Adverse events induced by durvalumab and tremelimumab combination regimens: a systematic review and meta-analysis

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have shown remarkable therapeutic outcomes among cancer patients. Durvalumab plus tremelimumab (DT) is under investigation as a new ICI combination therapy, and its efficacy has been reported in various types of cancer. However, the safety profile of DT remains unclear, especially considering rare adverse events (AEs).

Objective: We aimed to assess the frequency of AEs associated with DT.

Design: This study type is a systematic review and meta-analysis.

Data Sources and Methods: Four databases were searched for articles. Randomized trials, single-arm trials, and prospective and retrospective observational studies were included. The type of cancer, previous treatment, and performance status were not questioned. Major AE indicators such as any AE and the pooled frequency of each specific AE were used as outcomes. As a subgroup analysis, we also compared cases in which DT was performed as first-line treatment with those in which it was performed as second-line or later treatment. The protocol for this systematic review was registered on the University Hospital Medical Information Network (UMIN) Center website (ID: UMIN000046751).

Results: Forty-one populations including 3099 patients were selected from 30 articles. Pooled frequencies of key AE indicators are shown below: any AEs, 77.8% [95% confidence interval (CI): 67.9–87.6]; grade ⩾3 AEs, 29.3% (95% CI: 24.2–34.4); serious AEs, 34.9% (95% CI: 28.1–41.7); AE leading to discontinuation, 13.3% (95% CI: 9.3–17.4); treatment-related deaths, 0.98% (95% CI: 0.5–1.5). AEs with a frequency exceeding 15% are shown below: fatigue, 30.1% (95% CI: 23.8–36.3); diarrhea, 21.7% (95% CI: 17.8–25.6); pruritus 17.9% (95% CI: 14.4–21.3); decreased appetite, 17.7% (95% CI: 13.7–22.0); nausea, 15.6% (95% CI: 12.1–19.6). There were no significant differences in these pooled frequencies between subgroups.

Conclusions: The incidence of any AE in DT therapy was approximately 78%, and the incidence of grade 3 or higher AEs was approximately 30%, which was independent of prior therapy.

Keywords: clinical trial, drug-related adverse events, immune checkpoint inhibitor, monoclonal antibodies, neoplasms

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Introduction

It is well-established that immune checkpoint inhibitors (ICIs) block tumor cell signals that suppress T-cell activation. Importantly, the introduction of ICIs has drastically improved therapeutic outcomes among patients with cancer.

Tremelimumab, a monoclonal antibody targeting the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) protein receptor, inactivates T-cell recognition and cancer cell proliferation, diversifies T-cell responses, and promotes T-cell infiltration into tumors.[1,2] Durvalumab, another

known ICI, can enhance the antitumor effect of T cells by inhibiting the binding of programmed death ligand 1 (PD-L1) to programmed cell death protein-1 (PD-1).[3]

ICIs were initially used alone; however, clinical trials have revealed that combinations of cytotoxic agents or multiple ICIs can afford superior outcomes, resulting in the widespread application of nivolumab plus ipilimumab.

Currently, durvalumab plus tremelimumab (DT) is under investigation in clinical trials as a new ICI combination therapy, with efficacy reported in non-small cell lung cancer,[4] head and neck cancer,[5] and other types of cancers. However, the safety profile of DT remains unclear, especially considering rare adverse events (AEs).[6] DT has been associated with a greater number of grade $\geqslant 3$ AEs than monotherapy.[7–10] Considering AEs from combined ICI therapy, Somekawa *et al.*[11] have systematically reviewed the combined use of nivolumab, an anti-PD-1 antibody, and ipilimumab, an anti-CTLA-4 antibody. The authors reported that approximately 40% of patients who received a combination of nivolumab and ipilimumab experienced grade $\geqslant 3$ AEs. It is estimated that treatment with DT can also result in grade $\geqslant 3$ AEs than monotherapy.

Although DT is gaining momentum as a standard treatment for various malignancies, detailed toxicity profiles need to be established. Therefore, in the present systematic review and meta-analysis, we aimed to assess the patient-level frequency of AEs associated with DT therapy.

Methods

Protocol registration

The protocol for this systematic review was established in accordance with meta-analyses of observational studies in epidemiology guidelines and was registered on the University Hospital Medical Information Network (UMIN) Center website (ID: UMIN000046751).[12,13]

Study search

The electronic database search formulas for PubMed, Web of Science Core Collection, Cochrane Advanced Search, and EMBASE are described in Supplemental Text 1. A database search was conducted on 15 February 2022. Two authors (HM and KS) independently performed additional searches manually.

The identified articles (HM and KS) were screened and thoroughly assessed. In the case of any disagreement, a third reviewer was consulted.

Publication type and trial design

In addition to randomized and single-arm trials, prospective and retrospective observational studies were also considered. However, case reports and case series were excluded owing to unsuitable study designs for estimating AE frequency. Eligible articles were limited to those published in English. Full articles and conference abstracts were also considered.

Patients

There was no restriction on the type of cancer, as it did not substantially impact the safety profile when the same regimen was selected. Patients who had undergone previous chemotherapy were considered. No restrictions on performance status or age were implemented.

Treatment

DT regimens combined with other anticancer medications, such as cytotoxic anticancer drugs, molecular-targeted drugs, and other ICI combinations, were excluded. The present analysis also excluded patients who received combined chemoradiotherapy. Furthermore, we excluded sequential combinations, such as three courses of durvalumab followed by three courses of tremelimumab. There were no restrictions on the dose, schedule, or frequency of DT combination therapy. However, clinical trials in which the study protocol required only one course of DT therapy were excluded. Perioperative treatments, such as adjuvant and neoadjuvant therapies, were permitted.

Quality assessment

The Newcastle-Ottawa quality assessment scale for cohort studies was used for quality assessment.[14]

Outcomes

The binomial frequencies of major AE indicators (any AE, grade $\geqslant 3$ AEs, serious AEs, AE leading to discontinuation, and treatment-related death)

were pooled. In addition, 22 specific AEs, including elevated alanine aminotransferase levels and skin rash, were reported.

Data extraction

Two review authors (HM and KS) extracted key study characteristics, including author name, year of publication, country of origin, study title, and the number of patients. If a study evaluated different doses of durvalumab and tremelimumab accompanied by AE profiles, these regimens were counted as independent populations.

Subgroup analysis

The subgroup analysis focused on patients who received DT therapy as first-line treatment, as well as on those who received DT therapy as second-line or later treatment.

Statistics

The frequency of each AE was pooled by random model meta-analysis using the generic inverse variance method (RevMan ver 5.4.1.; Cochrane Collaboration, London, UK). Standard errors were calculated using Agrestia's method.[15] In addition to I^2 statistics, between-subgroup differences were expressed using p-values for heterogeneity based on the RevMan random model analysis, with a significance level of $p < 0.1$.

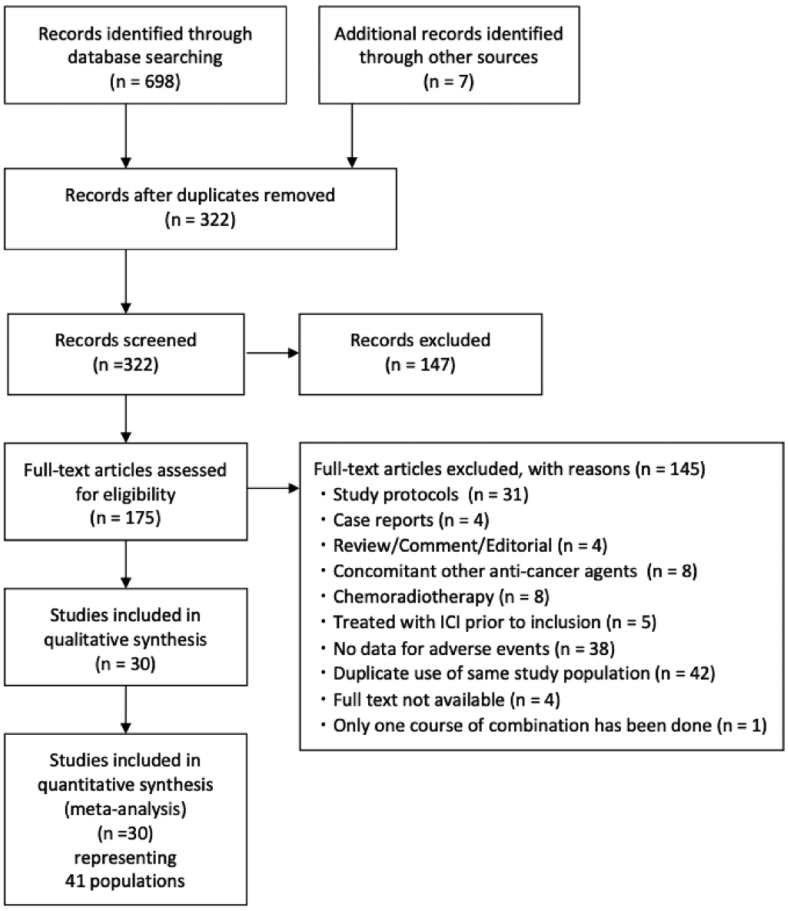

Figure 1. The preferred reporting items for systematic reviews and meta-analyses flow chart.

Results

Study selection process

An electronic search of four major databases retrieved 698 articles, and a manual search identified seven additional articles (Figure 1). After deduplication ($n = 147$), screening ($n = 322$), and full-text scrutiny ($n = 175$), 41 populations from 30 studies were included in the quantitative analysis. (Figure 1 and Supplemental Table 3).

Study characteristics

Among the 30 included papers, 17 were full articles and 13 were conference abstracts. More than 50% of included papers were from the U.S. ($n = 18$), followed by Canada ($n = 5$), France ($n = 3$), Italy, Korea, Spain, and the UK ($n = 1$ each). The studies included six phase I/IB studies, one phase Ib/II study, 14 phase II studies, six phase III studies, and one pilot study. However, some studies failed to describe the trial phase (Table 1).

Table 1 lists the target diseases identified in each study. The most frequently examined diseases were non-small cell lung cancer ($n = 5$), head and neck squamous cell cancer ($n = 3$), and hepatocellular carcinoma ($n = 2$). In addition, the present study included cancers such as small cell lung cancer and breast, colorectal, prostate, urinary tract, and rare cancers.

Approximately half ($n = 16$) of the included studies involved DT therapy as a second-line or later-line treatment. Three studies included only first-line therapy. In addition, three studies included adjuvant and neoadjuvant therapies, and one study failed to describe these therapies.

Based on the New-Ottawa Quality assessment scale, the median article quality was 4 (range 3–5). The analyzed population included 3099

Table 1. Characteristics of included populations.

Population	Country	Report	Design	Cancer	Stage	Regimen	Setting	*n*	NOS
Antonia 2016 T1	USA	FA	P1b	NSCLC	Locally advanced or metastatic	D10–20 q2w x26 or q4w x13 + T1 q4w x6 > q12w x3	1st or later	56	4
Antonia 2016 T10	USA	FA	P1b	NSCLC	Locally advanced or metastatic	D15 q4w x13 + T10 q4w x6 > q12w x3	1st or later	9	4
Antonia 2016 T3	USA	FA	P1b	NSCLC	Locally advanced or metastatic	D10–20 q2w x26 or q4w x13 + T3 q4w x6 > q12w x3	1st or later	34	4
Boilève 2021	France	FA	P2 RCT	Biliary tract carcinoma	Recurrent or advanced	D1500 + T75 q4w x4	2nd or later	10	4
Brohawn 2018 P1b	USA	CA	P1b	Gastric cancer	Recurrent or metastatic	D20 + T1 q4w > D10 q2w	2nd	6	4
Brohawn 2018 P2 ArmA	USA	CA	P2 RCT	Gastric cancer	Recurrent or metastatic	D20 + T1 q4w > D10 q2w	2nd	27	4
Brohawn 2018 P2 ArmD	USA	CA	P2 RCT	Gastric cancer	Recurrent or metastatic	D20 + T1 q4w > D10 q2w	3rd	25	4
Brohawn 2018 P2 ArmE	USA	CA	P2RCT	Gastric cancer	Recurrent or metastatic	D20 + T1 q4w > D10 q2w	2nd or 3rd	19	4
Calabro 2018	Italy	FA	Single arm P2	Mesothelioma	Unresectable	D20 + T1 q4w x4 > D20 q4w x9	1st or 2nd	40	5
Capdevila 2020	Spain	CA	Single arm P2	Lung carcinoid, G1/2 gastric, G1/2 pancreatic, G3NEN	Advanced	D1500 q4x13 + T75 q4w x4	2nd or later	123	4
Chen 2019	Canada	CA	P2 RCT	Colorectal carcinoma	Metastatic	D1500 + T75 q4w x4	2nd or later	118	5
Cho 2018	USA	CA	P1	SCLC	Extensive disease	D20 + T1 q4w	2nd or later	30	4
Edenfield 2021	USA	FA	Single arm P2	Rare cancers	Advanced	D1500 q4w x13 + T75 q4w x7 > q12w x2	2nd or later	44	4
Ferrarotto 2020	USA	FA	RCT	Oropharyngeal cancer	Stage 2–4A	D1500 + T75 day 1, 29	Neoadj	14	5
Ferris 2020	USA	FA	P3	HNSCC	Recurrent or metastatic	D20 + T1 q4w > D10 mg q2w	2nd-5th	246	4
Gao 2019	USA	CA	Single arm	Bladder cancer	cT2-T4a	D1500 + T75 q4w x2	Neoadj	28	4
Hotte 2019	Canada	CA	P2 RCT	Prostate cancer	Metastatic	D1500 + T75 q4w x4	2nd or later	39	4
Karakunnel 2016	USA	CA	P1	NSCLC	Advanced	D20 + T1 q4w	Unknown	102	4
Kelley 2020 T300 + D	USA	CA	P3	HCC	Unresectable	D1500 + T300 q4w	After sorafenib	74	5

(Continued)

Table 1. (Continued)

Population	Country	Report	Design	Cancer	Stage	Regimen	Setting	*n*	NOS
Kelley 2020 T75 + D	USA	CA	P3	HCC	Unresectable	D1500 + T75 q4w	After sorafenib	82	4
Kim 2020	Korea	FA	Single arm P2	Pulmonary sarcomatoid carcinoma	Recurrent or metastatic	D1500 + T75 q4w(x4) > D750 q2w(x18)	1st or adj	18	5
Leighl 2021	Canada	FA	P2 RCT	NSCLC	4	D1500 + T75 q4w x4 > D1500 q4w	Mainly chemo-naive	149	5
Nehra 2020	Canada	FA	P1B	Solid tumor	Advanced, unresectable, recurrent or metastatic	D1500 + T75 q4w x4	1st or 2nd	7'4	
O'Reilly 2019	USA	FA	P2 RCT	Pancreatic ductal adenocarcinoma	Recurrent or metastatic	D1500 q4w + T75 q4wx4 > D1500 q4w	2nd	32	4
Ornstein 2020 cohort2	USA	CA	P1b	RCC	High risk localized RCC (clinical stage T2b-4 and/or N1, M0 disease)	D + T- > D(x1dose), D + T- > D(x1 year), D + T- > D + T(x1dose) then D(x1 year), D1500 mgT75 mg	Neoadj, adj	6	4
Ornstein 2020 cohort2a	USA	CA	P1b	RCC	High risk localized RCC (clinical stage T2b-4 and/or N1, M0 disease)	D + T > D(x1dose), D + T > D(x1 year), D + T > D + T(x1dose) then D(x1 year), D1500 mgT75 mg	Neoadj, adj	8	4
Ornstein 2020 cohort3	USA	CA	P1b	RCC	High risk localized RCC (clinical stage T2b-4 and/or N1, M0 disease)	D + T > D(x1dose), D + T > D(x1 year), D + T > D + T(x1dose) then D(x1 year), D1500 mgT75 mg	Neoadj, adj	8	4
Planchard 2020	France	FA	P3	NSCLC	Stage3B/4	D20 mg/kg + T1 mg/kg q4w	3rd or later	173	4
Powles 2020	UK	FA	P3	Urothelial carcinoma	Unresectable, locally advanced, metastatic	D1500 + T75 q4w x4 > D1500 m q4w	1st	340	5
Ribrag 2021	France	FA	P1b	DLBCL	Relapsed/refractory	D20 + T1 q4w	2nd–5th	3	4
Rizvi 2020	USA	FA	P3	NSCLC	Stage4	D20 + T1 q4w	1st	371	5
Rubinstein 2019	USA	CA	P2 RCT	Endometrial carcinoma, carcinosarcoma	Persistent or recurrent	D1500 + T75 q4wx4 > D1500 q4w	2nd	28	4
Santa-Maria 2018	USA	FA	Single arm (pilot)	Breast cancer	Metastatic	D1500 + T45 q4w x4 > D750 q2w 1 year	2nd or later	18	3

(Continued)

Table 1. (Continued)

Population	Country	Report	Design	Cancer	Stage	Regimen	Setting	*n*	NOS
Sarfaty 2021	USA	FA	Single arm P2	Non-urothelial carcinoma of the urinary tract	Unresectable or metastatic	D1500 + T75 q4w x4 > D1500 q4w	1st–3rd	13	4
Seiwert 2016	USA	CA	P3	Head and neck cancer	Recurrent or metastatic	D1500 + T75 q4w > D1500 q4w	1st	408	4
Siu 2019	Canada	FA	P2 RCT	HNSCC	Recurrent or metastatic	D20 + T1 q4w x4	After 1 platinum regimen	133	4
Somaiah 2020	USA	CA	Single arm P2	Sarcoma	Advanced or metastatic	D1500 + T75 q4w x4 > D1500 q4w	1st or later	57	4
Song 2021 China Cohort	USA	CA	P2 RCT	HCC	Advanced	D20 + T1 q4w x4	After sorafenib	5	4
Song 2021 T1	USA	CA	P2 RCT	HCC	Advanced	D20 + T1 q4w x4	After sorafenib	40	4
Song 2021 T300	USA	CA	P2 RCT	HCC	Advanced	D1500 q4w + T300 x1	After sorafenib	74	4
Song 2021 T75	USA	CA	P2 RCT	HCC	Advanced	D1500 q4w + T75 q4w x4	After sorafenib	82	4

Adj, adjuvant therapy; CA, conference abstract; D10, durvalumab 10 mg/kg; D15, durvalumab 15 mg/kg; D1500, durvalumab 1500 mg/body; D20, durvalumab 20 mg/kg; FA, full article; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; 1L, first line; *n*, number of patients; NeoAdj, neo-adjuvant therapy; NOS, score of the Newcastle-Ottawa quality assessment scale for cohort studies wherein higher score means better quality; NS, not specified; NSCLC, non-small cell lung cancer; P1–4, phase 1–4; q2–6w, every 2–6 weeks; RCC, renal cell carcinoma; RCT, randomized controlled trial; T1, tremelimumab 1 mg/kg; T3, tremelimumab 3 mg/kg; T300, tremelimumab 300 mg/body; T45, tremelimumab 45 mg/body; T75, tremelimumab 75 mg/body; x1–26, administrated total 1–26 times; >, then.

patients (Table 1); five articles included multiple populations each, whereas others extracted one population each. Eventually, 41 independent populations were analyzed. The median population size was 34 patients (range 3–408).

Key AE indicators

In a random model meta-analysis with 19 populations and 1788 cases, the pooled frequency of all AEs was 77.8% [95% confidence interval (CI): 67.9–87.6, $I^2 = 97\%$, p for heterogeneity < 0.00001, Figure 2(a)]. Considering 21 populations ($n = 1855$) in which the presence or absence of grade ≥ 3 AEs was recorded, 29.3 cases experienced grade ≥ 3 AEs (95% CI: 24.2–34.4, $I^2 = 82\%$, p for heterogeneity < 0.00001, Figure 2(b)). The pooled frequency of serious AEs was 34.9% [24 populations, 95% CI: 28.1–41.7, $I^2 = 93\%$, p for heterogeneity < 0.00001, Figure 2(c)]. AE-related DT discontinuation occurred in 13.3% of patients [22 populations, 95% CI: 9.3–17.4, $I^2 = 84\%$, p for heterogeneity < 0.00001, Figure 2(d)]. Treatment-related deaths were documented in 0.98% of patients [28 populations, 95% CI: 0.5–1.5, $I^2 = 0\%$, p for heterogeneity = 1.00, Figure 2(e)].

Specific AEs

The most frequently observed AE was fatigue (30.1%, 95% CI: 23.8–36.3). AEs with a frequency exceeding 15% included diarrhea (21.7%, 95% CI: 17.8–25.6), pruritus (17.9%, 95% CI: 14.4–21.3), decreased appetite (17.7%, 95% CI: 13.7–22.0), and nausea (15.6%, 95%CI: 12.1–19.6) (Table 2).

The clinically important AEs included interstitial pneumonia, colitis, hyperthyroidism, hypothyroidism, and adrenal insufficiency. The pooled frequencies of these AEs were 2.3% for interstitial pneumonia (23 populations, 95% CI: 1.5–3.2), 3.9% for colitis (18 populations, 95% CI: 2.1–5.7), 4.3% for hyperthyroidism (14 populations, 95% CI: 2.9–5.7), 9.6% for hypothyroidism (22 populations, 95% CI: 7.6–11.6), and 0.67% for adrenal insufficiency (14 populations, 95% CI: 0.06–1.3).

Safety comparison of chemotherapy-naive and previously treated patients

A subgroup analysis of key AE indicators was conducted to compare the chemotherapy-naive and previously treated populations. There were no differences between subgroups for any AE (chemotherapy-naive 79.4% *versus* pretreated 70.8%, $I^2 = 0\%$, $p = 0.39$), grade ≥ 3 AEs (21.4% *versus* 27.4%, $I^2 = 30.9\%$, $p = 0.23$), serious AEs (23.7% *versus* 34.8%, $I^2 = 54.4\%$, $p = 0.14$), treatment discontinuation due to AEs (13.8% *versus* 7.1%, $I^2 = 54.7\%$, $p = 0.14$), or treatment-related deaths (1.1% *versus* 0.6%, $I^2 = 0\%$, $p = 0.38$) (Figure 3).

Discussion

Based on the results of the present systematic review, more than three-quarters of patients who received DT experienced AEs, and approximately 30% of patients experienced grade ≥ 3 AEs. Furthermore, AE-related treatment discontinuation was estimated to occur in 13% of patients, whereas treatment-related deaths occurred in less than 1% of patients. It is well-established that AEs are inevitable during cancer treatment, and combined therapy with two ICIs enhances toxicity.[7–9] Therefore, we believe that our data provide information necessary for healthcare providers and patients to balance the benefits and risks of DT therapy.

To date, three systematic reviews on DT have been published. In 2020, Wang *et al.*[6] reported the first meta-analysis on DT combination therapy. The authors analyzed data from 587 patients extracted from five trials and found that double immunotherapy was superior to tremelimumab alone in head and neck squamous cell carcinoma. In addition, the authors reported that there was no difference in efficacy between double immunotherapy and monotherapy in pancreatic ductal adenocarcinoma and gastric/gastroesophageal junction cancer. The study also found no differences in treatment-related AEs between the two groups. In addition, a systematic review by Arru *et al.*[16] in 2021 found that dual immunotherapy was superior to monotherapy in certain tumor subsets, although it failed to exhibit a consistent advantage over single-agent durvalumab. In 2022, Fahmy *et al.*[17] published a study analyzing AEs, concluding that combination therapy resulted in greater treatment discontinuation and treatment-related deaths than durvalumab monotherapy.

All three systematic reviews included studies on regimens combining immunotherapy with cytotoxicity; therefore, it remains unclear whether the observed AEs could be solely attributed to immunotherapy. Furthermore, two of these studies

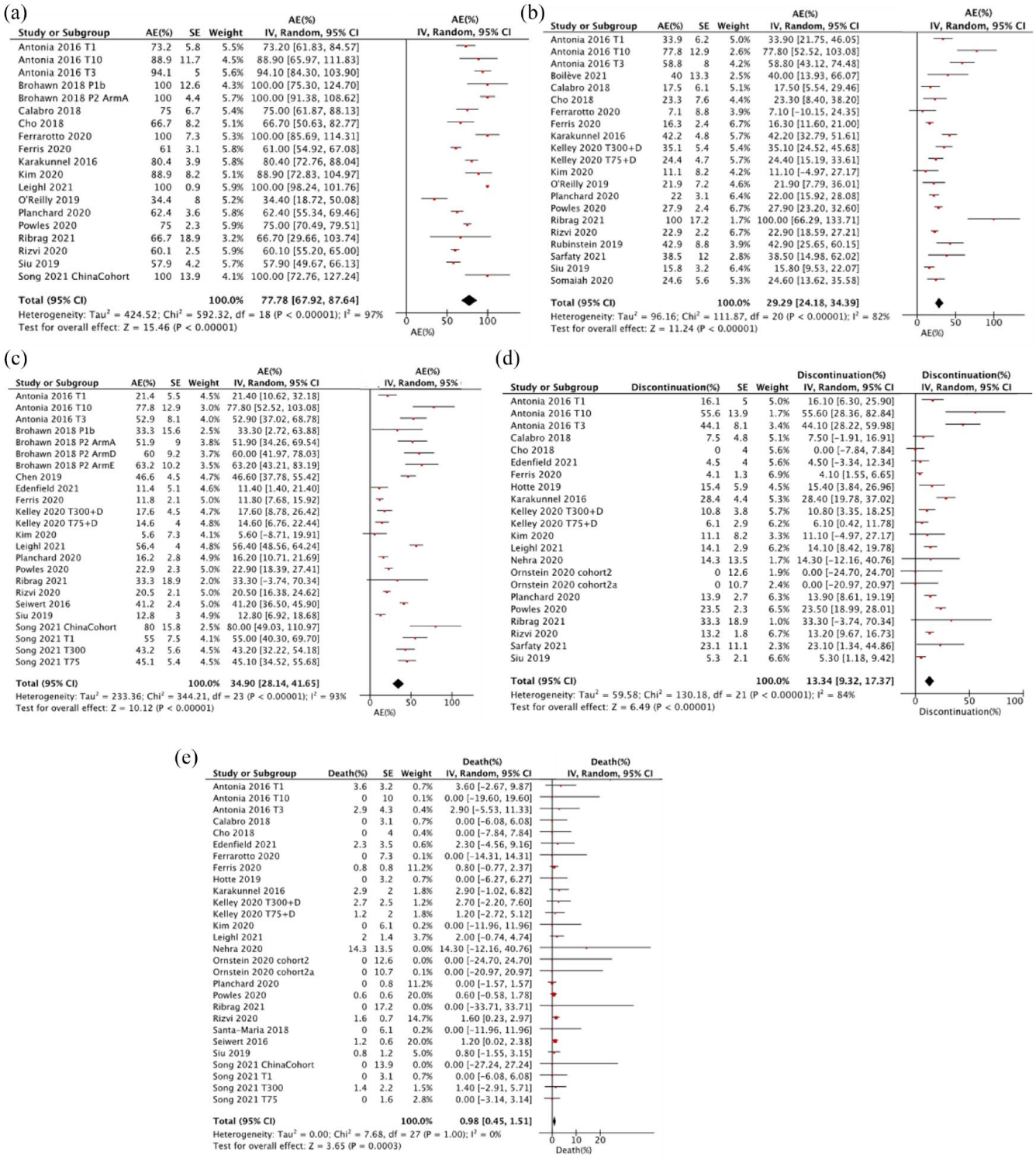

Figure 2. Forest plots to compare chemo-naive and pretreated for key adverse event indicators. (a) Any adverse event, (b) Grade 3 or higher adverse event, (c) Serious adverse event, (d) DT discontinuation due to adverse event and (e) Treatment-related deaths.

Table 2. Estimated incidence of adverse events.

Adverse event	*N*	*n*	Incidence (95% CI)
Key adverse event indicators			
Any AE	19	1788	77.8 (67.9–87.6)
Grade 3 or higher AE	21	1865	29.3 (24.2–34.4)
Serious AE	24	2536	34.9 (28.1–41.7)
AE leading to discontinuation	22	1977	13.3 (9.3–17.4)
Treatment-related death	28	2605	0.98 (0.45–1.5)
Gastrointestinal			
Aspartate aminotransferase	18	1332	8.3 (5.5–11.2)
Alanine aminotransferase	18	1560	10.6 (6.8–14.4)
Amylase	18	1349	7.0 (4.1–9.9)
Lipase	20	1569	7.0 (4.3–9.7)
Diarrhea	30	2720	21.7 (17.8–25.6)
Colitis	18	1677	3.9 (2.1–5.7)
Decreased appetite	20	2354	17.9 (13.7–22.0)
Nausea	25	2383	15.9 (12.1–19.6)
Vomiting	21	2118	10.8 (7.8–14.0)
Dermatological			
Rash	27	2357	14.8 (11.4–18.3)
Maculopapular rash	9	326	9.9 (3.8–16.1)
Vitiligo	4	201	0.5 (0–2.9)
Pruritus	29	2669	17.9 (14.4–21.3)
Hormonal			
Hypothyroidism	22	1965	9.6 (7.6–11.6)
Hyperthyroidism	14	1319	4.3 (2.9–5.7)
Adrenal insufficiency	14	1510	0.7 (0.06–1.3)
Hypopituitarism	7	1122	0.3 (0.2–0.8)
Other adverse events			
Fatigue	30	2740	30.1 (23.8–36.3)
Pyrexia	18	1708	12.1 (9.1–15.2)
Headache	14	916	5.7 (3.4–8.0)
Arthralgia	18	1177	7.2 (3.7–11.0)
Pneumonitis	23	1666	2.3 (1.5–3.2)

Incidence (95% CI), pooled incidence using random model meta-analysis and its 95% confidence interval.
AE, adverse event; NA, not available; *N*, number of populations; *n*, number of patients.

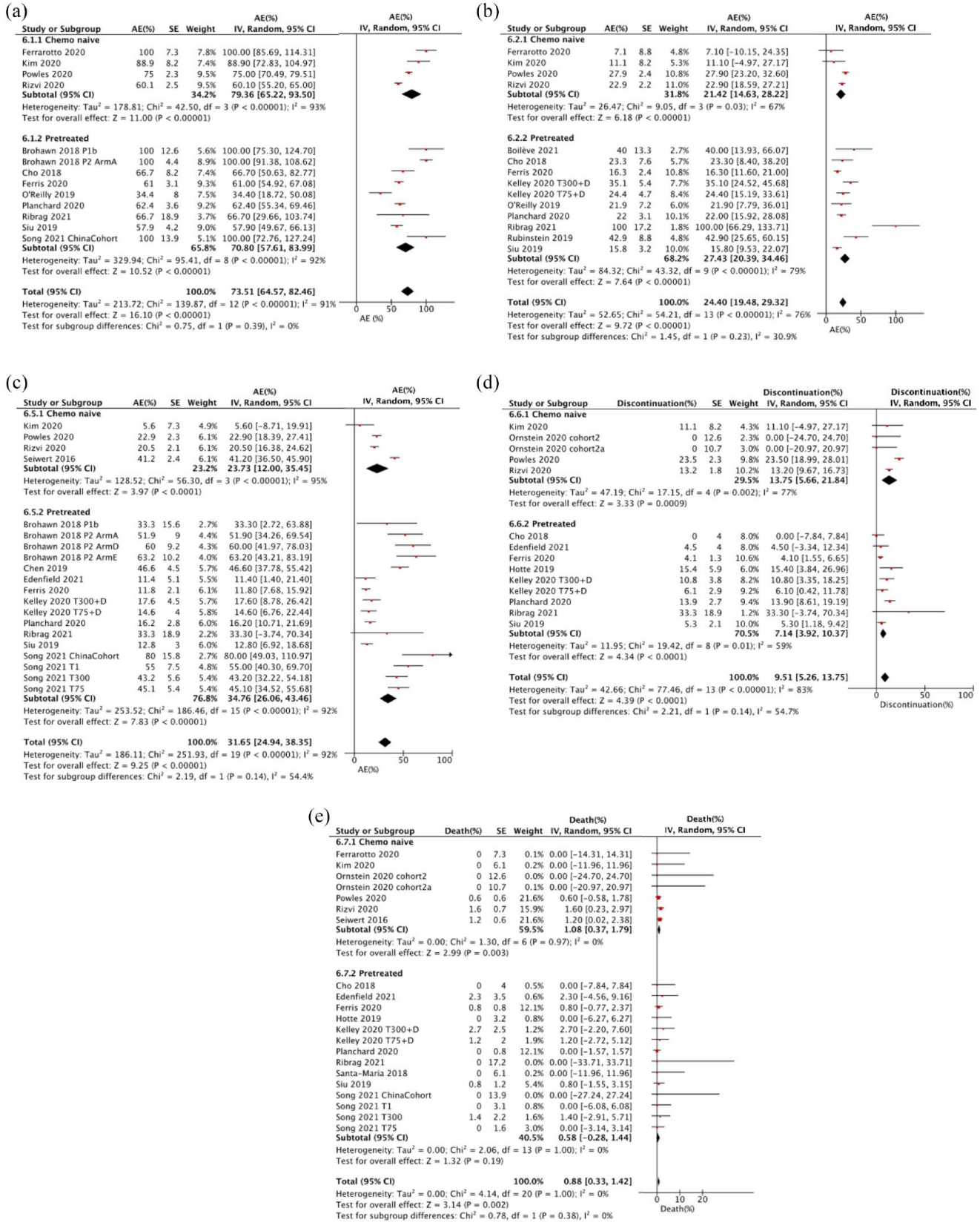

Figure 3. Forest plots to compare chemo-naive and pretreated for key adverse event indicators.
AE, adverse event; 95% CI, 95% confidence interval; IV, generic inverse variance.

focused on treatment efficacy and did not provide detailed data on AEs; therefore, data on AEs in DT-only regimens are required to establish the risks and benefits of DT therapy.

Standard dosing regimens and the optimal number of previous treatments for durvalumab and tremelimumab are yet to be established. Therefore, one of our main concerns was whether the safety profile was altered on administering the drug to patients who had never received chemotherapy when compared with those who had undergone prior therapy. The present systematic review did not reveal differences in the incidence of all AEs, grade ⩾ 3 AEs, serious AE, AEs leading to discontinuation, and treatment-related deaths between previously treated and untreated patients. Based on the findings of the present study, the DT regimen could be employed even in late-line treatment with the same safety profile as observed in first-line treatment.

One limitation of the present study was the inclusion of diverse tumor subtypes, therapeutic drug doses, dosing schedules, and lines of treatment. However, this may extend the external validity of the results.

In conclusion, this comprehensive systematic review summarized the AEs associated with DT therapy in ICI-naïve patients and incorporated 3099 cases from 41 populations. The data revealed the occurrence of AEs (77.8%), grade ⩾ 3 AEs (29.3%), serious AEs (34.9%), AEs resulting in treatment discontinuation (13.3%), treatment-related deaths (0.98%), documenting the occurrence of 22 specific AEs. Furthermore, no statistically significant differences in the safety profile were observed between chemotherapy-naive and chemotherapy-pretreated patients.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Hiromi Matsumoto: Data curation; Formal analysis; Investigation; Project administration; Visualization; Writing – original draft.

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Supplemental material

Supplemental material for this article is available online.

References

1. Johnson ML, Cho BC, Luft A, *et al.* Durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non-small-cell lung cancer: the phase III POSEIDON study. *J Clin Oncol* 2022; 41: 1213–1227.
2. Huang RR, Jalil J, Economou JS, *et al.* CTLA4 blockade induces frequent tumor infiltration by activated lymphocytes regardless of clinical responses in humans. *Clin Cancer Res* 2011; 17: 4101–4109.
3. Zhang H, Dai Z, Wu W, *et al.* Regulatory mechanisms of immune checkpoints PD-L1 and CTLA-4 in cancer. *J Exp Clin Cancer Res* 2021; 40: 184.
4. Rizvi NA, Cho BC, Reinmuth N, *et al.* Durvalumab with or without tremelimumab *versus* standard chemotherapy in first-line treatment of metastatic non-small cell lung cancer the MYSTIC phase 3 randomized clinical trial. *JAMA Oncol* 2020; 6: 661–674.
5. Siu LL, Even C, Mesía R, *et al.* Safety and efficacy of durvalumab with or without tremelimumab in patients with PD-L1-low/negative recurrent or metastatic HNSCC: the phase 2 CONDOR randomized clinical trial. *JAMA Oncol* 2019; 5: 195–203.
6. Wang DY, Salem JE, Cohen JV, *et al.* Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol* 2018; 4: 1721–1728.
7. Liu T, Jin B, Chen J, *et al.* Comparative risk of serious and fatal treatment-related adverse events caused by 19 immune checkpoint inhibitors used in cancer treatment: a network meta-analysis. *Ther Adv Med Oncol* 2020; 12: 175883592094092.
8. Zhou S, Khanal S and Zhang H. Risk of immune-related adverse events associated with ipilimumab-plus-nivolumab and nivolumab therapy in cancer patients. *Ther Clin Risk Manag* 2019; 15: 211–221.
9. Almutairi AR, McBride A, Slack M, *et al.* Potential immune-related adverse events associated with monotherapy and combination therapy of ipilimumab, nivolumab, and pembrolizumab for advanced melanoma: a systematic review and meta-analysis. *Front Oncol* 2020; 10: 91.
10. Chen J, Li S, Yao Q, *et al.* The efficacy and safety of combined immune checkpoint inhibitors (nivolumab plus ipilimumab): a systematic review and meta-analysis. *World J Surg Oncol* 2020; 18: 150.
11. Somekawa K, Horita N, Kaneko A, *et al.* Adverse events induced by nivolumab and ipilimumab combination regimens. *Ther Adv Med Oncol* 2022; 14: 175883592110583.
12. Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–2012.
13. UMIN Centor. UMIN crinical trial registry (UMIN-CTR), https://www.umin.ac.jp/ctr/ctr_regist.htm (accessed 24 November 2022).
14. Wells G, Shea B, O'Connell D, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses, https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (2000, accessed 24 November 2022).
15. Agresti A and Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. *Am Statist* 1998; 52: 119–126.
16. Arru C, De Miglio MR, Cossu A, *et al.* Durvalumab plus tremelimumab in solid tumors: a systematic review. *Adv Ther* 2021; 38: 3674–3693.
17. Fahmy O, Ahmed OAA, Khairul-Asri MG, *et al.* Adverse events and tolerability of combined durvalumab and tremelimumab *versus* durvalumab alone in solid cancers: a systematic review and meta-analysis. *Biomedicines* 2022; 10: 1101.