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Dynamic toxicity landscape of immunotherapy for solid tumors across treatment lines

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ABSTRACT

Objective: Immune checkpoint inhibitors (ICIs) targeting programmed cell death-1/ligand-1 (PD-1/PD-L1), cytotoxic T lymphocyte antigen-4 (CTLA-4), and lymphocyte-activation gene-3 (LAG-3) have been widely studied and applied throughout the course of cancer treatment. This study aimed to provide a comprehensive profile of ICI-associated toxicity and elucidate the toxicity patterns of ICIs across different treatment lines.

Methods: In total, 155 cohorts comprising 24 539 eligible patients were included in the safety analysis. Trial name, registration number, cancer type, trial phase, clinical setting, trial design, regimen, dosing schedule, age, sex and ethnicity distributions, number of patients, number of treatment-related adverse events (trAEs), and number of treatment-related death were extracted. We defined a timeline from the neoadjuvant setting to the third-line setting. We also introduced a synthesizing principle for adverse event rates (SPAER) of immunotherapy to ensure the comparability and reliability across different treatment lines. The study protocol was registered and approved by the PROSPERO protocol review committee (CRD42021242368).

Results: After excluding the neoadjuvant setting group, we observed a distinct reduction in the incidence of treatment-related adverse events (trAEs) with an advancement of the line of ICI treatment. The incidence of trAEs was negatively correlated with the line of treatment, irrespective of whether monotherapy or dual-ICI combination therapy was administered. Sensitivity analyses also confirmed the coincident negative correlations.

Conclusion: In summary, using a timeline-based concept centered around treatment lines, we revealed the dynamic landscape of ICI-associated toxicity and found that patients treated with ICIs during later lines of therapy may have a lower risk of trAEs.

1. Introduction

The emergence of immune checkpoint inhibitors (ICIs) targeting programmed cell death-1/ligand-1 (PD-1/PD-L1), cytotoxic T lymphocyte antigen-4 (CTLA-4), and lymphocyte-activation gene-3 (LAG-3) has led to a paradigm shift in cancer treatment.[1] ICIs reactivate effector T cells by blocking the PD-1/PD-L1 or CTLA-4 immune checkpoint pathways and preventing the immune escape of tumor cells.[2] ICIs are not only applied as second- or third-line therapies for previously treated[3] or heavily pretreated patients,[4] but are also being used as the first-line standard of care for treatment-naïve patients.[5] Moreover, the application of ICIs in neoadjuvant[6] and adjuvant therapies[7] is also being explored. However, ICIs can sometimes cause overactivation of host immunity, increasing the risk of treatment-related adverse events (trAEs) that manifest as immune-related toxicity in normal tissues.[8]

The human immune system is complex and sensitive to various factors. Hence, immune responses can often differ between untreated and treated patients.[9,10] Patients with treatment-refractory tumors show distinct immune system activity compared to those with previously untreated tumors[11]; thus, the incidence of trAEs can vary during different lines of treatment based on patients' immunological status. Given the increased adoption of ICI-based anticancer therapy, there is an ur-

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gent need to understand the dynamic safety landscape of ICIs and distinguish toxicity patterns across different lines of therapy. However, it is currently unclear whether the line of treatment influences the toxic effects of ICIs. In previous studies, the incidences of trAEs have been pooled without considering the changes in host immunity across different lines of treatment, leading to limited information and a potential risk of bias.[12,13]

Here, we performed a comprehensive analysis of immunotherapy-induced trAEs to provide a detailed profile of ICI-associated toxicities and elucidate ICI toxicity patterns across different treatment lines. We calculated the synthesizing principle of adverse event rates (SPAER) to reduce the heterogeneity of included studies and compared the toxicity of immunotherapies across different treatment lines. We extensively synthesized and analyzed evidence from clinical trials to delineate the trAEs caused by each regimen in different lines of treatment and uncover the dynamic changes in these trAEs.

2. Materials and methods

2.1. Data source and search strategy

The study protocol was registered and approved by the Prospective Register of Systematic Reviews (PROSPERO) protocol review committee (CRD42021242368, prospective study protocol in the Supplementary materials). We searched PubMed, Embase, Web of Science, and the Cochrane Library in June 2022 to identify relevant studies. We also reviewed online proceedings from major conferences, including the American Association for Cancer Research, the American Society of Clinical Oncology, and the European Society of Medical Oncology. Further, we searched the ClinicalTrials.gov database for additional eligible trials. The keywords used for the literature search were as follows: *immunotherapy, clinical trial, PD-1, PD-L1, CTLA-4, LAG-3, pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, ipilimumab, tremelimumab,* and *relatlimab* (Supplementary Table 1).

2.2. Study selection

Studies that met the following criteria were considered eligible for this study: (1) single-arm trials or randomized controlled trials, (2) single-agent ICI or dual-ICI combination regimens used for treatment, (3) regimen used across at least two lines of treatment, and (4) availability of trAE data. For combination therapies, considering the possibility of high heterogeneity and potential bias, we carefully excluded ICI plus chemotherapy combinations and only included dual-ICI combinations. The LAG-3 pathway has been established as the third immune checkpoint pathway, and its inhibition confers clinical benefits in patients with previously untreated melanoma. Considering the importance of LAG-3 inhibitors in current and future immunotherapy regimens, we also included trials investigating the safety of dual LAG-3 and PD-1 inhibition.

Subsequently, per the SPAER protocol, eligible trials were further classified into five groups based on when immunotherapy was administered. During this allocation process, alternative cohorts were labeled based on three tags - regimen, dosing schedule, and line of treatment, and only trials with matching regimens and dosing schedules were successfully included and allocated for further analysis. After excluding dosages that had been studied only in a single line of treatment, we finally included the following dosing schedules for further analyses: (1) pembrolizumab 200 mg, every 3 weeks, (2) nivolumab 3 mg/kg, every 2 weeks, (3) atezolizumab 1 200 mg, every 3 weeks, (4) avelumab 10 mg/kg, every 2 weeks, (5) durvalumab 10 mg/kg, every 2 weeks, (6) ipilimumab 3 mg/kg or 10 mg/kg, every 3 weeks, (7) nivolumab 1 mg/kg plus ipilimumab 3 mg/kg or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, every 3 weeks, (8) durvalumab 1500 mg plus tremelimumab 75 mg or durvalumab 20 mg/kg plus tremelimumab 1 mg/kg, every 4 weeks, and (9) nivolumab 480 mg plus relatlimab 160 mg, every 4 weeks.

2.3. Data extraction and outcomes

Included trials were double-checked online to ensure that updated data were being analyzed. The literature search and data extraction were independently performed by three researchers, and any discrepancies were resolved through a mutual consensus. We evaluated the main text and supplementary materials and performed extensive and detailed data extraction. The title and registration number of the trial, the cancer type studied, the trial phase, the clinical setting, the trial design, the regimen and dosing schedule, the age, sex, ethnicity and number of patients, and the number of trAEs and treatment-related deaths were obtained for each study.

The primary outcomes were trAEs, including (1) trAEs of any grade, (2) grade $\geq$ 3 trAEs, (3) trAEs leading to the discontinuation of ICIs, (4) trAEs leading to death, and (5) trAEs of special interest. Only treatment-, drug-, or immune-related adverse events (irAEs) were evaluated, and adverse events from any cause were carefully identified and excluded based on a thorough evaluation of the entire paper. TrAEs are those that occur during treatment and are defined according to standard guidelines.[13] However, irAEs represent all grades of adverse events associated with immune mechanisms, which result from the loss of immune homeostasis and off-target effects in peripheral tissues. In this study, both TrAEs and irAEs were identified from the included trials. The criteria for selecting the trAEs of special interest: toxicity events that had been widely reported, and the number of trials that did not report on trAEs of interest should not exceed 6% of all the trials included.

2.4. Data synthesis and statistical analysis

Incidences (denoted as p) of the main outcomes were first calculated using the number of patients with events (case) divided by the total number of patients (number), assuming that the data would follow binomial distributions. Results were then transformed to fit normal distributions in R software (version 4.0.3) with the *meta* package (version 4.18-0). Using the Shapiro–Wilk normality test, the W- and *P*-values were calculated for each dataset and the method providing the best normal distribution was selected for further data synthesis. A W-value close to 1.00 and a *P*-value greater than 0.10 were considered indicative of a normal distribution. Accordingly, an incidence matrix of trAEs, which was similar to a gene expression matrix, was constructed.[14]

A frequentist framework for synthesizing event rates was applied based on the transformed normally distributed data. Event rates and their corresponding 95% confidence intervals (CIs) were estimated using a fixed-effects or random-effects model. Statistical heterogeneity was assessed using the χ^2 and I^2 tests, with significance set at $P < 0.10$. An I^2 value greater than 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively; subsequently, a random-effects model was applied if significant heterogeneity was detected.[15] To avoid potential bias in the statistical model, event rates were pooled in a Bayesian framework using the OpenBUGS software (version 3.2.3). The joint posterior distributions of the model parameters were obtained using the Markov Chain Monte Carlo simulation for all Bayesian analyses. A Markov chain was established for running 5 000 burn-ins and 50 000 sample iterations at a step-size iteration of 1.

One-way analysis of variance (ANOVA) was used to compare the incidences of trAEs across different tumor types and the baseline clinical characteristics across the five line-of-treatment groups. If significant inter-group differences were observed, multiple comparisons were performed through Fisher's post-hoc least significant difference (LSD) test. In addition, Spearman's correlation analysis was performed using log2 transformed incidence data and the line of treatment based on ordinal scale data. Statistical analysis was performed using SPSS Statistics (version 26.0). To assess the stability of our results and rule out the possibil-

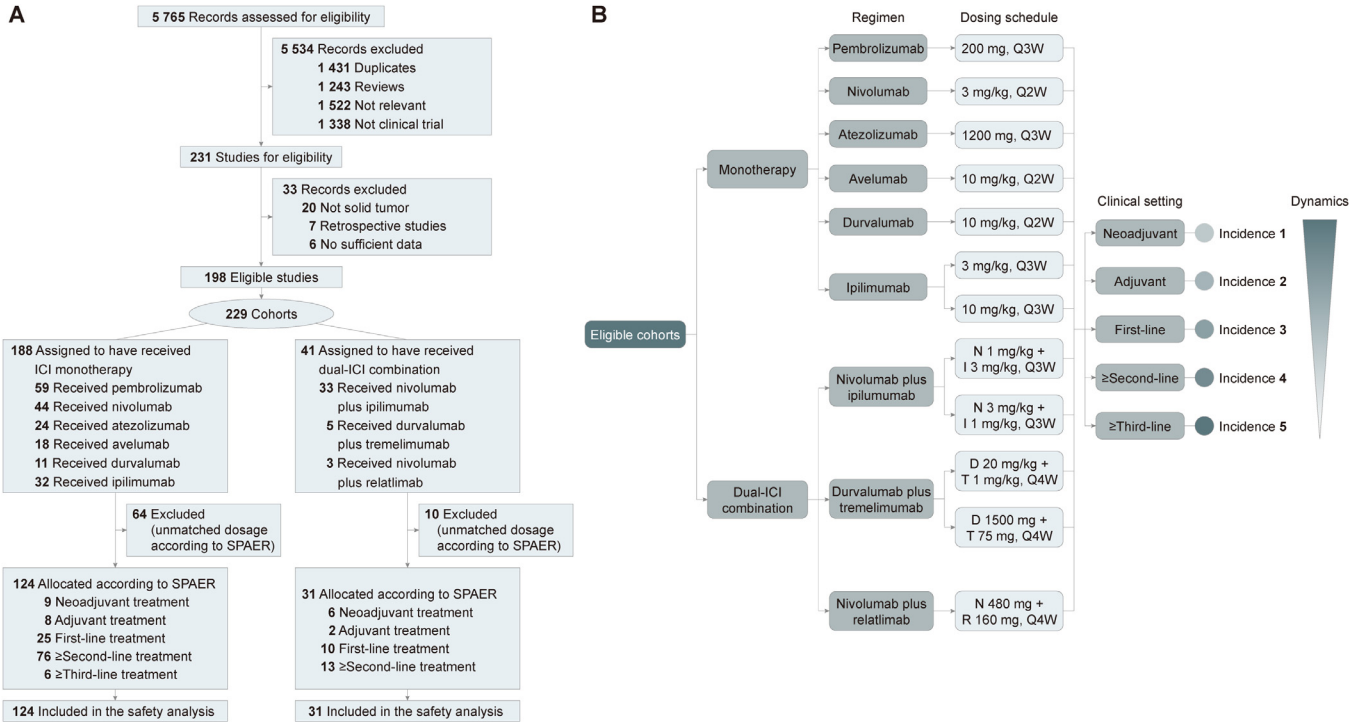


Fig. 1. Illustration of study design based on the synthesis principle for adverse event rate (SPAER) protocol. (A) Flowchart of the study selection and allocation process. (B) Illustration of the SPAER protocol and timeline concept. D, durvalumab; I, ipilimumab; N, nivolumab; T, tremelimumab, Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks.

ity that a particular drug contributed to the overall trend, we conducted a sensitivity analysis by omitting one study regimen each time. All tests were two-sided, and a *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Systematic review and characteristics

In total, 5 765 records were identified through a preliminary literature search. After screening the abstracts and reading the full text, 198 potential studies encompassing 229 cohorts that received immunotherapy were screened. Subsequently, 74 cohorts were considered ineligible and excluded from further analysis owing to a lack of matching dosing schedules based on the SPAER protocol. Through this allocation process, 127 studies encompassing 155 cohorts and a total of 24 539 eligible patients were finally included in the safety analysis (Fig. 1A and Supplementary Table 2). The baseline characteristics of the cohorts are listed in Supplementary Table 3. The SPAER protocol is illustrated in Fig. 1B.

We observed no significant difference in trAE incidence among the different tumor types (Supplementary Table 4 and Supplementary Fig. 1). One-way ANOVA showed that all baseline clinical characteristics, except the ECOG performance score, were largely comparable across the five line-of-treatment groups (Supplementary Table 5). Post-hoc multiple comparisons revealed inter-group differences in the proportion of patients with an ECOG performance score of 0 (Supplementary Table 6). Interestingly, Spearman's correlation analysis revealed that the proportion of patients with an ECOG performance score of 0 was negatively correlated with the line of treatment (Spearman's $r = -0.587$, $P < 0.01$). This finding indicated that the physical status of patients typically deteriorates through the course of treatment (Supplementary Table 7).

3.2. Dynamic incidence of overall treatment-related adverse events

To provide an overview of the safety profile of ICIs, we first focused on three primary outcomes that are widely reported in clinical trials: trAEs of any grade, grade ≥ 3 trAEs, and trAEs leading to drug discontinuation. Fig. 2 A-C summarized and depicted the incidences of all-grade toxicities associated with immunotherapy. According to the frequentist and Bayesian frameworks, patients receiving ICI monotherapy had a 0.70 (95% CI, 0.68–0.72), 0.17 (95% CI, 0.15–0.18), and 0.08 (95% CI, 0.07–0.09) probability of developing trAEs of any grade, grade ≥ 3 trAEs, and trAEs leading to discontinuation, respectively. In patients treated with dual-ICI combinations, the respective probabilities were 0.89 (95% CI, 0.85–0.93), 0.42 (95% CI, 0.36–0.49), and 0.20 (95% CI, 0.16–0.24) (Table 1 and 2).

Intriguingly, after introducing timelines based on the SPAER protocol, we observed a distinct reduction in the incidence of trAEs with an advancement of the line of treatment when the neoadjuvant setting group was excluded (Fig. 2D and Supplementary Fig. 2). For nivolumab (3 mg/kg, once every 2 weeks [Q2W]), the incidence of trAEs of any grade was 0.85 (95% CI, 0.82–0.88) in the adjuvant setting, 0.80 (95% CI, 0.71–0.88) in the first-line setting, 0.70 (95% CI, 0.66–0.75) in the ≥ second-line settings, and 0.59 (95% CI, 0.28–0.88) in the ≥ third-line settings. The incidences of grade ≥ 3 trAEs and trAEs leading to discontinuation showed similar trends in this group. Interestingly, dual-ICI combination therapies also showed similar patterns (Fig. 2E and Supplementary Fig. 3).

We further examined whether the incidence of trAEs was related to the line of treatment. Consistently, we found that the mean incidence of trAEs, including trAEs of any grade, grade ≥ 3 trAEs, and trAEs leading to discontinuation, was negatively correlated with the line of treatment, irrespective of whether monotherapy or combination therapy was administered (Fig. 2D and E). To further illustrate the patterns of immunotoxicity across different treatment lines, we also pooled incidences of any grade and grade ≥ 3 irAEs following immunotherapy. Interestingly,

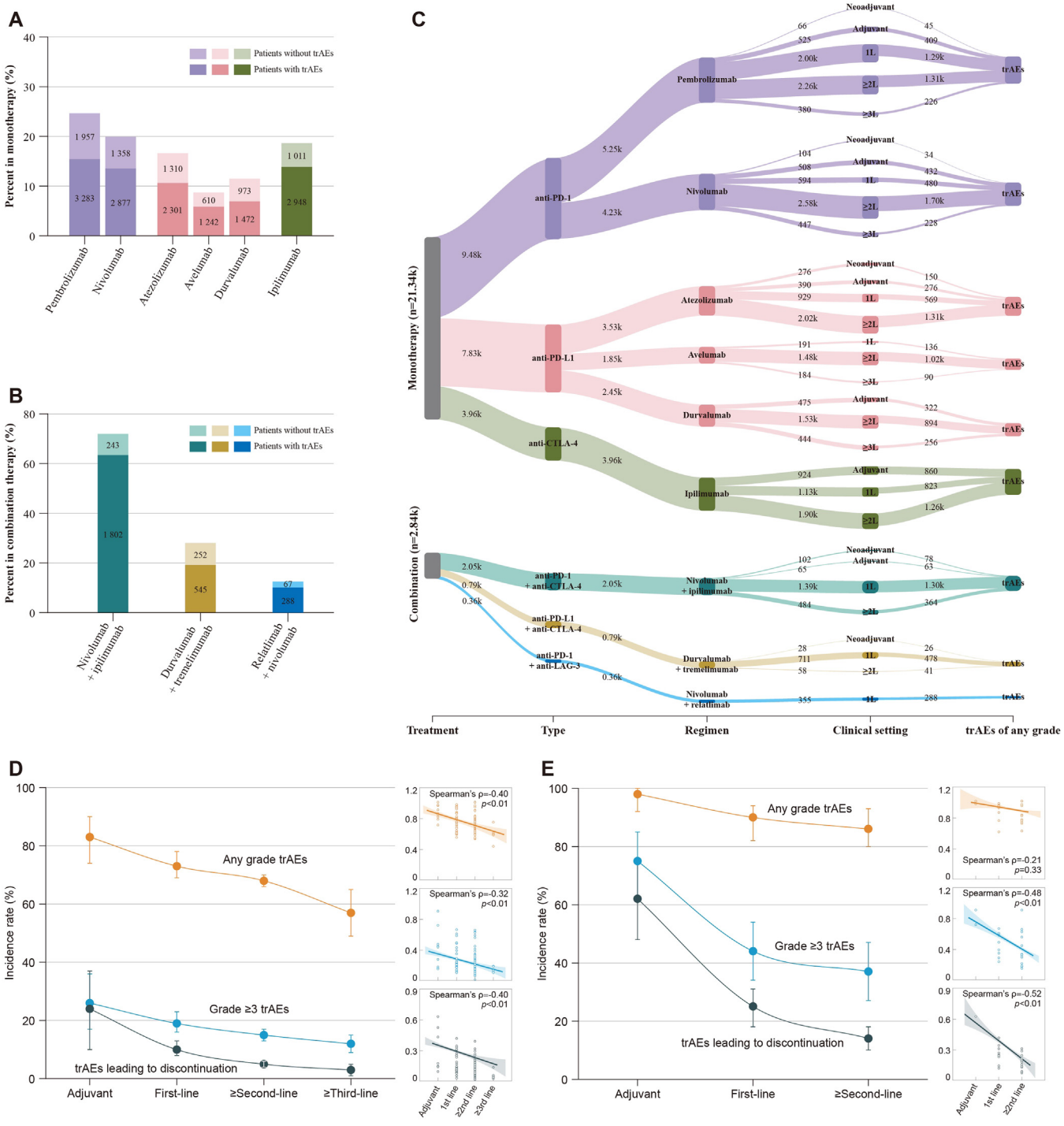


Fig. 2. Dynamic incidence of overall treatment-related adverse events. (A) Distribution of different regimens in monotherapy. (B) Distribution of different regimens in combination therapy. (C) Sankey plot of patient-level data for different regimens across different clinical settings. (D) Incidences of any grade trAEs, grade ≥ 3 trAEs, and trAEs leading to discontinuation during monotherapy across different clinical settings. (E) Incidences of any grade trAEs, grade ≥ 3 trAEs, and trAEs leading to discontinuation during combination therapy across different clinical settings. Incidences are presented as pooled rates combined with 95% CIs. 1 L, first-line; 2 L, second-line; 3 L, third-line; CIs, confidence intervals; trAEs, treatment-related adverse events.

the incidences of any grade irAEs (Supplementary Fig. 4A) and grade ≥ 3 irAEs (Supplementary Fig. 4B) were negatively correlated with the line of treatment.

To assess the validity of our results and rule out the possibility that a particular drug contributed to the overall trend, we conducted a sensitivity analysis by omitting one regimen at a time. The reduction in the overall incidence of trAEs remained consistent across these analyses, and correlation analyses also confirmed coincident negative associations (Supplementary Table 8, Supplementary Figs. 5 and 6).

3.3. Dynamic incidence of treatment-related adverse events of interest

To obtain a more comprehensive understanding of the safety profiles of immunotherapy, we developed a toxicity panel containing adverse events of special interest and reconstructed an incidence matrix based on

Table 1
Dynamic incidences of treatment-related adverse events in monotherapy by treatment line.

Clinical setting	Pembrolizumab	Nivolumab	Atezolizumab	Avelumab	Durvalumab	Ipilimumab	Ipilimumab	
	200 mg, Q3W (n = 5 240)	3 mg/kg, Q2W (n = 4 235)	1200 mg, Q3W (n = 3 611)	10 mg/kg, Q2W (n = 1 852)	10 mg/kg, Q2W (n = 2 445)	3 mg/kg, Q3W (n = 1 348)	10 mg/kg, Q3W (n = 2 611)	Overall (n = 21 342)
Any treatment-related adverse events, incidence (95% CI)								
Neoadjuvant	0.74 (0.47–0.94)	0.49 (0.20–0.79)	0.55 (0.48–0.62)	NA	NA	NA	NA	0.56 (0.43–0.69)
Adjuvant	0.79 (0.75–0.82)	0.85 (0.82–0.88)	0.71 (0.66–0.75)	NA	0.68 (0.63–0.72)	NA	0.93 (0.87–0.98)	0.83 (0.74–0.90)
First-line	0.66 (0.60–0.71)	0.80 (0.70–0.88)	0.64 (0.58–0.70)	0.74 (0.59–0.86)	NA	0.84 (0.73–0.93)	0.82 (0.78–0.85)	0.73 (0.69–0.78)
≥ Second-line	0.62 (0.60–0.64)	0.69 (0.64–0.75)	0.67 (0.64–0.69)	0.72 (0.67–0.76)	0.61 (0.57–0.64)	0.75 (0.65–0.83)	0.79 (0.70–0.88)	0.68 (0.66–0.70)
≥ Third-line	0.59 (0.54–0.64)	0.59 (0.28–0.86)	NA	0.49 (0.41–0.56)	0.58 (0.53–0.62)	NA	NA	0.57 (0.49–0.65)
Overall	0.65 (0.62–0.69)	0.70 (0.65–0.76)	0.65 (0.62–0.68)	0.71 (0.66–0.76)	0.61 (0.57–0.65)	0.79 (0.71–0.86)	0.84 (0.75–0.91)	0.70 (0.68–0.72)
Grade ≥ 3 treatment-related adverse events, incidence (95% CI)								
Neoadjuvant	0.29 (0.00–0.89)	0.09 (0.04–0.16)	0.08 (0.05–0.13)	NA	NA	NA	NA	0.12 (0.05–0.16)
Adjuvant	0.26 (0.03–0.58)	0.19 (0.07–0.31)	0.16 (0.13–0.20)	NA	0.13 (0.10–0.17)	NA	0.44 (0.41–0.48)	0.26 (0.17–0.36)
First-line	0.18 (0.15–0.21)	0.17 (0.11–0.25)	0.14 (0.12–0.16)	0.12 (0.07–0.16)	NA	0.24 (0.18–0.30)	0.46 (0.41–0.50)	0.19 (0.16–0.23)
≥ Second-line	0.15 (0.13–0.18)	0.13 (0.11–0.16)	0.15 (0.13–0.18)	0.09 (0.08–0.11)	0.10 (0.09–0.11)	0.19 (0.16–0.23)	0.34 (0.29–0.40)	0.15 (0.13–0.17)
≥ Third-line	0.16 (0.12–0.20)	0.13 (0.07–0.20)	NA	0.09 (0.05–0.14)	0.09 (0.07–0.12)	NA	NA	0.12 (0.09–0.15)
Overall	0.18 (0.15–0.20)	0.14 (0.12–0.16)	0.16 (0.14–0.17)	0.09 (0.08–0.11)	0.10 (0.09–0.11)	0.22 (0.20–0.24)	0.40 (0.36–0.46)	0.17 (0.15–0.18)
Treatment-related adverse events leading to discontinuation, incidence (95% CI)								
Neoadjuvant	0.05 (0.00–0.19)	0.09 (0.00–0.25)	0.05 (0.01–0.10)	NA	NA	NA	NA	0.04 (0.01–0.07)
Adjuvant	0.13 (0.10–0.16)	0.08 (0.06–0.11)	0.16 (0.12–0.20)	NA	NA	NA	0.46 (0.37–0.55)	0.24 (0.10–0.37)
First-line	0.07 (0.04–0.09)	0.12 (0.08–0.15)	0.06 (0.04–0.07)	0.07 (0.03–0.10)	NA	0.13 (0.08–0.18)	0.29 (0.25–0.34)	0.10 (0.08–0.13)
≥ Second-line	0.04 (0.03–0.06)	0.04 (0.03–0.05)	0.03 (0.01–0.05)	0.06 (0.04–0.08)	0.03 (0.02–0.04)	0.09 (0.07–0.12)	0.22 (0.20–0.24)	0.05 (0.04–0.06)
≥ Third-line	0.02 (0.00–0.07)	0.04 (0.03–0.07)	NA	0.04 (0.02–0.08)	0.02 (0.01–0.04)	NA	NA	0.03 (0.01–0.05)
Overall	0.05 (0.04–0.07)	0.05 (0.04–0.07)	0.05 (0.03–0.07)	0.06 (0.04–0.07)	0.03 (0.02–0.04)	0.10 (0.08–0.14)	0.26 (0.18–0.34)	0.08 (0.07–0.09)

Abbreviations: CI, confidence interval; NA, not available; Q2W, once every two weeks; Q3W, once every three weeks; Q4W, once every four weeks.

Table 2
Dynamic incidences of treatment-related adverse events in combination therapy by treatment line.

Clinical setting	Nivolumab plus ipilimumab		Durvalumab plus tremelimumab		Nivolumab plus relatlimab	
	N 1 mg/kg + I 3 mg/kg, Q3W (n = 920)	N 3 mg/kg + I 1 mg/kg, Q3W (n = 1 125)	D 1500 mg + T 75 mg, Q4W (n = 368)	D 20 mg/kg + T 1 mg/kg, Q4W (n = 429)	N 480 mg + R 160 mg, Q4W (n = 355)	Overall (n = 3 197)
Any treatment-related adverse events, incidence (95% CI)						
Neoadjuvant	0.97 (0.89–1.00)	0.97 (0.86–1.00)	0.93 (0.76–0.99)	NA	NA	0.96 (0.91–1.00)
Adjuvant	0.98 (0.92–1.00)	NA	NA	NA	NA	0.98 (0.92–1.00)
First-line	0.95 (0.93–0.97)	0.91 (0.85–0.96)	0.75 (0.70–0.80)	0.60 (0.55–0.65)	0.81	0.88 (0.79–0.94)
≥ Second-line	0.95 (0.92–0.99)	0.81 (0.69–0.90)	NA	0.72 (0.61–0.85)	NA	0.86 (0.80–0.93)
Overall	0.96 (0.94–0.97)	0.87 (0.82–0.93)	0.83 (0.64–0.97)	0.62 (0.57–0.66)	NA	0.89 (0.85–0.93)
Grade ≥ 3 treatment-related adverse events, incidence (95% CI)						
Neoadjuvant	0.67 (0.33–0.93)	0.15 (0.06–0.27)	0.21 (0.08–0.41)	NA	NA	0.41 (0.18–0.62)
Adjuvant	0.75 (0.63–0.85)	NA	NA	NA	NA	0.75 (0.63–0.85)
First-line	0.57 (0.50–0.63)	0.41 (0.30–0.51)	0.28 (0.23–0.33)	0.23 (0.19–0.28)	0.19	0.42 (0.31–0.52)
≥ Second-line	0.58 (0.41–0.74)	0.27 (0.22–0.32)	NA	0.17 (0.08–0.28)	NA	0.37 (0.27–0.47)
Overall	0.61 (0.53–0.68)	0.29 (0.21–0.37)	0.27 (0.23–0.32)	0.22 (0.18–0.26)	NA	0.42 (0.36–0.49)
Treatment-related adverse events leading to discontinuation, incidence (95% CI)						
Neoadjuvant	0.12 (0.02–0.27)	0.16 (0.05–0.32)	NA	NA	NA	0.14 (0.06–0.25)
Adjuvant	0.62 (0.48–0.75)	NA	NA	NA	NA	0.62 (0.48–0.75)
First-line	0.36 (0.32–0.40)	0.22 (0.19–0.25)	0.24 (0.19–0.28)	0.13 (0.10–0.17)	0.15	0.23 (0.18–0.29)
≥ Second-line	0.19 (0.13–0.25)	0.11 (0.07–0.15)	NA	0.10 (0.03–0.19)	NA	0.14 (0.10–0.18)
Overall	0.29 (0.22–0.37)	0.15 (0.11–0.20)	0.24 (0.19–0.28)	0.12 (0.09–0.15)	NA	0.20 (0.16–0.24)

Abbreviations: CI, confidence interval; D, durvalumab; I, ipilimumab; N, nivolumab; NA, not available; R, relatlimab; T, tremelimumab; Q3W, once every three weeks; Q4W, once every four weeks.

these selected adverse events. All these adverse events were treatment-related and reported by at least 10% of the included cohorts.

A dual-ICI combination generally caused higher toxicity than monotherapy. The most common irAEs of any grade were hypothyroidism (0.06 [95% CI, 0.06–0.07] in monotherapy; 0.14 [95% CI, 0.11–0.16] in combination therapy), pneumonitis (0.03 [95% CI, 0.02–0.03] in monotherapy; 0.06 [95% CI, 0.04–0.07] in combination therapy), and colitis (0.02 [95% CI, 0.01–0.03] in monotherapy; 0.07 [95% CI, 0.05–0.09] in combination therapy) (Fig. 3A). The most frequent trAEs of any grade were fatigue (0.19 [95% CI, 0.18–0.21] in monotherapy; 0.34 [95% CI, 0.28–0.40] in combination therapy), diarrhea (0.12 [95% CI, 0.11–0.14] in monotherapy; 0.27 [95% CI, 0.23–0.32] in combination therapy), pruritus (0.12 [95% CI, 0.10–0.13] in monotherapy; 0.27 [95% CI, 0.23–0.31] in combination therapy), and rash (0.10 [95% CI, 0.09–0.12] in monotherapy; 0.26 [95% CI, 0.21–0.30] in combination therapy) (Fig. 3B). A Forest plot was used to visualize toxicity-related events (Supplementary Fig. 7).

By introducing timelines based on the line of treatment, we also reconstructed a dynamic incidence matrix of adverse events of interest. Interestingly, we observed that the incidence of many specific adverse events tended to decrease with an advancement of the line of treatment (Fig. 3C). For monotherapy, the incidence of hyperthyroidism was the highest in the neoadjuvant setting, followed by the adjuvant and first-line settings; moreover, this value was the lowest in the ≥ second-line and ≥ third-line settings. A similar trend was also observed for other adverse events of interest, including hyperthyroidism, pneumonitis, colitis, hepatitis, alanine aminotransferase (ALT) elevation, and aspartate aminotransferase (AST) elevation. This tendency was not only observed for monotherapy overall but also for anti-PD-1, anti-PD-L1, and anti-CTLA-4 drugs alone. Moreover, combination therapy also yielded similar results. The dynamic incidences of adverse events of interest are listed in Supplementary Table 9.

3.4. Incidence of specific adverse events by cancer type

To understand the toxicity landscape of immunotherapy by cancer type, we integrated and pooled the mean incidences of ten specific ICI-induced toxicities, including cutaneous, endocrine, and gastrointestinal events.

We observed distinct trAE profiles across different cancer types (Table 3). Patients with melanoma who received monotherapy showed the highest risk of developing gastrointestinal toxicities, including colitis (0.06 [95% CI, 0.04–0.08]) and diarrhea (0.25 [95% CI, 0.20–0.30]). In addition, these patients were also more likely to experience cutaneous toxicities, such as rash (0.19 [95% CI, 0.15–0.22]) and pruritis (0.22 [95% CI, 0.18–0.25]). Nevertheless, the most common adverse event in patients with lung cancer was pneumonitis (0.04 [95% CI, 0.02–0.05]). Hypothyroidism occurred in 11% of patients with head and neck cancers and in about 6% of patients with other cancers. The mean incidence of hepatitis was comparable among patients with different cancer types. Regarding ICI combinations, the incidence of gastrointestinal toxicities was consistently higher in patients with melanoma, suggesting that irAEs were tissue-specific and tended to affect specific organs.

3.5. Dynamic incidence of fatal treatment-related adverse events

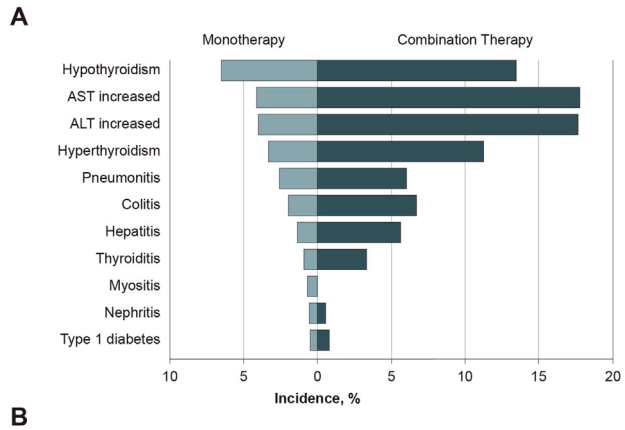
To first obtain the visible spectrum of fatal trAEs,[16] we developed a waterfall plot corresponding to an oncoprint[17] (Fig. 4). After screening the 155 included cohorts, we identified 71 (45.8%) with at least one fatal trAE. These 71 cohorts accounted for a total of 180 deaths. Among the 21 342 and 3 197 patients treated with ICI monotherapy and a dual-ICI combination, 150 (0.70%) and 30 (0.94%) developed fatal trAEs, respectively.

We further explored fatal trAE patterns across the different regimens. Pneumonitis was the only fatal trAE observed across all monotherapy regimens. Fatal hepatitis and cardiac failure were commonly

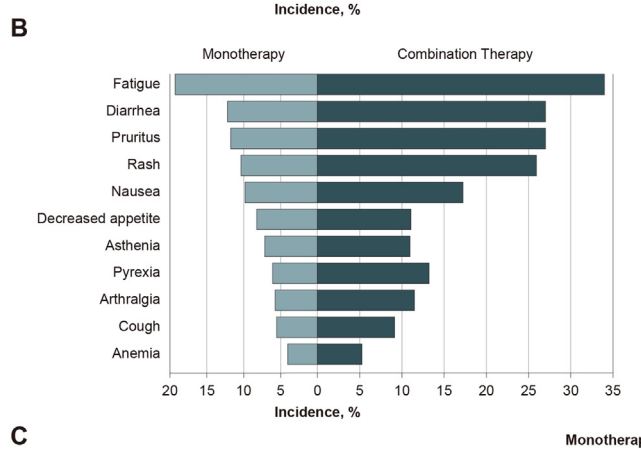
Table 3
Mean incidences of specific adverse events by cancer type.

Type	Monotherapy, incidence (95% CI)						Combination therapy, incidence (95% CI)			
	Gastrointestinal (n = 2 301)	Genitourinary (n = 4 604)	Head and neck (n = 953)	Lung (n = 5 674)	Melanoma (n = 5 027)	Other (n = 2 742)	Genitourinary (n = 1 009)	Lung (n = 525)	Melanoma (n = 1 334)	Other (n = 210)
Pneumonitis	0.02 (0.02–0.03)	0.02 (0.01–0.03)	0.02 (0.00–0.04)	0.04 (0.02–0.05)	0.01 (0.00–0.01)	0.02 (0.01–0.04)	0.04 (0.02–0.07)	0.06 (0.04–0.08)	0.06 (0.03–0.09)	0.04 (0.00–0.14)
Hepatitis	0.01 (0.00–0.02)	0.03 (0.00–0.09)	0.00 (0.00–0.01)	0.02 (0.01–0.04)	0.01 (0.00–0.01)	0.02 (0.01–0.02)	0.01 (0.00–0.02)	0.02 (0.01–0.04)	0.06 (0.01–0.14)	0.02 (0.01–0.04)
Colitis	0.02 (0.01–0.03)	0.02 (0.02–0.03)	0.00 (0.00–0.01)	0.01 (0.00–0.01)	0.06 (0.04–0.08)	0.02 (0.01–0.02)	0.04 (0.02–0.07)	0.02 (0.01–0.04)	0.09 (0.05–0.13)	0.04 (0.01–0.07)
Thyroiditis	0.01 (0.00–0.01)	0.01 (0.00–0.02)	0.01 (0.00–0.03)	0.01 (0.00–0.01)	0.01 (0.00–0.02)	0.01 (0.00–0.02)	0.02 (0.00–0.04)	0.02 (0.01–0.04)	0.03 (0.02–0.04)	0.03 (0.00–0.08)
Hypothyroidism	0.08 (0.06–0.10)	0.06 (0.04–0.08)	0.11 (0.06–0.17)	0.06 (0.05–0.07)	0.06 (0.04–0.08)	0.06 (0.05–0.07)	0.14 (0.07–0.22)	0.08 (0.06–0.10)	0.15 (0.13–0.17)	0.13 (0.08–0.19)
Hyperthyroidism	0.04 (0.02–0.05)	0.03 (0.02–0.05)	0.02 (0.01–0.03)	0.03 (0.02–0.04)	0.04 (0.02–0.07)	0.02 (0.01–0.04)	0.09 (0.05–0.14)	0.06 (0.01–0.10)	0.14 (0.09–0.20)	0.09 (0.04–0.13)
Rash	0.07 (0.06–0.09)	0.10 (0.06–0.14)	0.07 (0.06–0.09)	0.07 (0.06–0.09)	0.19 (0.15–0.22)	0.06 (0.05–0.07)	0.22 (0.16–0.28)	0.11 (0.08–0.13)	0.35 (0.26–0.44)	0.23 (0.16–0.29)
Pruritus	0.12 (0.08–0.16)	0.12 (0.08–0.16)	0.05 (0.04–0.07)	0.07 (0.05–0.09)	0.22 (0.18–0.25)	0.09 (0.07–0.10)	0.27 (0.24–0.30)	0.13 (0.10–0.15)	0.32 (0.26–0.37)	0.26 (0.11–0.45)
Fatigue	0.13 (0.10–0.16)	0.21 (0.17–0.25)	0.14 (0.12–0.16)	0.16 (0.13–0.19)	0.26 (0.21–0.32)	0.21 (0.17–0.25)	0.36 (0.20–0.55)	0.21 (0.12–0.32)	0.40 (0.32–0.48)	0.35 (0.17–0.56)
Diarrhea	0.10 (0.07–0.14)	0.14 (0.09–0.19)	0.07 (0.05–0.08)	0.08 (0.07–0.09)	0.25 (0.20–0.30)	0.08 (0.07–0.10)	0.25 (0.18–0.32)	0.18 (0.11–0.26)	0.33 (0.25–0.41)	0.29 (0.13–0.49)

Abbreviation: CI, confidence intervals.



Adverse events of interests	Incidence, % (95% CI)	
	Monotherapy	Combination therapy
Hypothyroidism	6.49 (5.68-7.37)	13.60 (11.47-16.24)
AST increased	4.10 (3.31-5.00)	17.80 (12.96-20.09)
ALT increased	3.98 (3.20-4.88)	17.66 (12.52-24.35)
Hyperthyroidism	3.30 (2.75-3.93)	11.31 (8.42-14.85)
Pneumonitis	2.57 (2.15-3.02)	5.68 (3.82-7.41)
Colitis	1.95 (1.47-2.53)	6.82 (4.98-8.78)
Hepatitis	1.38 (0.90-2.02)	6.23 (2.14-10.31)
Thyroiditis	0.92 (0.66-1.21)	3.32 (2.49-4.45)
Myositis	0.68 (0.47-0.96)	0.00 (0.00-0.00)
Nephritis	0.55 (0.38-0.77)	0.68 (0.21-1.44)
Type 1 diabetes	0.49 (0.34-0.66)	0.77 (0.41-1.30)



Adverse events of interests	Incidence, % (95% CI)	
	Monotherapy	Combination therapy
Fatigue	19.25 (17.65-20.98)	34.21 (28.25-40.32)
Diarrhea	12.16 (10.73-13.71)	27.16 (22.98-31.80)
Pruritus	11.79 (10.33-13.36)	27.11 (23.17-31.40)
Rash	10.33 (9.05-11.73)	25.88 (21.24-30.18)
Nausea	9.78 (8.82-10.85)	17.20 (13.66-21.27)
Decreased appetite	8.24 (7.54-8.99)	11.05 (9.15-13.04)
Asthenia	7.13 (6.26-8.08)	11.44 (8.01-15.56)
Pyrexia	6.09 (5.20-7.09)	13.24 (10.46-16.35)
Arthralgia	5.74 (5.06-6.48)	10.90 (7.09-15.79)
Cough	5.51 (3.87-7.59)	9.10 (6.84-11.95)
Anemia	3.96 (3.20-4.84)	5.23 (3.67-7.52)

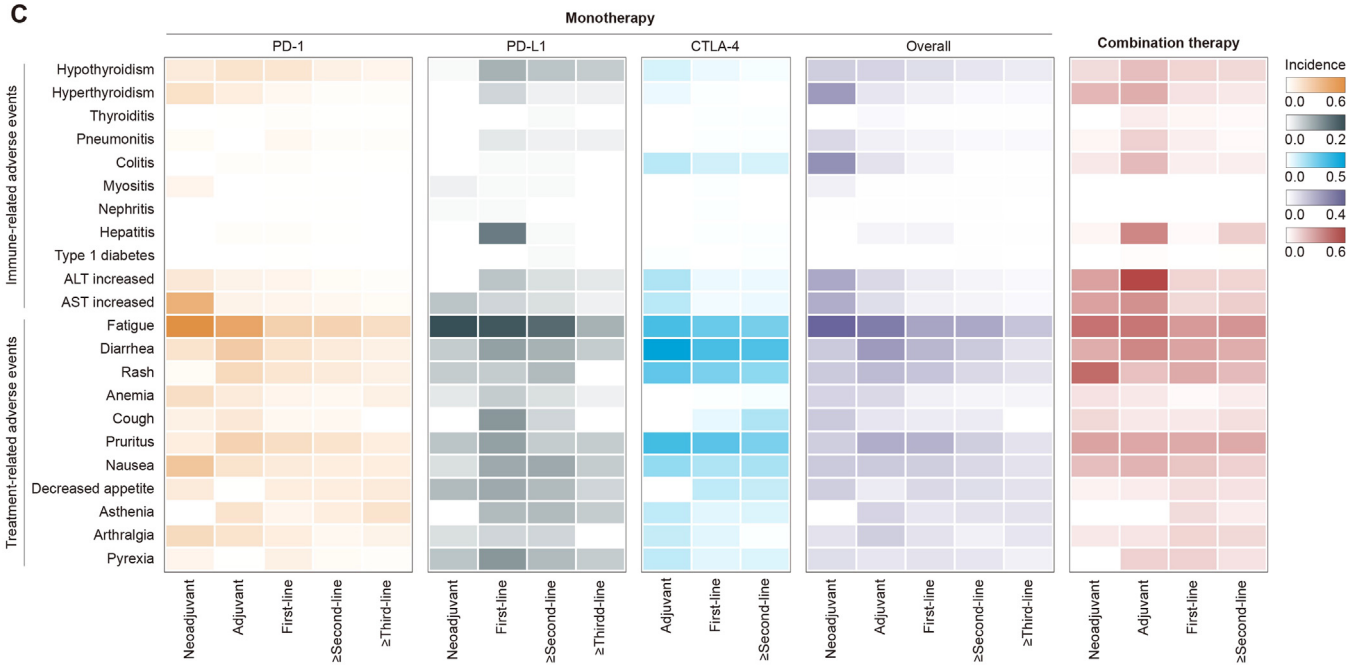


Fig. 3. Dynamic incidence of treatment-related adverse events of interest. (A) Incidences of the most common immune-related adverse events during monotherapy and combination therapy. (B) Incidences of the most common treatment-related adverse events during monotherapy and combination therapy. (C) Dynamic incidences of adverse events of interest during monotherapy and combination therapy across different clinical settings. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

observed across monotherapy regimens (Fig. 5A). Pembrolizumab (n = 49) was associated with the broadest distribution of fatal trAEs, including pneumonitis (n = 8, 16.3%), hyper progression (n = 7, 14.3%), sudden death (n = 4, 8.2%), myositis (n = 2, 4.1%), and neurologic events (n = 2, 4.1%). In contrast, avelumab was associated with the narrowest spectrum of lethal trAEs. Notably, gastrointestinal events, including intestinal perforation (n = 8, 19.0%), colitis (n = 5, 11.9%), and hepatic failure (n = 2, 4.8%), were the predominant cause of death in patients receiving ipilimumab monotherapy (n = 42) (Fig. 5A and Supplementary Fig. 8). More importantly, lethal trAEs caused by the dual-ICI combinations differed from those caused by monotherapy. Pneumonitis (n = 7, 23.3%), hep-

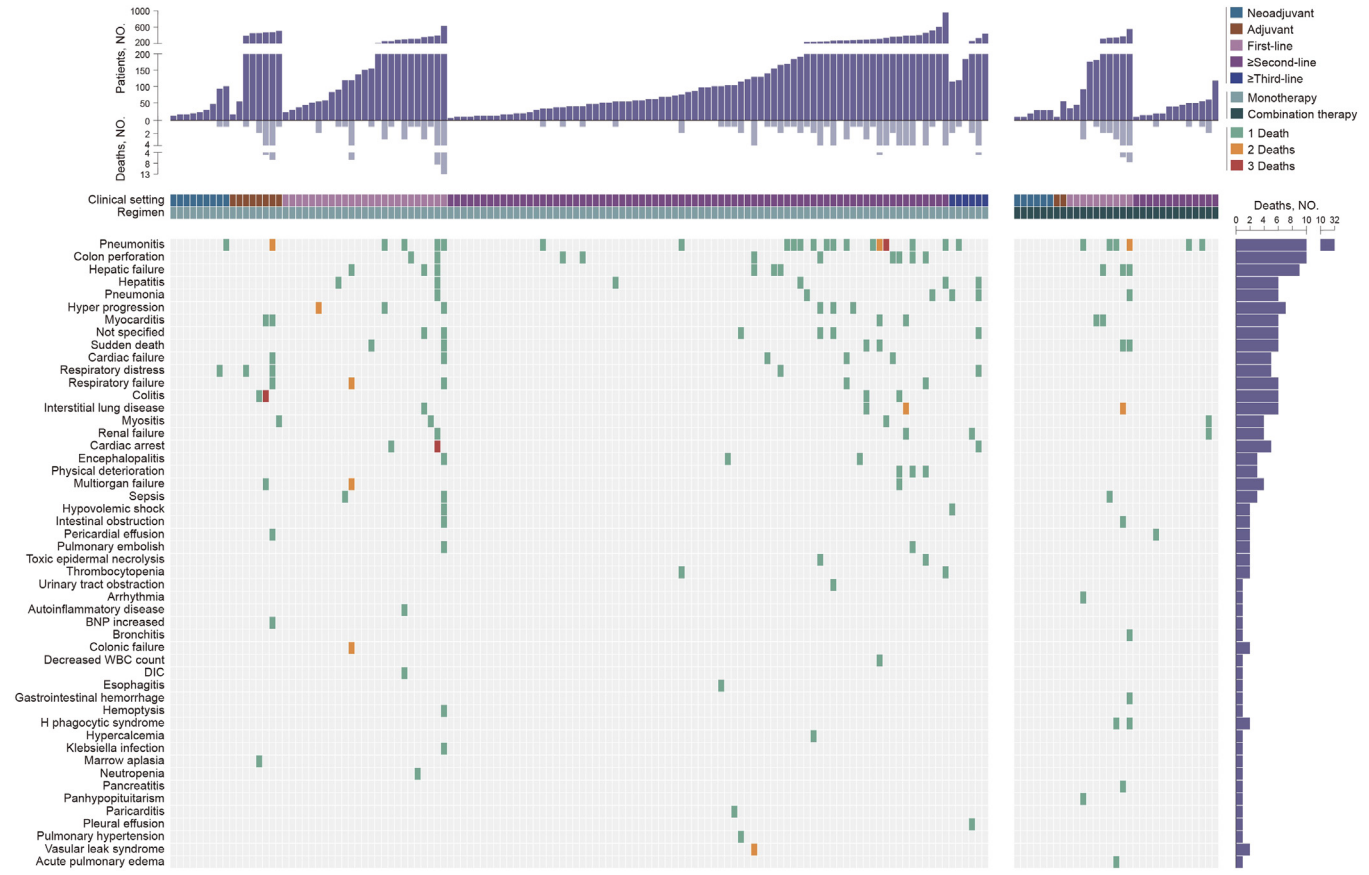


Fig. 4. Overview of fatal treatment-related adverse events. Waterfall plot depicting the distribution of fatal treatment-related adverse events across all cohorts. BNP, brain natriuretic peptide; DIC, disseminated intravascular coagulation; WBC, white blood cell.

atic failure (n = 3, 10.0%), and sudden death (n = 2, 6.7%) were the fatal events common to dual-ICI combinations (Supplementary Fig. 9).

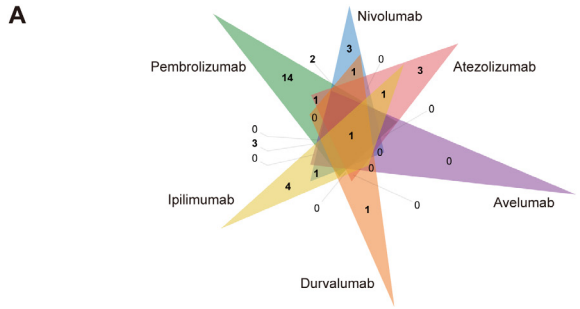
Next, we applied timelines to investigate the dynamics of fatal trAEs across different lines of treatment. Although neoadjuvant and adjuvant settings were associated with a higher incidence of trAEs overall, they showed a lower incidence of fatal trAEs. There were only two drug-related deaths (n = 2, 0.45%) during neoadjuvant treatment (n = 446), one due to pneumonitis (n = 1, 50.0%) and the other due to respiratory distress (n = 1, 50.0%). The first-line setting was associated with the highest incidence of lethal trAEs. Of the 4 854 patients who received ICI monotherapy as the first-line treatment, 47 experienced drug-related death (n = 47, 0.97%). Pneumonitis remained the only fatal event common to the different lines of treatment (Fig. 5B and Supplementary Fig. 8). For combination therapy, no drug-related deaths were observed in either the neoadjuvant or adjuvant settings. First-line treatment showed a wider distribution of fatal trAEs than second-line treatment, although pneumonitis was common across the two clinical settings (Supplementary Fig. 9).

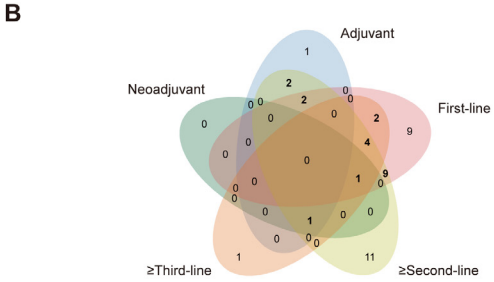
4. Discussion

Through a preplanned SPAER protocol, this study examined how trAE incidences differ across advancing lines of treatment based on a comprehensive analysis of data from clinical trials that assessed the safety of immunotherapy for solid tumors. We also balanced the age and sex across the five clinical setting groups, which might generate potential bias by influencing the immune status.[18] Using this approach, we not only provided a detailed overview of the static safety landscape of immunotherapy, but also unveiled the dynamic toxicity patterns associated with treatment timelines. To the best of our knowledge, this study is the first to provide direct evidence of the relationship between the incidence of trAEs and the line of treatment. Our results showed that patients treated with ICIs in later lines of therapy may have a lower risk of trAEs. This information could be incorporated into strategies for treatment counseling and decision-making and thus influence clinical practice in the future.[19]

Starting from the adjuvant setting, we observed that the incidences of trAEs of any grade, grade ≥ 3 trAEs, and trAEs leading to discontinuation generally decreased as the line of treatment advanced. The underlying timelines set in this study are meaningful as they indicate a change in patient status from treatment-naïve to treatment-refractory and terminally ill or heavily pretreated. Treatment duration is believed to influence the incidence of trAEs. However, we found that most trAEs tend to become less common with an advancement of the treatment line, irrespective of early or late toxicity events. For example, dermal toxicity usually appears first during treatment and may not be influenced by treatment duration. In this study, we consistently observed a negative correlation between the line of treatment and dermal toxicity, including rash and pruritus.

Although we observed that the mean incidences of all-grade and grade ≥ 3 trAEs were similar across different cancer types, the different cancer types were associated with different toxicity profiles, and the irAEs observed were tissue-specific and tended to involve a specific organ. Our results revealed a higher incidence of pneumonitis in patients with lung cancer and gastrointestinal toxicities in patients with melanoma, consistent with previous studies.[20,21] The activation or reactivation of tissue-resident autoreactive T cells is be-





	Pembrolizumab (n = 5 240)	Nivolumab (n = 4 235)	Atezolizumab (n = 3 531)	Avelumab (n = 1 852)	Durvalumab (n = 2 445)	Ipilimumab (n = 3 959)
Deaths, No. (%)	49 (0.94)	21 (0.50)	16 (0.45)	9 (0.49)	13 (0.53)	42 (1.06)
Fatal adverse events, No. (%)						
Pneumonitis	8 (16.3)	7 (33.3)	1 (6.3)	2 (22.2)	5 (38.5)	2 (4.8)
Respiratory distress	0	1 (4.8)	2 (12.5)	1 (11.1)	1 (7.7)	0
Myositis	2 (4.1)	1 (4.8)	0	0	0	0
Sepsis	1 (2.0)	0	1 (6.3)	0	0	0
Hepatitis	1 (2.0)	1 (4.8)	0	1 (11.1)	2 (15.4)	1 (2.4)
Pneumonia	1 (2.0)	2 (9.5)	1 (6.3)	0	0	1 (2.4)
Renal failure	1 (2.0)	0	0	1 (11.1)	0	1 (2.4)
Not specified	3 (6.1)	1 (4.8)	2 (12.5)	0	0	0
Myocarditis	1 (2.0)	0	0	1 (11.1)	1 (7.7)	1 (2.4)
Colitis	1 (2.0)	0	0	0	0	5 (11.9)
Respiratory failure	1 (2.0)	1 (4.8)	1 (6.3)	0	1 (7.7)	2 (4.8)
Encephalopalitis	2 (4.1)	1 (4.8)	0	0	0	0
Interstitial lung disease	1 (2.0)	0	1 (6.3)	2 (22.2)	0	0
Physical deterioration	0	0	1 (6.3)	0	0	2 (4.8)
Pulmonary embolish	1 (2.0)	0	0	0	0	1 (2.4)
Cardiac failure	1 (2.0)	1 (4.8)	1 (6.3)	0	1 (7.7)	1 (2.4)
Hepatic failure	0	0	1 (6.3)	1 (11.1)	0	4 (9.5)
Intestinal perforation	1 (2.0)	0	1 (6.3)	0	0	8 (19.0)
Thrombocytopenia	0	1 (4.8)	0	0	1 (7.7)	0
Hypovolemic shock	1 (2.0)	1 (4.8)	0	0	0	0
Cardiac arrest	0	1 (4.8)	0	0	0	4 (9.5)

	Neoadjuvant (n = 446)	Adjuvant (n = 2 822)	First-line (n = 4 854)	≥Second-line (n = 11 765)	≥Third-line (n = 1 455)
Deaths, No. (%)	2 (0.45)	16 (0.57)	47 (0.97)	75 (0.64)	10 (0.69)
Fatal adverse events, No. (%)					
Pneumonitis	1 (50.0)	2 (12.5)	4 (8.5)	17 (26.5)	1 (10.0)
Respiratory distress	1 (50.0)	2 (12.5)	0	1 (2.4)	1 (10.0)
Myositis	0	1 (12.5)	1 (2.1)	1 (1.2)	0
Multiorgan failure	0	1 (6.3)	2 (4.3)	1 (1.2)	0
Hepatitis	0	0	2 (4.3)	3 (3.6)	1 (10.0)
Pneumonia	0	0	1 (2.1)	2 (2.4)	2 (20.0)
Renal failure	0	0	1 (2.1)	1 (2.4)	1 (10.0)
Not specified	0	0	3 (6.4)	3 (3.6)	1 (10.0)
Myocarditis	0	2 (12.5)	0	2 (3.6)	0
Colitis	0	4 (25.0)	0	2 (2.4)	0
Respiratory failure	0	1 (6.3)	3 (6.4)	2 (3.6)	0
Encephalopalitis	0	0	1 (2.1)	2 (2.4)	0
Interstitial lung disease	0	0	1 (2.1)	3 (3.6)	0
Neoplasm progression	0	0	4 (8.5)	3 (3.6)	0
Pulmonary embolish	0	0	1 (2.1)	1 (1.2)	0
Cardiac failure	0	1 (6.3)	1 (2.1)	3 (4.8)	0
Hepatic failure	0	0	3 (6.4)	3 (3.6)	0
Intestinal perforation	0	0	2 (4.3)	8 (9.6)	0
Sudden death	0	0	1 (2.1)	2 (2.4)	0
Hypovolemic shock	0	0	1 (2.1)	0	1 (10.0)
Cardiac arrest	0	0	4 (8.5)	0	1 (10.0)

Fig. 5. Fatal treatment-related adverse events common among different regimens and treatment lines. (A) Common fatal trAEs across different regimens. (B) Common fatal trAEs across different treatment lines. Venn plots show the overlap between fatal events in different groups. BNP, brain natriuretic peptide; DIC, disseminated intravascular coagulation; WBC, white blood cell.

lieved to be a key contributor to the development of these autoimmune pathologies.[22] Antigens shared by tumors and normal tissues can induce *de novo* T cell activation and precipitate off-target toxicities.[23] Further, upregulated organ-specific transcripts can also lead to the aberrant activation of T cells.[24,25] Tumor cell death causes the release of additional antigens and peptides. The presentation of these antigens by antigen-presenting cells through epitope spread can also activate pre-existing autoreactive T cells. This phenomenon has been observed in skin toxicities associated with the enrichment of infiltrating T cells and epidermal cytokeratin peptides.[26] In addition, genetic determinants have also been linked to the development of disease-specific irAEs.[27,28] However, large genome-wide association studies are required to define the relationship between genetic factors and the risk of irAEs.

Growing evidence suggests that the development of irAEs is associated with tumor- and non-tumor-related factors.[29] For instance, tissue-resident $CD8^+$ T cells were reported to be highly abundant in colon tissues in patients with treatment-related colitis,[30] while cytotoxic memory $CD4^+$ T cells were found to be highly enriched in the brain of one patient with lethal ICI-induced encephalitis.[31] Moreover, the chronic expansion of effector memory $CD4^+$ T cells, which can be driven by viruses, toxic agents, inflammatory cytokines, and other clinical features, can lead to hepatitis after ICI treatment.[32] Microbiome- and tissue-specific factors can also contribute to the development of irAEs. Microbiota profiling has revealed an increased abundance of *Bacteroides intestinalis* in patients with irAEs, with upregulated IL-1β expression in patients with colitis and pre-clinical models.[33] Tumor factors such as tumor mutation burden are also thought to be associated with the development of irAEs.[34]

Immune-related toxicities usually develop within the first few weeks to months after treatment initiation; however, recent studies have reported that over 30% of patients treated with immunotherapy experience any grade late-irAEs, including a recurrence of early-irAEs and *de novo* late-irAEs.[35,36] Late-onset irAEs are mostly endocrine or rheumatological and can result from irreversible inflammation-induced damage to hormone-secreting cells, highlighting the importance of long-term monitoring and the necessity of urgent treatment. Overall, the general mechanisms responsible for the development of late-onset irAEs include aberrant T-cell activity, TCR diversity, and other pathogenic factors.[29,37] However, the specific mechanisms of early versus late ICI-induced toxicities remain poorly understood and need to be elucidated.

5. Limitations

Our study has several limitations. First, the sample sizes across the different clinical settings were not well-balanced, ranging from 446 for the neoadjuvant setting group to 11 765 for the second-line setting group. Given that immunotherapy as neoadjuvant treatment is still being explored, it was not feasible to balance the inter-group sample sizes in the present study. Nevertheless, correlation analyses were performed by excluding the neoadjuvant setting; thus, the sample size did not influence our results for the dynamic changes in the incidences of trAEs. Second, there were some missing data in the included studies on incidences of trAEs of interest; however, the censored data for the over-

all incidence of trAEs accounted for only about 6% of all the data included in the study. Moreover, we synthesized estimates simultaneously using the frequentist and Bayesian frameworks and employed exact inferences, avoiding any continuity correction for sparse binomial data.[21] Third, the treatment regimens were different across each clinical setting group, raising concerns that inter-group diversity could contribute to the instability of results. To address this issue, we performed a sensitivity analysis to rule out the possibility that a particular drug was responsible for the overall trends we observed. This analysis ruled out this concern to a certain acceptable degree. Finally, the duration of irAEs and the proportion of patients with ongoing toxicities at data cut-off were not specified in most published studies of ICIs, which is a major obstacle to the exploration of late-onset toxicity events. In this study, we used the most recently reported safety data from each trial to maximize the spectrum of observing late-onset adverse events.

6. Conclusions

The comprehensive analysis in this study provides a dynamic landscape of ICI-associated toxicities caused by different therapeutic regimens across different lines of treatment. By introducing the concept of timelines based on treatment lines, we demonstrate that except for in the neoadjuvant setting, the incidence of trAEs generally decreases as the line of treatment advances. These findings could be incorporated into strategies for treatment counseling and decision-making in routine clinical practice.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Data sharing statement

The data generated in this study are available from the corresponding author upon reasonable request.

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Author contributions

H.B and J. W. had full access to all the data from the study and took responsibility for the integrity of the data and the accuracy of the data analysis. L.L., S.L., H.B. and J.W. conducted the study conception and design. L.L., S.L., G.W. Y.Q., Z.W., D.C., C.W., P.X., X.Z. and Z.M. conducted the acquisition, analysis, or interpretation of data. L.L., S.L., G.W., Z.W., D.C. H.B. and J.W. drafted the manuscript. L.L., S.L., G.W. and Y.Q. conducted the critical reversion of the manuscript for important intellectual content. L.L., S.L., G.W. Y.Q., Z.W., D.C., C.W. and P.X. conducted the statistical analysis. H.B. and J.W. supervised the study.

Supplementary materials

Supplementary materials associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2023.07.002.

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