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Adverse Events of Immune Checkpoint Inhibitor-Based Therapies for Unresectable Hepatocellular Carcinoma in Prospective Clinical Trials: A Systematic Review and Meta-analysis

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Abstract

Background: To investigate the incidence and spectrum of adverse events in unresectable hepatocellular carcinoma (HCC) patients treated with immune checkpoint inhibitors (ICIs) or ICI-based combinations.

Summary: The study protocol was prospectively registered on PROSPERO (CRD42022319255). We searched PubMed, EMBASE, and the Cochrane Library for published clinical trials from database inception to April 22, 2022. Studies that included at least one group of unresectable HCC patients treated with ICIs or ICI-based combinations and reported the incidence or spectrum of treatment-related adverse events (trAEs) or immune-related adverse events (irAEs) were eligible. The incidence and spectra of all-grade and grade ≥3 trAEs were the primary outcomes. The profiles of irAEs, the incidence of trAEs leading to treatment discontinuation, and treatment-related mortalities were additional outcomes. We applied random-effects models to pool the incidence and spectra of adverse events. Subgroup analyses and meta-regression were performed. The literature search identified 2464 records. Twenty studies (4146 participants with HCC) met the eligibility criteria. The pooled incidences of all-grade trAEs, grade ≥3 trAEs, all-grade irAEs, and grade≥3 irAEs were 80.1% (95% CI 73.8-85.2), 35.4% (95% CI 27.2-44.6), 31.1% (95% CI 21.0-43.5), and 6.6% (95% CI 3.6-11.8), respectively. ICIs plus oral targeted agents (all-grade OR=17.07, 95% CI 6.05-48.16, $P<0.001$; grade ≥3 OR=9.35, 95% CI 4.53-19.29, $P<0.001$) and ICIs plus intravenous targeted agents (all-grade OR=4.91, 95% CI 1.80-13.42, $P=0.003$; grade ≥3 OR=4.21, 95% CI 1.42-12.48, $P=0.012$) were associated with increased trAEs compared with monotherapy. The all-grade trAEs with the highest pooled incidences were reactive capillary endothelial proliferation (49.2%, 95% CI 26.3-72.3), neutropenia (34.6%, 95% CI 17.1-57.5), and proteinuria (32.8%, 95% CI 19.8-49.2). The grade ≥3 trAEs with highest pooled incidences were hypertension (11.1%, 95% CI 4.0-29.0), neutropenia (10.5%, 95% CI 7.0-15.4), and aspartate aminotransferase increased (7.7%, 95% CI 6.3-9.4). The pooled incidence of trAEs leading to treatment discontinuation was 8.0% (95% CI 6.0-10.5), and the overall incidence of treatment-related mortalities was 1.1%.

Key Messages: This study comprehensively summarized the incidence and spectrum of trAEs in unresectable HCC patients receiving ICIs or ICI-based combinations in clinical trials. The results from this study will provide a useful reference to guide clinical practice.

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Introduction

Immune checkpoint blockade, which manipulates innate and adaptive immunity to reactivate or enhance the antitumor immune response, has broadened the choices of systemic therapies for various malignancies.[1] Currently, clinical immune checkpoint blockade mainly targets the PD-1/PD-L1 axis and has yielded favourable responses in non-small cell lung cancer [2, 3], melanoma [4, 5], and hepatocellular carcinoma (HCC).[6, 7]

Since 2017, immune checkpoint inhibitors (ICIs) and ICI-based combinations have become the new hope for improving the prognosis of unresectable HCC patients. Nivolumab and pembrolizumab achieved objective response rates of 20% and 17%, respectively, prolonged the survival of HCC patients after sorafenib failure or intolerable toxicity and were approved by the American Food & Drug Administration as second-line systemic treatment of unresectable HCC.[6, 8] The clinical utility of combinations of ICIs and targeted agents have also been explored for unresectable HCC patients. The phase III IMbrave150 trial reported that unresectable HCC patients without previous systemic therapy receiving atezolizumab combined with bevacizumab had prolonged median progression-free survival (6.9 months vs. 4.3 months) and an improved objective response rate (27.3% vs. 11.9%) over sorafenib with acceptable and manageable toxicity.[7] Favourable outcomes of unresectable HCC patients treated with a combination of ICIs and targeted agents were also reported by other clinical trials.[9, 10] Currently, ICI monotherapies and ICI-based combinations are recommended for the treatment of unresectable HCC by the NCCN and ESMO guidelines.[11, 12]

There are concerns about the toxicities of ICIs and ICI-based combinations. As adverse events generally require more careful monitoring and high-grade adverse events could lead to a worse prognosis, it is very important to systematically investigate the incidence and spectrum of adverse events of ICI-based combinations. In a previous systematic review and meta-analysis, the incidence of all-grade adverse events was 66.0%, and the incidence of grade ≥3 adverse events was 14.0% for cancer patients treated with single-agent PD-1 or PD-L1 inhibitors.[13] In another systematic review, the overall incidence of all-grade treatment-related adverse events (trAEs) was 94.5%, and the overall incidence of grade ≥3 trAEs was 47.3% for patients treated with PD-1 or PD-L1 inhibitors combined with targeted therapies.[14] Previous systematic reviews and meta-analyses summarized the adverse event profiles of ICIs or ICI-based combinations in pancancer settings. As few clinical trials of HCC were included in these reviews and many clinical trials for HCC have been published since these reviews, a summary of the adverse event profiles specifically for HCC patients is needed to provide an important reference for clinical practice.

The aim of this systematic review and meta-analysis was to investigate the incidence and spectrum of adverse events in unresectable HCC patients treated with ICIs or ICI-based combinations.

Materials and Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15] The study protocol was registered prospectively on PROSPERO (CRD42022319255). Two authors (Y. Z. and M. W.) independently performed the study selection and data extraction. All discrepancies were resolved by discussion with a third author (H. Z.) to reach a consensus.

Search strategy and selection criteria

We searched PubMed, EMBASE, and the Cochrane Library for published English-language clinical trials of unresectable hepatocellular carcinoma treated with ICIs or ICI-based combinations from database inception to April 22, 2022. The key search items included "hepatocellular carcinoma", "PD-1", "anti-PD-1", "PD-L1", "anti-PD-L1", "CTLA-4", "anti-CTLA-4", "immune checkpoint inhibitors", "nivolumab", "pembrolizumab", "atezolizumab", "ipilimumab", "tremelimumab", "sintilimab", "penpulimab", “dostarlimab”, “avelumab”, and “clinical trial”. The bibliographies of the included

studies and relevant reviews were manually screened to avoid omissions. The detailed search strategies are presented in **Supplementary Table 1.**
We applied the following selection criteria: (1) published reports of prospective clinical trials; (2) studies with at least one treatment group (arm) of unresectable HCC treated with ICIs as monotherapy or concomitantly combined with other agents; (3) studies that reported the incidence of trAEs or immune-related adverse events (irAEs) or tabulated data of the spectrum of trAEs or irAEs; (4) studies evaluating adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE); and (5) studies published in English. Studies that did not meet all of the selection criteria were excluded. Other exclusion criteria were as follows: (1) retrospective studies; (2) studies assessing ICIs other than anti-PD-1, anti-PD-L1, or anti-CTLA-4 agents; (3) studies reporting ICIs for HCC patients in neoadjuvant or adjuvant settings; (4) studies assessing ICIs combined with locoregional therapies, sequential therapies, or triplet combinations; (5) studies involving malignancies other than HCC and data of interest could not be extracted; (6) treatment groups including fewer than 10 patients; (7) conference abstracts without published reports; (8) commentaries, reviews, letters, and editorials; and (9) duplicate cohorts. Multiple publications reporting different cohorts of the same study without overlapping study populations were all included if eligible. If multiple reports of the same cohort were identified, only the most informative report was selected.

Data analysis

We extracted the following data from each included study: basic information (trial names, National Clinical Trial number, year of publication, first author), study methods (trial phase, randomization, blinding, treatment groups, line of systemic therapy, CTCAE version), participants (number of participants enrolled, names of ICIs, types of ICIs, doses of ICIs, type of treatment combination, name and dose of other drugs, number of participants included in the safety analyses), exposure (type of adverse events, criteria for reporting adverse events), and outcomes (number of participants with at least 1 CTCAE all-grade or grade ≥3 trAEs or irAEs, number of treatment-related mortalities, number of trAEs leading to treatment discontinuation, detailed types and frequencies of each all-grade or grade ≥3 trAEs or irAEs, treatment-related mortalities, and trAEs leading to treatment discontinuation). The data were extracted separately for each treatment group. Adverse events were coded according to the Preferred Terms in the Medical Dictionary for Regulatory Activities (MedDRA). To explore the relationship between drug exposure, progression-free survival (PFS), and overall survival (OS) and the incidence of adverse events, median exposure (duration of ICI treatment), median follow-up, the criteria for assessing PFS, median PFS, and median OS were also extracted for each eligible treatment group.

Outcomes

As prespecified in the study protocol, the primary outcomes of this study are the incidence and spectrum of all-grade and grade ≥3 trAEs. The incidence of adverse events was calculated from the number of participants with at least one adverse event divided by the number of participants included in the safety analysis. The spectrum of adverse events is defined as the incidence of each type of adverse event. Additional outcomes included the incidence of trAEs leading to treatment discontinuation and the incidence of treatment-related mortalities. The incidence and spectrum of all-grade and grade ≥3 irAEs were listed as additional outcomes in the study protocol.

Statistical analysis

All statistical analyses were performed based on treatment groups. The incidence of adverse events was the effect measure of the primary outcomes. We applied random-effects models with restricted maximum-likelihood estimation for the meta-analysis of the incidence and spectrum of adverse events. A continuity correction of 0.5 was applied to treatment groups with zero or all

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events, and the incidence was logit transformed before the meta-analysis. Adverse events in different treatment groups from one study were pooled separately. To limit the number of adverse events included in the primary analysis of the adverse event spectra, only the adverse events that are reported by at least 10% of the included treatment groups were pooled, regardless of the reported incidence. For the subgroup analyses of the adverse event spectra that only include no more than 20 treatment groups, adverse events that are reported by at least 2 treatment groups were pooled.

The incidence of trAEs leading to treatment discontinuation and the incidence of irAEs were also pooled. The incidence of treatment-related mortalities was calculated from the total number of treatment-related mortalities divided by the total number of participants included in the safety analyses as we expected frequent zero cells.

Prespecified subgroup analyses were performed according to the line of systemic therapy, type of treatment combination, and types of ICIs. Forest plots of results from the main and subgroup analyses, including the incidence and 95% CIs of subgroups with one single treatment group, were plotted for demonstration. The 95% CIs for subgroups with only one treatment group were calculated with the two-sided Clopper-Pearson method. We also performed multivariable meta-regression analysis to identify the factors associated with the incidence of all-grade and grade ≥3 trAEs and the sources of potential heterogeneity. Protocol-prespecified predictors were line of systemic therapy, type of treatment combination, and type of ICIs. As an exploratory analysis, the relationship between median OS, median PFS, and drug exposure and the incidence of adverse events was also analysed by separate multivariable meta-regression analysis after adjusting for the line of systemic therapy, type of treatment combination, and type of ICIs. The meta-regression models were also fitted with restricted maximum likelihood estimation and a continuity correction of 0.5 before logit transformation. Tests of individual coefficients in the meta-regression models were performed by the Knapp and Hartung method to obtain conservative results.[16] Likelihood ratio tests between the meta-regression model with all predictors and a model with all predictors except the one of interest were performed to give the overall *P* value of each predictor. Both models for the likelihood ratio test were fitted with the maximum likelihood estimator. We also performed post hoc multivariable meta-regression analyses, selecting ICIs combined with intravenous targeted agents as the referent of the type of treatment combination to compare the incidence of adverse events between ICIs combined with intravenous targeted agents and ICIs combined with oral targeted agents.

Heterogeneity across the included treatment groups was assessed with the χ^2 test and I^2 statistic. Publication bias was assessed with modified funnel plots of log odds against the number of participants included in the safety analyses, as the conventionally constructed funnel plots were inaccurate in the meta-analyses of proportion studies when the incidence was close to zero or one.[17] Egger's test with the number of participants included in the safety analyses as the predictor was also performed to assess publication bias.[18] The risk of bias of the randomized controlled trials was evaluated with the RoB 2 tool from the Cochrane Collaboration.[19] The risk of bias of nonrandomized cohort studies was assessed with the Newcastle–Ottawa scale.[20] Two authors (Y.D. and J.C.) independently performed the risk of bias assessment, and discrepancies were resolved by discussion with a third author (Q.C.) to reach a consensus. A two-sided *P* value of <0.05 indicated statistical significance. All statistical analyses were performed with R software (version 4.0.2) and *metafor* packages (version 3.0-2).[21]

Results

Characteristics of included studies

A total of 2464 records were identified in the systemic search. We identified 37 potentially eligible studies and performed full-text screening. Fourteen records were excluded by full-text assessment for lacking data for HCC (n=6), duplicate cohort (n=5), lacking required data of adverse events (n=2), or not clinical trial (n=1). Twenty-three reports of 20 studies (including 3 reports from

the CheckMate 040 study [6, 22, 23] and 2 reports from the KEYNOTE-224 study [24, 25]) involving a total of 4146 participants in the safety analyses were included (**Fig. 1**).[6, 9, 10, 22-41] Thirty-four treatment groups from the 20 studies reported adverse events of unresectable HCC patients treated with ICI monotherapy or ICI-based combinations and were included in the quantitative analyses. The characteristics of included studies were shown in **Supplementary Table 2**. The characteristics of included treatment groups were shown in **Supplementary Table 3**. Four treatment groups from 3 studies evaluated adverse events with CTCAE version 5.0.[37, 40, 41] The grading criteria of adverse events related to liver function (e.g. Aspartate aminotransferase, Alkaline phosphatase increased, and Alanine aminotransferase increased) were modified in CTCAE version 5.0 that patients with elevated test levels at baseline were compared to their baseline level instead of upper limits of normal in CTCAE version 4, which may lead to lower degree of these adverse events. We further excluded the treatment groups with CTCAE version 5.0 from the analyses of the incidence and spectra of trAEs/irAEs and trAEs leading to treatment discontinuation. These treatment groups were only included in the analysis of treatment-related mortalities. The risk of bias assessment was presented in **Supplementary Table 4-5**.

Among the 17 included studies with CTCAE version 4, 12 treatment groups involving 1251 participants assessed ICI monotherapy or ICI-based combinations as first-line systemic therapy for HCC, while 18 treatment groups involving 1580 participants enrolled patients previously treated with systemic therapies. For the types of treatment combination, 14 treatment groups involving 1616 participants assessed ICIs as monotherapy, four treatment groups involving 521 participants assessed ICIs combined with intravenous targeted agents, five treatment groups involving 343 participants assessed ICIs combined with oral targeted agents, five treatment groups involving 302 participants assessed dual ICIs combinations, one study assessed ICI combined with chemotherapy, and one study assessed ICI combined with an anti-CCR4 agent. For the type of ICIs, 16 treatment groups involving 1728 participants assessed anti-PD-1 agents (nivolumab, pembrolizumab, penpulimab, camrelizumab) as monotherapy or combined with other non-ICI agents, eight treatment groups involving 732 participants assessed anti-PD-L1 agents (durvalumab, atezolizumab, and avelumab) as monotherapy or combined with other non-ICI agents, one treatment group assessed anti-CTLA-4 agents (tremelimumab) as monotherapy, and five treatment groups assessed dual ICIs combinations (nivolumab combined with ipilimumab, durvalumab combined with tremelimumab).

The incidence of all-grade and grade ≥3 trAEs

Among the included studies with CTCAE version 4, 30 treatment groups involving 2831 participants reported the overall incidence of trAEs of ICIs as monotherapy or ICIs-based combinations were included in the analysis. The pooled incidence of all-grade trAEs was 80.1% (95% CI 73.8-85.2, I^2=92%, test for heterogeneity P<0.001). Among the included studies, 27 treatment groups in 18 studies involving 2668 participants reported the incidence of grade ≥3 trAEs were included in the analysis. The pooled incidence of grade ≥3 trAEs was 35.4% (95% CI 27.2-44.6, I^2=94%, test for heterogeneity P<0.001). The incidence of irAEs and grade ≥3 irAEs were reported in five treatment groups involving 273 participants. The pooled incidence of all-grade irAEs was 31.1% (95% CI 21.0-43.5, I^2=66%, test for heterogeneity P=0.011) and the pooled incidence of grade ≥3 irAEs was 6.6% (95% CI 3.6-11.8, I^2=25%, test for heterogeneity P=0.323) (**Fig. 2**).

In the treatment groups assessing ICIs monotherapy or ICI-based combinations as the first-line systemic therapy for unresectable HCC, the pooled incidence of all-grade trAEs was 82.7% (95% CI 68.0-91.5, I^2=96%, test for heterogeneity P<0.001) and the pooled incidence of grade ≥3 trAEs was 39.6% (95% CI 21.9-60.5, I^2=97%, test for heterogeneity P<0.001). In the treatment groups enrolled patients previously treated with systemic therapies, the pooled incidence of all-grade trAEs was 78.5% (95% CI 72.5-83.5, I^2=82%, test for heterogeneity P<0.001), and the pooled incidence of grade ≥3 trAEs was 32.5% (95% CI 25.2-40.7, I^2=88%, test for heterogeneity P<0.001).

In the treatment groups assessing ICIs as monotherapy for unresectable HCC, the pooled incidence of all-grade trAEs was 69.7% (95% CI 60.8-77.3, I^2=91%, test for heterogeneity *P*<0.001), and the pooled incidence of grade ≥3 trAEs was 22.3% (95% CI 18.1-27.1, I^2=72%, test for heterogeneity *P*<0.001). In the treatment groups of ICIs combined with intravenous targeted agents, the pooled incidence of all-grade trAEs was 82.9% (95% CI 73.1-89.6, I^2=76%, test for heterogeneity *P*=0.006) and the pooled incidence of grade ≥3 trAEs was 43.7% (95% CI 38.6-49.0, I^2=5%, test for heterogeneity *P*=0.465). In the treatment groups of ICIs combined with oral targeted agents, the pooled incidence of all-grade trAEs was 95.7% (95% CI 91.1-98.0, I^2=24%, test for heterogeneity *P*=0.186) and the pooled incidence of grade ≥3 trAEs was 64.2% (95% CI 41.3-82.1, I^2=92%, test for heterogeneity *P*<0.001). In the treatment groups assessing dual ICIs combinations, the pooled incidence of all-grade trAEs was 79.2% (95% CI 70.1-86.1, I^2=63%, test for heterogeneity *P*=0.033) and the pooled incidence of grade ≥3 trAEs was 34.5% (95% CI 25.6-44.7, I^2=67%, test for heterogeneity *P*=0.017).

In the treatment groups assessing anti-PD-1 agents as monotherapy or combined with other non-ICI agents, the pooled incidence of all-grade trAEs was 83.1% (95% CI 71.9-90.4, I^2=95%, test for heterogeneity *P*<0.001) and the pooled incidence of grade ≥3 trAEs was 35.9% (95% CI 23.5-50.5, I^2=96%, test for heterogeneity *P*<0.001). In the treatment groups assessing anti-PD-L1 agents as monotherapy or combined with other non-ICI agents, the pooled incidence of all-grade trAEs was 76.7% (95% CI 62.9-86.5, I^2=90%, test for heterogeneity *P*<0.001) and the pooled incidence of grade ≥3 trAEs was 33.6% (95% CI 16.3-56.8, I^2=95%, test for heterogeneity *P*<0.001). Results from the subgroup analyses for the incidence of all-grade trAEs and grade ≥3 trAEs were summarized in **Figure 3**. Due to the limited number of studies reporting the incidence of all-grade irAEs and grade ≥3 irAEs, these prespecified subgroup analyses were not performed.

Factors associated with the incidence of all-grade and grade ≥3 trAEs

We further excluded ICI plus chemotherapy and ICI plus anti-CCR4 agents from the multivariable meta-regression analysis as these two types of treatment combination only each include a single study with limited number of participants. The results from the multivariable regression analyses were summarized in **Table 1**. In the multivariable regression analysis, the line of systemic therapy and treatment type was associated with the risk of all-grade trAEs. Compared with treatment groups in the first-line setting, treatment groups enrolled patients previously treated with systemic therapies had an increased incidence of all-grade trAEs (OR=2.31, 95% CI 1.18-4.53, *P*=0.017) after adjusting for treatment type and type of ICIs. Compared with ICIs as monotherapy, ICIs combined with oral targeted agents (OR=17.07, 95% CI 6.05-48.16, *P*<0.001) and ICIs combined with intravenous targeted agents (OR=4.91, 95% CI 1.80-13.42, *P*=0.003) were associated with significantly increased risks of all-grade trAEs after adjusting for the line of systemic therapy and type of ICIs. Treatment type was associated with the risk of grade ≥3 trAEs. Compared with ICIs as monotherapy, ICIs combined with oral targeted agents (OR=9.35, 95% CI 4.53-19.29, *P*<0.001) and ICIs combined with intravenous targeted agents (OR=4.21, 95% CI 1.42-12.48, *P*=0.012) were associated with significantly increased risks of grade ≥3 trAEs after adjusting for the line of systemic therapy and type of ICIs.

To compare the risks of all-grade and grade ≥3 trAEs between ICIs combined with oral targeted agents and intravenous targeted agents, we performed post hoc multivariable regression analyses with the aforementioned predictors and selected ICIs combined with intravenous targeted agents as the referent of treatment type (**Supplementary Table 6**). After adjusting for the line of systemic therapy and type of ICIs, compared with ICIs combined with intravenous targeted agents, ICIs combined with oral targeted agents were associated with a trend of increased risk of all-grade trAEs (OR=3.48, 95% CI 0.96-12.64, *P*=0.058).

We also performed exploratory multivariable regression analyses to investigate the relationship between median OS, median PFS, and drug exposure and the incidence of all-grade and

grade ≥3 trAEs as prespecified in the protocol. Among the 28 treatment groups included in the multivariable regression analysis for the incidence of all-grade trAEs, median PFS was extracted from 25 treatment groups, median OS was reported in 28 treatment groups and was reached in 22 treatment groups, and drug exposure (median duration of ICIs treatment) was extracted from 20 treatment groups. Among the 25 treatment groups included in the multivariable regression analysis for the incidence of grade ≥3 trAEs, median PFS was extracted from 22 treatment groups, median OS was reported in 25 treatment groups and was reached in 19 treatment groups, and drug exposure was extracted from 19 treatment groups. The results from the exploratory multivariable regression analyses were summarized in **Table 2**. After adjusting for the line of systemic treatment, treatment type, and type of ICIs, median OS was positively associated with the incidence of all-grade trAEs (OR=1.13, 95% CI 1.03-1.23, *P*=0.010).

Spectra of all-grade and grade ≥3 trAEs

Tabulated data of the spectrum of trAEs were extracted from 26 treatment groups in 15 studies involving a total of 2579 participants in the safety analyses. We identified 180 different Preferred Terms in MedDRA as terminology of reported trAEs.

The all-grade trAEs with the highest pooled incidences were reactive capillary endothelial proliferation (49.2%, 95% CI 26.3-72.3), neutropenia (34.6%, 95% CI 17.1-57.5), and proteinuria (32.8%, 95% CI 19.8-49.2) (**Fig. 4a**). The grade ≥3 trAEs with highest pooled incidences were hypertension (11.1%, 95% CI 4.0-29.0), neutropenia (10.5%, 95% CI 7.0-15.4), and aspartate aminotransferase increased (7.7%, 95% CI 6.3-9.4) (**Fig. 4b**).

For ICIs monotherapies, the all-grade trAEs with highest pooled incidences were platelet count decreased (15.9%, 95% CI 11.8-21.0), pruritus (15.3%, 95% CI 11.9-19.4), and fatigue (14.7%, 95% CI 10.7-19.9). For ICIs combined with intravenous targeted agents, the all-grade trAEs with the highest pooled incidences were hypertension (23.1%, 95% CI 12.1-39.7), diarrhoea (17.3%, 95% CI 6.2-39.7), and fatigue (16.8%, 95% CI 13.3-21.1). For ICIs combined with oral targeted agents, the all-grade trAEs with the highest pooled incidences were hyperbilirubinaemia (61.9%, 95% CI 53.1-70.0), thrombocytopenia (59.9%, 95% CI 52.8-66.7), and hypertension (53.0%, 95% CI 25.0-79.2). For dual ICIs combinations, the all-grade trAEs with the highest pooled incidences were pruritus (30.2%, 95% CI 21.5-40.7), rash (22.5%, 95% CI 15.9-30.8), and aspartate aminotransferase increased (16.8%, 95% CI 12.9-21.4) (**Fig. 5a**). For ICIs monotherapies, the grade ≥3 trAEs with the highest pooled incidences were hypertransaminasaemia (6.2%, 95% CI 1.8-19.2), aspartate aminotransferase increased (6.1%, 95% CI 5.0-7.5), and lipase increased (4.5%, 95% CI 2.1-9.4). For ICIs combined with intravenous targeted agents, the grade ≥3 trAEs with the highest pooled incidences were hypertension (11.8%, 95% CI 8.8-15.5), aspartate aminotransferase increased (7.9%, 95% CI 2.8-20.2), and alanine aminotransferase increased (2.5%, 95% CI 1.3-4.8). For ICIs combined with oral targeted agents, the grade ≥3 trAEs with the highest pooled incidences were hypertension (27.2%, 95% CI 14.8-44.6), neutropenia (11.1%, 95% CI 7.3-16.4), and hyperbilirubinaemia (10.9%, 95% CI 6.3-18.1). For dual ICIs combinations, the grade ≥3 trAEs with the highest pooled incidences were aspartate aminotransferase increased (10.6%, 95% CI 7.5-14.8), lipase increased (7.6%, 95% CI 5.1-11.3), and alanine aminotransferase increased (4.9%, 95% CI 2.8-8.3) (**Fig. 5b**).

Results from subgroup analyses of the spectra of all-grade and grade ≥3 trAEs by line of systemic therapy and type of ICIs were summarized in **Supplementary Figure 1-4**. To investigate the impact of different types of treatment combinations on liver function, we also compared the pooled incidence of 7 hepatobiliary trAEs considered to be associated with liver function across different types of treatment combinations by a forest plot as a post hoc exploratory analysis (**Supp. Fig. 5**). We found that ICI plus oral target agents possessed numerically higher incidence of the hepatobiliary trAEs.

Tabulated data of the spectra of all-grade and grade ≥3 irAEs were extracted from only 4 treatment groups and these analyses planned in the protocol were not performed.

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TrAEs leading to treatment discontinuation and treatment-related mortalities

A total of 21 treatment groups involving 1906 participants reported the incidence of trAEs leading to treatment discontinuation. The pooled incidence of trAEs leading to treatment discontinuation was 8.0% (95% CI 6.0-10.5, I^2=60%, test for heterogeneity *P*<0.001, **Fig. 6**).

All 34 treatment groups including 4 treatment groups with CTCAE version 5.0 and involving 3308 participants reported the frequency of treatment-related mortalities. A total of 37 treatment-related mortalities were reported. The overall incidence of treatment-related mortalities was 1.1%. As the incidence of treatment-related mortalities was calculated from a division method involving multiple study populations, 95% CI was not applicable. The incidence of treatment-related mortalities was 0.7% for ICIs monotherapy, 1.7% for ICIs combined with intravenous targeted agents, 1.5% for ICIs combined with oral targeted agents, and 1.0% for dual ICIs combinations. The most common treatment-related mortalities were hepatic failure (n=6), hepatic function abnormal (n=6), and pneumonitis (n=4) (**Supplementary Table 7**).

Publication bias

We applied modified funnel plots of log odds against the number of participants to assess potential publication bias. Obvious asymmetry was not visually observed in the modified funnel plots for all-grade trAEs, grade ≥3 trAEs, grade ≥3 irAEs, and trAEs leading to treatment discontinuation, which was further confirmed by the modified Egger's test (**Supp. Fig. 6a, b, d, e**).[18] For all-grade irAEs, the funnel plot was visually asymmetrical and compacted at the right side. The modified Egger's test also indicated potential publication bias (*P*=0.038) (**Supp. Fig. 6c**).

Discussion

This systematic review and meta-analysis provided a comprehensive summary of the incidence and profile of adverse events of unresectable HCC patients treated with ICI-based therapy. Here, we made four conclusions that may promote the early identification and proper management of trAEs in unresectable HCC patients undergoing ICI-based therapy: (1) the incidences of all-grade and grade ≥3 trAEs (all-grade: 80.1%, 95% CI 73.8-85.2; grade ≥3: 35.4%, 95% CI 27.2-44.6) were comparable to previously published reports of other malignancies or pancancer studies [13, 14, 42]; (2) reactive capillary endothelial proliferation, neutropenia and proteinuria had the highest pooled incidence among all-grade trAEs, and hypertension, neutropenia, and increased AST had the highest pooled incidence among grade ≥3 trAEs; (3) 8.0% and 1.1% of patients discontinued or died because of intolerable trAEs, respectively, which is of high clinical concern; (4) multivariable regression analysis revealed that oral targeted agents are associated with a higher risk of developing all-grade trAEs compared to intravenous targeted agents in ICI-based combination therapy, and a correlation between mOS and the trAE incidence was observed.

In this study, the incidences of all-grade and grade ≥3 trAEs were generally consistent with previous reports [13, 14], and the difference mainly stems from the disproportionality of treatment strategies. Similar results were observed in subgroup analyses based on treatment line, type of ICI used or treatment modality.[13, 42, 43] As atezolizumab plus bevacizumab has become the standard-of-care first-line treatment for unresectable HCC, the systemic treatment landscape will experience a prominent revolution. We found that the addition of intravenous targeted agents to ICI treatment was associated with an increased risk of developing trAEs compared to ICI monotherapy (all-grade: OR = 4.91, 95% CI 1.80-13.42, *P*=0.003; grade ≥3: OR=4.21, 95% CI 1.42-12.48, *P*=0.012), which is similar to previous studies.[13, 14] Although the combination of oral tyrosine kinase inhibitors (TKIs) and ICIs has not been approved as first-line treatment in unresectable HCC patients, several trials have demonstrated its safety and clinical efficacy [9, 10, 35], and more promising trials are in progress (NCT04052152, NCT03418922, NCT03841201, NCT04042805, NCT04344158, NCT04542837, ChiCTR1900028295, NCT03347292). Accordingly, our results also showed that patients taking oral targeted agents with ICIs were at higher risk of developing trAEs than those treated with ICI alone

(all-grade: OR=17.07, 95% CI 6.05-48.16, *P*<0.001; grade ≥3: OR=9.35, 95% CI 4.53-19.29, *P*<0.001). Taken together, these findings suggest that clinicians should be aware of the trend of the trAE incidence increasing along with the shift of the treatment paradigm. It is becoming more important that clinicians timely identify patients with trAEs and initiate proper management to achieve a better clinical outcome.

We extracted tabulated data on the trAE spectrum and found that reactive capillary endothelial proliferation, neutropenia, and proteinuria had the highest pooled incidences among all-grade trAEs, and hypertension, neutropenia, and increased AST had the highest pooled incidences among grade ≥3 trAEs. Although the pooled incidence of reactive capillary endothelial proliferation was high, it was exclusively reported in trials adopting camrelizumab-based regimens. As most included studies only reported adverse events with an incidence higher than a specific value, we consider that this adverse event was highly heterogenous across the treatment groups included in the spectra analysis and its pooled incidence represents the risk of this adverse events among treatment groups that reported this adverse event (also the treatment groups involving camrelizumab). The pooled incidence of adverse events only reported by limited number of treatment groups should be interpreted cautiously as they may not represent a common risk across all included studies. Results from the subgroups analyses should also be considered and whether these treatment groups reporting the adverse events share common characteristics should be assessed. Similarly, neutropenia had high incidence among grade ≥3 trAEs, but this result was mostly due to the RESCUE trial, which adopted clustered preferred terms for neutropenia (including neutrophil count decreased, neutrophil percentage decreased, and granulocyte count decreased). Therefore, the incidence of grade≥3 neutropenia may be overestimated. Proteinuria had the third highest incidence among all-grade trAEs and hypertension had the highest incidences among grade ≥3 trAEs. Both adverse events are mainly reported for patients receiving ICI plus vascular endothelial growth factor (VEGF)-pathway inhibitors and this is of clinical concern due to their high incidence and clinical significance.[44-47] The addition of a targeted agent, which impedes the VEGF signalling pathway in most cases, might lead to disrupted production of vasodilators, inhibition of angiogenesis and dysregulation of the renin-angiotensin-aldosterone axis. These changes directly increase blood pressure and further damage the endothelial lining of the vessels, therefore leading to clinical hypertension and proteinuria.[46, 47] Patients with unresectable HCC often have comorbidities, including cirrhosis and portal hypertension. To preserve patients' renal function and avoid fatal cardiovascular events, it is necessary to evaluate whether patients would tolerate possible trAEs before administering combination therapy. Additionally, routine urine tests and regular blood pressure measurements are recommended for the early recognition of trAEs and the initiation of symptomatic treatment, dose modification or discontinuation when necessary.

As patients with unresectable HCC are commonly presented with impaired baseline liver function, they may develop hepatobiliary trAEs at a higher risk. Therefore, it is crucial for clinicians to understand the adverse events the patient would endure after administration of specific type of ICI-based therapy. In the post hoc exploratory analysis for the impact of different types of treatment combinations on liver function, we found that ICI plus oral target agents possessed numerically higher incidence of hepatobiliary trAEs. This result is consistent with our multivariable meta-regression analysis for factors associated with the overall incidence of trAEs, and adds to the evidence that oral target agents might lead to an increased incidence of hepatobiliary trAEs in ICI-based therapies for unresectable HCC patients. From a pharmacokinetic perspective, therapeutic monoclonal antibodies (mAbs, including anti-PD-(L)1 and anti-VEGF antibodies) undergo systemic degradation by phagocytic cells, while current evidence supports a major role of liver in metabolizing oral target drugs (mainly by CYP3A).[48-50] Thus, liver function is more prone to metabolic overload damage by oral target drugs. From a pharmacodynamic perspective, ICIs would pause immune tolerance and cause systemic adverse events in both nonspecific (systemic inflammatory response induced by boosted cytokines) and antigen-specific manner (proliferation of cross-reactive immune

cells and probably production of cross-reactive antibodies). Among all ICI-induced adverse events, liver impairment is not the most commonly observed, ranging from 1.8% in nivolumab to 9% in atezolizumab.[51] For targeted agents, a commonly targeted pathway is the VEGF pathway. The main difference is that mAbs (ramucirumab, bevacizumab, IBI305) are anti-VEGF-specific while oral target agents are exclusively multi-tyrosine kinase inhibitors (multi-TKI, targeting VEGF, FGF and PDGF pathways and etc.). As increased hepatotoxicity is observed in both oral target drug monotherapy and combination settings, the broad downstream impact of the targeted agents might partially explain the enhanced liver injury. We then questioned whether drug-drug interaction contributes to the high incidence of hepatobiliary trAEs in ICIs plus oral targeted agents. Theoretically, their metabolic pathway lacks intersection and the crosstalk between the two types of drugs largely remains unknown. Clinically, the addition of ICI to targeted therapy did not significantly increase hepatobiliary trAE incidence according to previous studies[52], indicating a less important role of synergistic effect. Collectively, these results might indicate a severer hepatotoxicity in patients receiving ICIs plus oral target agents compared to ICIs plus intravenous target agents, dual ICIs therapy or ICI monotherapy. The underlying mechanism probably involve hepatic metabolic overload and unspecific downstream inhibition of the target agents. Further researches are warranted to explore whether drug synergism contributes to hepatotoxicity development.

We further investigated whether the reverse of this statement is also correct, that is, whether patients' baseline liver function (as measured by Child-Pugh Score; or Albumin-Bilirubin grade, ALBI grade) might also affect trAE incidence under different combination regimens. This is of great importance in clinical settings, as most systemic therapies are only indicated in patients with preserved liver function (Child-Pugh A or B7 in some cases). If no significant difference in safety is observed, more patients with unresectable HCC might benefit from the treatment. However, as most trials included in our study do not provide subgroup analyses based on baseline liver function, we turned to published articles for relevant data. The indirect comparison of safety data between CheckMate 040 cohort 5 (Child-Pugh B7/8 patients, except 1 Child-Pugh A6 patient in sorafenib-naïve arm; nivolumab monotherapy) and CheckMate 040 cohort 1 and 2 (98% Child-Pugh A) did not show a significant difference in trAE incidence between Child-Pugh A or B patients (Child-Pugh B cohort v.s. Child-Pugh A cohort all-grade trAE incidence: 51% v.s. 59%).[22] Similar results were reported in a post-hoc analysis for GO30140 and IMbrave150 trial (Atezolizumab plus bevacizumab), where the investigators found patients with moderate hepatic impairment have similar trAE incidence compared to overall population (moderate hepatic impairment v.s. overall population: 96.4% v.s. 98.2%).[53] There are currently no published articles on the impact of baseline liver function on trAE in patients under dual ICI therapy or ICIs plus oral targeted agents, but analyses focusing on oral targeted agents monotherapies indicate that impaired liver function would raise important safety issues in this subpopulation.[54-56] These results are highly consistent with our finding and further supported that patients planning to receive ICIs plus oral targeted agents should carefully monitor trAE (both systemic and hepatobiliary), and should evaluate pre-treatment liver function carefully.

Another issue of great clinical importance is the patients' background liver disease (including alcoholic, viral and NAFLD), as etiology not only affect residual liver function, but also influence immune environment, and reactivity and tolerability to systemic therapy. However, as most clinical trials included in our study do not provide individual patient data, we could not perform detailed analysis on etiology. Comprehensive search on published articles also returned no relevant articles making direct comparison of trAE profiles among different etiology. Shemesh et al.[53] found that patients with different geographic regions receiving atezolizumab plus bevacizumab have similar safety profile. Further evidence is required on the effect of background liver disease on trAE profile. As results from the HCV and HBV cohort for CheckMate 040 remains unpublished (NCT01658878), we are also expecting more detailed results from this promising trial and other relevant researches. In addition, trAEs leading to treatment discontinuation and treatment-related mortalities remain major challenges for ICI-based therapies. We found that the incidences of trAEs leading to treatment

discontinuation and treatment-related mortalities were 8.0% and 1.1%, respectively, comparable to other malignancies.[14, 42, 57] Furthermore, the majority of patients with a fatal outcome suffered from deterioration of pulmonary and hepatic function. One report of the CheckMate 040 study only included Child–Pugh B (B7-B8) patients and reported no treatment-related mortality.[22] Consequently, these findings suggest that clinicians should closely monitor the dynamic changes in patients' lung and liver status to avoid acute exacerbation of symptoms or even mortality.

We performed multivariable regression analysis to evaluate the association between prespecified predictors (line of systemic treatment, types of combination, type of ICIs) and the incidence of trAEs. We found that ICIs combined with targeted agents were significantly associated with an increased risk of developing all-grade and grade ≥3 trAEs. Immune checkpoint inhibitors act on exhausted T cells to rejuvenate immunity against malignant cells, while targeted agents disrupt overactive cell proliferation pathways to suppress vascular and tumour growth.[58, 59] The complementarity in the underlying mechanism of the two agents might explain the additive toxicity as well.[23, 31, 58] In a post hoc analysis, we found that oral targeted agents (small molecule TKIs) combined with ICIs increased the risk of toxic events compared to intravenous targeted agents (anti-VEGF monoclonal antibodies), albeit statistical significance was not reached (oral vs. intravenous, all-grade: OR = 3.48, 95% CI 0.96-12.64, *P*=0.058; grade ≥3: OR = 2.22, 95% CI 0.70-7.01, *P*=0.162). The rationale behind this observation remains to be elucidated but may be related to anti-drug antibodies that decrease the bioavailability of the monoclonal antibodies.[60-62] Furthermore, a positive correlation between the occurrence of all-grade trAEs and treatment line was observed. This result possibly reflects the increased tumour burden and worsened performance status of the patient after first-line failure and is supported by the head-to-head comparisons of the included clinical trials (RESCUE, CheckMate 040 cohort 5, KEYNOTE-224). Overall, these results still require validation and warrant additional research to compare the safety of the two targeted regimens.

The impact of irAEs on survival has been extensively researched and is well characterized, but results are lacking for trAEs.[63, 64] Therefore, we next focused on unravelling the relationship between the incidence of trAEs and survival (PFS, mOS). A trend of a positive correlation was observed for the trAE incidence and mOS (all-grade: OR = 1.13, 95% CI 1.03-1.23, *P*=0.010; grade≥3: OR = 1.05, 95% CI = 0.995-1.11, *P*=0.071). While a higher trAE incidence might reflect an overactive immune system and contribute to increased overall survival, prolonged survival also increases the incidence of trAEs due to an extended follow-up time. This bidirectional correlation adds to the difficulty in elucidating their relationship. In addition, recent research on melanoma suggests that ICI-related toxicity can be decoupled from antitumor immunity [65], which indicates that adverse events and antitumor immunity might act through different downstream pathways. This adds to the heterogeneity of the relationship between adverse event development and clinical efficacy and emphasizes the importance of more basic oncology research to gain a better understanding of the underlying mechanisms. Interestingly, we also found that drug exposure was positively associated with trAE development, although statistical significance was not reached, which is discrepant with previous studies[42] and requires further validation.

This study has several limitations. First, the spectra analyses are limited by the heterogeneous criteria of reporting adverse events applied by the included studies and the substantial heterogeneity of some adverse events. The pooled incidence could underestimate the actual risks of adverse events with a low incidence that were not reported by some studies. The pooled incidences of adverse events that are only reported by limited number of treatment groups also require cautious interpretation and results from the subgroups analyses should be considered as well to assess whether these treatment groups share common characteristics. The risk of adverse events reported as a representative of a MedDRA Preferred Term cluster might be overestimated as well. Second, the incidence and spectrum of irAEs were listed in the study protocol as additional outcomes. Due to the low proportion of included studies reporting tabulated data of irAEs and potential publication bias, we judged that the pooled incidence of irAEs in this study may not reliably reflect the actual risk of

irAEs and that spectrum analyses could not be performed. IrAEs are characterized by their distinct spectrum and often involve immune-modulating agents, which is also of clinical significance. With more trials reporting the incidence and spectrum of irAEs in the future, an updated review would be able to summarize the irAE profiles more accurately.

Conclusion

This meta-analysis comprehensively summarized the incidence and spectrum of adverse events. We also summarized trAEs leading to treatment discontinuation and treatment-related mortalities in unresectable HCC patients with ICI-based therapies. Through multivariable regression analysis, we identified that ICIs combined with oral targeted agents were associated with an increased risk of trAEs compared with ICI monotherapies or ICIs combined with intravenous targeted agents, and overall survival was significantly associated with the risk of developing all-grade trAEs. The results of this study may become an important reference for clinical practice and guide clinicians in timely identifying patients with trAEs and initiating proper management for better clinical outcomes.

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Statements

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Statement of Ethics

Study approval statement: an ethics statement is not applicable because this study is based exclusively on published literature.

Consent to participate statement: Informed consent was not required as this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yizhou Zhang, Minghao Wang, Qichen Chen, Jianqiang Cai, and Hong Zhao designed the study. Yizhou Zhang, Minghao Wang, and Hong Zhao performed study selection and data extraction. Yiqiao Deng, Jinghua Chen, and Qichen Chen performed risk of bias assessment. Yizhou Zhang, Minghao Wang, Qichen Chen, and Sheng Luo performed statistical analysis, and all authors contributed to interpretation of data. Jianming Xu contributed to discussion of adverse events in different etiologies and background liver diseases and introduced a post hoc analysis for the impact of type of treatment combination on liver function. The manuscript was written by Yizhou Zhang, Minghao Wang, Qichen Chen, Yiqiao Deng, Jinghua Chen, and Yimin Dai, and was revised by all authors. All authors have full access to study data and approved the final version of the manuscript to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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Figure Legends

Fig. 1. **Flow diagram of study selection**. CTCAE: Common Terminology Criteria for Adverse Events.

Fig. 2. **Forest plot showing overall incidence of treatment-related adverse events and immune-related adverse events.** Random-effects model with restricted maximum-likelihood estimation was applied. AE: adverse event. TrAE: treatment-related adverse event. IrAE: immune-related adverse event.

Fig. 3. **Incidence of all-grade and grade 3-5 treatment-related adverse events based on the line of systemic treatment, treatment type, and ICI type.** ICI: immune checkpoint inhibitor. Random-effects model with restricted maximum-likelihood estimation was applied unless specified. *For subgroups with one treatment group, Clopper-Pearson method was applied to calculate 95% confidence interval. TrAE: treatment-related adverse event.

Fig. 4. **Spectrum and incidence of all-grade and grade 3-5 treatment-related adverse events.** (a) Spectrum and incidence of all-grade treatment-related adverse events. (b) Spectrum and incidence of grade 3-5 treatment-related adverse events. All extracted adverse events were converted to MedDRA preferred terms and ordered according to pooled incidence. Only ten adverse events with the highest incidence and reported by no less than 10% of treatment groups were included. TrAE: treatment-related adverse event. SOC: System Organ Class. RCEP: reactive capillary endothelial proliferation. PPES: palmar-plantar erythrodysesthesia syndrome. AST: aspartate aminotransferase. ALT: alanine aminotransferase. ALP: alkaline phosphatase. WBC: white blood cell. GGT: gamma-glutamyl transferase.

Fig. 5. **Spectrum and incidence of all-grade and grade 3-5 treatment-related adverse events based on treatment type.** (a) All-grade trAE spectrum and incidence based on treatment type. (b) Grade 3-5 trAE spectrum and incidence based on treatment type. Treatment type included immune checkpoint inhibitor (ICI) monotherapy, ICI plus oral targeted therapy, ICI plus intravenous targeted therapy, and dual ICI therapy. Only ten adverse events with the highest incidence and reported by at least two treatment groups were included. ICI plus chemotherapy and ICI plus anti-CCR4 therapy subgroups were excluded due to insufficient number of treatment groups. *Less than ten adverse events reported by at least 2 treatment groups. TrAE: treatment-related adverse event. AST: aspartate aminotransferase. ALT: alanine aminotransferase. PPES: palmar-plantar erythrodysesthesia syndrome. WBC: white blood cell. GGT: gamma-glutamyl transferase. ALP: alkaline phosphatase.

Fig. 6. **Incidence of treatment-related adverse events leading to treatment discontinuation based on treatment line, treatment type and ICI type.** ICI: immune checkpoint inhibitor. Random-effects model with restricted maximum-likelihood estimation was applied unless specified. *For subgroup analyses with one treatment group, Clopper-Pearson method was applied to calculate 95% confidence interval. TrAE: treatment-related adverse event.

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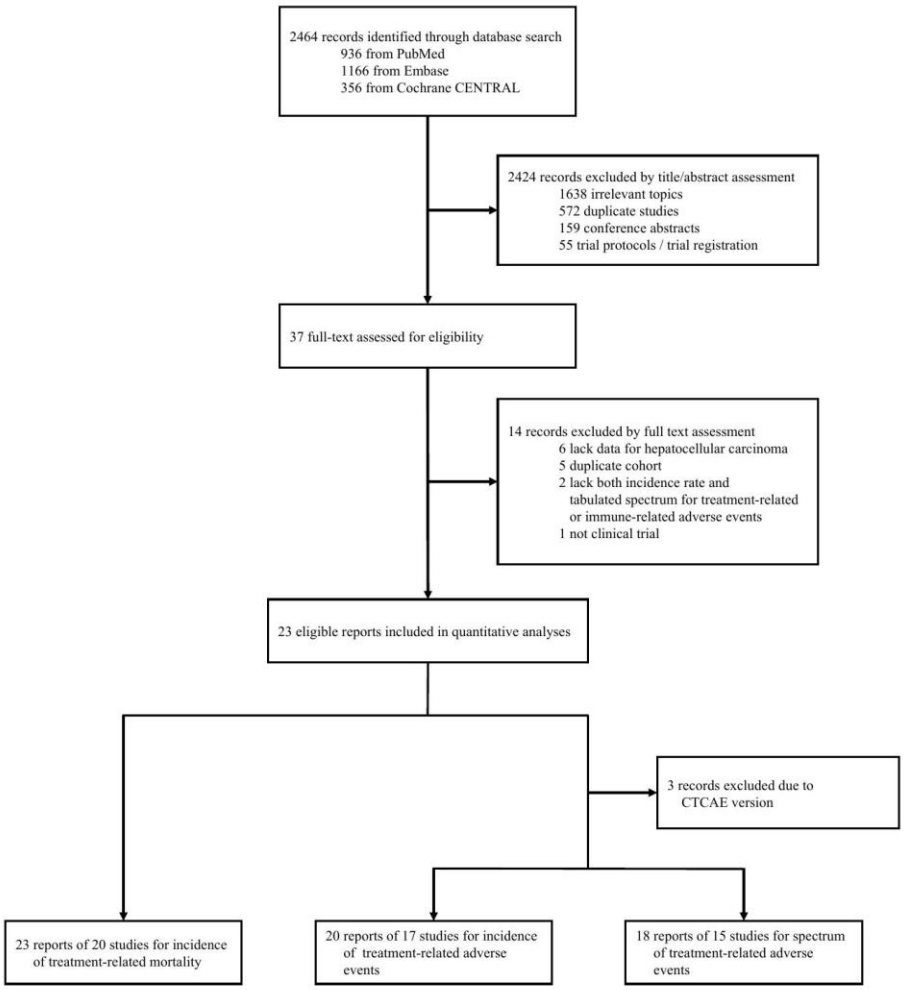
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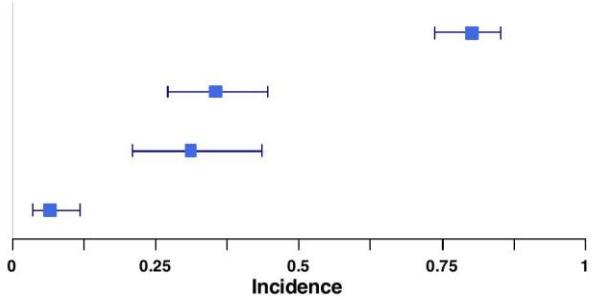
936 from PubMed
1166 from Embase
356 from Cochrane CENTRAL
2424 records excluded by title/abstract assessment
1638 irrelevant topics
572 duplicate studies
159 conference abstracts
55 trial protocols / trial registration
37 full-text assessed for eligibility
14 records excluded by full text assessment
6 lack data for hepatocellular carcinoma
5 duplicate cohort
2 lack both incidence rate and tabulated spectrum for treatment-related or immune-related adverse events
1 not clinical trial
23 eligible reports included in quantitative analyses
3 records excluded due to CTCAE version
23 reports of 20 studies for incidence of treatment-related mortality
20 reports of 17 studies for incidence of treatment-related adverse events
18 reports of 15 studies for spectrum of treatment-related adverse events

AEs category	No. of arms	Events/N	Incidence (95%CI)
trAE any grade	30	2201/2831	80.1 (73.8-85.2)
trAE grade 3-5	27	894/2668	35.4 (27.2-44.6)
irAE any grade	5	77/273	31.1 (21.0-43.5)
irAE grade 3-5	5	16/273	6.6 (3.6-11.8)



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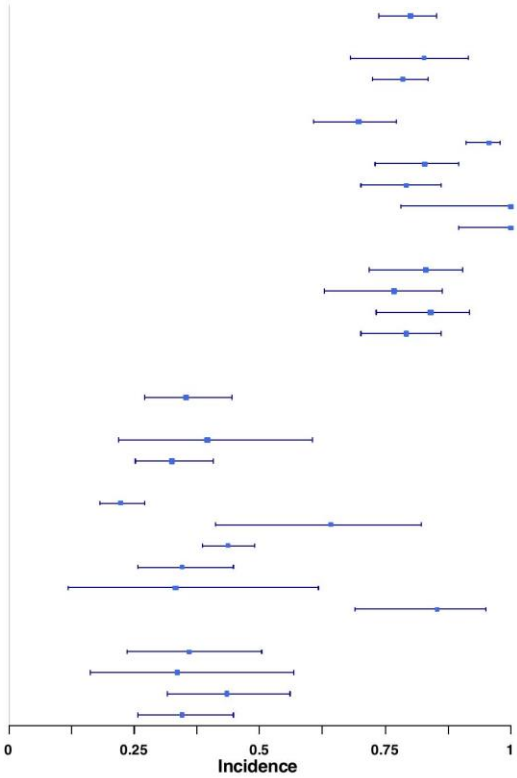
trAE subset	No. of arms	Events/N	Incidence (95%CI)
trAE Fullset	30	2201/2831	80.1 (73.8-85.2)
Treatment Line			
First-line	12	983/1251	82.7 (68.0-91.5)
Previously treated	18	1218/1580	78.5 (72.5-83.5)
Treatment Modality			
ICI Monotherapy	14	1141/1616	69.7 (60.8-77.3)
ICI+Target (oral)	5	333/343	95.7 (91.1-98.0)
ICI+Target (i.v.)	4	440/521	82.9 (73.1-89.6)
Dual ICI	5	238/302	79.2 (70.1-86.1)
ICI+anti-CCR4	1	15/15	100.0 (78.2-100.0)*
ICI+Chemotherapy	1	34/34	100.0 (89.7-100.0)*
ICI Type			
anti-PD-1	16	1336/1728	83.1 (71.9-90.4)
anti-PD-L1	8	569/732	76.7 (62.9-86.5)
anti-CTLA-4	1	58/69	84.1 (73.3-91.8)*
Dual ICI	5	238/302	79.2 (70.1-86.1)
trAE grade 3-5			
trAE grade 3-5 Fullset	27	894/2668	35.4 (27.2-44.6)
Treatment Line			
First-line	11	441/1147	39.6 (21.9-60.5)
Previously treated	16	453/1521	32.5 (25.2-40.7)
Treatment Modality			
ICI Monotherapy	12	338/1557	22.3 (18.1-27.1)
ICI+Target (oral)	5	236/343	64.2 (41.3-82.1)
ICI+Target (i.v.)	3	183/417	43.7 (38.6-49.0)
Dual ICI	5	103/302	34.5 (25.6-44.7)
ICI+anti-CCR4	1	5/15	33.3 (11.8-61.6)*
ICI+Chemotherapy	1	29/34	85.3 (68.9-95.0)*
ICI Type			
anti-PD-1	15	538/1699	35.9 (23.5-50.5)
anti-PD-L1	6	223/598	33.6 (16.3-56.8)
anti-CTLA-4	1	30/69	43.5 (31.6-56.0)*
Dual ICI	5	103/302	34.5 (25.6-44.7)



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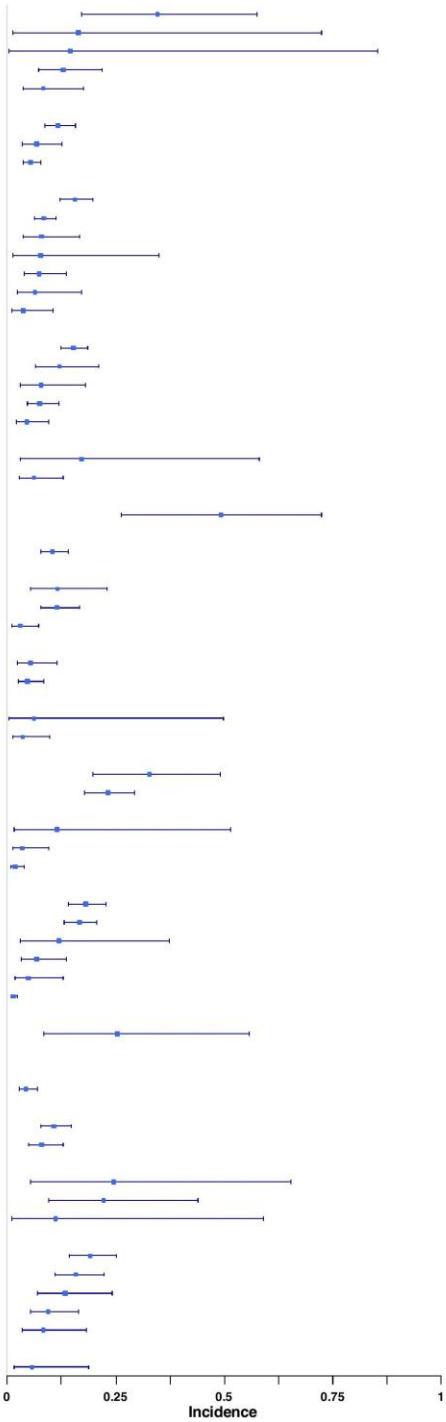
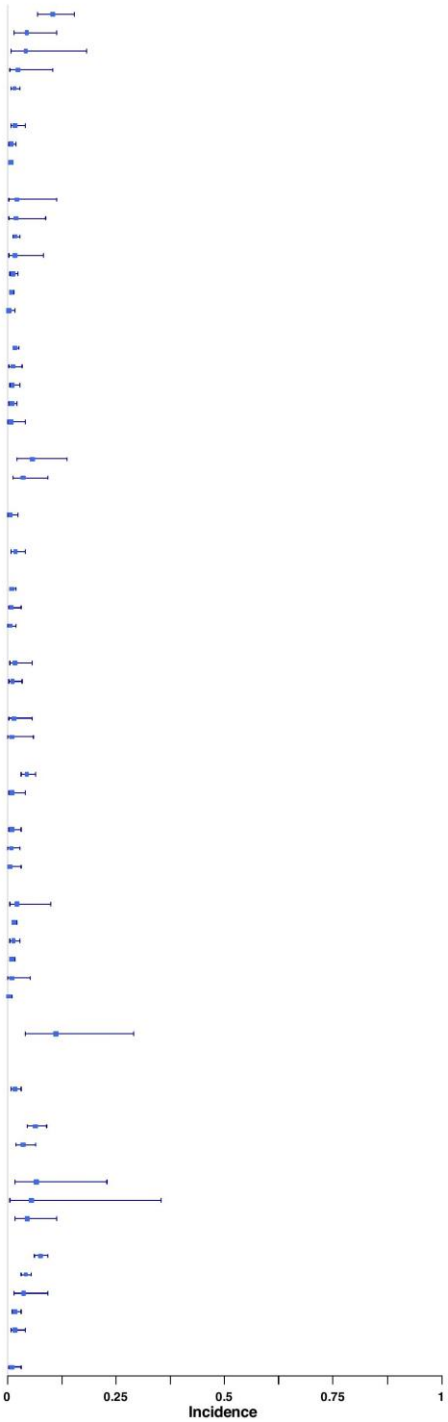
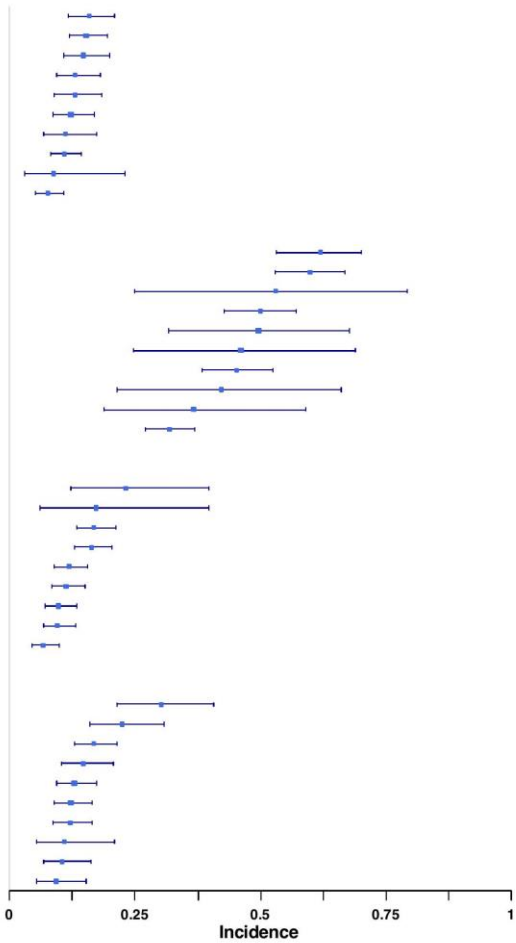
trAE SOC category	No. of arms	Events/N	Incidence (95%CI)
Blood and lymphatic system disorders			
neutropenia	3	90/219	34.6 (17.1-57.5)
thrombocytopenia	4	117/484	16.4 (1.4-72.5)
leukopenia	3	96/469	14.5 (0.5-85.4)
lymphopenia	3	26/205	12.9 (7.3-21.8)
anaemia	9	74/916	8.3 (3.6-17.7)
Endocrine disorders			
hypothyroidism	19	211/1852	11.7 (8.7-15.6)
adrenal insufficiency	5	17/272	6.8 (3.5-12.7)
hyperthyroidism	10	42/919	5.4 (3.8-7.7)
Gastrointestinal disorders			
diarrhoea	23	343/2496	15.6 (12.2-19.8)
nausea	16	128/1746	8.4 (6.3-11.2)
abdominal distension	3	6/82	7.9 (3.6-16.6)
stomatitis	4	15/347	7.7 (1.3-35.1)
abdominal pain	11	80/934	7.4 (3.9-13.6)
vomiting	4	17/356	6.4 (2.2-17.2)
dry mouth	3	19/541	3.7 (1.2-10.5)
General disorders and administration site conditions			
fatigue	20	347/2275	15.2 (12.3-18.5)
asthenia	11	131/1164	12.1 (6.6-21.2)
malaise	6	25/462	7.8 (3.1-18.0)
pyrexia	10	44/779	7.5 (4.6-11.9)
oedema peripheral	3	12/332	4.5 (2.1-9.6)
Hepatobiliary disorders			
hyperbilirubinaemia	5	123/343	17.1 (3.0-58.1)
hepatic function abnormal	6	45/785	6.2 (2.8-12.9)
Immune system disorders			
RCEP	4	226/441	49.2 (26.3-72.3)
Injury, poisoning and procedural complications			
infusion related reaction	3	38/366	10.4 (7.7-14.0)
Metabolism and nutrition disorders			
hypoalbuminaemia	5	59/484	11.6 (5.4-23.0)
decreased appetite	19	223/2153	11.5 (7.7-16.7)
hyponatraemia	4	8/371	3.0 (1.2-7.2)
Musculoskeletal and connective tissue disorders			
myalgia	5	18/478	5.3 (2.3-11.5)
arthralgia	6	18/480	4.7 (2.6-8.3)
Nervous system disorders			
dysgeusia	3	9/316	6.2 (0.4-49.9)
headache	4	8/360	3.6 (1.3-9.8)
Renal and urinary disorders			
proteinuria	7	298/892	32.8 (19.8-49.2)
haematuria	3	48/212	23.2 (17.9-29.4)
Respiratory, thoracic and mediastinal disorders			
dysphonia	4	38/520	11.4 (1.5-51.4)
cough	3	9/361	3.5 (1.3-9.5)
pneumonitis	3	5/325	1.8 (0.8-4.0)
Skin and subcutaneous tissue disorders			
pruritus	19	329/1959	18.0 (14-22.8)
rash	24	363/2530	16.6 (13.2-20.6)
PPES	8	157/1318	11.9 (3.0-37.3)
rash maculo-papular	10	46/870	6.8 (3.2-13.7)
dry skin	3	12/322	4.9 (1.8-12.9)
alopecia	4	13/1006	1.4 (0.8-2.4)
Vascular disorders			
hypertension	8	306/1284	25.4 (8.4-55.6)
Investigations			
Enzyme investigations			
blood alkaline phosphatase increased	8	36/882	4.3 (2.7-7.0)
Gastrointestinal investigations			
lipase increased	12	76/820	10.8 (7.8-14.8)
amylase increased	10	38/494	8.0 (4.8-13.0)
Haematology investigations			
white blood cell count decreased	4	61/311	24.5 (5.3-65.3)
platelet count decreased	6	108/655	22.2 (9.5-43.9)
neutrophil count decreased	4	53/561	11.1 (1.1-59.0)
Hepatobiliary investigations			
AST increased	24	463/2506	19.1 (14.2-25.2)
ALT increased	22	337/2039	15.8 (11.0-22.2)
bilirubin conjugated increased	3	30/282	13.4 (7.0-24.1)
blood bilirubin increased	10	92/938	9.5 (5.3-16.3)
gamma-glutamyltransferase increased	7	71/855	8.3 (3.5-18.3)
Physical examination and organ system status topics			
weight decreased	6	40/847	5.7 (1.6-18.7)



trAE SOC category	No. of arms	Events/N	Incidence (95%CI)
Blood and lymphatic system disorders			
neutropenia	3	22/219	10.5 (7.0-15.4)
lymphopenia	3	8/205	4.5 (1.6-11.5)
thrombocytopenia	4	19/484	4.2 (0.9-18.2)
leukopenia	3	8/469	2.4 (0.5-10.5)
anaemia	9	10/916	1.6 (0.8-3.0)
Endocrine disorders			
hypothyroidism	5	3/272	1.7 (0.7-4.2)
adrenal insufficiency	10	1/919	0.9 (0.4-2.0)
hyperthyroidism	19	2/1852	0.8 (0.4-1.4)
Gastrointestinal disorders			
stomatitis	4	2/347	2.2 (0.4-11.4)
vomiting	4	2/356	2.0 (0.4-8.8)
diarrhoea	23	34/2496	1.9 (1.2-2.9)
abdominal distension	3	0/82	1.8 (0.4-8.4)
abdominal pain	11	5/934	1.3 (0.6-2.4)
nausea	16	3/1746	0.9 (0.5-1.6)
dry mouth	3	0/541	0.3 (0.1-1.7)
General disorders and administration site conditions			
fatigue	20	29/2275	1.8 (1.3-2.7)
malaise	6	1/462	1.3 (0.4-3.5)
asthenia	11	6/1164	1.2 (0.5-2.9)
pyrexia	10	1/779	1.0 (0.4-2.2)
oedema peripheral	3	0/332	0.8 (0.2-4.1)
Hepatobiliary disorders			
hyperbilirubinaemia	5	22/343	5.7 (2.3-13.8)
hepatic function abnormal	6	25/785	3.7 (1.4-9.3)
Immune system disorders			
RCEP	4	1/441	0.7 (0.2-2.4)
Injury, poisoning and procedural complications			
infusion related reaction	3	6/366	1.9 (0.9-4.0)
Metabolism and nutrition disorders			
decreased appetite	19	11/2153	1.1 (0.6-2.1)
hyponatraemia	4	1/371	0.9 (0.3-3.1)
hypoalbuminaemia	5	1/484	0.7 (0.2-2.1)
Musculoskeletal and connective tissue disorders			
arthralgia	6	2/480	1.8 (0.5-5.8)
myalgia	5	2/478	1.2 (0.4-3.3)
Nervous system disorders			
headache	4	1/360	1.5 (0.4-5.8)
dysgeusia	3	0/316	1.1 (0.2-6.0)
Renal and urinary disorders			
proteinuria	7	32/892	4.5 (3.2-6.4)
haematuria	3	1/212	1 0 (0.3-4.0)
Respiratory, thoracic and mediastinal disorders			
pneumonitis	3	2/325	1.0 (0.3-3.2)
dysphonia	4	1/520	0.9 (0.2-2.9)
cough	3	0/361	0.6 (0.1-3.1)
Skin and subcutaneous tissue disorders			
PPES	7	24/1218	2.3 (0.5-9.9)
rash	24	15/2530	1.5 (1.0-2.2)
rash maculo-papular	10	4/870	1.4 (0.6-3.0)
pruritus	19	7/1959	1.0 (0.6-1.7)
dry skin	3	0/322	1.0 (0.2-5.3)
alopecia	4	0/1006	0.3 (0.1-1.1)
Vascular disorders			
hypertension	9	139/1284	11.1 (4.0-29.0)
Investigations			
Enzyme investigations			
blood ALP increased	8	8/882	1.7 (0.9-3.2)
Gastrointestinal investigations			
lipase increased	12	42/820	6.4 (4.5-9.1)
amylase increased	10	12/494	3.6 (2.0-6.4)
Haematology investigations			
WBC count decreased	5	21/326	6.7 (1.7-23.0)
neutrophil count decreased	4	29/561	5.5 (0.6-35.5)
platelet count decreased	6	22/655	4.6 (1.7-11.4)
Hepatobiliary investigations			
AST increased	24	170/2506	7.7 (6.3-9.4)
ALT increased	22	70/2039	4.2 (3.2-5.6)
GGT increased	7	33/855	3.8 (1.5-9.3)
blood bilirubin increased	10	11/938	1.8 (1.1-3.1)
bilirubin conjugated increased	3	4/282	1.7 (0.7-4.1)
Physical examination			
weight decreased	6	4/847	1.1 (0.4-3.1)



All-grade trAEs	No. of arms	Events/N	Incidence (95%CI)
ICI monotherapy			
platelet count decreased	2	39/246	15.9 (11.8-21.0)
pruritus	10	187/1260	15.3 (11.9-19.4)
fatigue	10	216/1479	14.7 (10.7-19.9)
AST increased	11	190/1477	13.1 (9.4-18.0)
rash	10	171/1479	13.0 (9.0-18.4)
white blood cell count decreased	2	30/246	12.2 (8.7-16.9)
ALT increased	10	134/1110	11.1 (6.9-17.4)
diarrhoea	10	145/1479	10.9 (8.2-14.4)
blood bilirubin increased	5	70/695	8.8 (3.0-23.1)
hypothyroidism	7	62/850	7.6 (5.2-10.9)
ICI combined with target (oral)			
hyperbilirubinaemia	2	117/190	61.9 (53.1-70.0)
thrombocytopenia	2	114/190	59.9 (52.8-66.7)
hypertension	5	194/343	53.0 (25.0-79.2)
leukopenia	2	95/190	50.0 (42.9-57.1)
ALT increased	3	111/221	49.6 (31.7-67.6)
AST increased	4	152/321	46.1 (24.7-69.0)
neutropenia	2	86/190	45.3 (38.3-52.4)
proteinuria	4	143/312	42.2 (21.5-66.1)
PPES	5	145/343	36.7 (18.9-59.0)
diarrhoea	5	106/343	31.8 (27.0-37.0)
ICI combined with target (i.v.)*			
hypertension	2	97/357	23.1 (12.1-39.7)
diarrhoea	2	44/357	17.3 (6.2-39.7)
fatigue	2	60/357	16.8 (13.3-21.1)
AST increased	2	58/357	16.3 (12.8-20.5)
ALT increased	2	42/357	11.8 (8.9-15.6)
decreased appetite	2	40/357	11.3 (8.4-15.0)
hypothyroidism	2	35/357	9.8 (7.1-13.4)
rash	2	34/357	9.5 (6.9-13.1)
nausea	2	24/357	6.7 (4.5-9.8)
dual ICI therapy			
pruritus	5	89/302	30.2 (21.5-40.7)
rash	5	68/302	22.5 (15.9-30.8)
AST increased	5	50/302	16.8 (12.9-21.4)
diarrhoea	5	43/302	14.7 (10.3-20.6)
ALT increased	5	38/302	12.9 (9.5-17.3)
fatigue	5	36/302	12.2 (8.9-16.5)
lipase increased	5	34/302	12.1 (8.8-16.5)
amylase increased	2	17/156	10.9 (5.4-21.0)
hypothyroidism	5	31/302	10.5 (6.8-16.1)
decreased appetite	3	13/146	9.2 (5.4-15.2)



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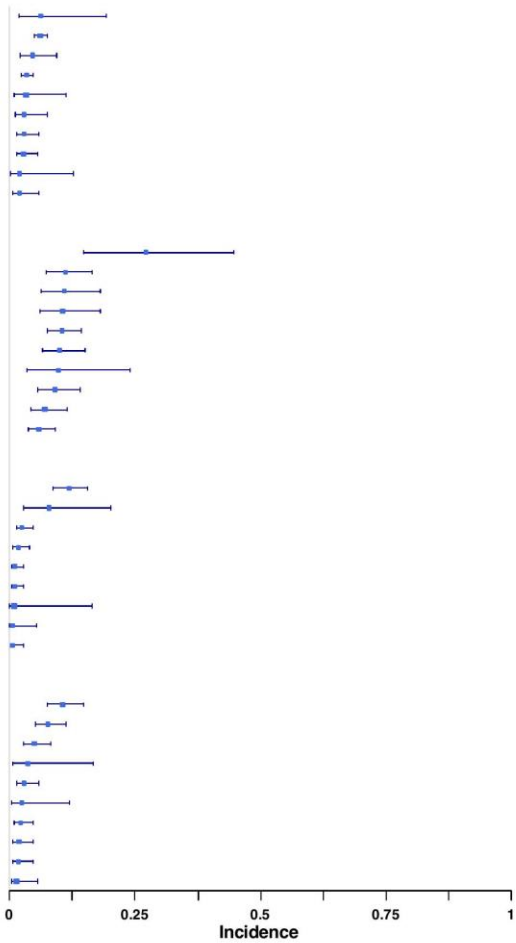
Grade 3-5 trAEs	No. of arms	Events/N	Incidence (95%CI)
ICI monotherapy			
hypertransaminasaemia	2	2/49	6.2 (1.8-19.2)
AST increased	11	85/1477	6.1 (5.0-7.5)
lipase increased	6	17/484	4.5 (2.1-9.4)
ALT increased	10	32/1110	3.4 (2.4-4.7)
platelet count decreased	2	6/246	3.3 (0.9-11.3)
amylase increased	5	5/267	3.0 (1.2-7.5)
WBC count decreased	2	7/246	2.9 (1.4-5.9)
hepatic function abnormal	3	7/266	2.8 (1.4-5.7)
liver function test increased	2	0/49	2.0 (0.3-12.6)
neutrophil count decreased	2	10/496	2.0 (0.7-5.8)
ICI combined with target (oral)			
hypertension	5	95/343	27.2 (14.8-44.6)
neutropenia	2	21/190	11.1 (7.3-16.4)
hyperbilirubinaemia	2	20/190	10.9 (6.3-18.1)
PPES	4	22/243	10.6 (6.0-18.0)
AST increased	4	31/321	10.4 (7.4-14.3)
thromboocytopenia	2	19/190	10.0 (6.5-15.1)
GGT increased	3	22/221	9.7 (3.5-23.9)
hepatic function abnormal	2	17/190	9.0 (5.7-14.0)
ALT increased	3	14/221	7.0 (4.2-11.4)
proteinuria	4	18/312	5.9 (3.8-9.2)
ICI combined with target (i.v.)*			
hypertension	2	42/357	11.8 (8.8-15.5)
AST increased	2	21/357	7.9 (2.8-20.2)
ALT increased	2	9/357	2.5 (1.3-4.8)
fatigue	2	6/357	1.8 (0.8-3.9)
decreased appetite	2	3/357	1.0 (0.4-2.8)
diarrhoea	2	3/357	1.0 (0.4-2.8)
hypothyroidism	2	1/357	0.9 (0-16.4)
rash	2	0/357	0.5 (0-5.3)
nausea	2	1/357	0.5 (0.1-2.7)
dual ICI therapy			
AST increased	5	30/302	10.6 (7.5-14.8)
lipase increased	5	22/302	7.6 (5.1-11.3)
ALT increased	5	12/302	4.9 (2.8-8.3)
amylase increased	2	6/156	3.6 (0.7-16.7)
rash	5	6/302	2.9 (1.4-5.9)
blood ALP increased	2	3/156	2.4 (0.4-11.9)
diarrhoea	5	6/302	2.2 (1.0-4.8)
rash maculo-papular	5	3/302	1.9 (0.7-4.7)
pruritus	5	2/302	1.7 (0.6-4.7)
adrenal insufficiency	3	1/146	1.4 (0.4-5.6)



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trAE discontinuation	No. of arms	Events/N	Incidence (95%CI)
trAE Fullset	21	143/1906	8.0 (6.0-10.5)
Treatment Line			
First-line	7	64/678	10.5 (6.5-16.5)
Previously treated	14	79/1228	7.0 (5.0-9.7)
Treatment Modality			
ICI Monotherapy	11	72/1249	6.0 (4.3-8.2)
ICI+Target (oral)	4	45/321	14.3 (10.1-20)
Dual ICI	5	26/302	8.9 (4.9-15.5)
ICI+Chemotherapy	1	0/34	0 (0-10.3)*
ICI Type			
anti-PD-1	14	100/1434	7.1 (4.8-10.4)
anti-PD-L1	1	8/101	7.9 (3.5-15.0)*
anti-CTLA-4	1	9/69	13.0 (6.1-23.3)*
Dual ICI	5	26/302	8.9 (4.9-15.5)

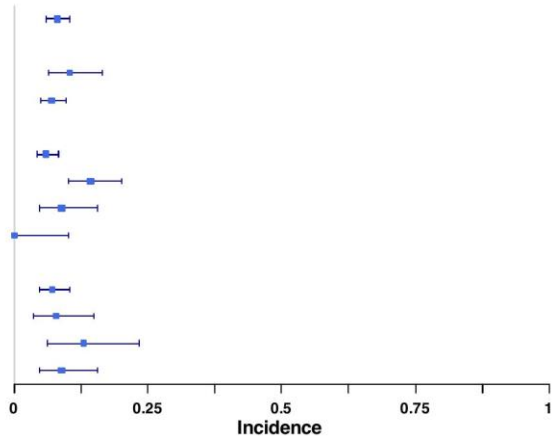

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Table 1 Multivariable regression analysis of study-level factors associated with the incidence of all-grade trAEs and grade ≥3 trAEs

Variable	All-grade trAEs (28 treatment groups)			Grade ≥3 trAEs (25 treatment groups)		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Line of systematic therapy			0.006*			0.077*
First-line	Ref			Ref		
Previously treated	2.31	1.18-4.53	0.017	1.55	0.83-2.89	0.159
Treatment type			<0.001*			<0.001*
ICI monotherapy	Ref			Ref		
ICI plus targeted agents (oral)	17.07	6.05-48.16	<0.001	9.35	4.53-19.29	<0.001
ICI plus targeted agents (iv)	4.91	1.80-13.42	0.003	4.21	1.42-12.48	0.012
Dual ICIs therapy	1.25	0.60-2.62	0.534	1.74	0.88-3.45	0.104
Type of ICIs			0.214*			0.060*
Anti-PD-1	Ref			Ref		
Anti-PD-L1	0.63	0.29-1.40	0.246	0.78	0.33-1.87	0.561
Anti-CTLA-4	1.69	0.43-6.66	0.434	2.54	0.75-8.63	0.126

***The overall P value of each predictor was calculated from a likelihood ratio test between the meta-regression model with all predictors and a model with all predictors except the one of interest. Both models for the likelihood ratio test were fitted with the maximum likelihood estimator.**

TrAE: treatment-related adverse event.

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Table 2 Protocol-prespecified exploratory analysis of the association between median progression-free survival, median overall survival, and exposure of immune checkpoint inhibitors and the incidence of all-grade trAEs and grade ≥3 trAEs after adjusting for the line of systemic treatment, treatment type, and type of ICIs

Variable	All-grade trAEs				Grade ≥3 trAEs			
	Number of treatment groups	OR	95% CI	*P* value	Number of treatment groups	OR	95% CI	*P* value
Median PFS	25	0.97	0.70-1.36	0.862	22	0.80	0.59-1.08	0.129
Median OS	22	1.13	1.03-1.23	0.010	19	1.05	0.995-1.11	0.071
Median exposure	20	1.14	0.96-1.35	0.128	19	1.07	0.98-1.17	0.114

TrAE: treatment-related adverse event. PFS: progression-free survival. OS: overall survival.

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