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Dose dependence of treatment-related adverse events for immune checkpoint inhibitor therapies: a model-based meta-analysis

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ABSTRACT

Programmed cell death-1 (PD-1) and/or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) immune checkpoint inhibitor (ICI) treatments are associated with adverse events (AEs), which may be dependent on ICI dose. Applying a model-based meta-analysis to evaluate safety data from published clinical trials from 2005 to 2018, we analyzed the dose/exposure dependence of ICI treatment-related AE (trAE) and immune-mediated AE (imAE) rates. Unlike with PD-1 inhibitor monotherapy, CTLA-4 inhibitor monotherapy exhibited a dose/exposure dependence on most AE types evaluated. Furthermore, combination therapy with PD-1 inhibitor significantly strengthened the dependence of trAE and imAE rates on CTLA-4 inhibitor dose/exposure.

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Introduction

Immune checkpoint inhibitors (ICIs) have shown efficacy across various cancers and are being evaluated in multiple clinical trials.¹ ICIs are associated with immune-mediated adverse events (imAEs), particularly in combination therapy.² Immunological checkpoints function to prevent autoimmune reactions; therefore, their inhibition can cause immune dysregulation and autoimmune-type reactions that lead to imAEs.^{3,4} Additional AEs, more typical of reactions to chemotherapy, have also been observed with programmed cell death ligand-1 (PD-L1) and programmed cell death-1 (PD-1) inhibitors.⁵ The management of AEs and patient safety using appropriate ICI dosing regimens is, therefore, an essential consideration in the optimization of ICI monotherapy and combination therapy.^{3,4}

Multiple clinical trials and reviews of the safety of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors, PD-1 inhibitors, and PD-L1 inhibitors, and their combinations using pooled and meta-analysis approaches have been published.^{1–35} Previously, AEs have been evaluated for various organ classes, including gastrointestinal,¹⁴ dermatologic,¹⁵ hepatic,⁹ renal,¹⁶ endocrine,¹⁷ pulmonary,^{18,19} and other rare immune-related AEs.²⁰ It has been shown that the type, incidence rate and severity of imAEs differ for the different ICIs classes and further increase under combination treatments with CTLA-4 and PD-(L)1 blocking antibodies.^{4,6,26}

However, despite such a substantial amount of clinical ICI safety data generated to date, a full mechanistic understanding on the pathophysiology of imAEs and a potential relationship

between imAE rates and ICI efficacy are still lacking.³⁶ To date, factors such as baseline T cell repertoire, cytokine and antibody profiles, as well as gut microbiota composition, have been found to be associated with a higher risk of imAEs in single studies.^{37,38} In terms of a relationship between AEs and ICI dose/exposure, analyses have focused on a limited number of doses, and dose dependence has not been systematically quantified for any of these organ classes. Trough levels at steady state have been used in a study of ipilimumab AE rates, based on individual-level data for 498 patients pooled from 4 phase 2 studies, where the dose-dependent effect was quantified using a logistic regression model.²⁵ However, these early modeling results have not been validated further in later studies. Therefore, in continuation of our previous work,²¹ we aimed to apply model-based meta-analysis methodologies for the quantitative study of the relationship between ICI dose and AEs.

Materials and methods

Literature search and data collection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for article search and selection.³⁹ Two investigators (BS and AO) independently searched and assessed the PubMed-Medline and Citeline Trialtrove⁴⁰ databases, along with the published American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) abstracts, to identify relevant PD-1 and CTLA-4 ICI safety data published from 2005 to 2018.

For the PubMed-Medline search, the following keywords were used: nivolumab OR pembrolizumab OR ipilimumab OR tremelimumab OR lambrolizumab OR ticilimumab OR (CTLA-4 OR PD-1) AND (safety OR adverse events) AND (oncology OR cancer). For the published ASCO abstracts search, the following keywords were used: nivolumab OR pembrolizumab OR ipilimumab OR tremelimumab, with a similar search performed for the published ESMO abstracts and the Citeline Trialrove database. In addition, we also reviewed references identified within published systematic reviews and meta-analyses. The AEs grouped by organ class have not been systematically reported for PD-L1 inhibitors; these trials were not included in the current analysis.

Adverse Events

Reporting of specific imAE types may vary across trials, thereby affecting the synthesis of evidence for each specific imAE.²⁹ In the current study, subgroup analyses were conducted for grade 3/4 imAEs for 5 organ classes: gastrointestinal, skin, pulmonary, hepatic, and endocrine. Rates of total treatment-related AEs (trAEs) and total grade 3/4 trAEs were also evaluated. The majority of studies included in the analysis classified AEs according to the Medical Dictionary for Regulatory Activities, and AE grades were defined according to CTCAE v4.03 guidance.

Immune checkpoint inhibitor dose/exposure

Two PD-1 inhibitors (nivolumab and pembrolizumab) and two CTLA-4 inhibitors (ipilimumab and tremelimumab) were evaluated in both monotherapy and combination therapy settings. To combine and compare AEs across different ICI dosing schedules, we proposed a novel methodology accounting for differences in ICI pharmacokinetics (PK) and potency (with respect to target receptor binding). We used population PK models for ICIs as published in the literature, along with documents from the United States Food and Drug Administration and the European Medicines Agency.⁴¹⁻⁵⁴ Based on parameter values derived from these PK models, we simulated exposure profiles in plasma for various sets of administered dosing regimens. Concentrations were averaged when steady-state conditions were assumed to have been reached. The simulated averaged concentration was next normalized by the drug concentration at which 50% inhibition of the native target receptor is achieved (IC_{50}). Published IC_{50} values have been measured in vitro. Normalization of drug exposure by the drug IC_{50} value allowed us to combine AE data from different ICIs acting on the same target receptor (refer to Supplemental Methods). All details of the PK models and derived parameter values are summarized in Supplemental Tables 1 and 2.

Statistical analysis

A meta-analysis was performed using trial-level data and based on a random-effects model. The Cochran Q test was used to detect heterogeneity across the different trials and between subgroups. Publication bias was evaluated by Funnel plots and Egger's test. To determine the relationship between dose/exposure and AEs, we performed a subgroup

analysis by splitting exposure intervals into high and low subgroups. Patients were assigned to subgroups based on the mean normalized drug exposure value calculated for each cohort. In fact, due to the reduced number of doses tested in the clinical programs considered, the 'low exposure' subgroup mostly included approved ICI dose levels, while the 'high' subgroup included cohorts with doses higher than the approved dosing and consequently closer to the MTD level. Logit-transformed AE rates were used and, when averaged AE rates for the subgroups were <5% for a particular organ class, AEs were considered to be rare. For rare AEs, the normal distribution assumption for within-trial variability is no longer valid and has been shown to lead to a bias in the estimation of the mean effect size.⁵⁵ Thus, for rare AEs, a normal-binomial general linear mixed model approach was used.⁵⁶

A meta-regression analysis was performed to derive a functional form of AE rate dependence on ICI dose/exposure to (i) quantitatively estimate parameters that would characterize dependence and (ii) evaluate the influence of patient baseline characteristics on dependence. The following models were tested to determine which model described the data with maximum likelihood:

Model 1, additive:

$$\text{logit}(Pr_{AE}) = \beta_0 + \beta_1 C_{norm, CTLA4} + \beta_2 C_{norm, PD1}$$

Model 2, supra-additive:

$$\text{logit}(Pr_{AE}) = \beta_0 + \beta_1 C_{norm, CTLA4} + \beta_2 C_{norm, PD1} + \beta_3 C_{norm, CTLA4} C_{norm, PD1}$$

Model 3, supra-additive with a binominal PD-1 inhibitor effect:

$$\text{logit}(Pr_{AE}) = \beta_0 + \beta_1 C_{norm, CTLA4} + \beta_2 C_{norm, PD1} + \beta_3 C_{norm, CTLA4} Factor_{PD1}$$

Model 4, CTLA-4 inhibitor-driven, with PD-1 inhibitor-dependent modulation:

$$\text{logit}(Pr_{AE}) = \beta_0 + \beta_1 C_{norm, CTLA4} + \beta_3 C_{norm, CTLA4} Factor_{PD1}$$

where $C_{norm, CTLA4}$ refers to the normalized averaged steady-state concentration of an anti-CTLA-4 drug, and $\text{logit}(AE)$ corresponds to the logit-transformed probability of a given AE averaged across studies. Supra-additive refers to a cross term in model equations, characterizing synergism between PD-1 inhibitor and CTLA-4 inhibitor effects. $Factor_{PD1}$ is set to 1 if a PD-1 inhibitor drug was given as monotherapy or in combination, and to 0 otherwise. To test sensitivity and to assess potential confounding factors, the following trial-level patient baseline characteristics were selected in a sequential (forward and backward) step-wise covariate search (see Supplemental Tables 1 and 3 for detailed explanations): line of therapy (first-line versus second-line or later therapy), cancer type (non-small cell lung cancer [NSCLC] versus melanoma versus others), ICI therapy combination + standard chemotherapy, ICIs (ipilimumab versus tremelimumab; nivolumab versus pembrolizumab), median age of patients in the study/cohort, percentage of males versus females, and

percentage of PD-L1-positive patients at baseline. PD-L1 positivity was defined according to the thresholds used in the included studies: PD-L1 threshold was 1% for 30 studies, 5% for 3 studies, and 50% for 1 study. The final model was chosen based on multiple criteria, including the value of the Akaike information criterion, with correction for small sample size, confidence intervals (CIs) of the regression coefficients, and different model diagnostic plots. Details of the meta-regression modeling and study-level characteristics are presented in Supplemental Table 1–4. The R statistics package *metafor*⁵⁷ was used to evaluate the statistical significance ($p < .05$) for dose dependence.

Results

Study selection and characteristics

A total of 417 data sources were selected for further analysis. Of these, we selected 102 eligible articles and abstracts (Supplemental Figure 1). Given the recent trend toward ICI studies having nonrandomized designs,⁵⁸ single-arm studies meeting the inclusion criteria were included.^{7,11,15,17,18} The selected articles included 153 treatment cohorts of 21,305 patients who received PD-1 or CTLA-4 ICI monotherapy or combination therapy across 80 clinical trials. A detailed description of the included studies is provided in Supplemental Table 5. Publication bias analysis revealed no significant asymmetry, indicating no obvious publication bias with respect to both total trAE and tissue-specific imAE types (Supplemental Figure 2).

AE analysis by ICI dose/exposure

The association between AE rates and dose/exposure was not statistically significant for PD-1 inhibitor monotherapy (Table 1; Supplemental Figure 3). For CTLA-4 inhibitor monotherapy, total grade 3/4 trAE rates were significantly higher in the high-dose/exposure subgroup versus the low-dose/exposure subgroup (37% versus 23%, respectively; $p < .001$), along with hepatic imAE rates (7.0% versus 1.1%, respectively; $p < .001$; Figure 1a and Table 1; Supplemental Figure 3). There was a significant association between the rates of total trAEs ($p < .05$), total grade 3/4 trAEs ($p < .001$), gastrointestinal imAEs ($p < .01$), hepatic imAEs ($p < .001$), and skin imAEs ($p < .05$) with PD-1 inhibitor + CTLA-4 inhibitor combination therapy dose/exposure (Figure 1b and Table 1; Supplemental Figure 3).

Meta-regression analyses

To provide a more formal quantification of AE dependencies upon ICI dose/exposure, as well as the testing of the different trial-level patient baseline characteristics, statistical meta-regression analyses were conducted. There was no significant increase in AE rates with increased dose/exposure of PD-1 inhibitor monotherapy, while increases in CTLA-4 inhibitor dose/exposure led to significant increases in total grade 3/4 trAEs, hepatic imAEs, and gastrointestinal imAEs (Figure 2). For PD-1 inhibitor + CTLA-4 inhibitor combination therapy, AE rates increased with a higher CTLA-4 inhibitor dose/

exposure only. The model that best described the total grade 3/4 trAE rate dependence on ICI dose/exposure was model 4 (see Methods), where the total grade 3/4 trAE rate was driven by CTLA-4 inhibitor exposure with a PD-1 inhibitor-dependent modulation. According to model 4, the regression coefficient describing the CTLA-4 inhibitor effect increased from 0.0015 (95% CI, 0.001–0.002; $p < .001$) to 0.0124 (95% CI, 0.0095–0.0153; $p < .001$) in the presence of a PD-1 inhibitor, which explained the significantly higher AE rate observed with the combination treatment, despite lower CTLA-4 inhibitor doses in combination therapy versus monotherapy (Figure 2). To further validate these results, we performed a similar analysis for gastrointestinal imAEs and hepatic imAEs. Similar to the total grade 3/4 trAE results, model 4 was shown to be the optimal model based on the objective function value and other diagnostic criteria (Figure 2).

Additional factors influencing AE rates

Meta-regression analysis was used to determine additional characteristics that affected AE rates during ICI treatment. Only grade 3/4 trAEs were evaluated, which included, but were not limited to, imAEs. Combining a PD-1 inhibitor with standard chemotherapy resulted in additive toxicity, which increased total grade 3/4 trAE rates from 17.7% (90% prediction interval [PI], 16.2%–19.4%) in monotherapy studies to 39.0% (90% PI, 29.4%–49.5%) in chemotherapy combination studies (Figure 3a). Additionally, first-line ICI therapy was shown to increase the regression coefficient for the CTLA-4 inhibitor dose/exposure effect from 0.0004 (95% CI, 0.0001–0.0011; $p < .001$) to 0.0034 (95% CI, 0.0031–0.0037; $p < .001$), corresponding to an increase in total grade 3/4 trAEs in studies evaluating CTLA-4 inhibitors in the first-line setting (Figure 3b). Incorporation of these two additional covariates into the final model did not change the functional form of the dependence of trAE rates on CTLA-4 inhibitor and PD-1 inhibitor dose/exposure. This allowed us to prospectively predict total grade 3/4 trAE rates for treatment options that have not yet been tested in clinical trials: a triple combination of PD-1 inhibitor + CTLA-4 inhibitor + standard chemotherapy was predicted to achieve a grade 3/4 trAE rate of 50% at lower doses than doses tested in clinical trials of ICI dual combination therapy (Figure 3c).

There were no statistically significant differences in AE rates across different cancer types (Supplemental Table 2). This finding suggests that ICI-related AE rates across cancer types may not significantly differ and supports the practice of pooling ICI AE data across different cancer types when performing meta-analyses. We did not observe any statistically significant effect when incorporating ICI type for a given target class as a covariate, illustrating that CTLA-4 inhibitors and PD-1 inhibitors exhibit similar safety profiles within their target class (Supplemental Table 2). Within the CTLA-4 target class, AE differences between tremelimumab and ipilimumab have been reported once.⁷ However, when the line of therapy and drug-specific normalized exposure were included as covariates in the present meta-analysis, no statistically significant

Table 1. Subgroup analysis of AE rates and ICI dose/exposure.

Target Dose/Exposure Subgroup	Total trAE		Total Grade 3/4 trAE		Gastrointestinal imAE		Hepatic imAE		Skin imAE		Endocrine imAE		Pulmonary imAE	
	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher
PD-1	AE % CI N	71 68-75 7506	74 70-77 2377	17 15-19 8899	19 15-22 2402	1.3 0.9-2.0 3557	3.4 1.3-8.8 227	1.9 1.4-2.5 3557	0.04 0-80 227	1.1 0.8-1.6 3644	1.3 0.3-6.2 247	0.4 0.2-0.9 2838	0.4 0.4-1.5 3577	1.2 0.2-8 247
PD-1 dose difference CTLA-4	AE % CI N	83 75-89 1934	89 85-92 4907	23 18-28 1934	37 32-42 4931	9.5 7.2-12 1549	13 10-16 2701	1.1 0.4-3.2 1652	7.0 5.3-9.1 2615	1.4 0.5-3.4 1652	2.9 1.8-4.5 2701	4.3 2.6-7.0 1652	0.14 0.02-1.0 719	1.0 0.5-2.0 817
CTLA-4 dose difference CTLA-4 + PD-1 (CTLA-4 dose)	AE % CI N	83 76-88 2064	92 86-95 654	35 30-41 2106	53 46-59 654	6.4 3.1-13 1183	20 14-20 509	9.5 7.1-13 1183	18 15-22 509	3.8 2.9-5.1 1203	6.3 4.5-8.6 544	5.3 3.7-7.6 1203	1.8 0.9-1.6 1203	1.6 0.8-3.1 509
CTLA-4 + PD-1 dose difference (CTLA-4 dose)		<i>p</i> = .016		<i>p</i> < .001		<i>p</i> = .008		<i>p</i> < .001		<i>p</i> = .02		<i>p</i> = .17		<i>p</i> = .8

Abbreviations: AE, adverse event; CI, confidence interval; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; ICI, immune checkpoint inhibitor; imAE, immune-mediated adverse event; PD-1, programmed cell death-1; trAE, treatment-related adverse event.

p < 0.05 was considered statistically significant for dose/exposure dependence.

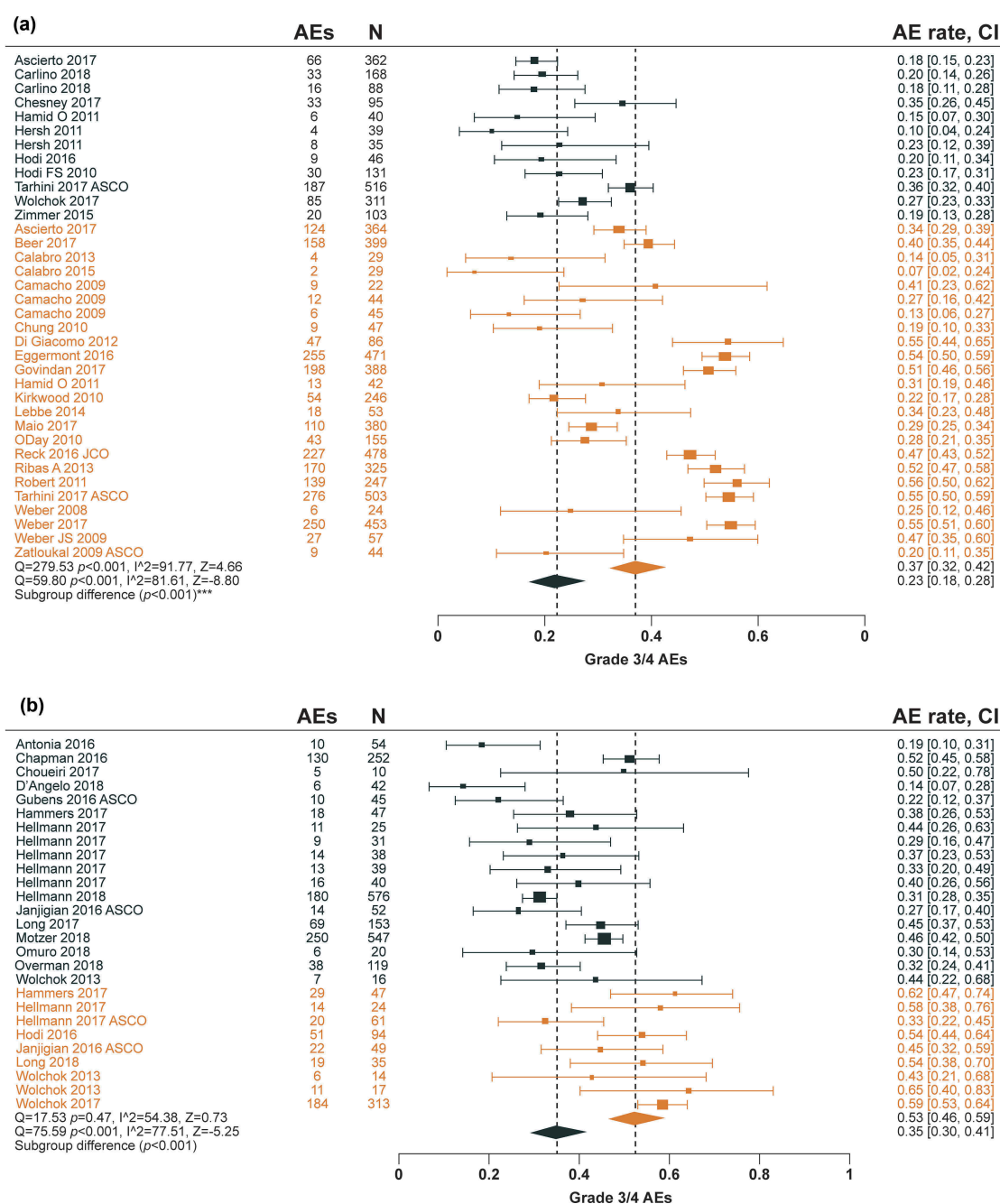


Figure 1. Forest plots of grade 3/4 AEs for (a) CTLA-4 inhibitors and (b) CTLA-4 inhibitor + PD-1 inhibitor.

Notes: Gray color denotes cohorts in the low-dose/exposure subgroup; orange color marks cohorts in the high-dose/exposure subgroup. Model results are shown as colored diamonds for each cohort. Note: in Figure (2A), there is a clear dependence on the line of therapy. Some of the high-dose/exposure cohorts are shifted to the right-hand side of the plot; most of these correspond to first-line therapy. The orange cohorts in the central and left-hand side parts of the plot mostly correspond to second-line or later therapy.

Abbreviations: AE, adverse event; ASCO, American Society of Clinical Oncology; CI, confidence interval; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; JCO, Journal of Clinical Oncology; PD-1, programmed cell death-1.

differences between tremelimumab and ipilimumab were found (Supplemental Tables 2 and 3).

Discussion

It is now well understood that autoimmunity is an integral part of the immune system and self-reactivity preserving in T cell repertoire despite the clonal selection controls many

aspects of lymphocyte biology.^{59,60} In the healthy state immune, autoreactive reactions are tightly controlled via multiple regulatory mechanisms, e.g., via expression of various immune checkpoint molecules.⁶¹ Therefore, the phenomenon of peripheral immune tolerance is in fact assembled by the dynamic ratio of multiple co-stimulatory and co-inhibitory interactions.⁶² These general immunological concepts formulated decades ago were supported nowadays with the results from the multiple clinical trials of CTLA-4, PD-1 and PD-L1

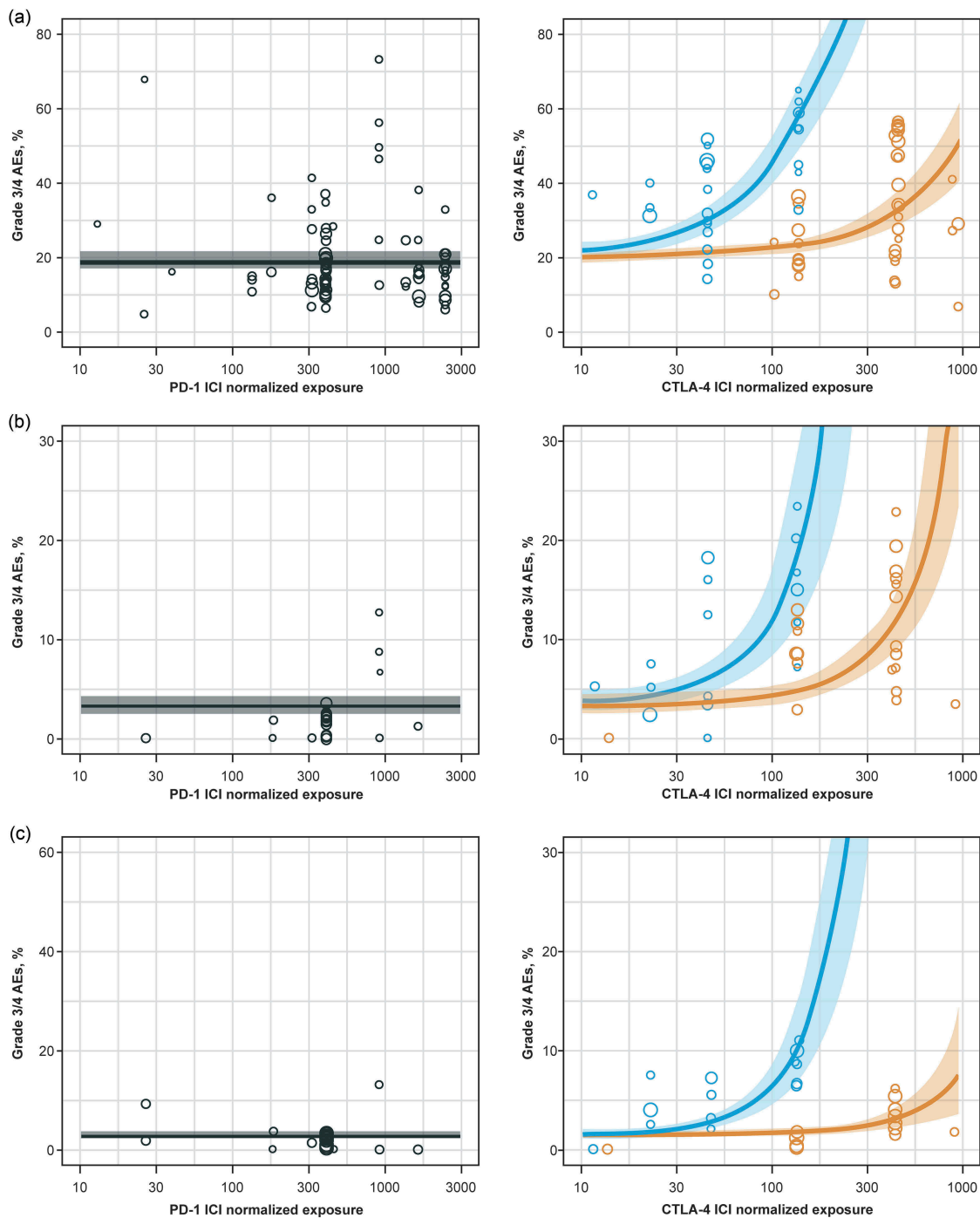


Figure 2. Dependencies of grade AEs upon ICI drug dose/exposure for (a) total trAEs, (b) gastrointestinal imAEs, and (c) hepatic imAEs.

Notes: Gray color denotes PD-1 inhibitors, orange color denotes CTLA-4 inhibitors, and blue color denotes treatment combinations. No dose/exposure dependence is predicted for PD-1 inhibitors; dose/exposure dependence is predicted for CTLA-4 inhibitor treatments, and an even stronger dose/exposure dependence is predicted for combination treatments.

Abbreviations: AE, adverse event; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; ICI, immune checkpoint inhibitor; imAE, immune-mediated adverse event; PD-1, programmed cell death-1; trAE, treatment-related adverse event.

blocking antibodies, which all in addition to remarkable anti-tumor responses have specific profiles of immune-mediated autoreactive AEs.^{4,6,26}

This model-based meta-analysis evaluated safety data from 80 published clinical trials (representing 21,305 patients from 153 dosing cohorts), which, to our knowledge, is the largest

analysis conducted to date and represents the first attempt to analyze the dose/exposure dependence of PD-1 and CTLA-4 ICI trAE and imAE rates upon the aggregation of all published AE data. Moreover, previous analyses of AE rate dose/exposure dependence for CTLA-4 inhibitors and PD-1 inhibitors have been limited to specific dosing regimens, without

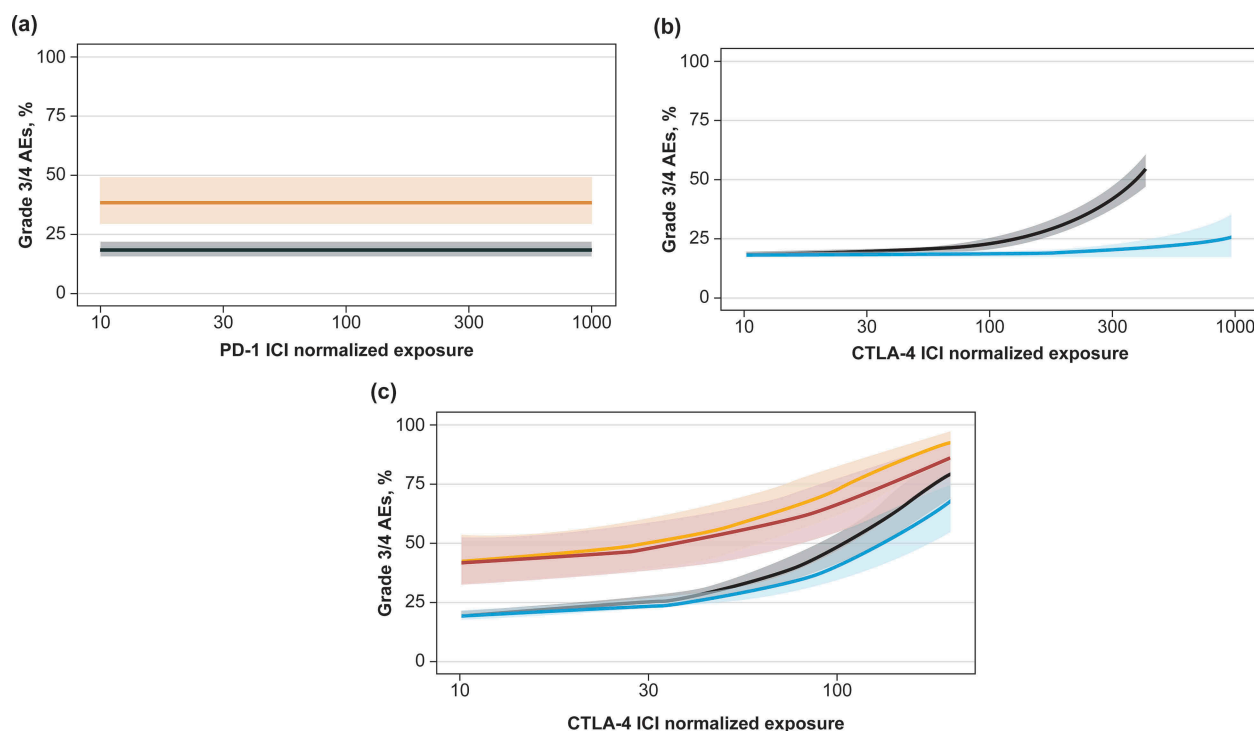


Figure 3. Dependencies of AEs on ICI dose/exposure and baseline characteristics.

Notes: Meta-regression results for (A) PD-1 inhibitors (gray color) and combinations of PD-1 inhibitors + chemotherapy (orange color), (B) CTLA-4 inhibitor monotherapy received as first-line therapy (gray color) and second-line or later therapy (blue color), and (C) CTLA-4 inhibitor + PD-1 inhibitor combination therapy in first-line (gray color) and second-line or later therapy (blue color), as well as triple combination of CTLA-4 inhibitor + PD-1 inhibitor + chemotherapy, received as first-line (orange color) and second-line or later therapy (red color).

Abbreviations: AE, adverse event; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; ICI, immune checkpoint inhibitor; PD-1, programmed cell death-1.

consideration of PK modeling and normalization by drug exposure.^{2,4,7,22} To analyze and compare AEs across trials, we proposed a novel methodology by deriving an average concentration at steady state as a measure of dose/exposure to the respective ICI, and further normalized average concentrations by drug-specific potencies (IC_{50} values). This allowed us to combine data for more than one ICI acting on the same target class (namely, PD-1 [nivolumab and pembrolizumab] or CTLA-4 [ipilimumab and tremelimumab]) and to perform meta-regression on dose for the quantitative characterization of dose/exposure dependence, while also evaluating the influence of patient baseline characteristics. Moreover, as opposed to AEs occurring within a specific organ class (e.g., colitis and diarrhea), the present study evaluated total trAE and imAE rates per organ class (e.g., gastrointestinal), which broadened the range of evaluated safety measures and showed that the effects observed (e.g., total AE measures) are in fact driven by events of immune-mediated origins.

The main results derived from our meta-analysis are in agreement with existing knowledge on AEs vs dose/exposure dependences, as observed in single drug development programs. For example, AE rates with PD-1 inhibitor monotherapy did not show dose/exposure dependence, which is probably due to the high specificity of PD-1 blocking antibodies and saturating biological effects (T-cell activation) with most doses tested in clinical trials. Thus, a 0.5 mg/kg Q3 W dose of pembrolizumab, which is nearly 10 times lower than the approved dose, shows 90% target engagement.⁶³ The absence of a dose/exposure vs efficacy dependence has also

been observed in pooled analyses of Phase 1 and Phase 2 trials of pembrolizumab.⁶⁴ Similar results have been observed in Phase 1 trials of nivolumab, another approved PD-1 blocking antibody, with a dosing regimen of 0.3 mg/kg Q2 W resulting in saturating target engagement.⁶⁵

In contrast to PD-1 blocking antibodies, CTLA-4 inhibitors as monotherapies or in combination with a PD-1 inhibitor exhibited robust AE dose/exposure dependence for most of the AE types evaluated. These results, obtained on aggregated clinical data, are in good agreement with earlier studies of ipilimumab^{22,66,67} and tremelimumab,⁶⁸ where AE rates, especially of grades 3 and 4, increased with drug exposure levels and were quantitatively described with population dose-exposure-safety modeling.²⁵ Such a robust dose-exposure safety relationship may be indicative of autoimmune reactions; for example, it has been shown that CTLA-4 blocking not only increases counts of activated CD4+ and CD8+ T cell subsets,⁶⁹⁻⁷¹ but also significantly increases the number of TCR clonotypes.⁷²⁻⁷⁴ The qualitative and quantitative boosting of peripheral T cell recruitment via CTLA-4 blocking would inevitably cause a higher probability of autoimmune reactions. In support of this mechanism, it has been shown recently that the increase of the number of circulating T-cell effector clones with CTLA-4 inhibition can be a strong driver of immune-mediated toxicity.⁷⁵

In accordance with accumulating clinical evidence,⁶ our analysis also indicates that combination therapy with CTLA-4 and PD-1 inhibitors may result in significantly higher AE rates. It should be noted that while AE rates with PD-1

inhibitor monotherapy did not exhibit any dose/exposure dependence, combination therapy with PD-1 and CTLA-4 inhibitors was found to significantly strengthen the dependence of trAE and imAE rates on CTLA-4 inhibitor dose/exposure. In fact, the functional form of the final meta-regression equation supports the addition of a multiplicative coefficient (β_3), and thus supports the view that combination treatment with CTLA-4 and PD-1 inhibitors increases AE rates beyond additivity. This would suggest that, similarly to the beyond-additive efficacy benefits observed in melanoma, NSCLC and renal cell carcinoma, a combination of these two classes of ICIs may cause immune-mediated toxicity through different mechanisms.^{76,77} For example, the addition of a PD-1 inhibitor may increase the immune sensitivity of peripheral compartments (including tumor) to the boosted recruitment of newly primed CD4+ and CD8+ cells caused by CTLA-4 inhibition in lymphoid organs;^{78,79} this, in turn, may lead to a higher rate of imAEs. Interestingly, the corresponding mathematical equation describing the dependence of various trAE and imAE rates on PD-1 and CTLA-4 drug exposure (*Model 4* in *Materials and Methods*) conceptually reflects autoimmune effects caused by lymphopenia-induced proliferation,⁸⁰ an autoreactive immune process experimentally shown to be amplified under PD-1 blockade.^{81,82}

Another interesting finding from the presented meta-analysis is that AE rates increased with increasing CTLA-4 ICI doses, in patients receiving first-line vs second-line or later therapy. Similar differences in rates of pneumonitis in NSCLC patients receiving first-line vs second-line or later therapy have been reported; however, no significant differences for other AEs have been observed.¹¹ A similar effect of therapy line has also been shown for grade 3/4 trAEs in patients with advanced melanoma treated with pembrolizumab or ipilimumab, coupled with a trend toward greater efficacy in the first-line setting.²⁸ The current data would not be sufficient to derive a clear mechanistic explanation for this observation. However, since the line of treatment (similarly to PD-1 inhibition – see the previous paragraph) may increase the sensitivity to CTLA-4 drug exposure (eTable3), it can be hypothesized that this effect may be dependent on the overall state of systemic immunity, which in fact can be compromised given a patient's treatment history, e.g., chemotherapy treatment⁸³ or progressive disease (increased tumor or metastatic burden), which all may affect both the efficacy and AE profiles of ICIs in subsequent therapies.^{84,85} Incorporation of a line-of-treatment covariate provides an opportunity for a more accurate comparison of safety profiles across ICIs. For example, we did not observe differences in AE dose dependence between ipilimumab and tremelimumab using our model-based framework, once the line of therapy was taken into account as a covariate (Supplemental Tables 2 and 3); this is in contrast to an early safety meta-analysis of anti-CTLA-4 antibodies, which showed lower AE rates for tremelimumab but did not take into account line of treatment as a covariate.⁷ Differences in AE rates for these two anti-CTLA-4 drugs were likely due to tremelimumab being mainly evaluated in patients receiving second-line or later therapy, while ipilimumab has been evaluated in both first-line and second-line or later

settings, with AE rates being higher in the first-line vs second-line or later setting, as shown in the present analysis.

Another covariate that independently affected AE rates was “combination of ICI with chemotherapy”; such combinations resulted in significantly higher AE rates vs ICI monotherapy treatment. Based on the currently available data, it would be challenging to conclude whether these increased AE rates are additive or beyond-additive, in such a combination setting with chemotherapy.^{86–88} A recently published meta-analysis of NSCLC trials revealed that combining a PD-1 inhibitor with chemotherapy affects both total trAEs and imAEs,⁸⁹ which would support the mechanistic hypothesis of a link between immunogenic cell death and its impact on systemic immunity; for example, specific types of chemotherapies may stimulate immunological effects, including a decrease in regulatory T-cell activity, an enhancement of tumor antigen presentation, and an induction of PD-L1 expression on tumor cells, which may increase ICI action and subsequently lead to increases in AE rates.⁹⁰

One additional limitation of the present work is that AEs have not been systematically reported by organ classes for all of the published clinical trials and, in particular, for PD-L1 inhibitors; these trials could not be included in the analysis. However, several meta-analyses suggest that treatments using PD-L1 inhibitors may exhibit lower imAE rates vs PD-1 inhibitors; thus, safety data for these two related ICI classes should not be pooled.^{91–93} More detailed analyses would be warranted to confirm such differences, including one making use of the same model-based methodology presented here (normalization by drug exposure and grouping AEs by organ class) and possibly augmented with patient-level AE data. Also, no published data on single-dose ICI therapies exist; hence, this analysis focused on settings making use of multiple dose regimens.

Despite a number of limitations, the present model-based approach provides a valuable quantitative framework for a joint analysis of clinical safety data from multiple ICIs currently available on the market or as tested in clinical trials. More importantly, this quantitative approach allows to extrapolate and predict safety outcomes for alternative treatment dosing regimens. This may be of special interest toward the development of therapeutic combinations, since efficacy and safety outcomes are only partially correlated for the various ICIs. Thus, it has recently been confirmed, in a Phase 3 trial, that reduction of dose and administration frequency of ipilimumab, down to a 1 mg/kg Q6 W regimen and in combination with a 240 mg Q2 W dose of nivolumab can significantly reduce Grade 3/4 total AEs rates while not compromising on efficacy, in those responding patients.⁹⁴ These results are in excellent agreement with a growing number of clinical reports, which indicate that an adequate reduction in dose does not compromise disease control or overall survival outcome measures.^{62,63,95–97} The present meta-analysis, combined with quantitative population PKPD analyses of patient-level clinical data may provide a very robust framework for the further optimization of ICI dosing regimens, especially in combination settings.

Conclusion

AE rates for PD-1 inhibitor monotherapy were not dose/exposure dependent. Significant AE dose/exposure dependence for CTLA-4 inhibitor monotherapy, CTLA-4 inhibitor + PD-1 inhibitor combination therapy, and ICI + chemotherapy combination therapy was observed for multiple AE types. Patients receiving first-line ICI therapy had higher AE rates vs patients receiving second-line or later ICI therapy. There was no influence of patient characteristics, such as PD-L1 status, on the observed relationships between AE rates and ICI dose/exposure. This novel model-based meta-analysis methodology provides a quantitative framework for positioning ICI doses and dosing regimens with respect to specific AE rates.

Abbreviations

AE	Adverse event
ASCO	American Society of Clinical Oncology
CI	Confidence interval
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
ESMO	European Society for Medical Oncology
IC ₅₀	Half maximal inhibitory concentration
ICI	Immune checkpoint inhibitor
imAE	Immune-mediated adverse event
NSCLC	Non-small cell lung cancer
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PI	Prediction interval
PK	Pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
trAE	Treatment-related adverse event

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Author contributions

All authors were involved in the concept and design of the study and data collection. BS, YK, AO, and KP conducted the analysis. All authors actively participated in manuscript development. All authors reviewed the manuscript drafts and approved the submission of the manuscript to this journal.

Declarations

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Disclosure statement

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