721, 1.9701]   | 0.4578         | 0.0185  |

Abbreviations: CI, confidence interval; irAE, immune-related adverse event.

## Covariate evaluation

A multiple meta-regression model on the basis of the base model for dose dependence was applied to evaluate the potential covariates influencing irAE rates. In the original database, covariates were missing from 0% to 30% of the trials and imputation was performed for the missing values. For studies that included patients receiving both first-line and second-line or later therapy, therapy lines were rounded off to 0 or 1 based on the percentage of patients receiving first-line versus second-line or later therapy. The distributions of the covariate values across trials are presented in Table S6. The final covariate models for both any grade and grade greater than or equal to 3 irAEs included an additive form of binominal effect of therapy line and combination with chemo or target therapy.

The parameters estimates and the odds ratio (OR) of final model are provided in Table 3. Patients receiving ICIs as second-line or later therapy had a lower incidence of irAEs compared with those receiving ICIs as first-line therapy (OR < 1,  $p < 0.05$ ; Figure 3a,b). Besides, combination of ICIs with chemo or target therapy would increase the incidence of irAEs (OR > 1,  $p < 0.05$ ; Figure 3c–f). No statistically significant effect was observed when introducing different drugs for a given target class as covariates, indicating similar incidence of irAEs within a same target class of ICIs in patients with advanced NSCLC. Besides, there were no statistically significant correlations between irAE rates and those continuous covariates like age as well as percentage of sex, PD-L1 status, smoking status, tumor stage, and histology.

## Model simulation

A model simulation was performed based on the final model for any grade and grade greater than or equal to 3 irAEs to predict the probability of irAEs in patients with NSCLC under diverse covariate combinations of PD-(L)1 inhibitor (Figure 4a,b) and some most common clinical dosing regimens of ipilimumab (Figure 4c). It can help clinicians to visually evaluate the probability of irAEs in patients with NSCLC under different treatment scenarios or dosing regimens, which allows for a suitable level of treatment monitoring for patients with NSCLC with regard to irAEs.

## DISCUSSION

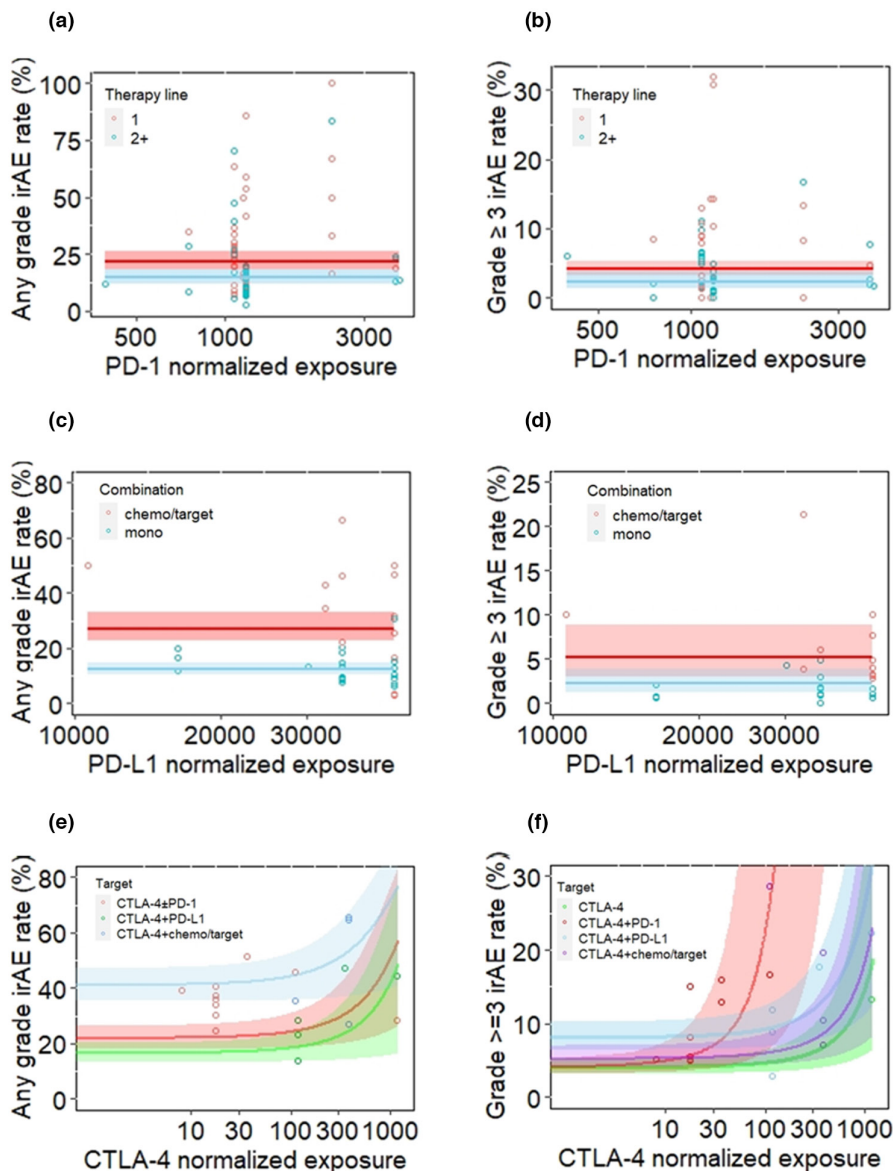
This comprehensive meta-analysis evaluated safety data from 120 publications across 81 clinical studies with 19,322 patients. To our knowledge, the present study was by far the largest model-based meta-analysis of irAEs during ICI treatment for NSCLC that covers the most types of clinical studies and we used meta-regression model to analyze the published data.

The majority of the conventional meta-analysis of irAEs are based on RCTs, which explore the OR or risk ratio (RR) calculated from both the experimental group and the control group. Strict inclusion and exclusion criteria for RCTs is able to reduce between-study heterogeneity. Nevertheless, rigorous eligibility criteria restrict the applicability of studies to the specific patient population and the experimental conditions of RCTs may not fully

**TABLE 3** Parameter estimates of the final model

| Parameter  | Estimate | 95% CI             | Standard error | <i>p</i> value | OR     |
|--|----------|--------------------|----------------|----------------|--------|
| <b>Any grade irAE</b>  |          |                    |                |                |        |
| $\beta_0$ (intercept)  | -1.2696  | [-1.5155, -1.0238] | 0.1255         | <0.0001        |        |
| $\beta_1$ (on factor <sub>PD-L1</sub> )                          | -0.3484  | [-0.6439, -0.0529] | 0.1508         | 0.0208         | 0.7058 |
| $\beta_2$ (on C <sub>CTLA-4</sub> )                              | 0.0013   | [0.0004, 0.0022]   | 0.0005         | 0.0049         | 1.0013 |
| $\beta_3$ (on line2+)  | -0.4757  | [-0.7587, -0.1926] | 0.1444         | 0.0010         | 0.6215 |
| $\beta_4$ (on chemo/target)                                      | 0.9093   | [0.6061, 1.1893]   | 1.2124         | <0.0001        | 2.4826 |
| <b>Grade <math>\geq 3</math> irAE</b>                            |          |                    |                |                |        |
| $\beta_0$ (intercept)  | -3.1445  | [-3.3936, -2.8954] | 0.1271         | <0.0001        |        |
| $\beta_1$ (on factor <sub>PD-L1</sub> )                          | -0.6271  | [-0.9508, -0.3035] | 0.1651         | <0.0001        | 0.5341 |
| $\beta_2$ (on C <sub>CTLA-4</sub> )                              | 0.0014   | [0.0006, 0.0022]   | 0.0004         | 0.0008         | 1.0014 |
| $\beta_3$ (on factor <sub>PD-L1</sub> C <sub>CTLA-4</sub> )      | 0.0176   | [0.0061, 0.0290]   | 0.0058         | 0.0027         | 1.0178 |
| $\beta_4$ (on factor <sub>PD-L1</sub> Factor <sub>CTLA-4</sub> ) | 1.3525   | [0.6803, 2.0247]   | 0.3430         | <0.0001        | 3.8671 |
| $\beta_5$ (on line2+)  | -0.6285  | [-0.9229, -0.3341] | 0.1502         | <0.0001        | 0.5334 |
| $\beta_6$ (on chemo/target)                                      | 0.8790   | [0.5686, 1.1893]   | 0.1583         | <0.0001        | 2.4085 |

Abbreviations: CI, confidence interval; OR, odds ratio.



**FIGURE 3** Dependencies of irAE rates on ICI normalized exposure and baseline characteristics. (a) Any grade and (b) grade greater than or equal to 3 irAEs for PD-1 inhibitor monotherapy received as first line compared with second line or later therapy; (c) any grade, and (d) grade greater than or equal to 3 irAEs for PD-L1 inhibitor first-line monotherapy compared with combinations of PD-L1 inhibitors and chemo/target therapy; (e) any grade and (f) grade greater than or equal to 3 irAEs for CTLA-4 inhibitor monotherapy, CTLA-4 plus PD-1 combinations, CTLA-4 plus PD-L1 combinations, and CTLA-4 plus chemo/target combinations. The dots and circles are observed values. The lines and shadow represent the prediction line and 95% confidence interval, respectively. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

reflect the realities of clinical practice.<sup>33</sup> This study extracted data from not only RCTs but also dose escalation trials, SATs, and RWSs, making our analyses closer to the clinical realities and applicable to a broader population. In addition, meta-regression model, the extension of regression models to the meta-analysis setting, provides a framework for explaining heterogeneity in effect sizes as well as examining potential moderators.<sup>34</sup> In addition, multiple meta-regression models allow us to integrate dose dependence of ICIs acting on different targets and additional influencing factors along with their interactions.

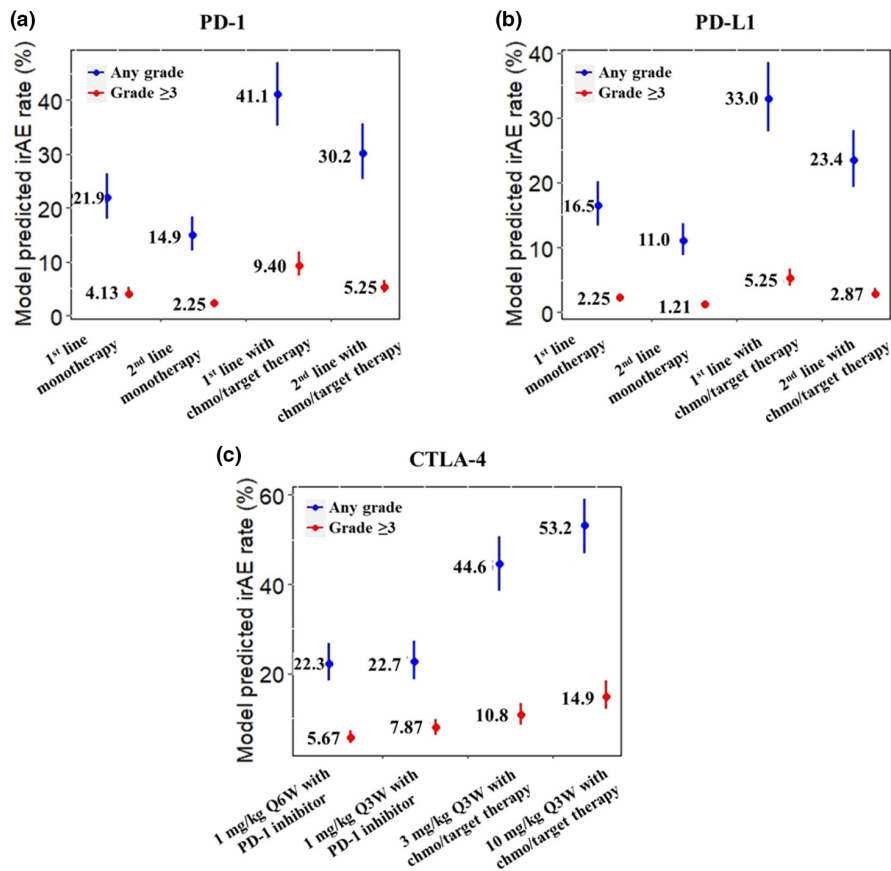
The forest plots (Figure S1) visually display the irAE rates (symbol centers), 95% CIs (whiskers) of each study and the overall means (symbol centers), and 95% CIs (symbol widths) estimated by random effects model.  $I^2$  and  $p$  are the statistical values of the heterogeneity test and  $\tau^2$  is the estimated value of between-study variance. The small  $p$  values ( $p < 0.05$ ) and large  $I^2$  values ( $I^2 \geq 50\%$ ,

except a close value of 47% for grade  $\geq 3$  irAEs in CTLA-4 plus PD-1 inhibitors) indicated a large between-study heterogeneity of irAEs in patients with NSCLC treated by ICIs. Consequently, a random effects model was applied to estimate the overall incidence of irAEs.

In the current analysis, there were several points outside the funnel (Figure S2), indicating a large between-study heterogeneity which is consistent with the results of the heterogeneity test in the forest plots. In addition, the points outside the funnel are always associated to the most relevant studies having heterogeneity in study characteristics. Taking funnel plot of any grade irAEs in CTLA-4 plus PD-1 inhibitor combination for example (Figure S2g), there were two studies (Michael 2021 and Neal 2019) outside the funnel. Michael 2021 was the only one using ipilimumab in combination with pembrolizumab instead of nivolumab in the other studies, and Neal 2019 was the only single arm trials whereas others were all RCTs.



**FIGURE 4** Model predicted any grade and grade greater than or equal to 3 irAE rates of (a) PD-1, (b) PD-L1 inhibitors with different therapy line and treatment combination, and (c) first-line CTLA-4 inhibitor (Ipilimumab) with different dosing regimens. The dots are model predicted values and the line segments represent the 95% confidence intervals, respectively. irAE, immune-related adverse event.



For ICI monotherapy, the descending order of the pooled irAE rates is CTLA-4 inhibitor, PD-1 inhibitor, and PD-L1 inhibitor. The results were in agreement with previous trials and meta-analysis that irAE rates were higher in patients across various cancer types receiving ICIs targeting CTLA-4 than PD-(L)1 inhibitors.<sup>6–8</sup> In addition, PD-L1 inhibitors exhibited lower irAE rates versus PD-1 inhibitors.<sup>35</sup> It was found that patients with NSCLC had a higher incidence of pneumonitis compared with other cancer types, such as melanoma and renal cell carcinoma.<sup>10</sup> But the overall incidence of irAEs in patients with NSCLC was similar with that in several cancers, including NSCLC. The patterns of irAEs in patients with NSCLC shown in this analysis were similar with studies including diverse cancer types.

In this study, PD-(L)1 inhibitors showed no dose or exposure dependence, which may be explained by the high affinity and saturating target engagement of PD-(L)1 inhibitors at regular clinical doses. For example, 0.04 µg/ml of nivolumab was sufficient to occupy more than 70% of PD-1 receptors on T cells,<sup>36</sup> which is nearly 100 times lower than the trough concentration at clinical dose. Low doses of pembrolizumab also showed elevated target engagement: ~90% for 0.5 mg/kg and 80% for 0.2 mg/kg.<sup>37</sup> The recommended dose of avelumab 10 mg/kg was associated with more than 90% target occupancy.<sup>38</sup> Besides, the trough concentrations of atezolizumab and durvalumab

at regular doses are more than 1000 times higher than the  $EC_{50}$  of target binding.<sup>22</sup>

In contrast, CTLA-4 inhibitors exhibited statistically significant exposure dependence when used alone or combined with PD-(L)1 inhibitors, which is in agreement with clinical studies of ipilimumab<sup>39</sup> and tremelimumab,<sup>40</sup> where incidence of irAEs, especially of grade greater than or equal to 3, increased with drug exposure levels. In an exposure-safety analysis of ipilimumab based on individual data pooled from four studies, higher doses of ipilimumab produced steady-state trough concentration ( $C_{min,ss}$ ) that associated with higher incidence of irAEs,<sup>41</sup> which suggested that the risk of irAEs in patients receiving ipilimumab was dose-dependent. Moreover, taking grade greater than or equal to 3 irAEs, for example, the coefficient of the CTLA-4 inhibitor normalized exposure ( $\beta_2$  in Equation 3) was close to that in the previous MBMA (0.0016 vs. 0.0015<sup>9</sup>), indicating a similar profile of irAE dose dependence in NSCLC compared to pooled cancer types.

According to the analysis, combination therapy with PD-1 and CTLA-4 inhibitors strengthen the dependence of irAE rates on normalized exposure of CTLA-4 inhibitors, whereas combination therapy with PD-L1 inhibitors and CTLA-4 inhibitors just increase the baseline of irAE rates. The coefficient of the interaction term ( $\beta_3$  in Equation 3) was similar to the publication (0.0176 vs. 0.011<sup>9</sup>). They

exhibited an alike synergistic effect of PD-1 and CTLA-4 inhibitors on grade greater than or equal to 3 irAEs both in NSCLC and pooled cancer types.

The OR was calculated by exponentiating the coefficient estimates to help with the interpretation. An OR greater than or equal to 1 indicates an increase in probability of irAEs and OR less than 1 indicates a decrease in probability of irAEs. One potential covariate found from the meta-regression is the therapy line where the ICI is used. Patients receiving ICIs as second-line or later therapy had a lower incidence of any grade and grade greater than or equal to 3 irAEs compared with those receiving ICIs as first-line therapy (OR <1,  $p < 0.05$ ). A similar effect of therapy line has been shown for grade greater than or equal to 3 irAEs in patients with advanced melanoma treated with pembrolizumab or ipilimumab.<sup>42</sup> The previous MBMA of PD-1 and CTLA-4 inhibitors adds the covariate in an interaction form with CTLA-4 inhibitor normalized exposure, characterizing the synergistic effect of therapy line and CTLA-4 inhibitors. In other words, it has no effect on irAEs of PD-1 inhibitors in the publication.<sup>9</sup> However, the covariate of therapy line in patients with NSCLC was added into the meta-regression model in a separate binomial term based on the current data, which demonstrated an impact of therapy line on irAE rates among PD-(L)1 and CTLA-4 inhibitors.

Another covariate significantly influencing irAE rates was the combination of ICIs with chemotherapy or target therapy. Combination of ICIs with chemo or target therapy would lead to higher incidence of any grade and grade greater than or equal to 3 irAEs compared to ICI monotherapy (OR >1,  $p < 0.05$ ). The previous MBMA just adds the covariate of “combination of ICI with chemotherapy” on factor<sub>PD-1</sub> in a binomial term,<sup>9</sup> indicating only an increase in irAE rate of PD-1 inhibitors. However, the current available data in this analysis would support a separate additive effect of both chemotherapy and target therapy on irAEs among PD-(L)1 and CTLA-4 inhibitors.

One limitation of the work is that this study just focused on trial-level and cross-sectional data, where the individual longitudinal data were not available to characterize the time course of exposure and irAE development. The results of trial-level meta-regression analyses would not be as robust as those of regression analyses using individual patient data in examining potential modifiers of treatment effects.<sup>43</sup> However, because therapy line and combination with chemotherapy or target therapy are both categorical covariates of which patients of the whole cohorts had the same value, the bias would be limited without potential confounding across studies. Besides, there is currently no standardized methodology to determine whether an AE is an irAE or an AE of other etiology. Incidence of irAEs

was obtained in this analysis if an adverse event was reported as “irAE,” “selected treatment-related AE,” “AE of special interest,” and the highest incidence of a potential irAE was used when the overall incidence is not given.<sup>14</sup> In this case, actual incidence of irAEs would be underestimated. Additionally, therapy lines were rounded off to 0 or 1 based on the percentage of patients receiving first-line versus second-line or later therapy for studies including both categories. This approximation may lead to biased assessments but there were no significantly difference in model parameters before and after imputations or rounding when using sensitivity analyses (Figure S3). Furthermore, although the patterns and dose dependence of irAEs in patients with NSCLC is similar to those across several cancer types, a large sample of clinical studies is needed in the future to compare the incidence and severity of irAEs among more tumor types.

In conclusion, a comprehensive model-based meta-analysis was conducted to quantify dose dependence and covariate effects of both any grade and grade greater than or equal to 3 irAEs in patients with NSCLC treated by ICIs. It was only an irAE rate dependence on normalized exposure of CTLA-4 inhibitors that had been observed. Therapy line and combination of ICIs with chemo or target therapy were significant covariates. This study provides quantitative evidence and a quantitative reference for the reasonable clinical application of ICI in patients with NSCLC from the perspective of irAEs.

## AUTHOR CONTRIBUTIONS

R.Z. and T.Z. wrote the manuscript. T.Z. designed the research. R.Z., D.K., R.C., Y.G., W.J., and M.H. performed the research. R.Z. and D.K. analyzed the data.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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