Original Article

The incidence of gastrointestinal adverse events in patients with advanced non-small cell lung cancer (NSCLC) treated with PD-1 inhibitors: a meta-analysis

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Background: We conducted a meta-analysis to evaluates the incidence of the gastrointestinal (GI) adverse events with the use of PD-1 inhibitors among patients with advanced non-small cell lung cancer (NSCLC).

Methods: The PICOs (participants, intervention, comparison, and outcomes) elements were used for the selection of studies to meet the inclusion and exclusion criteria. Google Scholar, PubMed, Science Direct and proceedings of major oncology conferences were systematically searched from their inception to December 2020, to identify studies which reported the GI adverse events of PD-1 inhibitors among patients with NSCLC. Risks of bias were assessed by using a revised methodological index for nonrandomized studies (MINORS). Pooled incidences and weighted relative risk (RR) estimate for GI adverse events, the incidence of treatment discontinuation due to GI adverse events was also calculated. To perform the analysis of qualified studies, the model of random effects was used and the inconsistency of studies with the I2 index was investigated. OpenMeta 10.10, Stata 11.0 and RevMan 5.3 software were used for data analysis.

Results: The research included 15 studies comprising of a total of 3,716 patients. The incidences of all-grade GI symptoms were: diarrhea 8.6% (95% CI: 6.6–10.6%), nausea 9.2% (95% CI: 7.3–11.0%), vomiting 3.2% (95% CI: 1.9–4.5%), constipation 2.8% (95% CI: 1.8–3.9%), colitis 0.7% (95% CI: 0.4–1.1%), stomatitis (95% CI: 1.0–2.7%), and decreased appetite 10.0% (95% CI: 8.3–11.7%). Therapy using PD-1 inhibitors was discontinued in 2.5% (95% CI: 0.0–5.1%) of patients with nausea, in 3.0% (95% CI: 0.7–5.3%) of those with diarrhea, and in 45.7% (95% CI: 20.6–70.7%) of patients with colitis. Compared with chemotherapy, the use of PD-1 inhibitors showed significant increase in the occurrence of grade 1–4 colitis (RR =3.90, 95% CI: 1.41–10.81, P=0.009) and grade 3–4 colitis (RR =3.76, 95% CI: 1.07–13.26, P=0.04).

Discussion: This meta-analysis provides a reliable estimate of the incidences of GI adverse events among NSCLC patients. Especially when colitis does occur, it often results in therapy discontinuation. Use of PD-1 inhibitors led to a higher incidence of colitis as compared to the use of chemotherapy.

Keywords: Non-small cell lung cancer (NSCLC); PD-1 inhibitors; gastrointestinal adverse events; meta-analysis

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Introduction

The GLOBOCAN study, conducted in 2018, reveals that lung cancer remains the leading cause of cancer-related mortality, causing an estimated 1.8 million deaths each year, globally (1). Depending on the histological features, lung cancers are classified as either small cell lung cancers (15–20%) or non-small cell lung cancers (NSCLCs) (80–85%) (2).

Novel approaches to the treatment of NSCLC include immunotherapy targeting programmed cell death receptor-1 and its ligand-1 and, hence, the use of PD-1/PD-L1 inhibitors as well as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). These innovative therapies have opened a new era in the treatment of lung cancer (3).

As immunotherapy continues to gain prominence in clinical practice, more and more adverse events are being observed. The adverse events associated with immunotherapy are different from those witnessed with the use of chemotherapy and small molecule targeted therapy. Reducing the incidence of adverse events is considered as important as is the prolongation of survival, especially for palliative treatment in some very late-stage cancer cases. Among adverse events, the incidence of gastrointestinal (GI) adverse events are second only to skin reactions among patients receiving immunotherapy.

GI adverse events may occur throughout the GI tract from upper involvement with oral aphthous ulcers, esophagitis, gastritis, to more distal involvement with enteritis and colitis (4). It is very important to further understand the incidence of GI adverse events in a larger scale of patients. This meta-analysis focuses on the incidence of GI adverse events with the use of PD-1 inhibitors and to find out if these adverse events were associated with treatment discontinuation. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-125).

Methods

Inclusion and exclusion criteria

The PICOs (participants, intervention, comparison, and outcomes) elements were used for selection of studies to meet the inclusion and exclusion criteria. Each letter represents a component: the patient population (P), the interventions or exposure (I), the comparator group (C), the outcome (O), and the study design chosen (S). Duplicate articles were removed from retrieved studies before screening articles by title and abstract to identify studies that met the following inclusion criteria: (I) published articles in English and Chinese language, (II) investigated the GI adverse events of PD-1 inhibitor for the management of advanced/metastatic NSCLC patients, (III) reported the occurrence of GI adverse events. Articles with insufficient detail in the title and abstract to make a clear decision were included for further review. The earliest publication was selected for studies that have the same methodological descriptions and results. Full-text versions of all included publications were retrieved. Exclusion criteria are as follows: a study that reported (I) the outcomes of more than one PD-1 inhibitors without distinction, (II) received concurrent radiation or chemotherapy at the same time as an PD-1 inhibitors therapy, (III) pharmacokinetic or pharmacodynamic investigation, (IV) *in vitro*, molecular, or experimental investigations, or (V) qualitative information. We used not only the full text but also the appendix and the references of each article would be used as the information resources.

Literature search

Several electronic databases, including Google Scholar, PubMed, Cochrane library, Embase Science Direct and proceedings of major oncology conferences, were explored by using specific search terms and medical subject headings. Primarily, the search terms PD-1 inhibitors, NSCLC, GI adverse events were used followed by several other extensions including, but not limited to, the words nivolumab, pembrolizumab, diarrhea, nausea, vomiting, constipation, colitis, stomatitis and decreased appetite. The scope of the search encompassed research articles published before December 2020. In addition, bibliographies of important related papers were also screened.

Quality assessment

The quality of included studies was assessed independently by three authors (WM Chen, HM Zhang and SS Jia) using a revised methodological index for nonrandomized studies (MINORS). This tool consisted of 8 criteria for all studies, and quality score consisted of eight questions: a clearly stated aim, inclusion of consecutive patients, prospective collection of data, endpoints appropriate to the aim of the

study, unbiased assessment of the study endpoint, follow-up period appropriate to the aim of the study, loss to follow up less than 5%, prospective calculation of the study size. Each item is scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate) (5).

Data collecting

Studies and data extraction were conducted independently by two authors (Y Song and R Zuo) who reviewed and screened all studies for eligibility according to the inclusion criteria described previously. If there were any different opinions, the difference would be discussed with the third author (FY Zhu). Information was recorded regarding the baseline demographics, clinical, including oncology, profile, study design, methodology, and the number of patients who reported to have GI adverse events of grade 1–5, classified by version 4.0 of the Common Terminology Criteria for Adverse Events (CTCAE 4.0) (6).

Statistical analyses

We performed statistical analysis using the statistical software OpenMeta (version 10.10, opensource: Brown University, Providence, RI, USA) and Review Manager 5.3 (Cochrane Collaboration 2014, Nordic Cochrane Center, Copenhagen, Denmark). The prevalence of GI adverse events reported by the individual studies were pooled under the DerSimonian-Laird random-effects models (7). The relative risk (RR) and the corresponding 95% confidence intervals (CIs) were calculated in patients assigned to PD-1 inhibitors exclusively compared with those assigned to chemotherapy in the same trial. RR >1.0 indicates a higher risk or higher incidence of GI adverse events in patients treated with PD-1 inhibitors exclusively than those treated with chemotherapy. For the calculation of the RR, random or fixed-effect models were used, depending on the heterogeneity of included studies. The existence of heterogeneity was tested using the Chi-square statistics. The heterogeneity was quantified using the I^2. For those variables with high heterogeneity ($P<0.05$ for I^2 analysis), the data were analyzed using the random effect model. Otherwise, fixed-effect model was used for the data analysis (8). The results are presented in forest plots, together with pooled summary estimates and their corresponding 95% CI. Subgroup analysis was conducted according to different PD-1 inhibitors to explore the source of heterogeneity. The funnel plots were used to assessing the publication bias. The Egger linear regression test and Begg rank correlation methods were applied to determine publication bias were performed using Stata 11.0 software (Stata A Corp., College Station, Texas, USA). A two-tailed P value of less than 0.05 was considered statistically significant.

Results

Literature search results

Using the research search strategy, a total of 1,426 potentially relevant records were identified from databases and conferences. The selection process and reasons for exclusion of ineligible studies are presented in *Figure 1*. Some 1,411 studies were excluded after screening the abstract and full text. Accordingly, a total of 15 studies were considered eligible for the meta-analysis. These were clinical trials published between 2015 and 2019 with the following distribution: six phase III trials, one phase II/III trial, four phase II trials and four phase I trials (9-23).

Characteristics of the selected studies

The socio-demographic and clinical profile of the patients in the studies included in the meta-analysis are presented in *Table 1*. A total of 3,716 patients with advanced unresectable recurrent or metastatic NSCLC were enrolled. Out of these, 1,693 patients received nivolumab whereas 2,023 patients were on treatment involving pembrolizumab. All of the PD-1 inhibitors were administered as monotherapy. The age range of the patients was 27–93 years and comprised of fewer females (34.8%). The minority of patients (18.8%) had never smoked before. All of the studies used the National Cancer Institute CTCAE, version 4.0 to define the grade of toxicity.

The MINORS was used to evaluate the quality of each study. As shown in *Table 1*, The quality of included studies was high. Treatment-related GI adverse events occurring in patients with advanced NSCLC treated with anti-PD-1 therapy are presented in *Table 2*.

Incidence of diarrhea associated with the use of PD-1 inhibitor

All the 15 studies evaluated the incidence of diarrhea associated with the use of PD-1 inhibitor in 3,716 patients

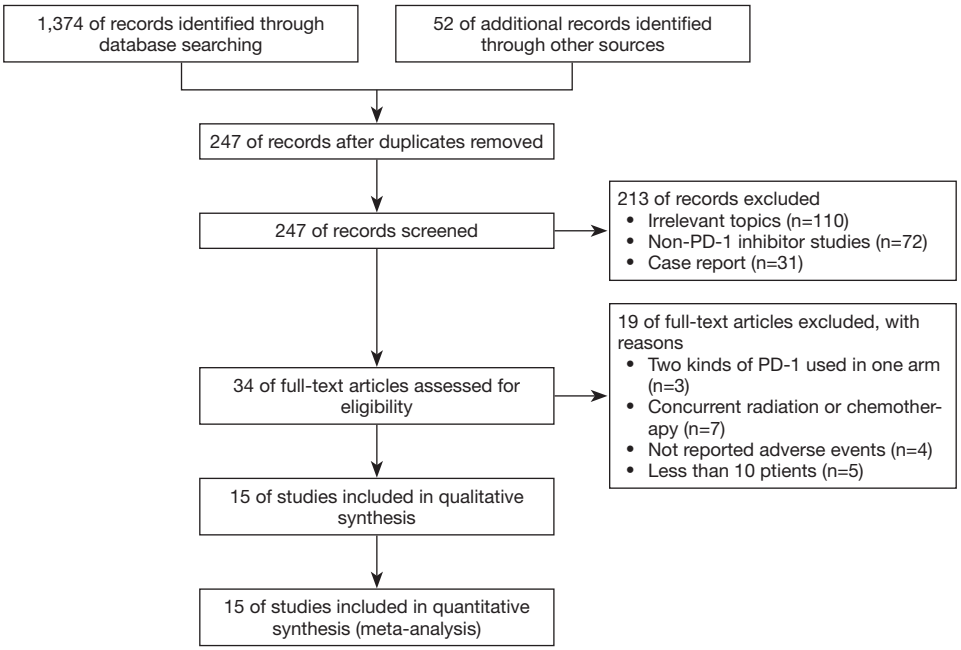

Figure 1 Flow diagram of included studies.

with advanced/metastatic NSCLC (*Table 3*). The incidence of all-grade [1–4] diarrhea associated with PD-1 inhibitors was 8.6% (95% CI: 6.6–10.6%). When stratified by severity of diarrhea, the incidence was 7.6% (95% CI: 5.8–9.4%) for grade 1–2 diarrhea and 0.5% (95% CI: 0.3–0.8%) for grade 3–4 diarrhea. Notably, the occurrence of diarrhea was similar in studies using either nivolumab or pembrolizumab, with incidences of 8.6% (95% CI: 5.3–12.0%) and 8.1% (95% CI: 5.7–10.5%), respectively.

Incidence of nausea associated with PD-1 inhibitor

Thirteen studies (9-13,15-22) evaluated the incidence of nausea associated with the use of PD-1 inhibitor in 3,361 patients with advanced/metastatic NSCLC (*Table 4*). The incidence of all-grade [1–4] nausea associated with PD-1 inhibitors was 9.2% (95% CI: 7.3–11.0%), 8.8% (95% CI: 7.0–10.6%) for grade 1–2 nausea and 0.2% (95% CI: 0.1–0.4%) for grade 3–4 nausea. Using nivolumab or pembrolizumab, with incidences of 10.4% (95% CI: 7.5–13.3%) and 7.9% (95% CI: 5.4–10.4%), respectively.

Incidence of vomiting associated with PD-1 inhibitor

Eleven studies (9-13,15,18,19,21-23) evaluated the incidence of vomiting associated with the use of PD-1 inhibitor in 2,943 patients with advanced/metastatic NSCLC (*Table 5*). The incidence of all-grade [1–4] vomiting was 3.2% (95% CI: 1.9–4.5%). 3.0% (95% CI: 1.7–4.4%) for grade 1–2 vomiting and 0.2% (95% CI: 0.0–0.3%) for grade 3–4 vomiting. Using nivolumab or pembrolizumab, with incidences of 3.8% (95% CI: 1.8–5.8%) and 2.6% (95% CI: 1.7–3.4%), respectively.

Incidence of constipation associated with PD-1 inhibitor

Eleven studies (1,9-13,15,17-19,21,22) evaluated the incidence of constipation associated with the use of PD-1 inhibitor in 2,641 patients with advanced/metastatic NSCLC (*Table 6*). The incidence of all-grade [1–4] constipation was 2.8% (95% CI: 1.8–3.9%), 2.7% (95% CI: 1.7–3.8%) for grade 1–2 constipation and 0.2% (95% CI: 0.0–0.3%) for grade 3–4 constipation. Using nivolumab or pembrolizumab, with incidences of 3.7% (95% CI: 2.0–5.4%) and 1.8% (95% CI: 0.8–2.8%), respectively.

Incidence of colitis associated with PD-1 inhibitor

Nine studies (9,10,14,16,18-21,23) evaluated the incidence of colitis associated with the use of PD-1 inhibitor in 2,359 patients with advanced/metastatic NSCLC (*Table 7*).

Table 1 Basic characteristics of included studies

Reference	Year	Study phase	ICI used	Patients (n)	Age, median [range] (years)	Males (%)	Never smokers (%)	Squamous (%)	Non-squamous (%)	Tumor PD-L1 expression			ECOG		Quality
										<1% (%)	≥1% (%)	Unknown (%)	0 (%)	1 (%)	
Borghaei (9)	2015	III	Nivolumab	287	61 [37–84]	52	20	0	100	37	42	21	29	71	14
Brahmer (10)	2015	III	Nivolumab	131	62 [39–85]	82	7	100	0	40	47	13	20	79	14
Garon (12)	2015	I	Pembrolizumab	495	64 [28–93]	52.7	25.5	17.2	81.0	14	52	34	35.2	64.4	13
Rizvi (22)	2015	II	Nivolumab	117	65 [57–71]	73	8	100	0	–	–	–	22	78	13
Gettinger (13)	2016	I	Nivolumab	52	67 [43–85]	50	21	25	75	26	62	12	–	–	13
Goldberg (14)	2016	II	Pembrolizumab	18	59 [33–82]	33	–	17	83	0	100	0	17	83	14
Herbst (16)	2016	II/III	Pembrolizumab	682	63 [56–69]	62	17.5	23	71	0	100	0	35	65	14
Reck (21)	2016	III	Pembrolizumab	154	64.5 [33–90]	59.7	3.2	18.8	81.2	0	100	0	35.1	64.3	14
Nishio 1 (19)	2017	II	Nivolumab	76	64 [39–78]	64.5	27.6	0	100	17	36	47	36.8	63.2	13
Carbone (11)	2017	III	Nivolumab	267	63 [32–89]	68	11	24	76	0	100	0	31	68	14
Hida (17)	2017	II	Nivolumab	35	65 [31–85]	91.4	2.9	100	0	–	–	–	51.4	48.6	12
Hellman (15)	2017	I	Nivolumab	391	64	69	13	30	70	0	100	0	36	64	13
Nishio 2 (20)	2019	I	Pembrolizumab	38	66 [41–78]	68	34	16	84	0	100	0	32	68	12
Mok (18)	2019	III	Pembrolizumab	636	63 [57–69]	71	22	38	62	0	100	0	31	69	15
Wu (23)	2019	III	Nivolumab	337	60 [27–78]	78	30	39	61	41	50	9	14	86	13

Table 2 Treatment-related gastrointestinal adverse events occurring in patients with advanced NSCLC treated with anti-PD-1 therapy

Reference	Patients (n)	Nausea				Vomiting				Diarrhea				Constipation				Nausea				Vomiting				Diarrhea				Constipation			
		Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)	Discontinuation (n)	Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)	Discontinuation (n)	Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)	Discontinuation (n)	Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)	Discontinuation (n)	Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)	Discontinuation (n)	Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)	Discontinuation (n)	Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)	Discontinuation (n)	Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)	Discontinuation (n)
Borghaei (9)	287	34	32	2	1	15	15	0	0	22	20	2	0	13	13	0	0	34	32	2	1	15	15	0	0	22	20	2	0	13	13	0	0
Brahmer (10)	131	12	12	0	0	4	4	0	0	10	10	0	0	2	2	0	0	12	12	0	0	4	4	0	0	10	10	0	0	2	2	0	0
Garon (12)	495	37	33	4	0	14	11	3	0	40	37	3	0	10	8	2	0	37	33	4	0	14	11	3	0	40	37	3	0	10	8	2	0
Rizvi (22)	117	18	18	0	–	7	7	0	–	12	9	3	1	6	6	0	–	18	18	0	–	7	7	0	–	12	9	3	1	6	6	0	–
Gettinger (13)	52	7	7	0	0	3	3	0	0	6	5	1	1	3	3	0	0	7	7	0	0	3	3	0	0	6	5	1	1	3	3	0	0
Goldberg (14)	18	–	–	–	0	–	–	–	0	3	3	0	0	–	–	–	0	–	–	–	0	–	–	–	0	3	3	0	0	–	–	–	0
Herbst (16)	682	68	65	3	–	–	–	–	–	46	44	2	–	–	–	–	–	68	65	3	–	–	–	–	–	46	44	2	–	–	–	–	–
Reck (21)	154	15	15	0	–	4	3	1	–	22	16	6	–	6	6	0	–	15	15	0	–	4	3	1	–	22	16	6	–	6	6	0	–
Nishio 1 (19)	76	9	9	0	0	4	4	0	0	5	5	0	0	6	6	0	0	9	9	0	0	4	4	0	0	5	5	0	0	6	6	0	0
Carbone (11)	267	31	30	1	1	15	15	0	0	37	34	3	1	9	9	0	0	31	30	1	1	15	15	0	0	37	34	3	1	9	9	0	0
Hida (17)	35	3	3	0	0	–	–	–	0	3	3	0	0	7	7	0	0	3	3	0	0	–	–	–	0	3	3	0	0	7	7	0	0
Hellmann (15)	391	21	20	1	–	10	9	1	–	44	41	3	4	6	6	0	–	21	20	1	–	10	9	1	–	44	41	3	4	6	6	0	–
Nishio 2 (20)	38	4	4	0	0	–	–	–	0	6	5	1	0	–	–	–	0	4	4	0	0	–	–	–	0	6	5	1	0	–	–	–	0
Mok (18)	636	31	31	0	–	15	15	0	–	34	29	5	–	8	8	0	–	31	31	0	–	15	15	0	–	34	29	5	–	8	8	0	–
Wu (23)	337	–	–	–	0	1	0	1	0	8	7	1	1	–	–	–	0	–	–	–	0	1	0	1	0	8	7	1	1	–	–	–	0

NSCLC, non-small cell lung cancer.

Table 3 Incidence of diarrhea with anti-PD-1 therapy

ICI	Studies (n)	Patients (n)	Grade of diarrhea								
			All			1–2			3–4		
			Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)
Anti-PD-1	15	3,716	8.6	6.6–10.6	78.3	7.6	5.8–9.4	76.0	0.5	0.3–0.8	0.0
Nivolumab	9	1,693	8.6	5.3–12.0	83.8	7.8	4.7–10.9	82.8	0.6	0.2–1.0	0.0
Pembrolizumab	6	2,023	8.1	5.7–10.5	65.2	6.9	5.0–8.9	54.9	0.6	0.1–1.1	33.4

ICI, immune checkpoint inhibitor.

Table 4 Incidence of nausea with anti-PD-1 therapy

ICI	Studies (n)	Patients (n)	Grade of nausea								
			All			1–2			3–4		
			Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)
Anti-PD-1	13	3,361	9.2	7.3–11.0	67.8	8.8	7.0–10.6	66.4	0.2	0.1–0.4	0.0
Nivolumab	8	1,356	10.4	7.5–13.3	63.6	10.2	7.3–13.1	64.1	0.4	0.4–0.7	0.0
Pembrolizumab	5	2,005	7.9	5.4–10.4	73.1	7.5	5.2–9.9	69.4	0.3	0.0–0.5	16.5

ICI, immune checkpoint inhibitor.

Table 5 Incidence of vomiting with anti-PD-1 therapy

ICI	Studies (n)	Patients (n)	Grade of vomiting								
			All			1–2			3–4		
			Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)
Anti-PD-1	11	2,943	3.2	1.9–4.5	80.0	3.0	1.7–4.4	83.8	0.2	0.0–0.3	0.0
Nivolumab	8	1,658	3.8	1.8–5.8	83.4	3.7	1.7–5.8	85.8	0.3	0.0–0.5	0.0
Pembrolizumab	3	1,285	2.6	1.7–3.4	0.0	2.2	1.4–3.1	0.0	0.2	0.0–0.6	26.2

ICI, immune checkpoint inhibitor.

Table 6 Incidence of constipation with anti-PD-1 therapy

ICI	Studies (n)	Patients (n)	Grade of constipation								
			All			1–2			3–4		
			Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)
Anti-PD-1	11	2,641	2.8	1.8–3.9	60.4	2.7	1.7–3.8	61.1	0.2	0.0–0.3	0.0
Nivolumab	8	1,356	3.7	2.0–5.4	63.1	3.7	2.0–5.4	63.1	0.2	0.0–0.4	0.0
Pembrolizumab	3	1,285	1.8	0.8–2.8	37.54	1.6	0.7–2.4	26.0	0.1	0.0–0.3	0.0

ICI, immune checkpoint inhibitor.

Table 7 Incidence of colitis with anti-PD-1 therapy

ICI	Studies (n)	Patients (n)	Grade of colitis								
			All			1–2			3–4		
			Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)
Anti-PD-1	9	2,359	0.7	0.4–1.1	0.0	0.4	0.1–0.6	0.0	0.4	0.2–0.7	0.0
Nivolumab	4	831	0.3	0.0–0.6	0.0	0.3	0.0–0.7	0.0	0.4	0.0–0.8	0.0
Pembrolizumab	5	1,528	1.1	0.5–1.6	0.0	0.4	0.1–0.7	0.0	0.7	0.3–1.1	0.0

ICI, immune checkpoint inhibitor.

Table 8 Incidence of stomatitis with anti-PD-1 therapy

ICI	Studies (n)	Patients (n)	Grade of stomatitis								
			All			1–2			3–4		
			Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)
Anti-PD-1	6	2,102	1.8	1.0–2.7	46.3	1.8	1.0–2.6	41.9	1.0	0.0–0.3	0.0
Nivolumab	3	630	1.6	0.3–2.9	31.7	1.6	0.3–2.9	31.7	0.2	0.0–0.5	0.0
Pembrolizumab	3	1,472	2.1	0.7–3.5	67.9	2.0	0.7–3.3	64.0	0.1	0.0–0.3	0.0

ICI, immune checkpoint inhibitor.

The incidence of all-grade [1–4] colitis was 0.7% (95% CI: 0.4–1.1%), 0.4% (95% CI: 0.1–0.6%) for grade 1–2 colitis and 0.4% (95% CI: 0.2–0.7%) for grade 3–4 colitis. Using nivolumab or pembrolizumab, with incidences of 0.3% (95% CI: 0.0–0.6%) and 1.1% (95% CI: 0.5–1.6%), respectively.

Incidence of stomatitis associated with PD-1 inhibitor

Six studies (9,11,16,18,19,21) evaluated the incidence of stomatitis associated with the use of PD-1 inhibitor in 2,102 patients with advanced/metastatic NSCLC (*Table 8*). The incidence of all-grade [1–4] stomatitis was 1.8% (95% CI: 1.0–2.7%), 1.8% (95% CI: 1.0–2.6%) for grade 1–2 stomatitis and 1.0% (95% CI: 0.0–0.3%) for grade 3–4 stomatitis. Using nivolumab or pembrolizumab, with incidences of 1.6% (95% CI: 0.3–2.9%) and 2.1% (95% CI: 0.7–3.5%), respectively.

Incidence of decreased appetite associated with PD-1 inhibitor

Fourteen studies (9-12,14-23) evaluated the incidence of decreased appetite associated with the use of PD-1 inhibitor in 3,664 patients with advanced/metastatic NSCLC (*Table 9*). The incidence of all-grade [1–4] decreased appetite was 10.0% (95% CI: 8.3–11.7%), 9.5% (95% CI: 7.8–11.2%) for grade 1–2 decreased appetite and 0.3% (95% CI: 0.1–0.5%) for grade 3–4 decreased appetite. Using nivolumab or pembrolizumab, with incidences of 10.5% (95% CI: 8.0–13.1%) and 9.5% (95% CI: 7.0–12.1%), respectively.

Incidence of treatment-related death and therapy discontinuation

No treatment-related deaths attributable to GI adverse events occurred with the use of PD-1 inhibitors. Discontinuation of treatment was evaluated in 8 studies (9-13,17,19,20) due to all-grade nausea. It was responsible for treatment discontinuation in 2.5% (95% CI: 0.0–5.1%) patients who developed nausea, whereas nausea led to termination of therapy in 0.14% of the patients on treatment using PD-1 inhibitors.

In 12 studies (9-15,17,19,20,22,23) comprising 2,244 patients, diarrhea was cited as the cause of treatment discontinuation in 3.0% (95% CI: 0.7–5.3%) patients who developed diarrhea. There was an overall discontinuation rate of 0.22% due to diarrhea among patients who received PD-1 inhibitors.

Among 887 patients (9,10,14,19,20,23) available for evaluation, 7 of them developed colitis. Out of these, three patients (45.7%, 95% CI: 20.6–70.7%) discontinued therapy.

Table 9 Incidence of decreased appetite with anti-PD-1 therapy

ICI	Studies (n)	Patients (n)	Grade of decreased appetite								
			All			1–2			3–4		
			Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)	Median (%)	Range (%)	I^2 (%)
Anti-PD-1	14	3,664	10.0	8.3–11.7	60.8	9.5	7.8–11.2	62.0	0.3	0.1–0.5	0.0
Nivolumab	8	1,641	10.5	8.0–13.1	63.1	10.2	7.8–12.7	60.1	0.2	0.0–0.4	0.0
Pembrolizumab	6	2,023	9.5	7.0–12.1	64.8	8.8	6.2–11.4	68.4	0.7	0.3–1.0	0.0

ICI, immune checkpoint inhibitor.

Table 10 Basic characteristics and the occurrence of colitis in the selected study of anti PD-1 monotherapy versus chemotherapy

Reference	Experimental arm	Control arm	Experimental arm patients/control arm patients (n)	Anti-PD-1			Chemotherapy		
				Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)	Any grade (n)	Grades 1–2 (n)	Grades 3–4 (n)
Borghaei (9)	Nivolumab	Docetaxel	287/268	2	1	1	0	0	0
Brahmer (10)	Nivolumab	Docetaxel	131/129	1	0	1	0	0	0
Herbst (16)	Pembrolizumab	Docetaxel	682/309	6	2	4	0	0	0
Reck (21)	Pembrolizumab	Investigator's choice of platinum doublet chemotherapy	154/150	3	1	2	0	0	0
Mok (18)	Pembrolizumab	Investigator's choice of carboplatin plus paclitaxel or pemetrexed chemotherapy	636/615	7	3	4	2	1	1
Wu (23)	Nivolumab	Docetaxel	337/156	1	1	0	0	0	0

Overall, discontinuation of treatment because of colitis occurred in 0.30% of all patients who received PD-1 inhibitors.

None of the patients treated with PD-1 inhibitors discontinued therapy because of vomiting, constipation, pancreatitis, stomatitis and decreased appetite.

Comparison of the incidence of colitis between PD-1 inhibitors and chemotherapy

Six studies reported the incidence of colitis between PD-1 inhibitors monotherapy and chemotherapy in patients with advanced/metastatic NSCLC. Collectively, there were 2,227 patients who were treated with PD-1 inhibitors monotherapy and 1,627 who were managed using chemotherapy (9,10,16,18,21,23) (*Table 10*).

The pooled results of the meta-analysis are presented in *Figure 2*. The heterogeneity test indicated that a fixed-effects model could be selected. Compared with chemotherapy, the use of a PD-1 inhibitor showed significant increase in the occurrence of grade 1–4 and grade 3–4 colitis, with pooled RR of 3.90 (95% CI: 1.41–10.81, P=0.009) and 3.76 (95% CI: 1.07–13.26, P=0.04), respectively. However, there was no significant increase in grade 1–2 colitis (RR =2.46, 95% CI: 0.68–8.88, P=0.17).

As shown in *Tables 11,12*, the sensitivity analysis was performed to detect whether the results could have an impact on the PD-1 inhibitors (grade 1–4, grade 3–4 colitis), respectively.

In addition, the funnel plots for the RR of grade 1–4 and grade 3–4 colitis showed that each of the studies was arranged symmetrically on either side of the funnel (*Figures 3,4*). The Egger linear regression test and Begg rank correlation method verified that there was no obvious publication bias (Egger's test: t=0.12, P=0.909; Begg' test: z=0.75, P=0.806). Collectively, there was no significant publication bias in our meta-analysis.

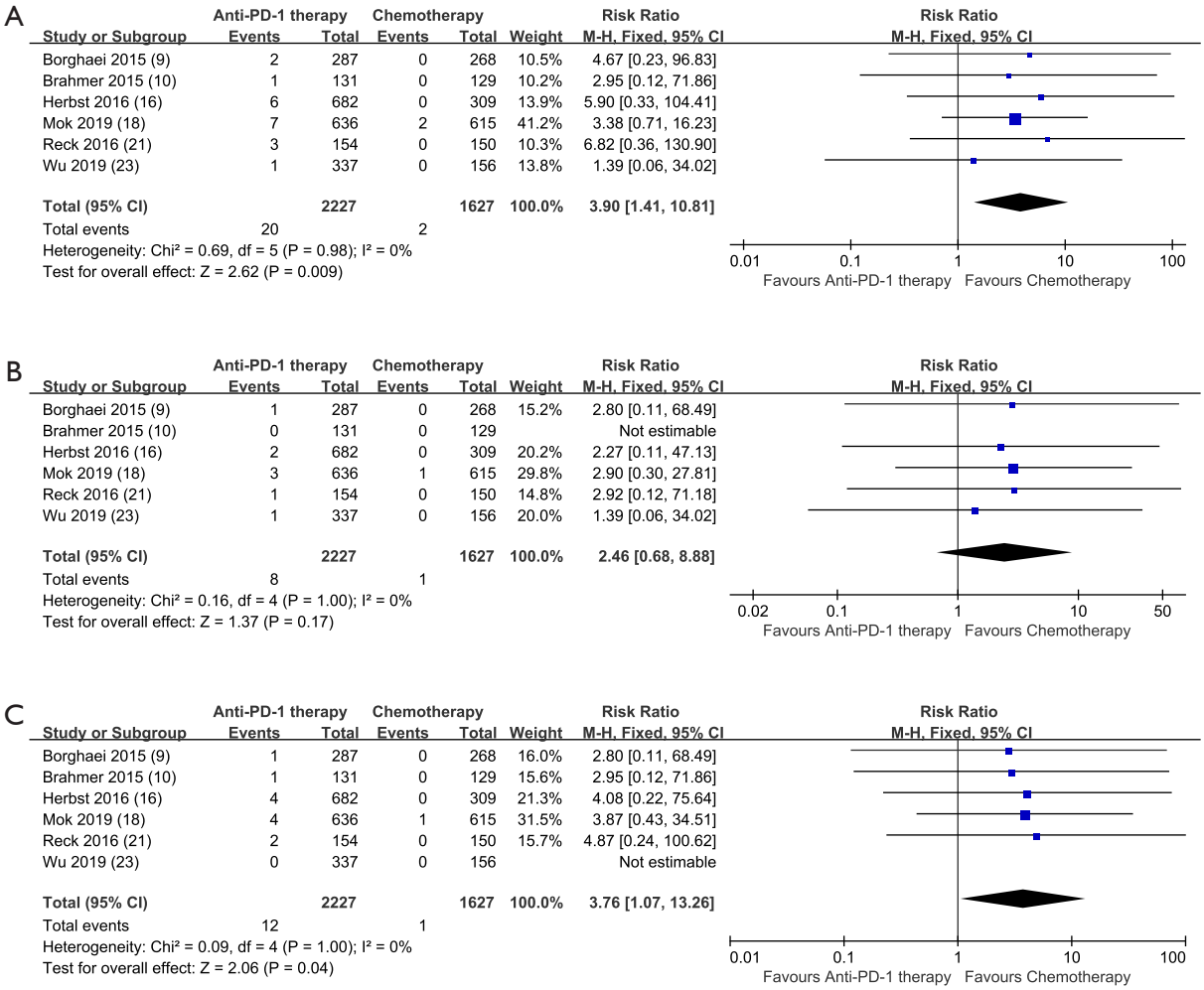

Figure 2 Forest plots for relative risk of all-grade colitis (A), grade 1–2 colitis (B) and grade 3–4 colitis (C) in advanced NSCLC patients treated with anti-PD-1 monotherapy compared with chemotherapy. NSCLC, non-small cell lung cancer.

Table 11 Sensitivity analysis for the incidence of colitis (grade 1–4) in treated with anti PD-1 monotherapy versus chemotherapy

Removed study	Studies (n)	Heterogeneity		RR (95% CI)	P
		P	I^2 (%)		
All study	6	0.98	0	3.9 (1.41–10.81)	0.009
Borghaei (9)	5	0.96	0	3.81 (1.29–11.25)	0.020
Brahmer (10)	5	0.96	0	4.01 (1.37–11.75)	0.010
Herbst (16)	5	0.97	0	3.58 (1.21–10.56)	0.020
Mok (18)	5	0.95	0	4.27 (1.12–16.25)	0.030
Reck (21)	5	0.97	0	3.57 (1.2–10.63)	0.020
Wu (23)	5	0.99	0	4.31 (1.45–12.77)	0.008

Table 12 Sensitivity analysis for the incidence of colitis (grade 3–4) in treated with anti PD-1 monotherapy versus chemotherapy

Removed study	Studies (n)	Heterogeneity		RR (95% CI)	P
		P	I^2 (%)		
All study	6	1.0	0	3.76 (1.07–13.26)	0.04
Borghaei (9)	5	1.0	0	3.94 (1.00–15.55)	0.05
Brahmer (10)	5	1.0	0	3.91 (0.99–15.40)	0.05
Herbst (16)	5	0.99	0	3.67 (0.91–14.74)	0.07
Mok (18)	5	0.99	0	3.71 (0.79–17.32)	0.10
Reck (21)	5	1.0	0	3.55 (0.89–14.25)	0.07
Wu (23)	5	1.0	0	3.76 (1.07–13.26)	0.04

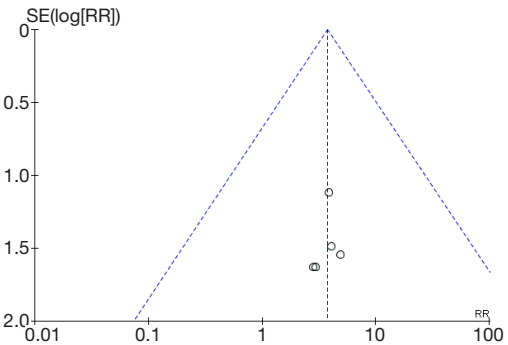

Figure 3 Funnel plots for grade 1–4 colitis in patients treated with PD-1 inhibitors versus chemotherapy.

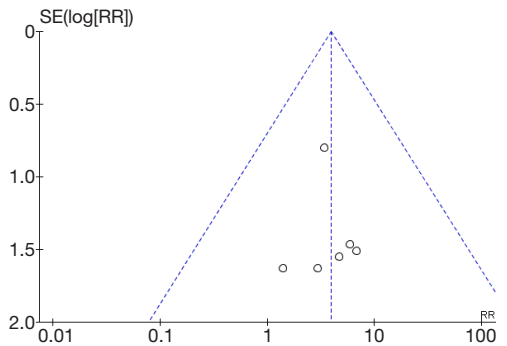

Figure 4 Funnel plots for grade 3–4 colitis in patients treated with PD-1 inhibitors versus chemotherapy.

Subgroup analysis of the incidence of colitis between PD-1 inhibitors and chemotherapy

To further investigate the effect of the specific type of PD-1 inhibitors on the RR of colitis, we performed subgroup analyses based on either nivolumab or pembrolizumab. The RR of colitis did not differ significantly between nivolumab and chemotherapy. In contrast, pembrolizumab showed a significant increase in grade 1–4 colitis, RR =4.46 (95% CI: 1.28–15.58, P=0.02), compared with chemotherapy (16,18,21) (*Figure 5*).

Discussion

To the best of our knowledge, the current meta-analysis involves the largest number of patients in assessing the rates of PD-1 inhibitor-related GI adverse events in advanced NSCLC.

Based on promising results of several landmark clinical trials, the US FDA approved nivolumab and pembrolizumab for the treatment of advanced NSCLC. Pembrolizumab has also been approved for patients who are naïve to chemotherapy when the expression of PD-L1 is greater than 50% (21,22). Besides appreciating the beneficial anti-cancer effects of PD-1 inhibitors, it is important to pay close attention to the occurrence of immune-related side reactions due to the use of these therapeutic interventions. Common drug-related adverse reactions involve the GI system and, when severe, can lead to treatment discontinuation.

Our study indicated that the most frequent GI adverse events among patients treated with PD-1 inhibitors are decreased appetite (10.0%, 95% CI: 8.3–11.7%), nausea (9.2%, 95% CI: 7.3–11.0%) and diarrhea (8.6%, 95% CI: 6.6–10.6%). Other manifestations of GI adverse effects, albeit occurring less frequently, include vomiting (3.2%, 95% CI: 1.9–4.5%), constipation (2.8%, 95% CI: 1.8–3.9%), stomatitis (1.8%, 95% CI: 1.0–2.7%) and colitis (0.7%, 95% CI: 0.4–1.1%). Of note, no patient

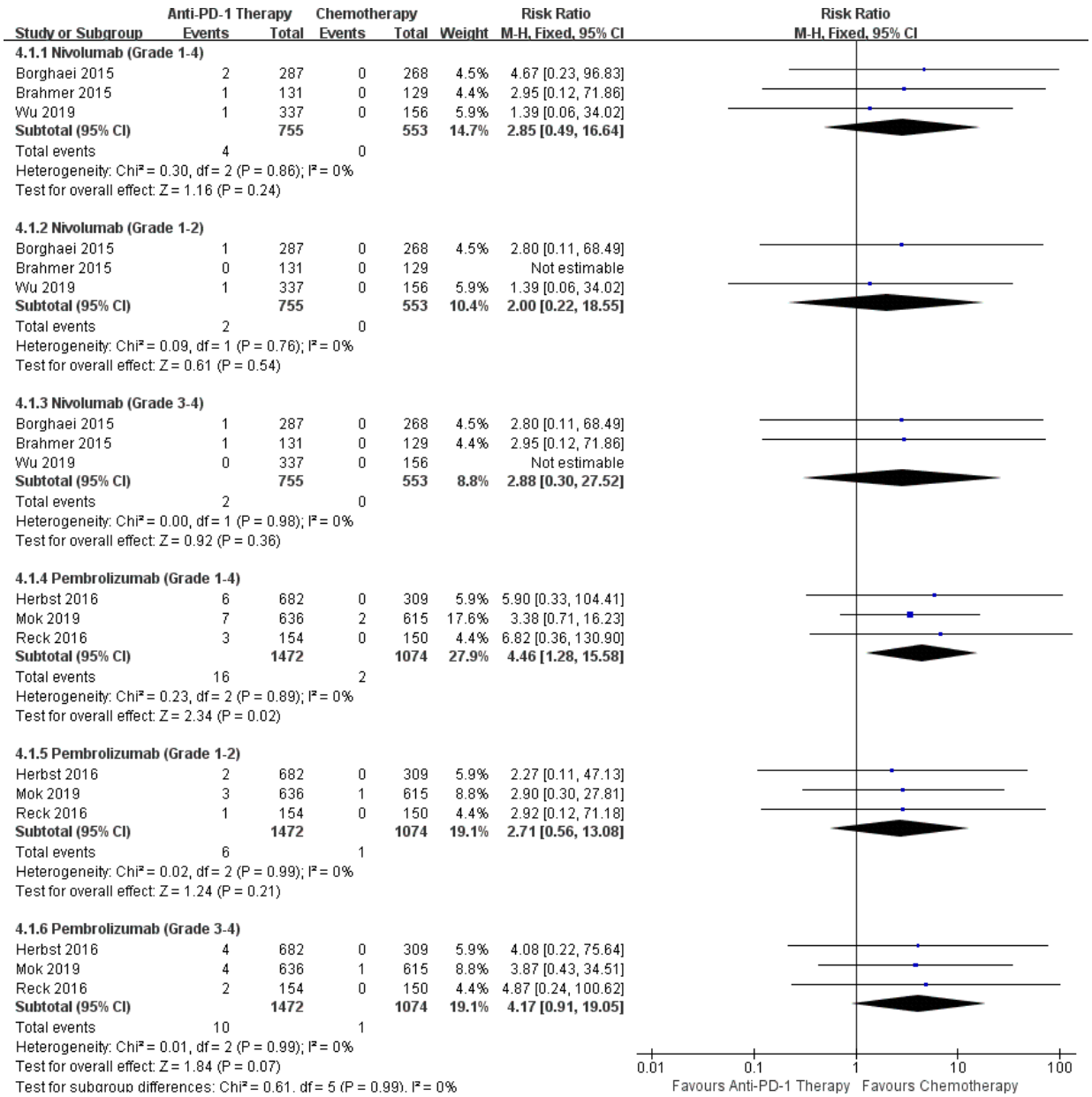

Figure 5 Forest plots analysis for colitis with different type of PD-1 inhibitors (nivolumab or pembrolizumab) monotherapy versus chemotherapy.

discontinued therapy due to decreased appetite. When compared to chemotherapy, the use of a PD-1 inhibitor carried a higher risk of all-grade colitis (RR =3.90, 95% CI: 1.41–10.81, P=0.009) as well as grade 3–4 colitis (RR =3.76, 95% CI: 1.07–13.26, P=0.04). Treatment discontinuation was also frequently experienced among patients with colitis (45.7%, 95% CI: 20.6–70.7%). Given that the incidence of colitis seems higher with the use of PD-1 inhibitors as opposed to the use of chemotherapy, and that nearly half of the patients discontinued therapy due to this unwanted effect, measures should be taken to monitor patients at risk of developing the condition to maximize clinical benefits of PD-1 inhibitor therapy.

The estimated incidences of GI adverse events as

observed in our study are consistent with the results published in the report by Li *et al.* (24), who cite an incidence of the various GI symptoms as follows: all-grade loss of appetite (10.8%), nausea (9.2%), diarrhea (8.2%), constipation (3.9%) and vomiting (3.7%). In their report, Wang *et al.* (25) gave the incidence of grade 1–4 and grade 3–4 colitis as 0.8% and 1.2%, respectively. Of note, the current meta-analysis is more comprehensive and comprises more patients compared to any of the previous studies.

In a meta-analysis by Almutairi and colleagues, nivolumab showed a significantly lower risk of nausea than pembrolizumab in patients with advanced NSCLC (26). This contradicts the results of our current study in which nivolumab had both a higher incidence of grade 1–4 and grade 3–4 nausea and colitis as compared to pembrolizumab. The discrepancy in the results of these two studies could be due to the sparse literature, only three, included in the study by Almutairi and co-workers who also conducted an indirect comparison between nivolumab and pembrolizumab.

Most manifestations of GI adverse events are easy to detect and can be identified early on. Implementing early diagnosis and prompt intervention is critical so as to optimize therapy and avoid treatment discontinuation. When adverse events occur, judicious assessments whether to suspend or to continue therapy, depending on the severity of the adverse event, should be made. When the severity of the adverse events is adequately mitigated and is no longer a threat, it is possible to consider re-introducing the use of immune checkpoint inhibitors except in special circumstances (27). Should the symptoms persist or worsen, steroids can be administered to counter the inflammation. Other treatment options include the use of mycophenolate or infliximab. Moreover, collaborative diagnosis and treatment by interdisciplinary teams that include gastroenterologists may reduce symptoms associated with these adverse events.

Although providing useful insights, we acknowledge that our study has some limitations. First, the studies that were included in the meta-analysis were conducted in an open-label manner without the use of a placebo control arm. These studies, therefore, are prone to bias. Second, almost all the patients in the studies considered in the meta-analysis were in good physical and health condition, with relatively high tolerance to toxicity. Clinically, it is anticipated that patients are likely to have other confounding medical conditions that may further complicate the occurrence and severity of GI adverse events. Therefore, real-world evidence is necessary, to complement the trial evidence, under conditions of greater heterogeneity in patients and treatment settings. Finally, we are unable to evaluate the relationship between the occurrence of adverse events and the duration of use of PD-1 inhibitors; this requires detailed data analysis and follow-up of individual patients.

In summary, our meta-analysis recruited 15 studies and has demonstrated the GI adverse events of PD-1 monotherapy in patients with advanced/metastatic NSCLC. Colitis often resulted in therapy discontinuation. The use of PD-1 inhibitors was associated with a higher incidence of colitis as compared to chemotherapy. These findings call for caution and provide insights that should guide clinical management of patients with PD-1 inhibitors.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/tcr-21-125

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-125). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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