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The risk of diarrhea and colitis in patients with lung cancer treated with immune checkpoint inhibitors: a systematic review and meta-analysis

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ABSTRACT

Background Immune checkpoint inhibitors (ICIs), including inhibitors of PD-1, PD-L1, and CTLA-4, are relatively novel therapies for lung cancer, although their use might be limited by gastrointestinal toxicity. The aim of the present study was to determine the risk of diarrhea and colitis associated with ICIs in lung cancer and the rates of discontinuation because of those toxicities.

Methods Electronic databases were searched for prospective trials reporting the risk of diarrhea and colitis in patients with lung cancer treated with PD-1, PD-L1, and CTLA-4 inhibitors. The incidences of diarrhea and colitis and their grades were assessed clinically using standardized reporting criteria. Pooled incidence and weighted relative risk estimates for diarrhea and colitis with 95% confidence intervals (CIs) were estimated using a random effects model. The incidence of discontinuations for GI toxicity was also calculated.

Results Twenty-seven studies were included: sixteen studies with PD-1 inhibitors, nine studies with PD-L1 inhibitors, and four studies combining PD-based strategies with CTLA-4 inhibitors. The incidence of all-grade diarrhea was 9.1% (95% CI: 7.8% to 10.5%) for anti–PD-1 therapy and 11.0% (95% CI: 7.5% to 14.5%) for anti–PD-L1 therapy. The incidence of all-grade colitis was 0.9% (95% CI: 0.4% to 1.3%) for anti–PD-1 therapy and 0.4% (95% CI: 0.0% to 0.8%) for anti–PD-L1 therapy. The relative risk for all-grade diarrhea was higher with combination anti–PD-1 and anti–CTLA-4 than with anti–PD-1 monotherapy (relative risk: 1.61; 95% CI: 1.14 to 2.29). Anti–PD-1 therapy was discontinued in 4.1% of patients with diarrhea (95% CI: 0.7% to 7.4%) and in 35.7% of those with colitis (95% CI: 0.0% to 81.1%); combination therapy was discontinued in 10.1% of patients with diarrhea (95% CI: 4.8% to 15.4%) and in 39.9% of those with colitis (95% CI: 3.9% to 75.9%).

Conclusions Diarrhea is a relatively frequently encountered GI toxicity when ICI therapy is used in lung cancer treatment. Colitis is less frequently encountered, although when it does occur, it often results in therapy discontinuation.

Key Words Lung cancer, checkpoint inhibitors, immunotherapy, diarrhea, colitis

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INTRODUCTION

Lung cancer accounts for 12.9% of all new cancer diagnoses and is the most common cause of cancer-related death[1–3]. Despite increasing efforts to prevent lung cancer through tobacco control, current smoking patterns suggest that lung cancer will remain a considerable cause of cancer-related death worldwide for several decades[4]. Novel therapies with immune checkpoint inhibitors (ICIs)—including antibodies against PD-1, PD-L1, and CTLA-4—have revolutionized the treatment of lung cancer. These therapies have the ability to disrupt mechanisms of immune tolerance to cancer cells by inhibiting key regulatory pathways in T lymphocytes[5].

Several pivotal trials have demonstrated the clinical efficacy of the anti–PD-1 agents nivolumab and pembrolizumab and the anti–PD-L1 agents durvalumab and

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atezolizumab, resulting in U.S. Food and Drug Administration approval of those treatments for advanced non-small-cell lung cancer (NSCLC)[6–9]. Although the Food and Drug Administration approved nivolumab and atezolizumab primarily for after failure of conventional therapy, pembrolizumab has also been approved for patients who are naïve to chemotherapy when the expression of PD-L1 is greater than 50%[6,10].

Although anti–PD-1 agents are a promising treatment strategy for lung cancer, they are associated with systemic immune-mediated side effects. Colitis and diarrhea are among the most frequently reported side effects, occurring in up to 50% of patients receiving anti–PD-1 agents according to a recent review article; when severe, those side effects could lead to substantial morbidity or death[11]. The reported incidence and severity of diarrhea and colitis associated with anti–PD-1 therapy in lung cancer varies between clinical trials, and how frequently anti–PD-1 agents are discontinued as a result of their side effects remains unclear. Given the recent approvals for anti–PD-1 agents in the treatment of lung cancer and the anticipated widespread uptake, we sought to systematically review the incidence of diarrhea and colitis with anti–PD-1 agents used either as monotherapy or in combination with a CTLA-4 inhibitor, and to determine the rates of therapy discontinuation because of those adverse events.

METHODS

This systematic review is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines[12]. The study followed an *a priori* established protocol. We used the *Cochrane Handbook for Systematic Reviews of Interventions* to guide the analysis[13].

Search Strategy and Study Selection

A search strategy was co-developed by members of the study team in conjunction with a health research librarian. We identified all studies that prospectively evaluated the risk of diarrhea or colitis in lung cancer treated with an ICI. A systematic search of multiple electronic databases [EMBASE, MEDLINE (OvidSP), the Cochrane Central Register of Controlled Trials, and MEDLINE (PubMed)] was conducted from inception to September 2018. Abstracts from all major conference proceedings were also reviewed. These MeSH descriptors were applied in the search strategy: ipilimumab OR CTLA-4 OR durvalumab OR avelumab OR BMS-936559 OR PD-L1 OR nivolumab OR PD-1 OR pembrolizumab OR tremelimumab OR lambrolizumab OR checkpoint block OR checkpoint block OR checkpoint inhibitor OR immune checkpoint OR immunomodulatory antibody OR programmed cell death 1 receptor OR CD274 AND colitis OR Colitis OR Diarrhea OR diarrhea OR diarrhoea OR gastrointestinal (toxic or complication or event or manifest or symptom) OR nausea OR vomiting AND lung cancer OR small cell lung cancer or SCLC or non–small cell lung cancer or NSCLC or adenocarcinoma or bronchogenic carcinoma. The complete search strategy can be found in supplementary Appendix A. To ensure completeness, the references from the included publications were manually reviewed to identify additional studies.

Selection Criteria

We included prospective open-label studies and randomized clinical trials that reported the risk of gastrointestinal (GI) adverse events in patients treated with ICI therapy for lung cancer. To ensure standardized comparisons for GI symptoms, studies were included if they reported GI toxicities according to the *Common Terminology Criteria for Adverse Events* (CTCAE), version 3.0 or 4.0[14]. Notably, although the CTCAE is widely used across trials, the definitions for colitis do not include endoscopic assessment. We included studies with adult patients more than 16 years of age diagnosed with lung cancer who were exposed to one or more of the following therapies: nivolumab, pembrolizumab, tremelimumab, ipilimumab, avelumab, atezolizumab, and durvalumab. We excluded studies that included patients who had previously been exposed to the same classes of ICI therapy or patients who had received concurrent radiation or chemotherapy at the same time as an ICI.

Data Extraction and Collection

Two investigators (KB, PT) independently reviewed identified relevant studies eligible for inclusion and used a standardized data collection template to extract data from each of the included studies. Disagreements on study inclusion were settled through consensus.

Study Definitions and Endpoints

The primary outcomes were the incidences of diarrhea and colitis stratified by class of checkpoint inhibitor (anti–PD-1 vs. anti–CTLA-4 vs. anti–PD-L1). The incidences of diarrhea and colitis were determined clinically for each therapy as defined by standardized CTCAE criteria (version 3.0 or 4.0)[14]. The severity of each adverse event was graded on a scale of 1–5, based on predefined criteria. Life-threatening diarrhea and colitis were defined as grades 3–5, with grade 5 indicating a fatal outcome. Secondary outcomes included the incidence and severity of GI toxicities associated with individual ICIs and each combination. Furthermore, we aimed to determine the rate of medication discontinuation in patients who experienced diarrhea or colitis.

Data Extraction and Study Quality

The following information was extracted: baseline study characteristics, including primary author, title of manuscript, year of publication, phase of clinical trial; patient characteristics, including median age and sex; subtype of lung cancer; therapy characteristics, including name and class of ICI, dose of therapy, and schedule, if available; incidence of any-grade (grades 1–5), low-grade (grades 1–2), and high-grade life-threatening (grades 3–5) diarrhea and colitis. Differences were resolved by consensus.

The tools in the Cochrane handbook for evaluating randomized controlled trials were used to assess sources of bias in each study[13]. Bias parameters included random sequence generation and allocation concealment (selection bias), blinding of outcome assessment (detection bias), incomplete outcomes data (attrition bias), selective

reporting (reporting bias), and other biases. Selection bias is introduced when patients, centres, or groups are selected in such a way that randomization is not achieved. Detection bias occurs when there are systematic differences between groups in how outcomes are assessed. Attrition bias occurs when there is an unequal loss of participants, changing the characteristics of the group. Finally, reporting bias occurs when the results of a trial influence the dissemination of the research findings. Each trial was categorized based on the risk of bias: low risk of bias (+), high risk of bias (–), and unclear (?). Single-arm trials have a high risk of bias by their nature, and they were therefore not further assessed for bias.

Statistical Analysis

The OpenMeta software application (version 10.10, open-source: Brown University, Providence, RI, U.S.A.) was used for the statistical analysis[15]. To account for heterogeneity across study populations and designs, the incidences of GI toxicities were determined using DerSimonian–Laird random-effects models. The results are presented in forest plots, together with pooled summary estimates and their corresponding 95% confidence intervals (CIs). Summary estimates were calculated for each class of checkpoint inhibitor and for each individual therapy, where applicable. Comparisons between ICI monotherapy (anti–PD-1 therapy) and combination therapy (anti–PD-1 agent and an anti–CTLA-4 agent) were assessed using weighted relative risk estimates.

RESULTS

The initial search strategy identified 1117 publications (Figure 1). After removal of duplicates, 950 publications underwent title and abstract review, with 117 of those studies being selected for full-text review. After applying the study criteria, twenty-four manuscripts[9,10,16–37] and three abstracts[38–40] were included. The coefficient of agreement between reviewers for article selection was 0.82 (95% CI: 0.70 to 0.95).

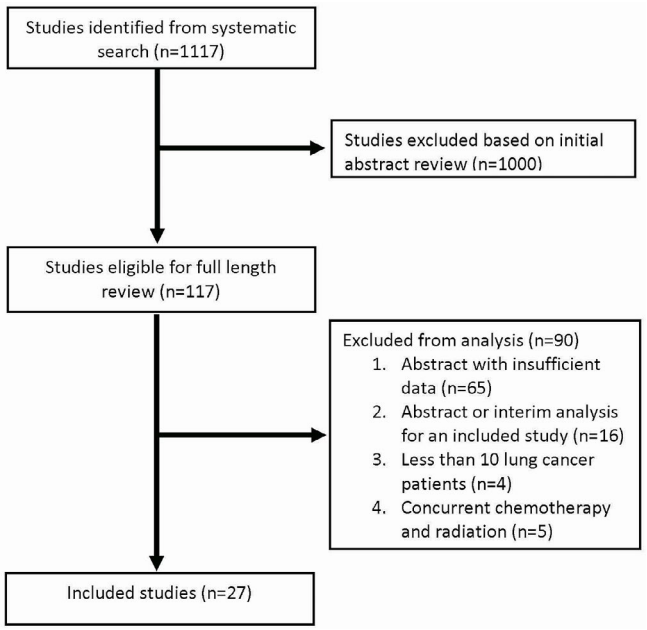

FIGURE 1 Flow diagram for study selection.

Table I summarizes the study characteristics. Included studies had been published between 2015 and 2018. All studies were clinical trials: eight were phase I[18,21,23,27,28,31,35,38], seven were phase II[19,22,24,29,30,33,36], eight were phase III[9,10,16,17,26,32,34,37], three were phase I/II[20,39,40], and one was a phase II/III trial[25]. Sixteen studies included rates of diarrhea or colitis for anti–PD-1 therapy[10,16–20,23–26,29–31,34,37,38]: nine for anti–PD-L1[9,22,27,32,33,35,39–41], three for combination anti–PD-1 and anti–CTLA-4[20,28,34], and one for combination anti–PD-L1 and anti–CTLA-4[21].

Incidence of Diarrhea Associated with ICIs

All 27 studies evaluated the incidence of diarrhea associated with ICI therapy in patients with lung cancer: sixteen studies with anti–PD-1 therapy[10,16–20,23–26,29–31,34,37,38] enrolling 3283 patients, and nine studies with anti–PD-L1 therapy[9,22,27,32,33,35,39–41] enrolling 2385 patients (Table II). The incidence of all-grade diarrhea associated with anti–PD-1 therapy was 9.1% (95% CI: 7.8% to 10.5%); it was 7.5% (95% CI: 5.4% to 9.6%) for low-grade diarrhea and 1.1% (95% CI: 0.5% to 1.8%) for high-grade diarrhea. Rates of diarrhea were similar for nivolumab and pembrolizumab, with incidences of 9.7% (95% CI: 8.2% to 11.2%) and 7.7% (95% CI: 5.9% to 9.4%) respectively. Similarly, the incidence of diarrhea with anti–PD-L1 therapy was 11.0% (95% CI: 7.5% to 14.5%); it was 11.4% (95% CI: 6.6% to 16.1%) for low-grade diarrhea and 0.6% (95% CI: 0.3% to 0.9%) for high-grade diarrhea. No treatment-related deaths attributable to diarrhea occurred with anti–PD-1 or anti–PD-L1 therapy.

Four studies reported the incidence of diarrhea with combination immunotherapy[20,21,28,34]. The incidence of all-grade diarrhea with combination anti–PD-1 and anti–CTLA-4 therapy was 13.2% (95% CI: 8.6% to 17.7%); it was 10.3% (95% CI: 3.9% to 16.6%) for low-grade diarrhea and 1.7% (95% CI: 0.9% to 2.6%) for high-grade diarrhea. In comparison, the incidence of all-grade diarrhea with anti–PD-L1 and anti–CTLA-4 was numerically higher at 40.4% (95% CI: 30.7% to 50.1%); it was 29.3% (95% CI: 20.3% to 38.3%) for low-grade diarrhea and 11.1% (95% CI: 4.9% to 17.3%) for high-grade diarrhea. Two studies compared combination therapy using anti–PD-1 plus anti–CTLA-4 with anti–PD-1 monotherapy[20,34]. The overall risk of developing diarrhea was higher when combination therapy was used (Figure 2): the relative risk for all-grade events was 1.51 (95% CI: 1.11 to 2.06); it was 1.44 for low-grade events (95% CI: 1.05 to 1.99) and 2.29 for high-grade events (95% CI: 0.70 to 7.52). No treatment-related deaths attributable to diarrhea were observed with combination immunotherapy regimens.

Incidence of Colitis Associated with ICI

Thirteen studies reported the incidence of colitis in patients treated with ICIs for lung cancer: eight with anti–PD-1 therapy[10,16,17,20,25,30,31,34] enrolling 1452 patients, and five with anti–PD-L1 therapy[22,32–34,39] enrolling 1195 patients (Table III). The incidence of all-grade colitis associated with anti–PD-1 therapy was 0.9% (95% CI: 0.4% to 1.3%); it was

TABLE I Study characteristics of included studies reporting gastrointestinal toxicity in patients with lung cancer receiving immune checkpoint inhibitors (ICIs)

Reference	Study Phase	ICI used	Patients (*n*)	Any grade (*n* patients)		Grades 1–2 (*n* patients)		Grades 3–4 (*n* patients)		Discontinuation (*n* patients)	
				Diarrhea	Colitis	Diarrhea	Colitis	Diarrhea	Colitis	Diarrhea	Colitis
Full publications											
Borghaei *et al.*, 2015[16]	III	Nivolumab	287	22	2	20	1	2	1	0	1
Brahmer *et al.*, 2015[17]	III	Nivolumab	131	10	1	10	0	0	1	0	0
Garon *et al.*, 2015[18]	I	Pembrolizumab	495	40	—	37	—	3	—	—	—
Rizvi *et al.*, 2015[19]	II	Nivolumab	117	12	—	9	—	3	—	—	—
Antonia *et al.*, 2016[20]	I/II	Nivolumab	98	7	0	7	0	0	0	0	0
		Nivolumab + ipilimumab	115	22	3	18	1	4	2	2	2
Antonia *et al.*, 2016[21]	I	Durvalumab + tremelimumab	99	40	12	29	3	11	9	5	9
Fehrenbacher *et al.*, 2016[22]	II	Atezolizumab	142	10	2	—	1	—	1	—	—
Gettinger *et al.*, 2016[23]	I	Nivolumab	52	6	—	5	—	1	—	1	—
Goldberg *et al.*, 2016[24]	II	Pembrolizumab	18	3	—	3	0	0	1	—	1
Herbst *et al.*, 2016[25]	II/III	Pembrolizumab	682	46	6	44	2	2	4	—	—
Reck *et al.*, 2016[10]	III	Pembrolizumab	154	22	3	16	1	6	2	—	—
Antonia *et al.*, 2017[9]	III	Durvalumab	476	87	—	84	—	3	—	—	—
Carbone *et al.*, 2017[26]	III	Nivolumab	267	37	—	3	—	34	—	1	2
Gulley *et al.*, 2017[27]	IB	Avelumab	184	13	—	13	—	0	—	0	0
Hellman *et al.*, 2017[28]	I	Nivolumab + ipilimumab	77	9	6	3	3	3	8	—	3
Hida *et al.*, 2017[29]	II	Nivolumab	35	3	—	3	—	0	—	0	0
Nishio *et al.*, 2017[30]	II	Nivolumab	76	5	1	5	0	0	1	—	1
Ott *et al.*, 2017[31]	IB	Pembrolizumab	24	3	1	3	0	0	0	—	—
Rittmeyer *et al.*, 2017[32]	III	Atezolizumab	609	94	2	90	2	4	0	—	—
Garassino *et al.*, 2018[33]	II	Durvalumab	444	27	2	24	2	3	0	1	—
Hellman *et al.*, 2018[34]	III	Nivolumab + ipilimumab	576	94	—	85	—	9	—	11	4
		Nivolumab	391	44	—	41	—	3	—	4	—
Horn *et al.*, 2018[35]	I	Atezolizumab	89	7	—	7	—	0	—	—	—
Spigel *et al.*, 2018[36]	II	Atezolizumab	137	25	—	22	—	3	—	—	—
Vokes *et al.*, 2018[37]	III	Nivolumab	418	37	—	33	—	4	—	—	—
Abstracts											
Kato *et al.*, 2016[38]	IB	Pembrolizumab	38	6	—	—	—	—	—	—	—
Antonia *et al.*, 2016[39]	I/II	Durvalumab	59	7	—	—	—	—	—	2	—
Balmanoukian *et al.*, 2017[40]	I/II	Durvalumab	245	20	—	—	—	—	5	—	—

TABLE II Incidence of diarrhea with anti–PD-1 and anti–PD-L1 monotherapy and combination therapy

Agent	Studies (*n*)	Patients (*n*)	Grade of diarrhea								
			All			1–2			3–4		
			(%)	Range (%)	I^2 (%)	(%)	Range (%)	I^2 (%)	(%)	Range (%)	I^2 (%)
Anti–PD-1	16	3283	9.1	7.8–10.5	30.9	7.5	5.4–9.6	81.2	1.1	0.5–1.8	69.5
Nivolumab	11	2026	9.7	8.2–11.2	21.4	7.4	4.6–10.2	84.5	1.6	0.6–2.6	75.3
Pembrolizumab	5	1257	7.7	5.9–9.4	10.0	7	5.6–8.4	0	0.4	0.0–0.7	0
Anti–PD-L1	9	2385	11.0	7.5–14.5	86.6	11.4	6.6–16.1	90.9	0.6	0.0–0.7	0
Anti–PD-1 + anti–CTLA-4	3	866	13.2	8.6–17.7	68.5	10.3	3.9–16.6	88.1	1.7	0.9–2.6	0
Anti–PD-L1 + anti–CTLA-4	1	99	40.4	30.7–50.1		29.3	20.3–38.3		11.1	4.9–17.3	

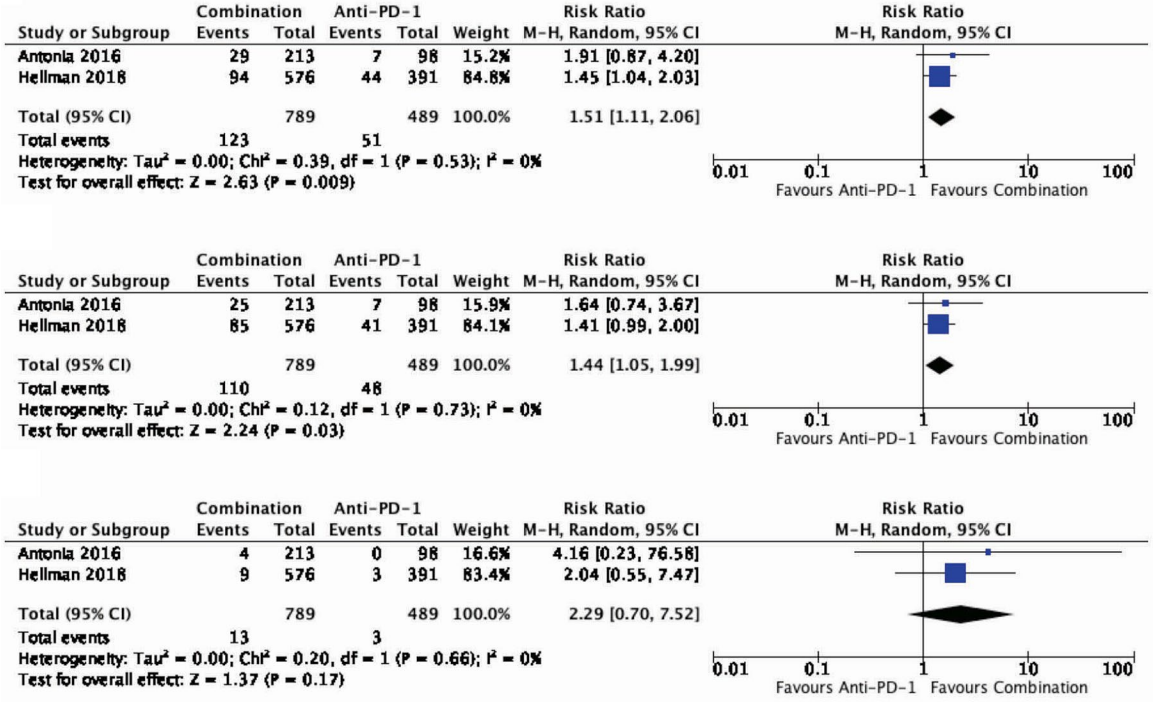

FIGURE 2 Forest plots for relative risk of (A) all-grade diarrhea, (B) low-grade diarrhea, and (C) high-grade diarrhea in patients treated with anti–PD-1 monotherapy compared with combined anti–PD-1 and anti–CTLA-4 therapy.

0.4% (95% CI: 0.1% to 0.7%) for low-grade colitis and 0.6% (95% CI: 0.2% to 0.9%) for high-grade colitis. Similarly, the incidence of all-grade colitis associated with anti–PD-L1 therapy was 0.4% (95% CI: 0.0% to 0.8%); it was 0.4% (95% CI: 0.0% to 0.8%) for low-grade colitis and 0.1% (95% CI: 0.0% to 0.3%) for high-grade colitis. The overall incidence of all-grade colitis was similar for individual ICIs within the same class. No treatment-related deaths attributable to colitis were observed with anti–PD-1 or anti–PD-L1 therapy.

Three studies reported rates of colitis associated with combination immunotherapy: two with anti–PD-1 plus anti–CTLA-4[20,28], and one with anti–PD-L1 plus anti–CTLA-4[21]. The incidence of all-grade colitis for combined anti–PD-1 and anti–CTLA-4 therapy was 7.3% (95% CI: 0% to 19.8%); it was 1.5% (95% CI: 0.0% to 4.6%) for low-grade colitis and 5.0% (95% CI: 0.0% to 14.2%) for high-grade colitis. The incidence of all-grade colitis for combined anti–PD-L1 and anti–CTLA-4 therapy was 12.1% (95% CI: 5.7% to 18.6%); it was 3.0% (95% CI: 0.0% to 6.4%) for low-grade colitis and 9.1% (95% CI: 3.4% to 14.8%) for high-grade colitis. One study reported a grade 5 adverse event attributable to colitis during pembrolizumab monotherapy[31]. No treatment-related deaths attributable to colitis were observed with combination immunotherapy regimens.

Incidence of Treatment Discontinuation

Thirteen studies reported rates of therapy discontinuation associated with all-grade diarrhea: eight for anti–PD-1 therapy[16,17,20,23,24,26,29,34], three for anti–PD-L1 therapy[27,33,39], and two for combination immunotherapy[20,21]. Of the 129 patients treated with anti–PD-1 who developed diarrhea, therapy was discontinued in 4.1% (95% CI: 0.7% to 7.4%). Overall, discontinuation because of diarrhea occurred in 0.4% of all patients who received anti–PD-1. Similarly,

therapy was discontinued in 4.4% (95% CI: 0% to 10.3%) of the 47 patients treated with anti–PD-L1 who had diarrhea (0.3% of all patients who received anti–PD-L1). Finally, of the 123 patients who received combination immunotherapy (anti–PD-1 and anti–CTLA-4) and who had diarrhea, therapy was discontinued in 10.1% (95% CI: 4.8% to 15.4%), representing 1.5% of all patients who received combination therapy.

Ten studies reported rates of therapy discontinuation associated with all-grade colitis: seven with anti–PD-1 therapy[16,17,20,24,29,30,34], one with anti–PD-L1[27], and three with combination immunotherapy regimens[20,21,28]. Of the 912 patients treated with anti–PD-1 therapy, 5 had to stop because of colitis. When colitis occurred, therapy was discontinued in 35.7% of the patients (95% CI: 0.0% to 81.1%). None of the patients treated with anti–PD-L1 therapy discontinued therapy in the only study that reported discontinuation from colitis. Finally, of 14 patients treated with combination immunotherapy who developed colitis, 5 (39.9%; 95% CI: 3.9% to 75.9%) discontinued therapy.

Study Quality Assessment

Figure 3 visually depicts the quality of all included studies. Fifteen studies included in the risk-of-bias assessment had a low risk of bias; two had higher risk. "Low risk of bias" was defined as 3 items or more in a study being evaluated as having a low risk of bias on the assessment tool. Random sequence generation and allocation concealment in the seventeen included studies were described in six and zero studies respectively, possibly introducing selection bias. No study reported blinding of study participants and blinding of the outcome assessment. No attrition or reporting bias was reported in any included study. Most studies had no additional biases.

DISCUSSION

The use of ICIs has improved progression-free and overall survival in patients with lung cancer. However, the utility of those agents can be limited by a range of immune-mediated adverse events, including diarrhea and colitis, and currently, no validated method to predict who will experience those adverse events has been developed. Our study demonstrated a number of important findings related to ICIs in lung cancer:

- Diarrhea occurs in 8%–10% of patients who are treated with inhibitors of the PD axis; colitis, defined clinically by the CTCAE, occurs in fewer patients than 1% of those receiving such treatment.
- Combining inhibitors of CTLA-4 and the PD axis resulted in a 51% higher incidence of diarrhea and a numerically higher incidence of colitis.
- The incidence of treatment discontinuation after anti–PD therapy was relatively modest for patients who developed diarrhea and numerically higher for patients who developed colitis.

TABLE III Incidence of colitis with anti–PD-1 and anti–PD-L1 monotherapy and combination therapy

Agent	Studies (*n*)	Patients (*n*)	Grade of colitis								
			All			1–2			3–4		
			(%)	Range (%)	I^2 (%)	(%)	Range (%)	I^2 (%)	(%)	Range (%)	I^2 (%)
Anti–PD-1	7	1452	0.9	0.4–1.3	0	0.4	0.1–0.7	0	0.6	0.2–0.9	0
Nivolumab	5	146	0.8	0.2–1.5	0	0.5	0–0.9	0	0.5	0–1.0	0
Pembrolizumab	2	706	0.9	0.2–1.6	0	0.2	0–0.7	0	0.6	0–1.2	0
Anti–PD-L1	4	1195	0.4	0–0.8	0	0.1	0–0.3	0	0.1	0–0.3	0
Anti–PD-1 + anti–CTLA-4	2	290	7.3	0.0–19.8	90.0	1.5	0.0–4.6	56.7	5.0	0.0–14.2	86.0
Anti–PD-L1 + anti–CTLA-4	1	99	12.1	5.7–18.6		3.0	0–6.4		9.1	3.4–14.8	

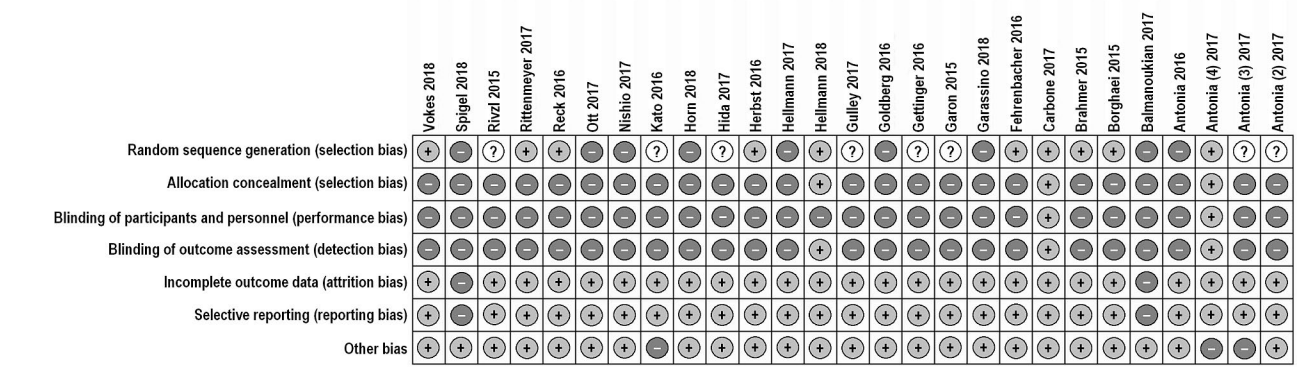

FIGURE 3 Study quality assessment for all included studies. Each trial was categorized based on the risk of bias: low (+), high (–), and unclear (?).

Two previous meta-analyses assessing the incidences of diarrhea and colitis in patients treated with ICIs have been published: one involving patients with any solid tumour[42], and the other restricted to patients with melanoma[43]. The sole meta-analysis that included patients with NSCLC included only a small number of studies because the search strategy was completed in 2016. Moreover, that meta-analysis did not assess the risk of GI toxicities after treatment with combination ICIs. Finally, neither study assessed rates of therapy discontinuation.

The incidence estimates for diarrhea and colitis in our study are consistent with the results from the previous two meta-analyses. Wang *et al.*[42] reported an incidence of all-grade colitis of 1.4% with anti–PD-1 therapy and 1.0% with anti–PD-L1 therapy. Likewise, the incidence of grades 3–4 diarrhea was 1.3% with anti–PD-1 therapy and 0.3% with anti–PD-L1 therapy. When assessing gastrointestinal adverse events in NSCLC being treated with either anti–PD-1 or anti–PD-L1 monotherapy, the authors reported an incidence of 0.8% for colitis and 1.2% for grades 3–4 diarrhea. None of the studies included in the meta-analysis assessed combination therapy with a CTLA-4 inhibitor. The updated comprehensive results of our meta-analysis are comparable to the previously described incidences of colitis and high-grade diarrhea in patients receiving an ICI for lung cancer. Additionally, the incidences of all-grade colitis and diarrhea appear similar for pembrolizumab and nivolumab, suggesting that GI toxicity is a class effect rather than a specific drug effect. Similarly, the incidences of colitis and diarrhea also appear to be comparable for anti–PD-1 and anti–PD-L1 therapy.

Anti–CTLA-4 therapy is not currently approved in the treatment of lung cancer, but ongoing trials are assessing the utility of combination therapy in the treatment of NSCLC[44]. The results of our study show that the risk of developing diarrhea is higher with combination therapy than with monotherapy. The risk of developing colitis also appears higher with combination therapy than with monotherapy. That observation is comparable to results from a meta-analysis by Tandon *et al.*[43], who addressed the incidence of GI-related adverse events in patients with melanoma receiving ICI therapy. In that patient population, the risk of developing diarrhea or colitis was higher in patients receiving anti–CTLA-4 monotherapy than in those receiving anti–PD-1 monotherapy. Furthermore, the risk of developing all-grade diarrhea was higher with combination therapy than with ipilimumab monotherapy. The results of the present meta-analysis and of the Tandon *et al.* study suggest that combination therapy involving an inhibitor of the PD axis plus anti–CTLA-4 is associated with a higher risk of GI toxicity regardless of malignancy type. It will therefore be important to keep that concept in mind as the role of ICIs expands into other malignancies such as lymphoma, colorectal cancer, and renal cell carcinoma[45]. In particular, we demonstrated a rate of therapy discontinuation as high as 54.9% among patients who develop symptomatic immune-related colitis during combination immunotherapy. Early recognition of GI toxicity and prompt management by interdisciplinary teams that include gastroenterologists might reduce the morbidity associated with those adverse events.

In the present review, we comprehensively assessed the incidence of GI adverse events associated with ICI therapy in patients with advanced lung cancer. The major strength of our study is the inclusion of prospective studies with a common method of reporting GI toxicities and their severity. Not only does that approach ensure consistency between studies, it also allows us to reach an accurate estimate of GI toxicity.

Our study also has a number of notable limitations. First, all studies took open-label approaches, without placebo control arms; it is therefore not possible to estimate the baseline incidence of diarrhea and colitis in the patient populations being studied. We were not able to assess for confounding variables such as prior exposure to chemotherapy regimens, antibiotics, and infections, all of which are common in these vulnerable patients. A future avenue of research includes the effect of concurrent antibiotic use in particular, because antibiotics are known to alter the gut microbiome and could affect the likelihood of diarrhea and colitis developing in patients receiving ICIs. Likewise, the constipating effect of medications such as narcotics can mask milder symptoms of diarrhea. Therefore, the reported GI toxicities should be regarded as all-cause events and cannot be directly attributed to ICI therapy. Second, substantial heterogeneity was detected between the included studies, which could in part be related to differences in drug dosing and timing, or other unrelated factors such as concomitant medications and infections. Despite the heterogeneity, similar summary estimates for diarrhea and colitis were observed for individual medications within the same class of therapy. Not only do those observations suggest a class effect for GI toxicity, they provide reassurance for the accuracy of the summary estimates. Third, our estimates for colitis were based on clinical criteria (the CTCAE), without endoscopic confirmation. It is therefore likely that our study underestimated the true incidence of colitis. In a recent retrospective study by Wang *et al.*[46], 81% of patients with clinically relevant symptoms of diarrhea who underwent an endoscopic assessment had evidence of inflammation, despite only 60% of patients meeting the CTCAE for colitis (grade 2–3 criteria).

CONCLUSIONS

To summarize, our study demonstrates that diarrhea occurs in a substantial number of patients with lung cancer after receipt of ICI therapy and that the risk appears substantially higher with combination ICI therapy. Although the risk of colitis appears more modest, future prospective studies using objective measures of inflammation rather than clinical scores are required to establish the true incidence. Our summary estimates are important for patient counselling and for increasing awareness on the part of health care providers about the potential GI toxicities associated with ICI therapy. As the use of ICI therapies becomes more frequent and expands into other disease types, care providers will have to become more familiar with the common adverse events. Early recognition of toxicities is critical to ensure timely diagnosis and appropriate management. A multidisciplinary approach with collaboration between specialists in medical oncology and gastroenterology is

essential to recognize and treat affected patients appropriately as the use of ICI therapy in lung cancer becomes increasingly common.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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