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 \geq 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 Ther Adv Med Oncol

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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 ≥ 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 ≥ 3 AEs. It is estimated that treatment with DT can also result in grade \geq 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 \geq 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.

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,

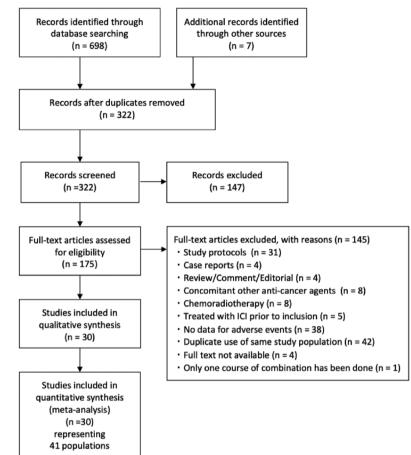


Figure 1. The preferred reporting items for systematic reviews and metaanalyses flow chart.

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 laterline 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

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Table 1. Characteristics of included populations.	s of inclue	led popul	ations.						
Population	Country	Report	Design	Cancer	Stage	Regimen	Setting	u	SON
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	NSA	FA	P1b	NSCLC	Locally advanced or metastatic	D15 q4w x13 + T10 q4w x6 > q12w x3	1st or later	6	4
Antonia 2016 T3	NSA	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	NSA	CA	P1b	Gastric cancer	Recurrent or metastatic	D20 + T1 q4w > D10 q2w	2nd	6	4
Brohawn 2018 P2 ArmA	NSA	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	NSA	CA	P2RCT	Gastric cancer	Recurrent or metastatic	D20+T1 q4w>D10 q2w	2nd or 3rd	19	4
Calabro 2018	ltaly	FA	Single arm P2	Mesothelioma	Unresectable	D20 + T1 q4w x4 > D20 q4w x9	1st or 2nd	40	Ъ
Capdevila 2020	Spain	СА	Single arm P2	Lung carcinoid, 61/2 gastric, 61/2 pancreatic, 63NEN	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	D
Cho 2018	NSA	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	D
Ferris 2020	NSA	FA	P3	HNSCC	Recurrent or metastatic	D20+T1 q4w>D10mg q2w	2nd-5th	246	4
Gao 2019	NSA	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	NSA	CA	P1	NSCLC	Advanced	D20+T1 q4w	Unknown	102	4
Kelley 2020 T300 + D	NSA	CA	P3	НСС	Unresectable	D1500 + T300 q4w	After sorafenib	74	വ
								(C	(Continued)

Population	Country	Report	Design	Cancer	Stage	Regimen	Setting	u	NOS
Kelley 2020 T75 + D	USA	CA	P3	НСС	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	2 2
Leighl 2021	Canada	FA	P2 RCT	NSCLC	4	D1500 + T75 q4w x4 > D1500 q4w	Mainly chemo- naive	149	Q
Nehra 2020	Canada	FA	P1B	Solid tumor	Advanced, unresectable, recurrent or metastatic	D1500 + T75 q4w x4	1st or 2nd	7.4	
0'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[x1year], D + T- > D + T[x1dose] then D(x1year], D1500 mgT75 mg	Neoadj, adj	9	4
Ornstein 2020 cohort2a	USA	CA	P1b	RCC	High risk localized RCC [Clinical stage T2b-4 and/ or N1, M0 disease]	D + T > D(x 1 dose), D + T > D(x 1 year), D + T > D + T(x 1 dose) then D(x 1 year), $D1500 mgT75 mg$	Neoadj, adj	8	4
Ornstein 2020 cohort3	USA	СА	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	ω	4
Planchard 2020	France	FA	P3	NSCLC	Stage3B/4	D20 mg/kg + T1 mg/kg q4w	3rd or later	173	4
Powles 2020	NU	FA	P3	Urothelial carcinoma	Unresectable, locally advanced, metastatic	D1500 + T75 q4w x4 > D1500 m q4w	1st	340	വ
Ribrag 2021	France	FA	P1b	DLBCL	Relapsed/refractory	D20 + T1 q4w	2nd–5th	c	4
Rizvi 2020	NSA	FA	P3	NSCLC	Stage4	D20 + T1 q4w	1st	371	വ
Rubinstein 2019	NSA	СА	P2 RCT	Endometrial carcinoma, carcinosarcoma	Persistent or recurrent	D1500 + T75 q4wx4 > D1500 q4w	2nd	28	4
Santa-Maria 2018	NSA	FA	Single arm (pilot)	Breast cancer	Metastatic	D1500 + T45 q4w x4 > D750 q2w 1 year	2nd or later	18	с

Population	Country	Report	Design	Cancer	Stage	Regimen	Setting	u	NOS
Sarfaty 2021	NSA	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	ЪЗ	Head and neck cancer	Recurrent or metastatic	D1500 + T75 q4w > D1500 q4w	st	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	НСС	Advanced	D20 + T1 q4w x4	After sorafenib	ы	4
Song 2021 T1	NSA	CA	P2 RCT	НСС	Advanced	D20 + T1 q4w x4	After sorafenib	40	4
Song 2021 T300	NSA	CA	P2 RCT	НСС	Advanced	D1500 q4w + T300 x1	After sorafenib	74	4
Song 2021 T75	NSA	CA	P2 RCT	НСС	Advanced	D1500 q4w + T75 q4w x4	After sorafenib	82	4
Adj, adjuvant therapy; CA, conference abstract; D10, durvalumab 10 mg/kg; D15, durvalumab HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; IL, first li Ottawa quality assessment scale for cohort studies wherein higher score means better qualit 2-6 weeks; RCC, renal cell carcinoma; RCT, randomized controlled trial; T1, tremelimumab 15 mg/body; x1-26, administrated total 1-26 times; >, then.	 λ, conferent λ, c	ce abstract ISCC, head r cohort stu na; RCT, ra mg/body; :	t; D10, durvalun l and neck squa udies wherein h indomized contr x1-26, administ	nab 10 mg/kg; D15, durv; mous cell carcinoma; 1L igher score means bette olled trial; T1, tremelim rated total 1–26 times; >	alumab 15 mg/kg; D1500, du ., first line; <i>n</i> , number of pat er quality: NS, not specified; numab 1 mg/kg; T3, tremelirr >, then.	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; 11, first line; <i>n</i> , 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 2–6weeks; 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.	umab 20 mg/kg; F NOS, score of the P1-4, phase 1-4; 300 mg/body; T45	A, full art Newcast ק2–6w, ev , tremeli	icle; le- ery mumab

Table 1. [Continued]

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, $I^2 = 97\%$, Þ 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 \geq 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 treatmentrelated 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

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a)	AE(%)	AE(%) (b))		AE(%)	AE(%)
Antonia 2016 T1 73.2 5.8 Antonia 2016 T10 88.9 11.7 Antonia 2016 T3 94.1 5 Brohawn 2018 P1b 100 12.6 Brohawn 2018 P2 ArmA 100 4.4 Calabro 2018 P2 ArmA 100 4.4 Calabro 2018 66.7 8.2 Ferrarotto 2020 100 7.3 Karakunnel 2016 80.4 3.9 Karakunnel 2016 80.4 3.9 Kim 2020 88.9 8.2 Leighl 2021 100 0.9 O'Reilly 2019 34.4 8 Planchard 2020 75 2.3 Ribrag 2021 66.7 18.9 Ribrag 2021 60.1 2.5 Song 2021 ChinaCohort 100 13.9 Total (95% CI) Heterogeneity: Tau ² = 424.52; Chi ² = 5	Weight IV, Random, 95% CI 5.5% 73.20 [61.83, 84.57] 4.5% 88.90 [65.97, 111.83] 5.6% 94.10 [84.30, 103.90] 4.3% 100.00 [75.30, 124.70] 5.7% 100.00 [75.30, 124.70] 5.7% 100.00 [75.30, 124.70] 5.7% 100.00 [53.63, 82.77] 5.3% 66.70 [50.63, 82.77] 5.8% 80.40 [72.76, 88.04] 5.8% 80.40 [72.76, 88.04] 5.8% 80.40 [72.76, 88.04] 5.8% 80.40 [72.76, 88.04] 5.8% 80.40 [72.76, 88.04] 5.8% 80.40 [72.76, 88.04] 5.8% 60.00 [54.27, 65.00] 5.8% 60.00 [54.27, 60.13] 3.2% 667.01 [29.66, 103.74] 5.9% 75.00 [70.49, 79.51] 3.2% 66.01 [55.20, 65.00] 5.7% 57.90 [49.67, 66.13] 4.11 100.00 [72.76, 127.24] 100.0% 77.78 [67.92, 87.64] 92.32, df = 18 (P < 0.00001); l ² = 97%	IV, Random, 95% CI	Antonia 2016 T3 58.8	6.2 5.0% 33.9% 12.9 2.6% 77.80 8 4.2% 58.81 13.3 2.5% 40.00 6.1 5.1% 17.1 7.6 4.4% 23.3 8.8 3.9% 7.10 2.4 6.7% 16.3 8.8 3.9% 7.10 2.4 6.7% 16.3 8.8 3.9% 7.10 2.4 6.7% 16.3 8.2 4.2% 12.11 7.2 4.6% 22.00 2.4 6.7% 27.9% 3.1 6.4% 22.00 2.4 6.7% 27.9% 1.1 7.2 1.7% 100.00 2.2 6.7% 22.9% 32.5 3.2 6.4% 15.5 5.3% 24.64 15.6 5.3% 24.64 100.0% 29.25	andom, 95% Cl 012.75, 46.05] [52.52, 103.08] [43.12, 74.48] [13.93, 66.07] 50 [5.54, 29.46] 50 [5.54, 29.46] 50 [5.54, 29.46] 50 [5.54, 29.46] 10 [14.00, 21.00] 122.79, 51.61] 124.52, 45.68] 50 [15.19, 33.61] 14.49, 72, 71, 71 10 [7.59, 36.01] 51.59, 28.08] 15.23, 02.60] [66.29, 133.71] 125.56, 60.15] 124.52, 45.02] 80 [9.53, 22.07] 114.98, 62.02] 80 [9.53, 22.07] 114.98, 62.02] 80 [24.18, 34.39] P < 0.00001; l ² = 82% -	IV, Random, 95% CI
Test for overall effect: Z = 15.46 (P < 0.	.00001)	(d)	Test for overall effect: Z = 11.	24 (P < 0.00001)		AE(%)
Study or Subgroup AE(%) SE Wei Antonia 2016 T1 21.4 5.5 4 Antonia 2016 T1 21.4 5.5 4 Antonia 2016 T1 77.8 12.9 3 Antonia 2016 T3 52.9 8.1 4 Brohawn 2018 P1b 3.3 15.6 2 Brohawn 2018 P2 ArmD 60 9.2 3 Genfield 2021 11.4 5.1 4 Kelley 2020 T300+D 17.6 4.5 4 Kim 2020 2.6 7.3 4 Leighl 2021 5.6 7.3 4 Leighl 2021 5.6 4 4 Xizu 2020 2.2 2.3 5	15% 21.40 110.62, 22.18 05% 7.80 52.52, 10.30.81 10% 52.90 [37.02, 68.78] 10% 52.90 [37.02, 68.78] 10% 52.90 [37.02, 68.78] 10% 52.90 [37.02, 68.78] 10% 52.90 [37.02, 68.78] 10% 52.90 [37.02, 68.78] 15% 63.20 [43.21, 83.19] 17% 46.60 [37.78, 55.42] 1.80 [7.68, 15.92] - 1.7% 1.76.06 [8.78, 26.42] 1.80 [7.68, 15.92] - 1.7% 1.76.06 [8.78, 26.42] 1.80 [7.64, 24.40] - 1.80 [7.64, 19.91] - 1.85 56.40 [4.55, 64.24] 1.9% 1.28.01 [6.32, 24.62] - 0.9% 1.28.01 [6.92, 18.68] - 2.5% 80.00 [4.93, 110.97] - 1.5% 43.20 [34.22, 55.68] <	AEC0 AEC0 Antoni Antoni Antoni Antoni Calabr Calabr Cho 20 Hotts 2 Hotts 2	118 118 114 2021 1020 1020 1029 1020	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{r} \textbf{16,10} \ (\textbf{6,30}, \textbf{25,90}) \\ \textbf{55,60} \ (\textbf{28,36}, \textbf{82,84}) \\ \textbf{44,10} \ (\textbf{28,22}, \textbf{59,38}) \\ \textbf{7,50} \ [-1,31, 16,91] \\ \textbf{0,00} \ [-7,84, 7,84] \\ \textbf{4,50} \ [-3,34, 12,34] \\ \textbf{4,10} \ [1,55, 6,65] \\ \textbf{15,40} \ [3,84, 26,96] \\ \textbf{28,40} \ [13,76, 37,02] \\ \textbf{10,80} \ [3,35, 18,25] \\ \textbf{6,10} \ [0,42, 11,78] \\ \textbf{11,10} \ [-4,97, 27,17] \\ \textbf{14,30} \ [16,40,76] \\ \textbf{-0,00} \ [-24,70, 24,70] \\ \textbf{-0,00} \ [-24,70, 24,70] \\ \textbf{-0,00} \ [-24,70, 24,70] \\ \textbf{-0,00} \ [-24,77, 7,73] \\ \textbf{13,20} \ [16,61, 19,19] \\ \textbf{23,50} \ [18,99, 28,01] \\ \textbf{33,20} \ [-3,74, 70,34] \\ \textbf{13,20} \ [16,74, 7,73] \\ \textbf{23,10} \ [1,34, 44, 86] \\ \textbf{5,30} \ (1,18, 9,42] \\ \textbf{13,34} \ [\textbf{43,24} \ [\textbf{17,37}] \end{array}$	Discontinuation(%) IV, Random, 95% Cl
(e)	Study or Subgroup Death(%) SE Antonia 2016 T1 3.6 3.2 Antonia 2016 T3 2.9 4.3 Calabro 2018 0 3.1 Cho 2018 0 4 Edenfield 2021 2.3 3.5 Ferrarotto 2020 0.8 8 Hotte 2019 0.3.2 Xarakunnel 2016 2.9 2 Karakunnel 2016 2.9 2 Karakunnel 2016 2.9 2 Karakunnel 2016 2.9 2 Karakunnel 2016 2.9 2 Karakunnel 2016 2.9 1.2 Karakunnel 2016 2.9 2 Karakunnel 2016 2.9 1.2 Karakunnel 2020 0 6.1 Leighl 2021 2 1.4 1.3.5 Ornstein 2020 0 6.1 Nehra 2020 14.3 13.5 Ornstein 2020 0.6 6.6 Ribrag 2021 0 16.7 7.2 Rizvi 2020 1.6 6.7 Send 2021 1.6 <	Death(%) Weight IV, Random, 95% Cl 0.7% 3.60 [-2.67, 9.87] 0.1% 0.00 [-19.60, 15.60] 0.4% 2.90 [-5.53, 11.33] 0.7% 0.00 [-7.84, 7.84] 0.7% 0.00 [-4.32, 14.31] 0.4% 0.00 [-14.31, 14.31] 0.4% 0.00 [-14.31, 14.31] 0.5% 2.30 [-4.56, 9.16] 0.5% 2.30 [-4.56, 9.16] 0.7% 0.00 [-1.43, 11.43] 11.2% 0.80 [-0.77, 2.37] 0.7% 0.00 [-1.2, 6.82] 1.2% 2.70 [-2.07, 4.60] 1.8% 1.20 [-2.72, 5.12] 0.2% 0.00 [-1.21, 6.40.76] 0.0% 0.00 [-3.71, 3.371] 0.1% 0.00 [-3.71, 3.371] 1.2% 0.00 [-3.7, 1.371] 0.0% 0.00 [-3.7, 3.371] 1.4% 1.60 [0.23, 2.97] 0.2% 0.00 [-1.55, 1.15] 0.2% 0.00 [-1.55, 1.57] 0.0% 0.00 [-1.55, 3.17] 0.2% 0.00 [-1.96, 1.96] 0.2% 0.00 [-2.3, 2.7]	Death(%) IV, Random, 95% CI IV,			

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.

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(a) AE(%) AE(%) Study or Subgroup 6.1.1 Chemo naive Ferrarotto 2020 Kim 2020 AE(%) SE Weight IV, Random, 95% CI IV, Random, 95% CI 100 7.3 88.9 8.2 75 2.3 60.1 2.5 7.8% 100.00 [85.69, 114.31] 7.4% 88.90 [72.83, 104.97] 9.5% 75.00 [70.49, 79.51] 9.5% 60.10 [55.20, 65.00] 34.2% 79.36 [65.22, 93.50] Powles 2020 Rizvi 2020 Subtotal (95% CI) Subtotal (95% CI) Heterogeneity: Tau² = 178.81; Chi² = 42.50, df = 3 (P < 0.00001); i² = 93%Test for overall effect: Z = 11.00 (P < 0.00001) Test for overall effect: 2 = 11.00 (P < 0.00001) **6.12 Pretreated** Broham 2018 P1b 100 12.6 5.6% 100.00 [75.30, 124.70] Broham 2018 P2 ArmA 100 4.4 8.9% 100.00 [91.38, 108.62] Cho 2018 66.7 8.2 7.4% 66.70 [50.63, 82.77] Ferris 2020 61 3.1 9.3% 61.00 [54.92, 67.08] O'Reilly 2019 34.4 8 7.5% 34.40 [18.72, 50.08] Planchard 2020 62.4 3.6 9.2% 62.40 [55.34, 69.46] Ribrag 2021 66.7 18.9 3.7% 66.70 [29.66, 103.74] Subtotal (95% C) Heterogeneity: Tau² = 329.94; Chi² = 95.41, df = 8 (P < 0.00001); i² = 92% Test for overall effect: 2 = 10.52 (P < 0.00001) Total (95% Ch 100.0% 73.51 (64.57.83.46) 1

10(a) (33/6 C)	100.0% /3.51 [04.57, 82.40]			
Test for overall effect: Z = 16.10 (F	$P^{2} = 139.87$, df = 12 (P < 0.00001); $P^{2} = 9$ P < 0.00001) $P^{2} = 0.75$, df = 1 (P = 0.39), $P^{2} = 0\%$	0	50 E (%)	100

				AE(%)	AE(%)
Study or Subgroup	AE(%)	SE	Weight	IV, Random, 95% CI	IV, Random, 95% (
6.2.1 Chemo naive					
Ferrarotto 2020	7.1	8.8	4.8%	7.10 [-10.15, 24.35]	
Kim 2020	11.1	8.2	5.3%	11.10 [-4.97, 27.17]	
Powles 2020	27.9	2.4	10.8%	27.90 [23.20, 32.60]	-
Rizvi 2020 Subtotal (95% CI)	22.9	2.2	11.0% 31.8%		•
Heterogeneity: $Tau^2 =$	26.47:0	Chi ² =	9.05, df	$= 3 (P = 0.03); I^2 = 67\%$	
Test for overall effect:					
6.2.2 Pretreated					
Boilève 2021	40	13.3	2.7%	40.00 [13.93, 66.07]	
Cho 2018	23.3	7.6	5.7%	23.30 [8.40, 38.20]	
Ferris 2020	16.3	2.4	10.8%	16.30 [11.60, 21.00]	-
Kelley 2020 T300+D	35.1	5.4	7.7%	35.10 [24.52, 45.68]	
Kelley 2020 T75+D	24.4	4.7	8.4%	24.40 [15.19, 33.61]	
O'Reilly 2019	21.9	7.2	6.0%	21.90 [7.79, 36.01]	
Planchard 2020	22	3.1	10.1%	22.00 [15.92, 28.08]	-
Ribrag 2021	100	17.2	1.8%	100.00 [66.29, 133.71]	
Rubinstein 2019	42.9	8.8	4.8%	42.90 [25.65, 60.15]	
Siu 2019 Subtotal (95% CI)	15.8	3.2	10.0% 68.2%	15.80 [9.53, 22.07] 27.43 [20.39, 34.46]	-
Heterogeneity: Tau ² =	84.32:0	chi ² =	43.32. df	$= 9 (P < 0.00001); I^2 = 79\%$	
Test for overall effect:					
Total (95% CI)			100.0%	24.40 [19.48, 29.32]	•
Heteroneneity: Tau ² =	52.65:0	hi ² =	54.21. df	$I = 13 (P < 0.00001); I^2 = 76\%$	0 50 100

Test for subgroup differences: $Ch^2 = 1.45$, df = 1 (P = 0.23), $I^2 = 30.9\%$

)				AE(%)	AE(%)
Study or Subgroup	AE(%)	SE	Weight	IV, Random, 95% CI	IV, Random, 95%
6.5.1 Chemo naive					
Kim 2020	5.6	7.3	4.9%	5.60 [-8.71, 19.91]	
Powles 2020	22.9	2.3	6.1%	22.90 [18.39, 27.41]	-
Rizvi 2020	20.5	2.1	6.1%	20.50 [16.38, 24.62]	-
Seiwert 2016	41.2	2.4	6.1%	41.20 [36.50, 45.90]	-
Subtotal (95% CI)			23.2%	23.73 [12.00, 35.45]	•
Heterogeneity: Tau ² = 12	8.52; Ch	i ² = 5	6.30, df =	$= 3 (P < 0.00001); I^2 = 95\%$	1.6
Test for overall effect: Z =	3.97 (P	< 0.0	001)		
6.5.2 Pretreated					
Brohawn 2018 P1b		15.6	2.7%	33.30 [2.72, 63.88]	· · · · ·
Brohawn 2018 P2 ArmA	51.9	9	4.4%	51.90 [34.26, 69.54]	
Brohawn 2018 P2 ArmD	60	9.2	4.3%	60.00 [41.97, 78.03]	
Brohawn 2018 P2 ArmE	63.2	10.2	4.0%	63.20 [43.21, 83.19]	
Chen 2019	46.6	4.5	5.7%	46.60 [37.78, 55.42]	
Edenfield 2021	11.4	5.1	5.5%	11.40 [1.40, 21.40]	
Ferris 2020	11.8	2.1	6.1%	11.80 [7.68, 15.92]	-
Kelley 2020 T300+D	17.6	4.5	5.7%	17.60 [8.78, 26.42]	
Kelley 2020 T75+D	14.6	4	5.8%	14.60 [6.76, 22.44]	
Planchard 2020	16.2	2.8	6.0%	16.20 [10.71, 21.69]	-
Ribrag 2021	33.3	18.9	2.2%	33.30 [-3.74, 70.34]	
Siu 2019	12.8	3	6.0%	12.80 [6.92, 18.68]	-
Song 2021 ChinaCohort	80	15.8	2.7%	80.00 [49.03, 110.97]	
Song 2021 T1	55	7.5	4.8%	55.00 [40.30, 69.70]	
Song 2021 T300	43.2	5.6	5.4%	43.20 [32.22, 54.18]	
Song 2021 T75	45.1	5.4	5.4%		
Subtotal (95% CI)			76.8%	34.76 [26.06, 43.46]	•
Heterogeneity: Tau ² = 25	3.52; Ch	i ² = 1	86.46, df	= 15 (P < 0.00001); I ² = 92%	
Test for overall effect: Z =	7.83 (P	< 0.0	0001)		
Total (95% CI)			100.0%	31.65 [24.94, 38.35]	•
Heterogeneity: Tau ² = 18	6 11 Ch	$i^2 = 7$	51 93 df	= 19 (P < 0.00001); I ² = 92%	0 50

Subtotal (95% CI)	45.1 5.4		45.10 [34.52, 55			
Heterogeneity: $Tau^2 = 2$	253.52; Chi ² = 1					
Test for overall effect: 2	Z = 7.83 (P < 0.0)	0001)				
Total (95% CI)		100.0%	31.65 [24.94, 38	.35]	•	
Heterogeneity: Tau ² = 1			= 19 (P < 0.00001	.); I ² = 92% -	1	50
Test for overall effect: 2					AE(%)	50
Test for subgroup difference	rences: $Chi^2 = 2$.	19. $df = 1$	$(P = 0.14), I^2 = 5$	4.4%	1 111 (19)	

Study or Subgroup	Discontinuation(%)	SE	Weight	IV, Random, 95% CI	IV, Random, 95% C
6.6.1 Chemo naive					
Kim 2020	11.1	8.2	4.3%	11.10 [-4.97, 27.17]	+
Ornstein 2020 cohort2	0	12.6	2.3%	0.00 [-24.70, 24.70]	+
Ornstein 2020 cohort2a	0	10.7	3.0%	0.00 [-20.97, 20.97]	+
Powles 2020	23.5	2.3	9.8%	23.50 [18.99, 28.01]	-
Rizvi 2020	13.2	1.8	10.2%	13.20 [9.67, 16.73]	-
Subtotal (95% CI)			29.5%	13.75 [5.66, 21.84]	•
Heterogeneity: $Tau^2 = 47$	7.19; Chi ² = 17.15, df =	= 4 (P	= 0.002);	$I^2 = 77\%$	
Test for overall effect: Z	= 3.33 (P = 0.0009)				
6.6.2 Pretreated					
Cho 2018	0	4	8.0%	0.00 [-7.84, 7.84]	+
Edenfield 2021	4.5	4	8.0%	4.50 [-3.34, 12.34]	+
Ferris 2020	4.1	1.3	10.6%	4.10 [1.55, 6.65]	-
Hotte 2019	15.4	5.9	6.0%	15.40 [3.84, 26.96]	
Kelley 2020 T300+D	10.8	3.8	8.2%	10.80 [3.35, 18.25]	
Kelley 2020 T75+D	6.1	2.9	9.2%	6.10 [0.42, 11.78]	-
Planchard 2020	13.9	2.7	9.4%	13.90 [8.61, 19.19]	-
Ribrag 2021	33.3	18.9	1.2%	33.30 [-3.74, 70.34]	
Siu 2019	5.3	2.1	10.0%	5.30 [1.18, 9.42]	-
Subtotal (95% CI)			70.5%	7.14 [3.92, 10.37]	•
Heterogeneity: $Tau^2 = 11$.95; Chi ² = 19.42, df =	= 8 (P =	= 0.01); 1	² = 59%	
Test for overall effect: Z	= 4.34 (P < 0.0001)				
Total (95% CI)			100.0%	9.51 [5.26, 13.75]	•
Heterogeneity: $Tau^2 = 42$.66; Chi ² = 77.46, df =	= 13 (P	< 0.000	01); I ² = 83%	0 50 10
Test for overall effect: Z	= 4.39 (P < 0.0001)				0 50 10 Discontinuation(%)
Test for subgroup differe	nces: Chi ² = 2.21, df =	= 1 (P =	= 0.14), 1	= 54.7%	Discontinuation(%)

Discontinuation(%)

				Death(%)	Death(%)
Study or Subgroup	Death(%)	SE	Weight	IV, Random, 95% CI	IV, Random, 95% C
6.7.1 Chemo naive					
Ferrarotto 2020	0	7.3		0.00 [-14.31, 14.31]	
Kim 2020	0	6.1		0.00 [-11.96, 11.96]	
Ornstein 2020 cohort2	0	12.6	0.0%	0.00 [-24.70, 24.70]	
Ornstein 2020 cohort2a	0	10.7	0.1%	0.00 [-20.97, 20.97]	-
Powles 2020	0.6	0.6	21.6%	0.60 [-0.58, 1.78]	+
Rizvi 2020	1.6	0.7	15.9%	1.60 [0.23, 2.97]	-
Seiwert 2016	1.2	0.6	21.6%	1.20 [0.02, 2.38]	-
Subtotal (95% CI)			59.5%	1.08 [0.37, 1.79]	•
Heterogeneity: Tau ² = 0.0				0.97 ; $I^2 = 0\%$	
Test for overall effect: Z =	= 2.99 (P =)	0.003)			
6.7.2 Pretreated					
Cho 2018	0	4	0.5%	0.00 [-7.84, 7.84]	+
Edenfield 2021	2.3	3.5	0.6%	2.30 [-4.56, 9.16]	
Ferris 2020	0.8	0.8	12.1%	0.80 [-0.77, 2.37]	+
Hotte 2019	0	3.2	0.8%	0.00 [-6.27, 6.27]	+
Kelley 2020 T300+D	2.7	2.5	1.2%	2.70 [-2.20, 7.60]	+
Kelley 2020 T75+D	1.2	2	1.9%	1.20 [-2.72, 5.12]	
Planchard 2020	0	0.8	12.1%	0.00 [-1.57, 1.57]	+
Ribrag 2021	0	17.2	0.0%	0.00 [-33.71, 33.71]	
Santa-Maria 2018	0	6.1	0.2%	0.00 [-11.96, 11.96]	
Siu 2019	0.8	1.2	5.4%	0.80 [-1.55, 3.15]	+
Song 2021 ChinaCohort	0	13.9	0.0%	0.00 [-27.24, 27.24]	+
Song 2021 T1	0	3.1	0.8%	0.00 [-6.08, 6.08]	+-
Song 2021 T300	1.4	2.2	1.6%	1.40 [-2.91, 5.71]	
Song 2021 T75	0	1.6	3.0%	0.00 [-3.14, 3.14]	+
Subtotal (95% CI)			40.5%	0.58 [-0.28, 1.44]	•
Heterogeneity: $Tau^2 = 0.0$	0; $Chi^2 = 2$.06, df	f = 13 (P	$= 1.00$; $l^2 = 0\%$	
Test for overall effect: Z =	= 1.32 (P =)	0.19)			
Total (95% CI)			100.0%	0.88 [0.33, 1.42]	,
Heterogeneity: $Tau^2 = 0.0$	0; $Chi^2 = 4$.14, di	F = 20 (P	$= 1.00$; $I^2 = 0\%$	
Test for overall effect: Z =	3.14 (P =)	0.002)			0 10 20 Death(%)

(d)

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.

Discontinuation(%)

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 vet 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 \geq 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.

Kohei Somekawa: Formal analysis; Investigation.

Nobuyuki Horita: Conceptualization; Investigation; Supervision; Writing – review & editing.

Suguru Ueda: Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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