Received: 13 March 2020 | First decision: 29 March 2020 | Accepted: 6 July 2020

DOI: 10.1111/apt.15998

AP&T Alimentary Pharmacology & Therapeutics WILEY

Systematic review with meta-analysis: effectiveness of anti-inflammatory therapy in immune checkpoint inhibitor-induced enterocolitis

Hajir Ibraheim[1,2] | Samantha Baillie[3] | Mark A. Samaan[4] | Hamzah Abu-Sbeih[5] | Yinghong Wang[6] | Nicholas J. Talley[7] | Michael P. Jones[8] | Nick Powell[1,2]

[1]Division of Digestive Diseases, Faculty of Medicine, Imperial College London, London, UK

[2]The Royal Marsden Hospital, London, UK

[3]Kings College Hospital, London, UK

[4]Department of Gastroenterology, Guy's and St Thomas' Hospital, London, UK

[5]University of Missouri-Kansas City, Kansas City, MO, USA

[6]The University of Texas MD Anderson Cancer Cente, Houston, TX, USA

[7]University of Newcastle, New Lambton, NSW, Australia

[8]Psychology Department, Macquarie University, North Ryde, NSW, Australia

Correspondence
Dr Nick Powell, Division of Digestive Diseases, Faculty of Medicine, Imperial College London, London, UK.
Email: npowell@ic.ac.uk

Summary

Background: Immune checkpoint inhibitors have revolutionised cancer treatment, but at the cost of off-target immune-mediated organ damage. This includes checkpoint inhibitor-induced enterocolitis which frequently requires hospitalisation and may be life-threatening. Empiric treatment typically includes corticosteroids and infliximab, although no large-scale studies have confirmed their effectiveness.

Aim: To investigate the effectiveness of anti-inflammatory therapy in checkpoint inhibitor-induced enterocolitis

Methods: We performed a systematic review and meta-analysis of studies reporting clinical outcomes of checkpoint inhibitor-induced enterocolitis in adult cancer patients treated with anti-inflammatory agents. We searched Medline, EMBASE, and the Cochrane library through April and extracted the proportion of patients responding to anti-inflammatory therapy. Variation in effect size was studied using a random-effects meta-regression analysis, with checkpoint inhibitor agent and tumour type as the variables.

Results: Data were pooled from 1210 treated patients across 39 studies. Corticosteroids were effective in 59% (95% CI 54- 65) of patients, with response significantly more favourable in patients treated with anti-PD-1/L1 monotherapy, compared with anti-CTLA-4 containing regimens (78%, 95% CI 69-85 vs 56 %, 95% CI 49-63, $P = 0.003$), and more favourable in lung cancer patients compared with melanoma patients (88%, 95% CI 62-97 vs 55%, 95% CI 47-63, $P = 0.04$). Infliximab was effective in 81% (95% CI 73-87) of patients, and vedolizumab in 85% (95% CI 60-96).

Conclusion: Corticosteroids, infliximab and vedolizumab, are effective in the treatment of checkpoint inhibitor-induced enterocolitis. Checkpoint inhibitor regimen and cancer type were significant moderators in response to corticosteroid therapy.

Hajir Ibraheim, Samantha Baillie, Michael Jones and Nick Powell: Equal contribution.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y. Yuan. The Handling Editor for this article was Professor Jonathan Rhodes, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Immune checkpoint inhibitors including monoclonal antibodies targeting cytotoxic T-lymphocyte–associated-4 (CLTA-4), eg ipilimumab, and programmed cell death protein-1 (PD-1) or its ligand PD-L1, eg nivolumab and pembrolizumab, have transformed the treatment landscape for cancer by incurring a durable survival benefit.[1-5] Their success is hampered by immune-mediated toxicity, particularly with anti-CTLA-4 containing regimens. Checkpoint inhibitor-induced enterocolitis is one of the most serious immune-mediated complications and is especially common in combination regimens (ipilimumab plus nivolumab), affecting >40%.[5-7] It is the most common cause of checkpoint inhibitor discontinuation and treatment-related death.[7,8] Symptoms include diarrhoea, faecal urgency and rectal bleeding[9-12] Endoscopic features include erythema, loss of vascular pattern, oedema, with around 30% of cases exhibiting ulcerated mucosa.[10-17] Histological features include acute inflammation, epithelial apoptosis, crypt abscess formation and infiltration of immune cells, most notably neutrophils and lymphocytes.[10-17]

Checkpoint inhibitor-induced enterocolitis is typically treated with high-dose systemic corticosteroids while second-line treatments include the anti-TNF monoclonal antibody infliximab, the anti-α4β7 integrin monoclonal antibody vedolizumab[15,18] or other immunosuppressants such as mycophenolate mofetil, and tacrolimus.[13,19-22] These agents can incur significant side effects including life-threatening infections.[23-25] However, there are no randomised controlled studies evaluating the efficacy of anti-inflammatory therapy in this setting, with data mainly arising from small observational studies.

Collins et al[17] published a recent systematic review which offered insights into the management of this evolving mucosal disease. The current study complements this work, by providing an updated systematic review and the first meta-analysis with meta-regression to quantify the efficacy of anti-inflammatory therapy in checkpoint inhibitor-induced enterocolitis.

2 | METHODS

2.1 | Search strategy

A systematic search of the medical literature (from 2002 to 6th April 2020) was conducted using MEDLINE, EMBASE and Cochrane library, which were accessed via Pubmed, Ovid and Cochrane. Studies were identified with MESH terms and free text including 'immune check point inhibitor*', 'immune checkpoint antagonis*' as well as specific checkpoint inhibitor drug names. These were combined using the set operator AND with studies identified with the terms: immune-related adverse event*, immune-related toxicit*, diarrh*, colitis, enterocolitis and gastrointestinal (see Appendix A for full search strategy). Where possible, searches were filtered to human studies. There were no language restrictions. Additionally, abstracts from conference proceedings from DDW, UEGW, BSG, ASCO, SITC and ESMO from 2011 were manually searched to identify eligible studies published in abstract form.

Potentially relevant papers were obtained and evaluated in detail, with the reference lists used to carry out a recursive search of the literature. Articles were assessed independently by two investigators (HI and MAS) according to the predefined eligibility criteria. Any disagreement between investigators was resolved by consensus or discussion with a third investigator (NP), if a consensus was not reached.

2.2 | Outcomes of interest

In this study, the term 'checkpoint inhibitor-induced enterocolitis' is used to denote inflammation of the gastrointestinal tract that is usually associated with diarrhoea.

The inclusion criteria included: adult patients with any solid or haematological malignancy receiving at least one dose of any checkpoint inhibitor; availability of data for rate of checkpoint inhibitor-induced enterocolitis and response to anti-inflammatory therapy and studies where more than 5 patients received anti-inflammatory therapy. Studies where checkpoint inhibitor therapy was delivered in combination with other therapies (eg radiotherapy, chemotherapy, etc.) were excluded.

For studies that were close to fulfilling the inclusion criteria, corresponding authors were contacted by email to see if additional data were available that might qualify the study as eligible. For example, in studies where there was ambiguity in the number of patients responding to anti-inflammatory therapy.

The main outcomes of interest included the anti-inflammatory agent used (with regimen and dose—if available) and number or proportion of patients 'responding' to anti-inflammatory therapy. 'Response' was taken to be the definition used by authors in their respective studies.

2.3 | Data extraction

Data were extracted by two authors in duplicate, according to a predefined protocol and recorded in a table. Data extracted included author and publication year, study design, sample size (number of patients with enterocolitis), checkpoint inhibitor agent/s, underlying cancer, anti-inflammatory agent/s and rate of response/remission to therapy. Other data extracted where available, included diagnostic criteria used for defining cases, definition of response to anti-inflammatory therapy, time to response and any safety signals/adverse events identified.

Missing outcome data for patients who had received anti-inflammatory therapy were excluded from analysis.

2.4 | Assessment of study quality

The methodological quality of studies was evaluated using a quality appraisal tool by Moga et al.[18] This uses an 18-point checklist

to evaluate the domains of study objective, study population, interventions and co-interventions, outcome measures, statistical analysis, results and conclusions and competing interests. Studies were awarded points according to preset criteria agreed between two authors (Appendix B).

2.5 | Data synthesis and statistical methods

Due to substantial between-study variance in effect size, a random effects meta-analysis model, according to the method of DerSimmonian and Laird,[19] was used to calculate the pooled estimate proportion of checkpoint inhibitor-induced enterocolitis patients who responded to each anti-inflammatory agent (rounded to the nearest significant figure). Each proportion was logit transformed prior to analysis and then the pooled estimate and 95% confidence interval boundaries were back transformed to a proportion scale using the antilogit formula. Heterogeneity was assessed using the I^2 method, with a threshold of ≥50% to define a substantial heterogeneity,[20] and the Cochrane chi-squared test with a $P \leq 0.10$, used to define a significant degree of heterogeneity.[26]

Comparisons between checkpoint inhibitor regimens and between cancer types were performed using random-effects meta-regression.[21] Dummy variables representing type of cancer and checkpoint inhibitor regimen (anti-CTLA-4 containing regimen [which includes both anti-CTLA-4 monotherapy and the combination anti-CTLA-4 plus anti-PD-1 regimen] and anti-PD-1/PD-L1 monotherapy) were included as independent variables in the model. Some studies included cohorts with a mixed population of patients on a range of checkpoint inhibitor regimens and across a range of cancers, with limited individual data available. For the subgroup analysis, it was agreed that when at least 75% of the study population had a particular cancer or were on a particular checkpoint inhibitor regimen, they were included in that respective subgroup category for analysis (eg if one study had 80% of patients treated with an anti-CTLA-4 containing regimen, that study was included in the anti-CTLA-4 group). If a study did not fulfil this criterion, it was depicted on the forest plot under the label 'mixed'.

Funnel plots were produced for the principal outcome for each comparison, and Egger's test of funnel plot asymmetry was used to assess publication bias.[27] All statistical analyses described above were performed using the STATA (version 16) software. Reporting of this study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

3 | RESULTS

3.1 | Search

After de-duplication, the search strategy identified a total of 4093 citations, of which 98 were potentially relevant and retrieved for further assessment (Figure 1). Of these, 59 were excluded for various reasons leaving 39 eligible studies (Table 1). Thirteen were abstracts and 26 were full articles. One article was translated from Japanese.[22] The majority of studies were either observational studies (prospective and retrospective) or case series. Detailed characteristics of included studies are shown in Table 1. Of note there were no discrepancies between authors, in terms of studies deemed suitable for inclusion.

Corticosteroids and infliximab were the most frequently administered anti-inflammatory agents.

All but one study[22] included patients with melanoma, with 21 of these primarily assessing melanoma patients. Other studies included NSCLC (non-small cell lung cancer), 'lung cancer' (subtype not specified), urothelial cancer, prostate cancer, renal cell carcinoma, 'other solid tumours,' Hodgkin's lymphoma and 'other haematological' malignancies. One study included thymoma and oral squamous cell carcinoma.[11]

Fourteen studies looked exclusively at anti-CTLA-4 monotherapy (ipilimumab or tremelimumab) and 9 at anti-PD1/anti-PD-L1 monotherapy (either nivolumab, pembrolizumab or anti-PD-L1). The combination regimen, ipilimumab and nivolumab, was used in 15 studies but not exclusively. Across all studies, there were 1210 checkpoint inhibitor-induced enterocolitis patients treated with anti-inflammatory therapy. In all but one study, outcomes were based on unique patients. Foppen et al[10] report outcomes on 'episodes' of diarrhoea/colitis where theoretically one patient may have multiple episodes of diarrhoea/colitis recorded. However, this was only the case in four patients who had two different episodes of diarrhoea.

3.2 | Study quality

Studies scored between 5/18 and 17/18 points on the quality assessment for case series checklist (see Appendix B), with an average score of 11. Studies scoring lower marks were predominantly abstracts which lacked the detail to achieve points in the relevant categories.

Points were also frequently deducted for studies being single centre, and lack of reporting for length of follow up and adverse events.

3.3 | Publication bias

Funnel plots did not show significant asymmetry for any cohorts (cancer type, checkpoint inhibitor regimen) for either corticosteroids or infliximab, with Eggers test P value ≥ 0.5 in all cases.

3.4 | Efficacy of corticosteroids

Thirty-three studies reported outcomes on 1104 checkpoint inhibitor-induced enterocolitis patients treated with corticosteroids. Just over half of data were contributed by 6 studies; Abu-Sbeih et al[9] (n = 141), Wang et al, 2019[23] (n = 109), Nahar et al, 2019[24]

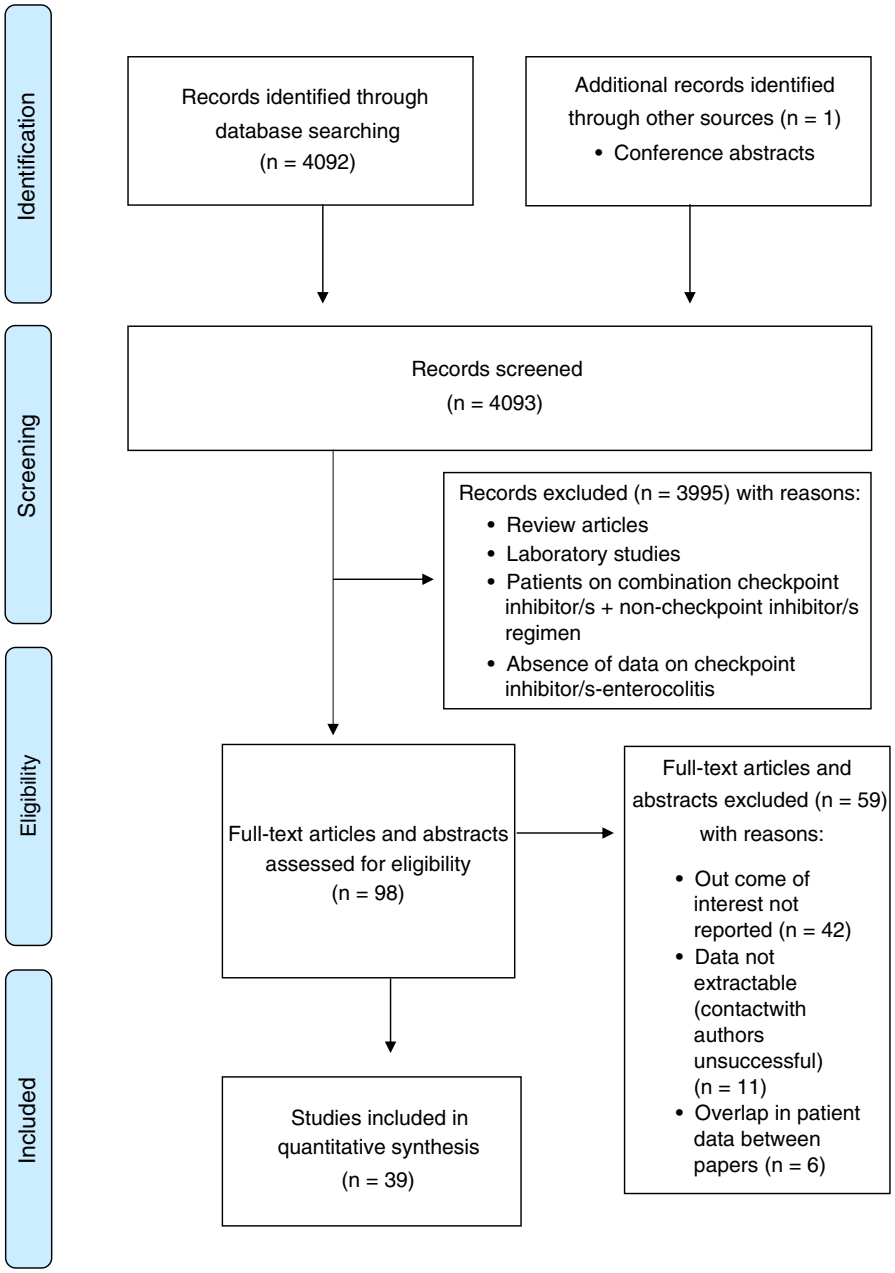

FIGURE 1 Flow diagram of assessment of studies identified in the systematic review and meta-analysis

(n = 106) Foppen et al[10] (n = 92), Spain et al[25] (n = 72) and Hughes et al(II), 2019[28] (n = 57). Reporting of the corticosteroid dose and regimen used was inconsistent and described in 20 studies. Most studies incorporated a range of regimens including prednisolone (14 studies), hydrocortisone (3 studies), methylprednisolone (6 studies) and budesonide (5 studies). Three of the 6 largest aforementioned studies provide a more detailed description of the corticosteroid regimen employed, with Hughes et al(II)[28] reporting that 87.5% of patients received at least 1 mg/kg prednisone or equivalent; Foppen et al[10] describing budesonide use in 12 episodes and "high dose corticosteroids" in 92 episodes (32 episodes at a dose of <1 mg/kg, 57 at 1 mg/kg and 3 at >1 mg/kg) and Wang et al[23] reporting that anti-PD-1 monotherapy and combination regimen treated patients received a median of 1.0 and 1.5 mg/kg prednisone equivalent respectively.

Overall, the pooled response to corticosteroids was 59% (95% CI 54-65), which was associated with a high degree of statistically significant heterogeneity between studies (I^2 = 61%, P < 0.001) (Figure 2A). The median time to response was defined in seven studies,[27-33] varying between 1 day[27] and 95[29] days, although most studies reported a median time of around several weeks. Mir et al report two outcomes—median time to grade 1 colitis (11.5 days) and median time to symptom resolution (43 days).[34]

Stratification according to the type of checkpoint inhibitor regimen included 19 studies, with anti-CTLA-4 containing regimen-treated patients accounting for the majority of patients in the meta-analysis (13 with only anti-CTLA-4 containing regimen-treated patients and 6 studies that included at least 75% of anti-CTLA-4 containing regimen-treated patients). Nine studies included anti-PD-1/L1 monotherapy-treated patients (8 with only anti-PD-1/L1 treated patients,

TABLE 1 Characteristics of included studies (n = 39)

Study	Publication	Design	Agent/s used	Malignancy	No of enterocolitis cases	Diagnostic criteria	CS use n (%)	CS response n (%)	CS regimen/s	IFX in CS refractory cases n (%)	IFX response n (%)	Vedo in CS refractory cases n (%)	Vedo response n (%)
Harding et al, 2012[36]	Abstract	Retrospective cohort	Ipilimumab	Melanoma						36/36 (100%)	26/35[a] (74%)		
Arriola et al, 2015[39]	Abstract	Retrospective cohort	Ipilimumab	Melanoma	27		21/27 (78%)	14/21 (67%)	Oral steroids, escalated to IV MP (1-2 mg/kg)	7/7 (100%)	7/7 (100%)		
De Felice et al, 2015[30]	Article	Retrospective cohort	Ipilimumab	Melanoma	30	≥CTCAE grade 2 diarrhoea requiring CS therapy	23/30 (77%)	22/23 (96%)	Prednisolone <1 mg/kg, prednisolone 1-2 mg/kg, IV MP, budesonide	1/1[b] (100%)	1/1 (100%)		
Horvat et al, 2015[37]	Article	Retrospective cohort	Ipilimumab	Melanoma	87	Symptoms	50/87 (57%)	21/50 (42%)	Prednisolone 1 mg/kg equivalent'	29/29 (100%)	21/29 (72%)		
Rastogi et al, 2015[27]	Article	Case series	Ipilimumab	Melanoma	7	Symptoms	6/7 (86%)	4/6 (66%)	Budesonide, MP, prednisolone	2/2[b] (100%)	2/2 (100%)		
Hillock et al, 2016[13]	Article	Retrospective cohort	Ipilimumab	Melanoma	13	Negative stool cultures, endosopic + histological inflammation			At least 3-5 d IV dexamethasone, HC, MP	13/13 (100%)	4/13 (31%)		
Marthey et al, 2016[15]	Article	Prospective cohort	Ipilimumab, tremelimumab	Melanoma, prostate, lung	39	Negative stool cultures + endoscopic inflammation	35/39 (90%)	13/35 (37%)	Median dose 60 mg prednisolone/ day	12/22 (55%)	10/12 (83%)		
O'Connor et al, 2016[35]	Article	Retrospective cohort	Ipilimumab	Melanoma	16	Symptoms	8/16 (50%)	4/8 (50%)	Prednisolone 0.75-1 mg/kg, IV HC 100 mg QDS	4/4[b] (100%)	4/4 (100%)		
Salgado et al, 2016[32]	Abstract	Retrospective cohort	Anti-CTLA-4, anti-PD-1, combination	Melanoma	46	≥CTCAE grade 3	44/46 (96%)	27/44 (61%)		17/17 (100%)	17/17 (100%)		
Siakavellas et al, 2016[61]	Abstract	Retrospective cohort	Ipilimumab	Melanoma	9	Symptoms	9/9 (100%)	6/9 (66%)		3/3[b] (100%)	3/3 (100%)		
Sidhu et al, 2016[31]	Abstract	Retrospective cohort	Ipilimumab, combination, anti-PD-1		30		29/30 (97%)	14/29 (48%)		15/15 (100%)	15/15 (100%)		
Verschuren et al, 2016[16]	Article	Retrospective cohort	Ipilimumab	Melanoma, prostate	27	Diarrhoea + endoscopic inflammation	26/27 (96%)	14/26 (54%)	Budesonide, HC, prednisone 40-60 mg	12/12 (100%)	12/12 (100%)		

(Continues)

TABLE 1 (Continued)

Study	Publication	Design	Agent/s used	Malignancy	No of enterocolitis cases	Diagnostic criteria	CS use n (%)	CS response n (%)	CS regimen/s	IFX in CS refractory cases n (%)	IFX response n (%)	Vedo in CS refractory cases n (%)	Vedo response n (%)
Bamias et al, 2017[14]	Article	Case series	Ipilimumab	Melanoma	9	Symptoms	8/9 (100%)	4/8 (50%)	Prednisolone, budesonide	4/4[b] (100%)	4/4 (100%)		
Bergqvist et al, 2017[44]	Article	Case series	Ipilimumab, nivolumab	Melanoma, lung	7	Endoscopic inflammation			IV MP up to 2 mg/kg			7/7 (100%)	6/7 (86%)
Collins et al, 2017[29]	Article	Retrospective cohort	Anti-PD-1/L1	Melanoma, NSCLC, Hodgkins lymphoma, other solid tumours	20	Negative stool cultures + histological inflammation	19/20 (95%)	14/19 (74%)	Budesonide, 'systemic CS'				
Franklin et al, 2017[41]	Article	Retrospective cohort	Anti-PD-1, anti-CTLA-4, combination	Melanoma	41	Symptoms	34/41 (83%)	23/34 (68%)	MP 1-2 mg/kg	10/11 (91%)	6/10 (60%)		
Gonzalez et al, 2017[11]	Article	Case series	Anti-PD-1/L1	Melanoma, lung, oral squamous cell carcinoma, urothelial, thymoma	20 (follow up available for 19)		15/19 (79%)	12/15 (80%)		2/3[b] (66%)	2/2 (100%)		
Iafolla et al, 2017[62]	Abstract	Retrospective cohort	Ipilimumab	Melanoma	22	Symptoms	11/22 (50%)	9/11 (82%)	Prednisolone 1-2 mg/kg	2/2[b] (100%)	2/2 (100%)		
Jain et al, 2017[40]	Article	Retrospective cohort	Ipilimumab	Melanoma	16	≥CTCAE grade 2	16/16 (100%)	7/16 (44%)	Prednisolone 1-2 mg/kg per day or equivalent	9/9 (100%)	8/9 (89%)		
Kim et al, 2017[42]	Abstract	Case series	Nivolumab, pembrolizumab	Melanoma, lung, RCC	25	Endoscopic inflammation	23/25 (92%)	17/23 (74%)		6/6 (100%)	6/6 (100%)		
Mir et al, 2017[34]	Abstract	Retrospective cohort	Ipilimumab, pembrolizumab, combination	Melanoma	18	≥CTCAE grade 3	8/18 (44%)	0/8 (0%)		8/18 (100%)	8/8 (100%)		
Abu-Sbeih et al, 2018[9]	Article	Retrospective cohort	Anti-PD-1, anti-CTLA-4, combination	Melanoma, other solid tumours, hamatological cancers	182	Clinical, endoscopic ± histological features	141/182 (77%)	88/141 (62%)		43/53 (81%)	36/43 (84%)		
Arai et al, 2018[64]	Abstract	Retrospective cohort	Nivolumab, pembrolizumab, ipilimumab		10	≥CTCAE grade 2 diarrhea requiring treatment	10/10 (100%)	7/10 (70%)					
Foppen et al, 2018[10]	Article	Retrospective cohort	Anti-PD-1, anti-CTLA-4, combination	Melanoma, NSCLC	92 (96 episodes)	Diarrhoea + negative stool cultures.	92 (100%)	38/92 (41%)	Prednisone 0.5-2 mg/kg, budesonide	54/54 (100%)	51/54 (94%)		

(Continues)

TABLE 1 (Continued)

Study	Publication	Design	Agent/s used	Malignancy	No of enterocolitis cases	Diagnostic criteria	CS use n (%)	CS response n (%)	CS regimen/s	IFX in CS refractory cases n (%)	IFX response n (%)	Vedo in CS refractory cases n (%)	Vedo response n (%)
Mitome et al, 2018[22]	Article	Retrospective cohort	Pembrolizumab, nivolumab	Lung cancer	14	Symptoms	10/11 (91%)	10/10 (100%)	Prednisolone <0.5-1 mg/kg				
So et al, 2018[60]	Article	Retrospective cohort	Pembrolizumab	Melanoma	29	Symptoms	6/29 (21%)	6/6 (100%)					
Spain et al, 2018[25]	Abstract	Retrospective cohort	Ipilimumab, pembrolizumab, nivolumab, combination	Melanoma	117	Symptoms	72/117 (62%)	55/72 (76%)		17/17 (100%)	13/17 (76%)		
Abu-Sbeih et al(II), 2019[43]	Article	Retrospective cohort	Anti-PD-1, anti-CTLA-4, combination	Melanoma, GU, lung, head and neck	179	Symptoms ± endoscopic ± histological inflammation						34/84 (40%)	32/34 (94%)
Cañete et al, 2019[66]	Article	Case series	Nivolumab	Lung cancer, melanoma	6	Diarrhoea + endoscopic inflammation	6/6 (100%)	5/6 (83%)	Prednisolone 1 mg/kg oral or IV (or equivalent)	1/6[b] (17%)	1/1 (100%)		
Herlihy et al, 2019[67]	Article	Retrospective cohort	Ipilimumab	Melanoma	33	Endoscopic ± histological inflammation	32/33 (97%)	13/32 (41%)	125 mg/day IV MP for 3 d, followed by a 4-week prednisone taper	19/19 (100%)	17/19 (89%)		
Hughes et al, 2019[33]	Article	Retrospective cohort	Ipilimumab, combination, anti-PD-1	Lung cancer, melanoma, other solid tumours	38	Endoscopic ± histological inflammation	38/38 (100%)	22/38 (68%)	Budesonide (for microscopic colitis), 'systemic glucocorticoids'	16/16 (42%)			
Hughes et al(II), 2019[28]	Article	Retrospective cohort	Ipilimumab, combination, pembrolizumab, nivolumab	Melanoma	60	Clinical ± histological inflammation	57/60 (95%)	27/57 (47%)	≥1 mg/kg prednisolone or equivalent				
Lesage et al, 2019[38]	Article	Retrospective cohort	Anti-PD-1, anti-CTLA-4, combination	Melanoma	27	≥CTCAE grade 3 and CS resistant enterocolitis				27	20/27 (74%) complete response. 6/27 (22%) partial response		
Nahar et al, 2019[24]	Abstract	Retrospective cohort	Combination, anti-PD-1	Melanoma	106	Clinically significant colitis (requiring systemic CS)	106/106 (100%)	49/106 (46%)					
Wang et al, 2019[23]	Article	Retrospective cohort	Combination, anti-PD-1	Melanoma	109	≥CTCAE grade 3 or persistent grade 2 treated with CS	109/109 (100%)	65/109 (60%)	Prednisolone 1-1.5 mg/kg or equivalent				

(Continues)

TABLE 1 (Continued)

Study	Publication	Design	Agent/s used	Malignancy	No of enterocolitis cases	Diagnostic criteria	CS use n (%)	CS response n (%)	CS regimen/s	IFX in CS refractory cases n (%)	IFX response n (%)	Vedo in CS refractory cases n (%)	Vedo response n (%)
Yutsudo et al, 2019[65]	Abstract	Retrospective cohort	Anti-PD-1	Lung cancer, RCC, melanoma, other solid tumours	9	Endoscopic inflammation	6/9 (66%)	5/6 (84%)		1/6 (11%)			
Harris et al, 2020[45]	Abstract	Retrospective cohort	Combination, anti-PD-1/L1	GU, lung, melanoma	9							9/9 (100%)	6/9 (66%)
Miyahara et al, 2020[63]	Article	Case series	Anti-PD-1		9	≥CTCAE grade 2	8/9 (89%)	6/8 (75%)		2/2[b] (100%)	2/2 (100%)		
Zhang et al, 2020[68]	Article	Retrospective cohort	Anti-PD-1/L1, combination	Melanoma, lung, colorectal, other solid tumours	29	Symptoms, excluding other causes, + improvement after immunosuppressive therapy	26/29 (50%)	13/26 (50%)		13/13 (100%)			

Note: Combination refers to ipilimumab + nivolumab.

Empty fields denote data that was not reported- or not applicable.

Abbreviations: CS, corticosteroid; GU, genitourinary; HC, hydrocortisone; IFX, infliximab; IV, intravenous; MP, methylprednisolone; n, number; NSCLC, non small cell lung cancer; RCC, renal cell carcinoma; Vedo, vedolizumab.

[a]One patient not evaluable.

[b]Not included in meta-analysis as n <5.

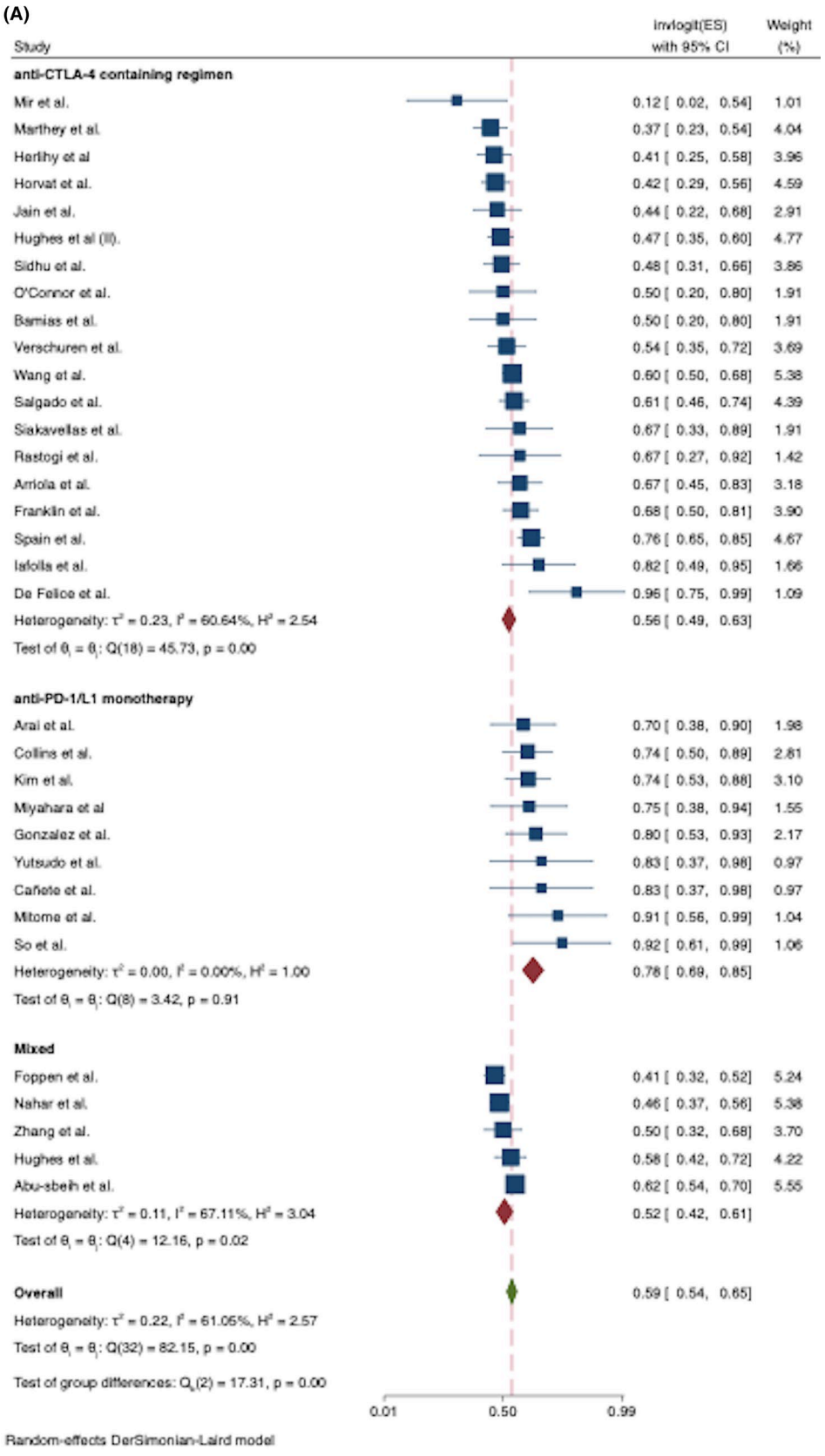

FIGURE 2 Forest plot of pooled response rate to corticosteroid therapy in patients with checkpoint inhibitor induced-enterocolitis according to checkpoint inhibitor regimen (2A) and underlying cancer (2B). 'Mixed' cohorts refer to those where the variable of interest (ie checkpoint inhibitor regimen or underlying cancer) was not represented in at least 75% of the group study. 'Unknown' refers to studies where the variable of interest was not quantified within the group

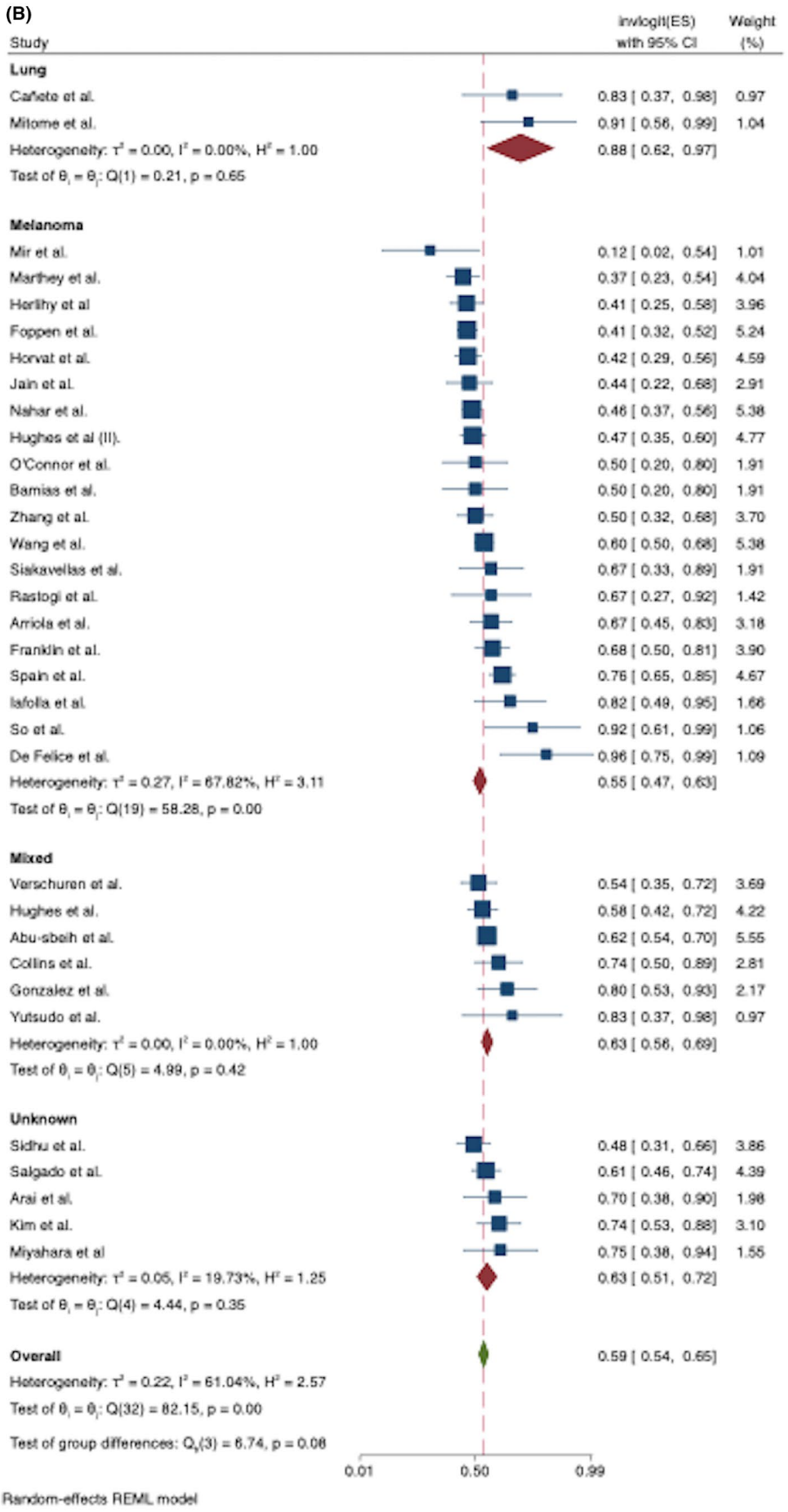

FIGURE 2 (Continued)

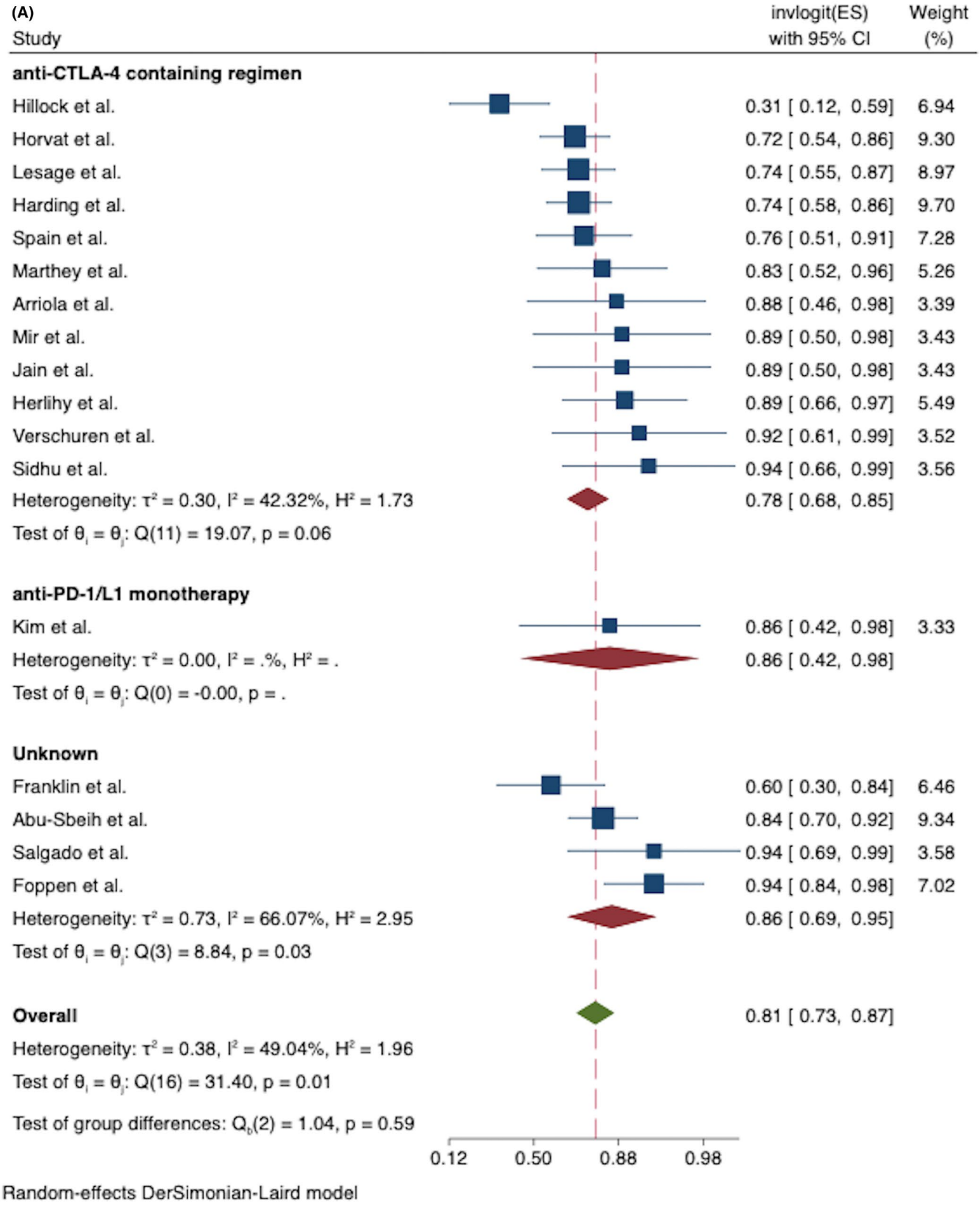

FIGURE 3 Forest plot of pooled response rate to infliximab in patients with checkpoint inhibitor induced-enterocolitis according to checkpoint inhibitor regimen (3A) and underlying cancer (3B). 'Mixed' cohorts refer to those where the variable of interest (ie checkpoint inhibitor regimen or underlying cancer) was not represented in at least 75% of the group study. 'Unknown' refers to studies where the variable of interest was not quantified within the group

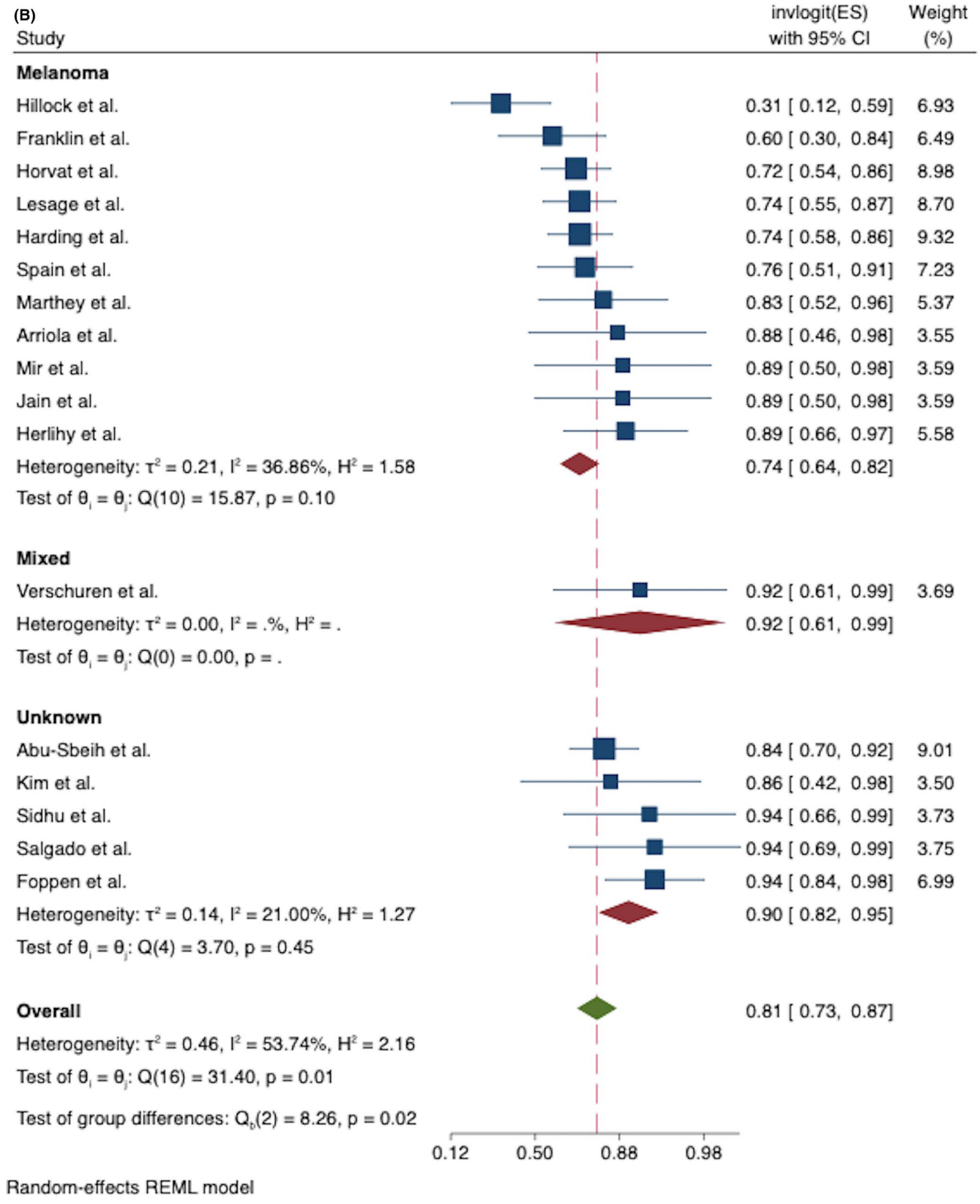

FIGURE 3 (Continued)

and one study where >75% cohort were on anti-PD-1/L1 monotherapy). The remaining studies included a cohort of patients treated with a range of checkpoint inhibitor regimens ('mixed') (Figure 2A).

The response to corticosteroid therapy was more favourable in anti-PD-1/L-1-treated patients (78%, 95% CI 69-85), compared with the anti-CTLA-4 containing regimen group (56%, 95% CI 49-63), with the

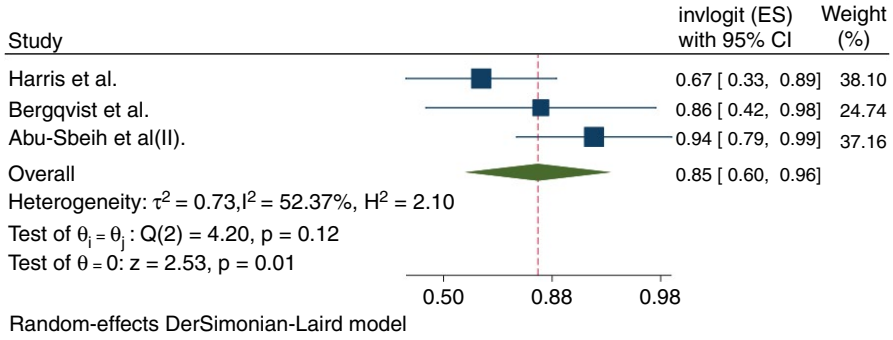

FIGURE 4 Forest plot of pooled response rate to vedolizumab in patients with checkpoint inhibitor-induced enterocolitis.

anti-CTLA-4 subgroup accounting for at least some of the heterogeneity seen ($I^2 = 61\%$, $P < 0.001$ vs $I^2 = 0\%$, respectively). Meta-regression confirmed a statistically significant association between checkpoint inhibitor regimen and response to corticosteroids ($P = 0.003$).

Subgroup analysis according to underlying malignancy included 20 studies for melanoma and two for lung, with the remainder studies comprising 'mixed' cancers, or studies where the cohorts underlying cancers were not clearly defined ('unknown') (Figure 2B).

While the proportion of patients responding to corticosteroid therapy in the melanoma studies was similar to the overall pooled proportion (55% ,95% CI 47-63), it was markedly lower than the 88% (95% CI 62-97) response rate seen within the two lung cancer studies. Meta-regression showed a statistically significant association between cancer type (melanoma vs lung) and response rate ($P = 0.04$), with the melanoma subgroup accounting for some of the heterogeneity seen ($I^2 = 68\%$, $P < 0.001$ vs $I^2 = 0\%$, $P = 0.61$).

3.5 | Efficacy of infliximab

Seventeen studies reported outcomes of infliximab therapy in 333 patients not achieving an adequate response to corticosteroids. The exception was in the O'Connor et al study[35] where one patient was given infliximab as primary therapy due to "severity of symptoms" and a previous serious adverse effect related to corticosteroid use. Over half of the pooled cohort was contributed by 5 studies, Foppen et al[10] (n = 54), Abu-Sbeih et al[9] (n = 43), Harding et al[36] (n = 35), Horvat et al[37] (n = 29) and Lesage et al[38] (n = 27).

Overall, the pooled response to infliximab was 81% (95% CI 73-87), with a moderate degree of statistically significant heterogeneity between studies ($I^2 = 49\%$, $P = 0.01$) (Figure 3A).

Where dose of infliximab used was defined, it was 5 mg/kg.[9,13,14,16,38-40] The number of infliximab doses administered was reported in 14 studies,[9,10,13,14,16,25,32,35-41] with three of these not included in the quantitative analysis as too few patients were treated. In most studies, the number of infusions varied between one and three depending on the clinical response, although two studies were less specific using either 'more than one dose'[10] or 'more than two doses'.[36] Only Bamias et al administered infliximab in a predefined classical IBD induction regimen at weeks 0-2-6,[14] although this was not included in the quantitative analysis as only four patients were treated (100% response rate). The time to response after infliximab therapy, was defined in 5 studies ranging between a median of 2-14 days.[10,25,31,34,40]

A response rate of 78% (95% CI 68-85) was observed in the 12 studies of anti-CTLA-4 containing regimen-treated groups, which was associated with a moderate degree of statistically significant heterogeneity ($I^2 = 42\%$, $P = 0.06$) (Figure 3A). Only Kim et al[42] reported outcomes in patients exclusively receiving anti-PD-1/L1 monotherapy (n = 6, response rate 100%), and so a pooled response could not be generated in this subgroup.

Subgroup analysis according to underlying cancer was only possible in melanoma and included 186 infliximab-treated patients from 11 studies (Figure 3B). The remainder studies included 'mixed' or mainly 'unknown' cancer cohorts. The pooled response rate in melanoma-treated patients was 74% (95% CI 64-82), which was associated with a moderate degree of statistically significant heterogeneity (I^2 37%, $P = 0.1$), and thus may partly account for the overall heterogeneity seen.

3.6 | Efficacy of vedolizumab

Three studies (two articles and one abstract) reported outcomes of vedolizumab in checkpoint inhibitor-induced enterocolitis,[43-45] in a total of 50 patients. The overall pooled response was 85% (95% CI 60-96) with a high degree of heterogeneity that was not statistically significant ($I^2 = 52\%$, $P = 0.12$) (Figure 4). All studies reviewed patients across a range of cancers and checkpoint inhibitor agents including anti-CTLA-4 monotherapy, anti-PD-1 monotherapy, and combination therapy. Bergqvist et al reported a case series of 7 endoscopically proven corticosteroid refractory patients with checkpoint inhibitor-induced enterocolitis (one had prior infliximab), who received 2-4 doses of vedolizumab (300 mg). Prednisolone was successfully tapered in 6 of 7 patients. Of note, the one patient who did not respond had inflammatory bowel disease and was given vedolizumab prophylactically prior to checkpoint inhibitor therapy. The median time from start of vedolizumab treatment to corticosteroid-free remission from enterocolitis symptoms was 56 days (range 52-92 days).[44]

In the larger Abu-Sbeih et al study,[43] 34 corticosteroid refractory patients (2 had prior exposure to infliximab) received a median of 3 doses (range 1-6) of vedolizumab, incurring a response rate of 32/34. Improvement of symptoms was defined as a reduction in symptoms of at least one CTCAE grade.

In the Harris et al study,[45] of the 9 corticosteroid refractory patients treated with vedolizumab, 7 had previously failed an anti-TNF agent. The median time for a clinical response to vedolizumab in the 6 patients who responded (defined as improvement in diarrhoea to ≤CTCAE grade 1 or less) was 7 days (IQR 5-14), with a median of 2 doses administered. The median time taken for sustained clinical remission (defined as resolution of diarrhoea with no further flares in 30 days) was 15 days (IQR 5-43).

There were too few studies to perform subgroup analysis or meta-regression.

4 | DISCUSSION

Despite the success of checkpoint inhibitor therapy in an expanding number of malignancies, immune-related adverse events are an important clinical challenge limiting their use. Checkpoint inhibitor-induced enterocolitis is a common complication, associated with disabling symptoms and intestinal injury. It frequently requires hospitalisation, and is associated with life-threatening complications, including intestinal perforation. Until the results of prospective clinical trials are available, data regarding the efficacy of anti-inflammatory therapy in this context are urgently needed to provide an evidence-based framework for management. In this study, we pooled data from 39 studies across a range of tumours and checkpoint inhibitor regimens and performed a systematic review and meta-analysis with meta-regression. To our knowledge this is the largest study to address this question. A key finding was that all the anti-inflammatory agents evaluated appeared to be effective in checkpoint inhibitor-induced enterocolitis, with success rates of 59% (95% CI 54-65) for corticosteroids, 81% for infliximab (95% CI 73-87) and 85% for vedolizumab (95% CI 60-96).

Interestingly, the efficacy of corticosteroids in checkpoint inhibitor-induced enterocolitis is broadly comparable to response rates observed in patients with acute, severe ulcerative colitis.[46-48] A potentially important and previously unrecognised insight from our study, was that clinical response to corticosteroids was significantly diminished in patients treated with anti-CTLA-4 containing regimens compared with anti-PD-1/L1-treated patients. Two key endoscopy-based studies also identified high risk endoscopic features (extensive colitis and/or presence of mucosal ulcers) as predictors of corticosteroid failure.[9,10] In keeping with this observation, one of the studies reporting the lowest response rate to corticosteroids (37.1%) was from a cohort where mucosal ulceration was present in 79% of patients.[15] Taken altogether, it may be reasonable to consider more intensive treatment, including early escalation to biological therapy in patients developing checkpoint inhibitor-induced enterocolitis following anti-CTLA-4 containing regimens, especially if high-risk endoscopic features are present.

A tumour-specific effect on incidence of checkpoint inhibitor-induced enterocolitis has been described, with melanoma patients appearing to have higher rates of colitis.[54] This prompted us to probe whether a differential response to anti-inflammatory therapy may also be linked to tumour type. The current study shows that cancer type—namely, melanoma and lung cancer—were significant moderators in effect size, with melanoma patients experiencing a less favourable response to corticosteroid therapy.

Another important finding pertains to the clinical utility of budesonide- a topical corticosteroid that has a well documented role in the management of IBD. Although prophylactic budesonide, was not effective in preventing ipilimumab-induced diarrhoea in a phase 2 randomised placebo-controlled trial,[49] our study highlights the potential for budesonide as a primary therapeutic strategy in checkpoint inhibitor induced-enterocolitis. Eight studies report the use of budesonide,[10,14,16,27,29,30,33,37] although few describe the clinical outcomes related to its administration. De Felice et al report that 5 of 6 prednisolone refractory patients achieved a 'complete response' after treatment with budesonide (9-12 mg).[30] Hughes et al used budesonide to successfully treat over 50% (exact rate not extractable) of 12 patients with checkpoint inhibitor-induced microscopic colitis.[33] Other studies report a few cases where budesonide was successfully used as the primary corticosteroid.[27,29]

In line with this, a small case series (n = 2) also demonstrated that Clipper, another type of topical corticosteroid, was effective in inducing clinical and histological remission in two patients with checkpoint inhibitor-induced enterocolitis.[50] The favourable side effect profile of topical corticosteroids over systemic corticosteroids such as prednisolone, positions it as an attractive option for the management of these patients, although more work is needed to determine which subgroup may benefit the most.

Infliximab has an established role as second-line therapy in corticosteroid refractory cases, or some instances of corticosteroid relapse.[17,51] Other anti-TNF agents have not been extensively studied, although successful use of adalimumab has been reported.[15,52] There is evidence that timely initiation of infliximab is associated with a shorter time to resolution, shorter duration on corticosteroids as well as lower rates of recurrence.[9]

In terms of dose, 5 mg/kg has been widely adopted, with the number of infusions administered seeming to depend on clinical response, but generally not exceeding 3 doses, before alternative therapeutic strategies are sought.

There is a movement towards adopting a 'top-down' approach, as used in the IBD paradigm. One study introduced early infliximab to checkpoint inhibitor-induced enterocolitis patients in a predefined schedule, administering three or more infusions regardless of response to corticosteroids.[43] This was associated with a reduced length of hospital stay, reduced need for re-hospitalisation, increased likelihood of successful corticosteroid taper and a lower recurrence rate compared to patients who received less than three infliximab infusions, and at a later time course in their disease.

A differential response to infliximab based on checkpoint inhibitor regimen was less apparent than in the corticosteroid subgroup, although this was challenging to ascertain given there was only one anti-PD-1/L1 treated study included.[42] Notably, all 6 infliximab treated patients experienced a response,[42] compared

to a pooled response of 78% from 12 studies of anti-CTLA-4 containing regimen treated patients. Similarly, limited cancer data for the infliximab subgroup made it difficult to assess the influence of cancer type. To inform a precision medicine approach to management, further studies are needed to evaluate the impact of checkpoint inhibitor regimen and cancer type on response to infliximab therapy.

The quantitative synthesis for vedolizumab consisted of only 3 studies, although outcomes were fairly comparable. In line with the therapeutic efficacy of vedolizumab in this context, Bergqvist et al also reported a significant biochemical response in the 6 (of 7 treated) vedolizumab responders. Post vedolizumab, CRP and faecal calprotectin decreased from 14.0 mg/L (range 2.0-28.0) and 382 mg/kg (range 54-1268) to 6.5 mg/L (range 0.3-16.0) and 76 mg/kg (range 15-199) respectively.[44]

Additional insights into the efficacy of vedolizumab can be gauged from a retrospective study reporting outcomes in 28 vedolizumab-treated checkpoint inhibitor-induced enterocolitis patients by Abu-Sbeih et al[53] (which we excluded due to overlap of patients with their larger more recently published study in 2019[43]). The authors describe clinical remission, as well as endoscopic remission and histological remission in 84%, 54% and 29% of patients, respectively, highlighting a lag in endoscopic and histological remission.

Interestingly, there may be a role for prophylactic vedolizumab as either a primary or secondary prophylaxis strategy. Abu Sbeih et al(II)[43] describe 14 patients who resumed checkpoint inhibitor therapy after resolution of enterocolitis. Of the 8 who received vedolizumab concurrently with checkpoint inhibitor infusions, only one experienced recurrence of enterocolitis, compared to 3 of 6 patients who did not receive vedolizumab.

The gut-specific mechanism of action, favourable safety profile and effectiveness of vedolizumab in this evolving mucosal disease render this an attractive agent in the management of checkpoint inhibitor induced-enterocolitis. However, to delineate its role further, there is a need for larger prospective trials which include a focus on optimal dosing schedules and impact on cancer outcomes.

Although our study did not set out to define side effects associated with the different checkpoint inhibitor-induced colitis treatments, we believe this is a particularly important metric of treatment success. Reassuringly, most data suggest that the beneficial anticancer effect of checkpoint inhibitor therapy is not negated in patients treated with immunosuppressive agents.[8,37,39,55-57] However, there are some data indicating that the anticancer efficacy may be compromised in patients treated with corticosteroids. In melanoma patients developing autoimmune hypophysitis (another well-recognised immune-mediated complication of checkpoint inhibitor therapy) following ipilimumb treatment, overall survival was reduced in patients treated with high-dose corticosteroids compared to those treated with low-dose corticosteroids.[58] Similarly, PD-L1-treated non-small cell lung cancer patients had reduced overall and progression free survival if they were taking corticosteroids immediately prior to checkpoint inhibitor initiation, as compared to patients not exposed to corticosteroids.[59] This study was a retrospective analysis, and so it could be argued that patients requiring corticosteroids at baseline might have had an increased burden of comorbidity and reduced performance status as a potentially important confounding issue for survival. In addition to their potential impact on checkpoint inhibitor efficacy, it is also important to consider other potential side effects of immunosuppressive therapy in cancer patients treated with checkpoint inhibitors.

Five studies reported safety outcomes in corticosteroid monotherapy, including no 'major adverse events' in 16 corticosteroid-treated patients,[40] corticosteroid-induced diabetes mellitus in a cohort of 12 treated patients,[60] adrenal insufficiency (n = 5), hyperglycaemia (n = 4), musculoskeletal issues (n = 3), volume overload (n = 2), hypertension, psychosis, insomnia and clostridium difficile colitis of 109 treated patients,[23] hyperglycaemia, labile mood and vaginal candidiasis,[40] and one study reporting infectious colitis in 2 patients alongside the other commonly documented corticosteroid complications in 23 corticosteroid-treated patients.[30]

Six studies reported safety outcomes in the context of infliximab [10,25,36-38,40] across 171 infliximab-treated patients. Of 36 infliximab-treated corticosteroid refractory patients, Harding et al describe hypersensitivity reactions in two and a fungal pneumonia in one patient.[36] In another study with 17 corticosteroid refractory patients receiving infliximab, infection occurred in 10 episodes, prompting antibiotic therapy in 9, including two cases of Pneumocystis jirovecii pneumonia.[25] An infusion reaction after the second dose of infliximab was reported.[37] Three studies report an absence of 'serious' or 'major' adverse effects.[10,38,40] It is worth highlighting the challenges of extrapolating the infection risk incurred by infliximab in this context, given the additive effect of corticosteroids.

In relation to vedolizumab, one study noted an absence of adverse events.[44] The 2018 vedolizumab Abu-Sbeih et al study, which included patients from the cohort in their most recent series, describes one patient who developed a skin rash and another with diffuse joint pain after one dose leading to discontinuation.[53]

While our study focused on the most widely used agents currently used to treat checkpoint inhibitor-induced colitis, other therapies such as 5-aminosalicylic acid (5-ASA), calcineurin inhibitors and mycophenolate mofetil (MMF) have been described, albeit with relatively sparse data.[13,19-22,49,50] The success of 5-ASA therapy has been variable,[49,50] but given these agents have a lower cost and toxicity profile, prospective data on the value of 5-ASA intervention would be welcome.

This study has some important limitations. Meta-analyses of observational studies are prone to biases and confounding factors that are inherent in the original studies. Notably, we observed a significant degree of heterogeneity between studies, which may be partly explained by differences in their inclusion criteria. For example, many studies included patients with any gastrointestinal symptom,[14,22,25,27,35,37,41,60-62] while others were more stringent and only included patients exhibiting at least CTCAE grade 2[40,63,64] or 3[23,34] diarrhoea, endoscopic and/or histological evidence of

inflammation,[16,33,42,44,65-67] patients requiring corticosteroids[24,30] or having some response to immunosuppressive therapy.[68]

Moreover, there was marked variation between studies in how treatment response was recorded and the time points of perceived disease resolution. Although these studies employed pragmatic endpoints of treatment success that are likely to be clinically relevant in real world datasets, the lack of standardisation of definitions across the different studies is a weakness of this review, and likely an important source of the observed heterogeneity. For example, Mitome et al[22] considered an 'improvement in symptoms' to correspond to a response to corticosteroids, while Marthey et al[15] used 'complete clinical remission' as their endpoint. This may explain the discrepancy in response rates of 100% and 37% respectively. Other potential sources of heterogeneity include differences in corticosteroid regimens, immunotherapy exposure and the baseline characteristics of the study population (especially around disease extent and severity of mucosal injury).

Of note, apart from melanoma and lung cancer it was not possible to evaluate the impact of other cancers, although clearly this is an important consideration for future studies.

Finally, in the subgroup analysis we included some studies where not all the study group belonged to the covariate being analysed. It may be argued that this may 'dilute' the true effect size, but reassuringly when we removed these studies and only analysed those that exclusively reported patients with melanoma, or a particular checkpoint inhibitor regimen there were no considerable differences in the response rate seen (data not shown).

In conclusion, administration of anti-inflammatory therapy with corticosteroids, infliximab and vedolizumab, are effective in inducing a favourable clinical response in patients with checkpoint inhibitor-induced enterocolitis. Checkpoint inhibitor regimen and cancer type influenced the magnitude of response to corticosteroid therapy. Responses to infliximab and vedolizumab were especially favourable, challenging current management paradigms.

These data emphasise the need for high-quality, prospective comparator studies to inform optimal management strategies for this emerging clinical problem.

ACKNOWLEDGEMENTS

Declaration of personal interest: HI, SB: Nil. MAS: reports personal fees from Takeda, personal fees from Janssen, personal fees from MSD, personal fees from Falk, outside the submitted work. HAS: Nil. YW: reports consulting work with Tillotts Pharma, outside the submitted work. NJT: reports personal fees from Allergans PLC (GI Development Programs), personal fees from Viscera Labs (IBS), personal fees from IM Health Sciences (FD), personal fees from Napo Pharmaceutical (IBS), personal fees from Outpost Medicine (IBS), personal fees from Progenity Inc San Diego (capsule SIBO), personal fees from Allakos (gastric eosinophilic disease), personal fees from Samsung Bioepis (IBD), personal fees from Synergy (IBS), personal fees from Takeda (gastroparesis), personal fees from Theravance (gastroparesis), grants and personal fees from Vis-cera USA (IBS), grants from Commonwealth Diagnostics (International) Inc (IBS), nonfinancial support from HVN National Science Challenge NZ (IBS), grants and personal fees from GI therapies (constipation), personal fees from Cadila Pharmaceuticals (CME), personal fees from Planet Innovation (Gas capsule), personal fees from Danone (Probiotic), personal fees from Pfizer (IBS), personal fees from Dr. Reddy's Laboratories (Webinar), personal fees from Arlyx (IBS), personal fees from Sanofi (Probiotic), outside the submitted work; In addition, Dr. Tal-ley has a patent Biomarkers of IBS licensed, a patent Licensing Questionnaires Talley Bowel Disease Questionnaires licensed to Mayo/Talley, a patent Nestec European Patent licensed, a patent Singapore Provisional Patent "Microbiota Modulation Of BDNF Tissue Repair Path-way" issued, and a patent Nepean Dyspepsia Index licensed to Talley copyright and Commit-tees: Australian Medical Council (AMC) [Council Member]; Australian Telehealth Integration Programme; MBS Review Taskforce; NHMRC Principal Committee (Research Committee) Asia Pacific Association of Medical Journal Editors. Boards: GESA Board Member, Sax Institute, Committees of the Presidents of Medical Colleges. Community group: Advisory Board, IFFGD (International Foundation for Functional GI Disorders). Miscellaneous: Avant Foundation (judging of research grants). Editorial: Medical Journal of Australia (Editor in Chief), Up to Date (Section Editor), Precision and Future Medicine, Sungkyunkwan University School of Medicine, South Korea. MJ: Nil. NP: Served as a speaker for Allergan, Falk, Janssen, Tillotts and Takeda a consultant and/or an advisory board member for AbbVie, Allergan, Debiopharm International, Ferring and Vifor Pharma. Has received personal fees as a speaker for Allergan, Bristol-Myers Squibb, Falk, Janssen, Tillotts and Takeda, and as a consultant and/or an advisory board member for AbbVie, Allergan, Celgene, Ferring and Vifor Pharma.

Infrastructure support for this research was provided by the NIHR Imperial Biomedical Research Centre (BRC). NP is funded through the Wellcome trust.

AUTHORSHIP

Guarantor of the article: Hajir Ibraheim.

Author contributions: Hajir Ibraheim—study design, literature search, data collection, data interpretation, figures, writing. Samantha Baillie—literature search, data interpretation, figures, writing. Nick Powell—study design, data interpretation, figures, writing. Mark Samaan—literature search, data collection, data interpretation, writing. Nicholas Talley—data interpretation, writing. Michael Jones—data interpretation, figures, writing. Hamzah Abu-Sbeih—data interpretation, writing. Yinghong Wang—data interpretation, writing. All authors approve the final version of the manuscript.

ORCID

Hajir Ibraheim https://orcid.org/0000-0002-0563-2547
Mark A. Samaan https://orcid.org/0000-0002-4057-9200
Yinghong Wang https://orcid.org/0000-0002-5148-6130
Nicholas J. Talley https://orcid.org/0000-0003-2537-3092
Nick Powell https://orcid.org/0000-0003-3231-6950

REFERENCES

1. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389:67–76.
2. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803–1813.
3. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372:311–319.
4. Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol*. 2015;16:257–265. Clinical Trial, Phase II Multicenter Study Research Support, Non-U.S. Gov't.
5. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373:23–34.
6. Zhang B, Wu Q, Zhou YL, Guo X, Ge J, Fu J. Immune-related adverse events from combination immunotherapy in cancer patients: a comprehensive meta-analysis of randomized controlled trials. *Int Immunopharmacol*. 2018;63:292–298.
7. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377:1345–1356.
8. Schadendorf D, Wolchok JD, Stephen Hodi F, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials. *J Clin Oncol*. 2017;35:3807–3814.
9. Abu-Sbeih H, Ali FS, Luo W, Qiao W, Raju GS, Wang Y. Importance of endoscopic and histological evaluation in the management of immune checkpoint inhibitor-induced colitis. *J Immunother Cancer*. 2018;6:95.
10. Foppen MHG, Rozeman EA, van Wilpe S, et al. Immune checkpoint inhibition-related colitis: symptoms, endoscopic features, histology and response to management. *ESMO Open*. 2018;3:e000278.
11. Gonzalez RS, Salaria SN, Bohannon CD, Huber AR, Feely MM, Shi C. PD-1 inhibitor gastroenterocolitis: case series and appraisal of 'immunomodulatory gastroenterocolitis'. *Histopathology*. 2017;70:558–567.
12. Wang Y, Abu-Sbeih H, Mao E, et al. Immune-checkpoint inhibitor-induced diarrhea and colitis in patients with advanced malignancies: retrospective review at MD Anderson. *J Immunother Cancer*. 2018;6:37.
13. Hillock NT, Heard S, Kichenadasse G, Hill CL, Andrews J. Infliximab for ipilimumab-induced colitis: a series of 13 patients. *Asia Pac J Clin Oncol*. 2017;13:e284–e290.
14. Bamias G, Delladetsima I, Perdiki M, et al. Immunological characteristics of colitis associated with Anti-CTLA-4 antibody therapy. *Cancer Invest*. 2017;35:443–455.
15. Marthey L, Mateus C, Mussini C, et al. Cancer immunotherapy with anti-CTLA-4 monoclonal antibodies induces an inflammatory bowel disease. *J Crohns Colitis*. 2016;10:395–401.
16. Verschuren EC, van den Eertwegh AJ, Wonders J, et al. Clinical endoscopic and histologic characteristics of ipilimumab-associated colitis. *Clin Gastroenterol Hepatol*. 2016;14:836–842.
17. Collins M, Soularue E, Marthey L, Carbonnel F. Management of patients with immune checkpoint inhibitor-induced enterocolitis: a systematic review. *Clin Gastroenterol Hepatol*. 2020;18:1393–1403.e1.
18. Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Delphi technique. *Institute of Health Economics*. 2012.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
21. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. *Stat Med*. 1995;14:395–411.
22. Mitome N, Saito H, Shibata Y, et al. Clinical, endoscopic and histologic features of lung cancer patients with programmed cell death protein 1 (PD-1) inhibitor-associated diarrhea and colitis. [Japanese] *Japanese Journal of Lung Cancer*. 2018;58:262–270.
23. Wang DY, Mooradian MJ, Kim D, et al. Clinical characterization of colitis arising from anti-PD-1 based therapy. *OncoImmunology*. 2019;8:e1524695.
24. Nahar KJ, Rawson RV, Sandanayake N, et al. Clinicopathologic characteristics of immune colitis in melanoma patients treated with combination ipilimumab and anti-PD1 (IPI1PD1) and PD1 monotherapy. *Ann Oncol*. 2019;30:v552.
25. Spain L, Clark J, Au L, et al. Infliximab use in immune-related diarrhoea/colitis (IRD/C). *Gut*. 2018;67:A64–A65.
26. Cochrane Handbook for Systematic Reviews of Interventions. https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm. Accessed May 10, 2020.
27. Rastogi P, Sultan M, Charabaty AJ, Atkins MB, Mattar MC. Ipilimumab associated colitis: an IpiColitis case series at MedStar Georgetown University Hospital. *World J Gastroenterol*. 2015;21:4373–4378.
28. Hughes MS, Zheng H, Zubiri L, et al. Colitis after checkpoint blockade: a retrospective cohort study of melanoma patients requiring admission for symptom control. *Cancer Med*. 2019;8:4986–4999.
29. Collins M, Michot JM, Danlos FX, et al. Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies. *Ann Oncol*. 2017;28:2860–2865.
30. De Felice KM, Gupta A, Rakshit S, et al. Ipilimumab-induced colitis in patients with metastatic melanoma. *Melanoma Res*. 2015;25:321–327.
31. Sidhu M, Mersaides A, Liniker E, et al. Infliximab for the treatment of ipilimumab (anti CTLA-4) and nivolumab/pembrolizumab (anti-PD-1) associated colitis. *J Gastroenterol Hepatol*. 2016;30:139.
32. Salgado AC, Campo M, Giobbie-Hurder A, et al. Management of immune-mediated diarrhea and the impact of infliximab on outcome. *Journal for Immunotherapy of Cancer Conference: 31st Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer, SITC*. 2016;4.
33. Hughes MS, Molina GE, Chen ST, et al. Budesonide treatment for microscopic colitis from immune checkpoint inhibitors. *J Immunother Cancer*. 2019;7:292.
34. Mir R, May Shaw H, Kuhan H, et al. Cumulative corticosteroid exposure in patients experiencing checkpoint inhibitor toxicity. *J Clin Oncol*. 2017;35:e21010.
35. O'Connor A, Marples M, Mulatero C, Hamlin J, Ford AC. Ipilimumab-induced colitis: Experience from a tertiary referral center. *Therap Adv Gastroenterol*. 2016;9:457–462.
36. Harding JJ, Callahan M, Postow M, et al. Infliximab (infliximab) for ipilimumab (IPI)-induced colitis in melanoma patients (pts). *Pigment Cell Melanoma Res*. 2012;25:862.
37. Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol*. 2015;33:3193–3198.
38. Lesage C, Longvert C, Prey S, et al. Incidence and clinical impact of anti-TNFalpha treatment of severe immune checkpoint inhibitor-induced colitis in advanced melanoma: the Mecolit survey. *J Immunother*. 2019;42:175–179.
39. Arriola E, Wheater M, Karydis I, Thomas G, Ottensmeier C. Infliximab for IPILIMUMAB-related colitis-letter. *Clin Cancer Res*. 2015;21:5642–5643.
40. Jain A, Lipson EJ, Sharfman WH, Brant SR, Lazarev MG. Colonic ulcerations may predict steroid-refractory course in patients with

ipilimumab-mediated enterocolitis. *World J Gastroenterol*. 2017;23:2023–2028.
41. Franklin C, Rooms I, Fiedler M, et al. Cytomegalovirus reactivation in patients with refractory checkpoint inhibitor-induced colitis. *Eur J Cancer*. 2017;86:248–256.
42. Kim J, Shia J, Schattner MA, et al. Anti-PD-1 induced colitis: a case series of 25 patients. *Gastroenterology*. 2017;152:S811.
43. Abu-Sbeih H, Ali FS, Wang X, et al. Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor-induced colitis. *J Immunother Cancer*. 2019;7:93.
44. Bergqvist V, Hertervig E, Gedeon P, et al. Vedolizumab treatment for immune checkpoint inhibitor-induced enterocolitis. *Cancer Immunol Immunother*. 2017;66:581–592.
45. Harris J, Faleck D. P086 effectiveness of vedolizumab in patients with refractory immunotherapy-related colitis: a case series. *Gastroenterology*. 2020;158:S119.
46. Truelove SC, Witts L. Cortisone in ulcerative colitis. *BMJ*. 1955;2:1041–1048.
47. Lennard-Jones J, Ritchie JK, Hilder W, Spicer CC. Assessment of severity in colitis: a preliminary study. *Gut*. 1975;16:579–584.
48. Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*. 2001;121:255–260.
49. Weber J, Thompson JA, Hamid O, et al. A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clin Cancer Res*. 2009;15:5591–5598. Clinical Trial, Phase II; Comparative Study; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't.
50. Ibraheim H, Green M, Papa S, Powell N. Topical beclometasone dipropionate in the management of immune checkpoint inhibitor-induced microscopic colitis. *BMJ Case Rep*. 2019;12:e226481.
51. Haanen J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv119–iv142.
52. Bertha M, Bellaguara E, Kuzel T, Hanauer S. Checkpoint inhibitor-induced colitis: a new type of inflammatory bowel disease? *ACG Case Rep J*. 2017;4:e112.
53. Abu-Sbeih H, Ali FS, Alsaadi D, et al. Outcomes of vedolizumab therapy in patients with immune checkpoint inhibitor-induced colitis: a multi-center study. *J Immunother Cancer*. 2018;6:142. Multicenter Study.
54. Wang DY, Ye F, Zhao S, Johnson DB. Incidence of immune checkpoint inhibitor-related colitis in solid tumor patients: a systematic review and meta-analysis. *OncoImmunology*. 2017;6:e1344805.
55. Barbee MS, Ogunniyi A, Horvat TZ, Dang T-O. Current status and future directions of the immune checkpoint inhibitors ipilimumab, pembrolizumab, and nivolumab in oncology. *Ann Pharmacother*. 2015;49:907–937.
56. Attia P, Phan GQ, Maker AV, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti–cytotoxic T-lymphocyte antigen-4. *J Clin Oncol*. 2005;23:6043–6053.
57. Garant A, Guilbault C, Ekmekjian T, Greenwald Z, Murgoi P, Vuong T. Concomitant use of corticosteroids and immune checkpoint inhibitors in patients with hematologic or solid neoplasms: a systematic review. *Crit Rev Oncol Hematol*. 2017;120:86–92.
58. Faje AT, Lawrence D, Flaherty K, et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. *Cancer*. 2018;124:3706–3714.
59. Ferrara R, Lai WV, Hendriks L, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non–small-cell lung cancer. *J Clin Oncol*. 2018;36:2872–2878.
60. So AC, Board RE. Real-world experience with pembrolizumab toxicities in advanced melanoma patients: a single-center experience in the UK. *Melanoma Manag*. 2018;5:MMT05.
61. Siakavellas SI, Bamias G, Delladetsima I, et al. Ipilimumab-induced colitis: Clinical, endoscopic, and histological characteristics. *J Crohns Colitis*. 2016;10:S386.
62. Iafolla MAJ, Pond GR, McWhirter E. Retrospective analysis of ipilimumab-induced diarrhea and/or colitis: a single centre review. *J Clin Oncol*. 2017;35:e21064.
63. Miyahara K, Noda T, Ito Y, et al. An investigation of nine patients with gastrointestinal immune-related adverse events caused by immune checkpoint inhibitors. *Digestion*. 2020;101:60–65.
64. Arai M, Taida T, Fan MM, Imai C, Tawada A, Takiguchi Y. Evaluation of diarrhea as immune-related adverse event by colonoscopy. *Ann Oncol*. 2018;29:VII56.
65. Yutsudo K, Tanaka A, Komaki Y, et al. The efficacy of early treatment in immune checkpoint inhibitor-related colitis: clinical outcomes in a retrospective case series. *Am J Gastroenterol*. 2019;114:S29.
66. Canete F, Manosa M, Lobaton T, et al. Nivolumab-induced immune-mediated colitis: an ulcerative colitis look-alike—report of new cases and review of the literature. *Int J Colorectal Dis*. 2019;34:861–865.
67. Herlihy JD, Beasley S, Simmelink A, et al. Flexible sigmoidoscopy rather than colonoscopy is adequate for the diagnosis of ipilimumab-associated colitis. *South Med J*. 2019;112:154–158.
68. Zhang ML, Neyaz A, Patil D, Chen J, Dougan M, Deshpande V. Immune-related adverse events in the gastrointestinal tract: diagnostic utility of upper gastrointestinal biopsies. *Histopathology*. 2020;76:233–243.

How to cite this article: Ibraheim H, Baillie S, Samaan MA, et al. Systematic review with meta-analysis: effectiveness of anti-inflammatory therapy in immune checkpoint inhibitor-induced enterocolitis. *Aliment Pharmacol Ther*. 2020;52:1432–1452. https://doi.org/10.1111/apt.15998

APPENDIX A

Search strategy

PubMed

(immune checkpoint inhibit* OR immune checkpoint block* OR "immunotherapy" OR "ipilimumab"[MeSH Terms] OR "nivolumab"[MeSH Terms] OR "pembrolizumab"[Supplementary Concept] OR "atezolizumab"[Supplementary Concept] OR "avelumab"[SupplementaryConcept]OR"durvalumab"[Supplementary Concept] OR "cemiplimab"[Supplementary Concept])) OR ("anti-PD-1"[Title/Abstract] OR "anti PD-L1"[Title/Abstract] OR "anti ctla-4"[Title/Abstract])))) AND (colitis[Title/Abstract] OR enterocolitis[Title/Abstract] OR diarrh*[Title/Abstract] OR "immune- related adverse event*"[Title/Abstract] OR "immune- related toxicit*"[Title/Abstract] OR gastrointestinal[Title/Abstract]) AND "humans"[MeSH Terms]

APPENDIX B

Risk of bias

TABLE A1 Risk of bias evaluated with the quality appraisal tool by Moga et al which uses 18 criteria (✓ criterion met; x criterion not met)

Study	Study Objective	Study population					Intervention and co-intervention		Outcome measures			Statistical analysis	Results and conclusions					Competing interest and source of support	Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Zhang et al, 2020	✓	✓	x	✓	✓	x	x	✓	x	✓	✓	✓	✓	✓	x	x	✓	x	11
Yutsudo et al, 2019	✓	x	x	✓	✓	x	x	✓	x	✓	✓	✓	✓	✓	x	x	x	x	9
Wang et al, 2019	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	x	x	x	x	✓	✓	13
Verschuren et al, 2016	✓	✓	x	✓	✓	x	✓	✓	✓	✓	✓	✓	x	x	x	x	✓	✓	12
Spain et al, 2018	✓	x	x	✓	✓	x	x	✓	x	✓	✓	✓	x	x	x	x	✓	x	8
So et al, 2018	✓	x	x	✓	✓	x	x	✓	x	✓	✓	✓	✓	✓	x	x	✓	✓	11
Sidhu et al, 2016	✓	x	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	x	x	x	x	✓	x	11
Siakavellas et al, 2016	✓	✓	x	✓	✓	x	x	✓	✓	✓	✓	✓	x	x	x	x	✓	x	10
Salgado et al, 2016	✓	x	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	x	✓	x	✓	x	12
Rastogi et al, 2015	✓	✓	x	✓	✓	x	x	✓	✓	✓	✓	✓	x	x	x	x	✓	x	10
O'Connor et al, 2016	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	✓	x	x	x	x	✓	✓	11
Nahar et al, 2019	✓	x	x	✓	✓	x	x	✓	x	x	x	x	x	x	x	x	✓	x	5
Miyahara et al, 2020	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	x	x	x	x	✓	✓	13
Mitome et al, 2018	✓	✓	x	✓	✓	x	x	✓	✓	✓	✓	✓	x	x	x	✓	✓	✓	12
Mir et al, 2017	✓	x	x	✓	✓	x	x	✓	✓	✓	✓	✓	x	x	x	x	✓	x	9
Marthey et al, 2016	✓	✓	✓	✓	✓	x	✓	✓	x	✓	✓	✓	x	x	x	x	✓	✓	12
Lesage et al, 2019	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	17
Kim et al, 2017	✓	✓	x	✓	✓	x	x	✓	x	✓	✓	✓	x	x	x	x	✓	x	9

(Continues)

TABLE A1 Continued

Study	Study Objective	Study population					Intervention and co-intervention		Outcome measures			Statistical analysis	Results and conclusions					Competing interest and source of support	Total
Jain et al, 2017	✓	✓	x	✓	✓	x	x	✓	✓	✓	✓	✓	✓	x	x	✓	✓	x	12
Iafolla et al, 2017	✓	X	x	✓	✓	x	x	✓	x	x	x	x	x	x	x	x	✓	x	5
Hughes et al(II), 2019	✓	✓	x	✓	✓	x	x	✓	✓	✓	✓	✓	✓	✓	x	x	✓	✓	13
Hughes et al, 2019	✓	✓	x	✓	✓	x	x	✓	✓	✓	✓	✓	✓	x	x	x	✓	✓	12
Horvat et al, 2015	✓	✓	x	✓	✓	x	x	✓	✓	✓	✓	✓	✓	✓	x	x	✓	✓	13
Hillock et al, 2016	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	x	x	✓	x	14
Herlihiy et al, 2019	✓	✓	x	✓	✓	x	✓	✓	✓	✓	x	x	x	x	x	x	✓	✓	10
Harris et al, 2020	✓	✓	x	✓	✓	x	x	✓	✓	✓	✓	✓	✓	✓	x	x	✓	x	12
Harding et al, 2012	✓	x	x	✓	✓	x	✓	✓	✓	✓	✓	✓	x	✓	x	✓	✓	x	12
Gonzalez et al, 2017	✓	✓	✓	✓	✓	x	x	✓	x	✓	✓	✓	✓	✓	x	x	✓	✓	13
Franklin et al, 2017	✓	✓	X	✓	✓	x	x	✓	✓	✓	✓	✓	x	x	x	x	✓	✓	11
Foppen et al, 2018	✓	✓	x	✓	✓	x	✓	✓	x	✓	✓	✓	x	x	x	x	✓	✓	11
De Felice et al, 2015	✓	✓	x	✓	✓	x	✓	✓	✓	✓	✓	✓	x	x	x	✓	✓	✓	13
Collins et al, 2017	✓	✓	✓	✓	✓	x	x	✓	✓	✓	✓	✓	✓	x	x	x	✓	✓	13
Canete et al, 2019	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	x	x	x	x	✓	✓	13
Bergqvist et al, 2017	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	x	x	✓	✓	✓	14
Bamias et al, 2017	✓	✓	x	✓	✓	x	x	✓	x	✓	✓	✓	x	x	x	x	✓	✓	10

(Continues)

TABLE A1 Continued

Study	Study Objective	Study population					Intervention and co-intervention		Outcome measures			Statistical analysis	Results and conclusions					Competing interest and source of support	Total
Arriola et al, 2015	✓	x	x	x	x	x	x	✓	x	✓	✓	✓	x	x	✓	x	✓	✓	8
Arai et al, 2018	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	x	x	x	✓	x	12
Abu Sbei et al, 2018	✓	✓	x	✓	✓	x	x	✓	✓	✓	✓	✓	✓	x	✓	x	✓	✓	13
Abu Sbeih et al, 2019	✓	✓	x	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	15

Note: **Study Objective** 1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction or methods section? **Study population** 2. Are the characteristics of the participants included in the study described? 3. Were the cases collected in more than one centre? 4. Are the eligibility criteria (inclusion and exclusion criteria) to enter the study explicit and appropriate? 5. Were participants recruited consecutively? 6. Did participants enter the study at a similar point in the disease? **Intervention and co-intervention** 7. Was the intervention clearly described in the study? 8. Were additional interventions (co-interventions) clearly reported in the study? **Outcome measures** 9. Are the outcome measures clearly defined in the introduction or methods section? 10. Were relevant outcomes appropriately measured with objective and/or subjective methods? 11. Were outcomes measured before and after intervention? **Statistical analysis** 12. Were the statistical tests used to assess the relevant outcomes appropriate? **Results and conclusions** 13. Was the length of follow-up reported? 14. Was the loss to follow-up reported? 15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes? 16. Are adverse events reported? 17. Are the conclusions of the study supported by results? **Competing interest and source of support** 18. Are both competing interest and source of support for the study reported?