



# Five-year review of corticosteroid duration and complications in the management of immune checkpoint inhibitor-related diarrhoea and colitis in advanced melanoma

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## ABSTRACT

**Background** Immune-related diarrhoea/colitis (ir-D/C) is a common adverse event of immune checkpoint inhibitor (ICI) therapy. Guidelines recommend corticosteroid (CS) treatment; however, the average treatment duration for ir-D/C remains poorly defined.

**Methods** All advanced melanoma patients treated with ICI therapy at the Royal Marsden Hospital between 2011 and 2016 were reviewed to identify ir-D/C cases alongside clinical variables.

**Results** 117 any-grade ir-D/C episodes occurred in 109 (21%) patients out of a total of 519 patients treated (ipilimumab=77 episodes, anti-PD1=17 (nivolumab or pembrolizumab), ipilimumab and nivolumab=23 (ipi+nivo) (seven patients had ir-D/C more than once on different lines of treatment) and  $\geq$  grade 3 ir-D/C occurred most frequently (63/519 patients (12%) vs 29/519 (5%) grade 1, and 25/519 (5%) grade 2). Median onset (days) of all-grade ir-D/C after starting ICI therapy was 41 for ipilimumab (IQR 24 to 59, n=77), 91 for anti-PD1 (IQR 46 to 355, n=17) and 45 for ipi+nivo (IQR 24 to 67, n=23). In 71/117 (61%) patients, ir-D/C episodes were treated with CS (17% grade 2; 79% grade 3/4): 54 being steroid-responsive; 17 being steroid-refractory and received additional anti-tumor necrosis factor (TNF) treatment. Median grade 3 ir-D/C CS duration was similar across treatments, averaging 58 days. Median overall CS duration (days) was longer in the grade 3/4 D/C steroid-refractory group (94 vs 45 days). Infection developed in 11/71 (15%) CS recipients and in 6/17 (35%) anti-TNF recipients. In 65/117 (55%) patients, ir-D/C episodes were investigated with flexible sigmoidoscopy. Of these patients, 38/65 (58%) had macroscopic colitis and 12/65 (18%) had microscopic colitis. The steroid-refractory group had more macroscopic changes, 13/17 (76%), than the steroid-responsive group, 22/41 (54%).

**Conclusion** Rates of grade 3 ir-D/C were higher than reported in clinical trials. The 58-day median duration of CS therapy for grade 3 ir-D/C places a significant number of patients at risk of complications. We demonstrate that microscopic colitis is an important subgroup, advocating biopsies in ir-D/C even with macroscopically normal bowel.

## Key questions

### What is already known about this subject?

► Immune-related diarrhoea and/or colitis (ir-D/C) are among the most common immune-related adverse events associated with immune checkpoint inhibitor therapy. Current treatment algorithms recommend upfront high-dose corticosteroid (CS) administration for patients with an increase of 4 or more stools over baseline or the presence of abdominal pain, mucus or blood. Once symptoms resolve, weaning of steroids is recommended; however, the average total duration of CS for ir-D/C remains poorly defined.

### What does this study add?

► We show that the median duration of CS treatment for grade 3 ir-D/C is 58 days, placing a significant number of patients at risk of iatrogenic complications (most commonly infection and mood changes) and reinforcing the need for steroid-specific supportive care. Additionally, we demonstrate that microscopic colitis is an important subgroup in patients with ir-D/C, and thus advocate for biopsies in patients even with macroscopically normal bowel.

### How might this impact on clinical practice?

► Increased awareness for the need as well as the initiation of steroid-specific supportive care in patients receiving CS therapy for ir-D/C. Performing bowel biopsies in all ir-D/C patients who undergo an endoscopy, regardless of whether the bowel appears macroscopically normal.

## INTRODUCTION

Immune-related diarrhoea and/or colitis (ir-D/C) is among the most common and severe<sup>1</sup> immune-related adverse events (irAEs) associated with immune checkpoint inhibitor (ICI) therapy. Rates of all-grade diarrhoea and colitis attributed to nivolumab and pembrolizumab in patients with advanced melanoma range from 10% to 20% and 1% to



4%, respectively.<sup>2-5</sup> These figures are much higher for the combination of ipilimumab and nivolumab (ipi+nivo), with all-grade diarrhoea impacting 44% and all-grade colitis 12%.<sup>4</sup> Interestingly, ir-D/C may be an independent predictor for improved survival, regardless of subsequent treatment requirements.<sup>6</sup> There is less data on rates of ir-D/C outside of clinical trials. ICIs now have European Medicines Agency approval for several different cancers, including non-small cell lung cancer. Therefore, the impact of immune-related toxicities on health services is significant and will continue to rise as more patients are treated.

Current treatment algorithms recommend upfront high-dose corticosteroid (CS) administration for grade 2 or greater symptoms, as well as for persistent grade 1 cases.<sup>7</sup> Once symptoms resolve, weaning of steroids is recommended over approximately 4 to 6 weeks; however, the average total duration of CS for ir-D/C remains poorly defined. Courses of high-dose CS render patients susceptible to significant iatrogenic toxicities such as insomnia, mood changes, osteoporotic fractures, diabetes and infection. The risk of infection is compounded by the use of additional immunomodulatory agents such as anti-tumor necrosis factor alpha (TNF) antibodies in steroid-refractory cases of ir-D/C.<sup>8</sup>

We sought to review the clinical features and the management of all advanced melanoma patients under the care of our institution who received approved ICI regimens and who were treated for ir-D/C. In particular, we aimed to describe the duration of CS received, differences between steroid-responsive and refractory cases, side effects attributed to the use of CS and features seen at endoscopy.

## METHODS

All patients treated at the Royal Marsden Hospital with ipilimumab, nivolumab (administered every 2 weeks), pembrolizumab (administered every 3 weeks) and the combination of ipi+nivo for advanced melanoma between 2011 and 2016 were identified from pharmacy records. Patients recruited to published clinical trials (Checkmate-067, Checkmate-037 and Checkmate-066) as

well as ipilimumab and pembrolizumab expanded access programmes were also included.

Electronic medical records were reviewed and the patients treated for ir-D/C were identified, even if management of ir-D/C occurred in an external institution. Demographic information and the worst grade of ir-D/C by CTCAE version 4.0 was recorded for each episode, as were the duration of CS use and administration of anti-TNF and other immune-modulators (IMM). Patients who received an anti-TNF antibody or other IMM were labelled as steroid-refractory (as opposed to steroid-responsive). CS toxicities (new onset or worsening hyperglycaemia (ie, in the setting of pre-existing diabetes), hypertension, osteoporosis and related fractures, mood change, insomnia and infection) attributed to the course of treatment from the ir-D/C episode were recorded.

Patients who had a flexible sigmoidoscopy (FS) were labelled as having either macroscopic±microscopic changes (macro changes), microscopic changes alone (micro changes) or no changes (normal) based on review of endoscopy and histology reports. Descriptive statistics were used, with median and IQR reported. The unpaired Student's *t*-test was used to compare groups. The logrank test was used to analyse Kaplan-Meier survival analyses.

## RESULTS

During the study period, 519 immune checkpoint therapy treatment courses were administered in 492 patients: 285/519 (54%) treatment courses were ipilimumab monotherapy, 166/519 (31%) were nivolumab or pembrolizumab (grouped as anti-PD1 in this study), and 68/519 (13%) were combination ipi+nivo. In total, the incidence of ir-D/C in the study population was 117/519 (22%). **Table 1** provides further details about the frequency and severity of ir-D/C by treatment type. Although only 68/519 (13%) of the patients during the study period received ipi+nivo, they comprised 19/61 (31%) of the grade 3 diarrhoea episodes.

In total, there were 117 episodes of ir-D/C of any grade occurring in 109 patients. A total of 77/117 ir-D/C episodes (66%) were due to ipilimumab monotherapy, 17/117 (14%) to anti-PD-1 monotherapy and 23/117

**Table 1** Frequency and severity of immune-related toxicity by type of immune checkpoint therapy during study period

	All	Ipilimumab	Anti-PD1	Ipi+nivo
Total number treated	519	285	166	68
Number with ir-D/C (%)	117/519 (22)	77/285 (27)	17/166 (10)	23/68 (34)
Grade 1	29/519 (5)	25/285 (9)	3/166 (2)	1/68 (2)
Grade 2	25/519 (5)	17/285 (6)	5/166 (3)	3/68 (4)
Grade 3	61/519 (11)	33/285 (11)	9/166 (5)	19/68 (28)
Grade 4	1/519 (<1)	1/285 (<1)	0	0
Grade 5	1/519 (<1)	1/285 (<1)	0	0

ipi+nivo, ipilimumab and nivolumab; ir-D/C, immune-related diarrhoea/colitis.

**Table 2** Study patient characteristics (n=117 episodes of D/C in n=109 patients)

	Ipilimumab (n=77 episodes)		Anti-PD1 (n=17 episodes)		Combination ipi+nivo (n=23 episodes)	
	N	%	N	%	N	%
Age (mean)	58	–	56	–	58	–
Male	43/77	56	11/17	65	8/23	35
Cutaneous melanoma	55/77	71	13/17	76	18/23	78
BRAF mutation	27/77	35	9/17	53	13/23	57
Performance status*						
0/1	70/77	91	14/17	82	22/23	96
≥2	7/77	9	3/17	18	1/23	4
Stage*						
M1a	11/77	14	5/17	29	4/23	17
M1b	11/77	14	4/17	24	7/23	30
M1c	55/77	71	8/17	47	12/23	52
Clinical trial participant†	7/77	9	3/17	18	7/23	30
First-line therapy	29/77	38	3/17	18	18/23	78
Median number cycles‡	3	–	14	–	3	–
Objective response (CR or PR)	9/77	12	7/17	41	12/23	52
Stopped due to ir-D/C	31/77	40	8/17	47	13/23	57
Stopped due to other ir-toxicity	2/77	3	0/17	0	2/23	9

The listed numbers (N) refer to immune checkpoint inhibitor D/C episodes (some patients had >1 line of treatment during which they developed gastrointestinal toxicity on >1 line of treatment).

\*At start of ICI therapy.

†Expanded access programmes are not included in this.

‡For ipi+nivo this includes maintenance nivolumab.

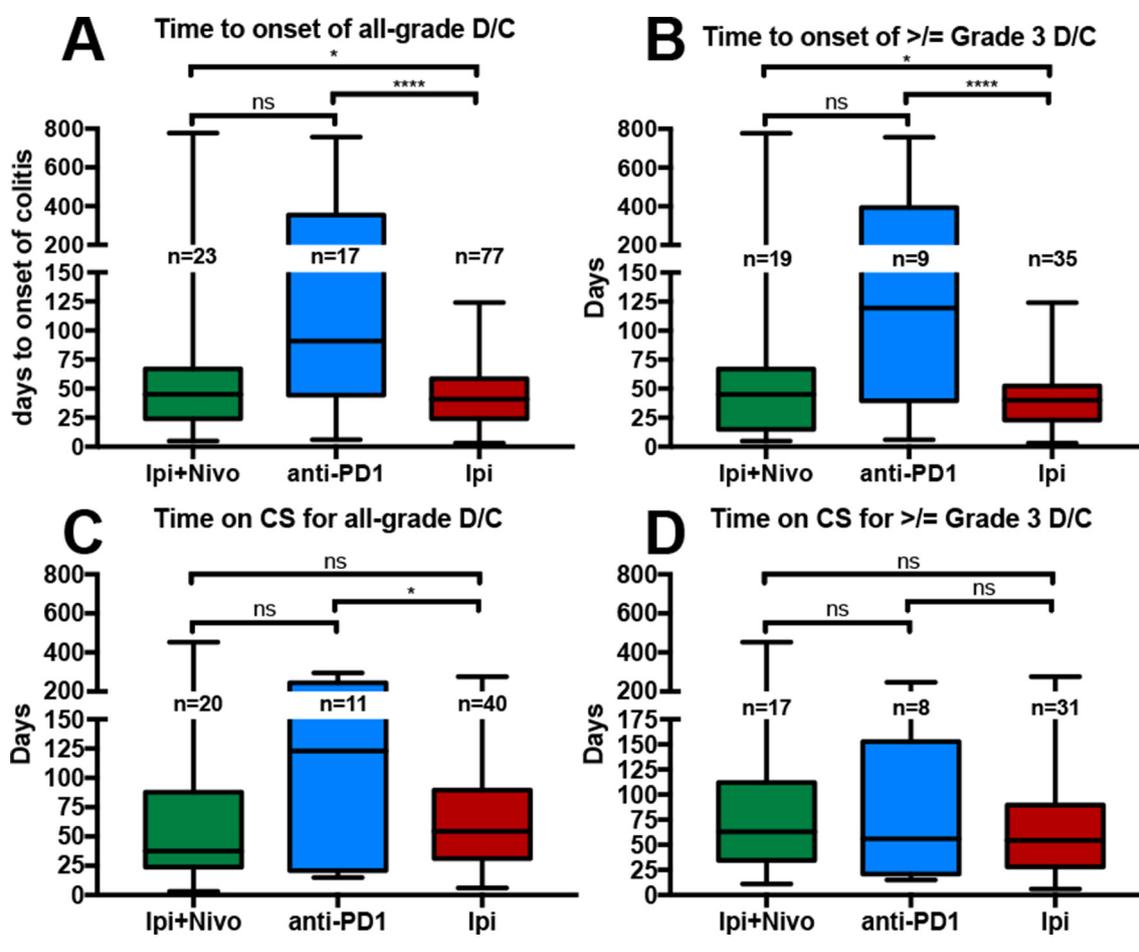
CR, complete response; ipi+nivo, ipilimumab and nivolumab; ir, immune-related; ir-D/C, immune-related diarrhoea/colitis; PR, partial response.

(20%) to ipi+nivo. Seven patients (6%) developed ir-D/C episodes on multiple ICI regimens: 6 patients developed ir-D/C on two subsequent ICI regimens (anti-PD1, ipilimumab) and one patient developed ir-D/C on all three regimens. **Table 2** summarises the clinical characteristics of all ir-D/C episodes by treatment type. There were higher numbers of clinical trial patients in the ipi+nivo group (30% compared with 9% for ipilimumab and 18% for anti-PD1), and most of these patients (78%) received first-line treatment, in contrast to patients in the ipilimumab and anti-PD1 groups (38% and 18%, respectively). Of the 117 episodes of ir-D/C, 29/117 (25%) were grade 1, 25/117 (21%) grade 2 and 63/117 (54%) ≥grade 3 (**table 1**). Of those patients who developed ir-D/C, treatment was stopped in 31/77 (40%) of ipilimumab patients (the majority being patients on second-line therapy), in 8/17 (47%) of patients taking anti-PD1 monotherapy, and in 13/23 (57%) of patients treated with combination ipi+nivo therapy (the majority being on first-line therapy) (**table 2**).

Fifty-four per cent of patients were admitted to hospital for management of ir-D/C, with a median length of stay of 9 days (IQR 4 to 16). The onset of all-grade ir-D/C occurred at a median of 41 days from the commencement of ipilimumab (IQR 24 to 59; n=77) 91 days from

anti-PD1 (IQR 46 to 355; n=17) and 45 days for ipi+nivo (IQR 24 to 67; n=23) (**figure 1A**). The onset of ≥grade 3 ir-D/C occurred at a similar median time to all-grade ir-D/C, except for the anti-PD1 group, which had an extended median of 120 days (IQR 40 to 294; n=9) (**figure 1B**) (ipilimumab 40 days (IQR 23 to 53; n=19), ipi+nivo 45 days (IQR 15 to 67; n=35)).

In total, 71/117 (61%) ir-D/C episodes were treated with CS treatment, with 12/71 (17%) of these being for grade 2 ir-D/C and 56/71 (79%) for grade 3/4 ir-D/C (**table 3**). The median CS treatment duration for all-grade ir-D/C was: ipilimumab 54.5 days (range 31 to 90), anti-PD1 123 days (range 21 to 244) and ipi+nivo 37.5 days (range 24 to 88) (**figure 1C**). For grade ≥3 ir-D/C, median duration of CS treatment was similar across all treatment types: ipilimumab 55 days (range 6 to 276), anti-PD1 56 days (range 15 to 247) and ipi+nivo 63 days (range 11 to 453) (**figure 1D**). Seventeen patients (24% of the 71 requiring CS treatment) were steroid-refractory and required anti-TNF alpha therapy (**table 3**), 8 (47%) of whom received ipi+nivo. The majority of these (16/17, 94%) were of grade 3/4 severity. There was no difference in the median time to development of ir-D/C in the steroid-responsive and steroid-refractory groups (unpaired Student's t-test p=0.9) (**table 3**). Median



**Figure 1** (A) Time to onset of D/C across all grades. The anti-PD1 group consist of nivolumab or pembrolizumab. Unpaired Student's *t*-test  $p = 0.1$  (ipi+nivo vs anti-PD1),  $p = 0.01$  (ipi+nivo vs ipi),  $p < 0.0001$  (anti-PD1 vs ipi). (B) Time to onset of  $\geq$  grade 3 D/C. Unpaired Student's *t*-test  $p = 0.1$  (ipi+nivo vs anti-PD1),  $p = 0.045$  (ipi+nivo vs ipi),  $p < 0.0001$  (anti-PD1 vs ipi). (C) Time on corticosteroid treatment for all grade D/C. Unpaired Student's *t*-test  $p = 0.1$  (ipi+nivo vs anti-PD1),  $p = 1$  (ipi+nivo vs ipi),  $p = 0.04$  (anti-PD1 vs ipi). (D) Time on corticosteroid treatment for  $\geq$  grade 3 D/C. Unpaired Student's *t*-test  $p = 0.8$  (ipi+nivo vs anti-PD1),  $p = 0.2$  (ipi+nivo vs ipi),  $p = 0.5$  (anti-PD1 vs ipi). Abbreviations: CS, corticosteroids; D/C, diarrhoea and colitis; ICI, immune checkpoint inhibitor therapy; Ipi+Nivo, ipilimumab and nivolumab.

duration of CS was greater in the steroid-refractory group in grade 3/4 cases (94 vs 45 days) (unpaired Student's *t*-test  $p=0.001$ ) (table 3) with too few cases of grade 2 severity to reliably comment. Notably, the median time to progressive disease was longer in the steroid-refractory group (170 vs 101 days) (table 3). Kaplan-Meier survival analyses revealed no statistically significant differences in progression-free survival in patients with grade 3 ir-D/C who had received anti-TNF alpha antibodies (figure 2).

Side effects of CS were inconsistently recorded; however, at least 15% of patients receiving CS developed an infection, including 35% of patients receiving anti-TNF agents. All these cases required antibiotics. Two cases of *Pneumocystis jirovecii* pneumonia were noted, both in patients who had received an anti-TNF alpha agent and who were on antibiotic prophylaxis during their steroid wean (mean total CS time 33 weeks). Table 4 summarises the documented CS toxicities.

Investigation of ir-D/C with flexible endoscopy was undertaken in 65/117 ir-D/C episodes (56%). Among this group, 38/65 (58%) had a macroscopic abnormality consistent with colitis and 12/65 (18%) had a microscopic abnormality only (ie, identified on histological assessment). A greater proportion of patients in the ipilimumab and ipi+nivo groups had macroscopic changes consistent with colitis (63% and 61%, respectively) compared with anti-PD-1 (29%) (table 5). A greater proportion of cases with macroscopic changes at endoscopy were noted in the steroid-refractory group (76% vs 54%) (table 3). One-quarter of patients with macroscopic colitis were also noted to have duodenitis; however, the timing of upper endoscopy in relation to lower endoscopy was highly variable. Initial stool cultures were negative for all 37 patients (%) who had stool microscopy sent at our institution. However, following initial steroid treatment for ir-D/C,

**Table 3** Steroid-responsive and steroid-refractory patients

	Steroid-refractory (n=17)		Steroid-responsive (n=54)	
	n (range)	%	n (range)	%
Ipilimumab	8/17	47	32/54	59
Anti-PD1	1/17	6	10/54	19
Ipi+nivo	8/17	47	12/54	22
Days from start of ICI to onset of D/C	43	–	45	–
Grade 2	1/17	6	11/54	20
Grade 3/4	16/17	94	40/54	74
Median days from start of D/C to steroids (range)	5	–	4	–
Days from start steroids to anti-TNF	14 (1–100)	–	NA	–
Median duration CS		–		–
Grade 2	160 (160–160)	–	48 (6–295)	–
Grade 3/4	94 (24–453)	–	45 (9–204)	–
Additional IMM (eg, vedolizumab)	1	6	0	0
Macro abnormality on scope	13/17	76	22/41	54
Micro abnormality on scope	1/17	6	9/41	22
Normal scope	2/17	12	7/41	17
Unknown scope finding	1/17	6	3/41	7
Number of patients who PD on Rx	12/17	71	42/54	78
Median days to progressive disease	170	–	101	–

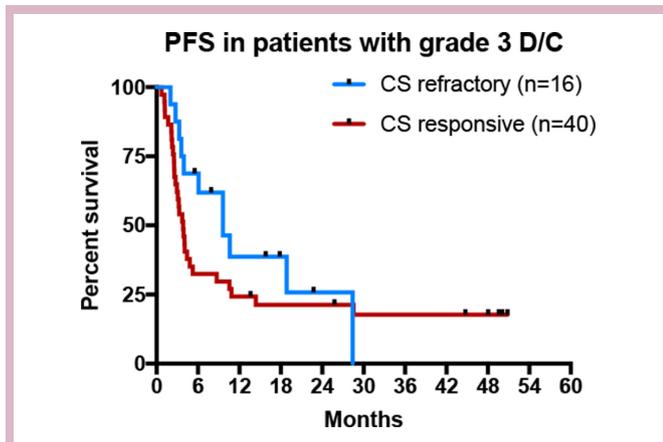
CS, corticosteroid; D/C, diarrhoea/colitis; ICI, immune checkpoint inhibitor; IMM, immune-modulators; ipi+nivo, ipilimumab and nivolumab; PD, progressive disease; Rx, treatment.

one patient developed *Clostridium difficile* while two had *Cytomegalovirus* (CMV; biopsy positive).

**DISCUSSION**

We present clinical information on a large, single-institution series of patients with immune-related ir-D/C due to ipilimumab, anti-PD1 or ipi+nivo, the majority

of whom (85%) were managed outside of clinical trials. Where several studies have focussed on the assessment of patients with macroscopic changes consistent with colitis on endoscopy, we included any patient who was managed for ir-D/C. Such real-world practice data is useful for this common irAE, given that around half of patients experiencing this toxicity cease treatment as a consequence.<sup>9 10</sup>



**Figure 2** Anti-TNF therapy does not worsen PFA. Progression free survival in grade 3 D/C between steroid refractory and responsive groups. Logrank test  $p = 0.2$  (Hazard Ratio 0.7; 95% CI 0.4–1.3). Abbreviations: CS, corticosteroids; D/C, diarrhoea/colitis; PFS, progression free survival.

**Table 4** Steroid-related side effects (n=71/117 ir-D/C episodes (61%) required steroids)

	Number	% (of n=71)	Infliximab-requiring (n=17)	% (of n=17)
Diabetes	7	10		
Hypertension	2	3		
Osteoporosis	1	1		
AVN	0	0		
Mood change	12	17		
Psych referral	4	6		
Insomnia	7	10		
Infection	11	15	6	35
PJP infection	2	3	2	12
Antibiotics required	11	15	6	35

AVN, avascular necrosis; PJP, *Pneumocystis jiroveci* pneumonia.

**Table 5** Flexible sigmoidoscopy (FS) findings (n=65/117 ir-D/C episodes (56%))

	N (%)	Ipi* (%)	anti-PD-1* (%)	Ipi +nivo* (%)	Had CS (%)	Median CS duration days	On CS at 3 months (%)	Received anti-TNF (%)	Duodenitis on gastroscopy (%)
<b>Macroscopic abnormality</b> (±micro)	38/65 (58)	24/38 (63)	2/7 (29)	11/18 (61)	35/38 (92)	64	14/38 (37)	13/38 (34)	6/23 (26)
<b>Microscopic abnormality only</b> (ie, no macro change)	12/65 (18)	6/38 (16)	3/7 (43)	3/18 (17)	10/12 (83)	74	4/12 (33)	1/12 (8)	2/8 (25)
Normal FS	9/65 (14)	5/38 (13)	2/7 (29)	2/18 (11)	9/9 (100)	47	2/9 (22)	2/9 (22)	2/6 (33)
Unknown FS findings	6/65 (9)	3/38 (8)	0/7 (0)	2/18 (11)	5/6 (83)	n/a	n/a	1/6 (17)	n/a

\*Proportion of patients who had a lower endoscopy.

CS, corticosteroids; ipi, ipilimumab; ipi+nivo, ipilimumab and nivolumab.

The differences in demographic characteristics between the ipilimumab, anti-PD1 and ipi+nivo treatment groups (eg, in BRAF mutation rate, male gender) are most likely attributable to the small number of cases in each subgroup, rather than underlying biology. The rates of grade 3 ir-D/C in our cohort were higher than those reported in the clinical trial literature, most notably for ipi+nivo (28% vs 9% for diarrhoea and 8% for colitis).<sup>4</sup> In a series of 64 patients treated with ipi+nivo as part of an expanded access programme, Shoushtari *et al* reported a rate of 20% for grade 3/4 colitis with a rate of 14% for grade 2. Our rate of 5% for grade 3 ir-D/C due to anti-PD-1 is also higher than reported in clinical trials (<1% to 3%).<sup>11</sup> The time to onset of ir-D/C (all grades) was reasonably consistent with other reports (5 to 7 weeks for ipi+nivo<sup>12</sup>; 7 to 14 weeks for anti-PD1.<sup>13 14</sup> Steroid-responsive and steroid-refractory patients did not differ in their time to onset (43 and 45 days, respectively) suggesting this is not likely to be a useful distinguishing feature.

CS were prescribed in 56/60 grade 3/4 ir-D/C episodes (93%) and in 12/25 grade 2 ir-D/C episodes (48%), with a median duration of 8 to 9 weeks for those experiencing ir-D/C of grade 3/4 severity. Worst 'grade' of ir-D/C was captured, and therefore some cases may have improved spontaneously without the need for CS treatment or admission. One-quarter were steroid-refractory, a figure consistent with the 22% reported by Shoushtari *et al* in their series.<sup>15</sup> Of note, 8/20 patients (40%) with ipi+nivo ir-D/C who were prescribed CS were steroid-refractory. In this group, earlier use of additional IMM such as anti-TNF alpha antibodies may be helpful. Of note, a retrospective series from MD Anderson showed that early anti-TNF alpha treatment with CS resulted in a shorter time to symptom resolution and steroid titration compared with treatment with CS alone, suggesting that early anti-TNF alpha treatment should be considered in appropriate patients.<sup>16</sup> Our study incorporates patients managed at an early timepoint in the use of ICI and recommendations have changed in recent years, perhaps accounting for this difference.

There is a significant impact on the health system for the management of ir-D/C. Over half of the affected patients (54%) were admitted for inpatient management with intravenous steroids, observation or to obtain an endoscopy, with a median length of stay of 9 days. Infections and mood disturbance occurred in 15% and 17% of patients on CS, respectively, but are likely to be under-reported due to the retrospective nature of this study. Supportive care for patients on steroids should become a core part of management, including education regarding common side effects (such as insomnia, documented to occur in at least 10% of our cohort).

Macroscopic colitis appeared to be most frequent in anti-CTLA-4-containing regimens. In a series of 16 patients with ipilimumab-mediated colitis,<sup>17</sup> 7/8 patients with colonic ulcers received infliximab as opposed to 2/6 without. We demonstrated a preponderance of

macroscopic colitis in the steroid-refractory group but clinicians are probably biased to the use of anti-TNF agents in this setting. Interestingly, patients with macroscopic and microscopic colitis had similar median steroid durations (64 and 74 days, respectively) but patients with a completely normal flexible endoscopy had a shorter median duration (47 days). This highlights the fact that a normal endoscopy may enable clinicians to more rapidly taper steroids.

Four categories of gastrointestinal irAEs have been recognised: acute colitis, microscopic colitis, upper gastrointestinal tract inflammation and pseudo-obstruction.<sup>18</sup> Our data also suggest that 18% of patients have microscopic colitis and this may be underestimated as not all patients with a normal macroscopic FS underwent biopsy. Thus, series that only include cases with endoscopic changes will miss this important subgroup.<sup>19</sup> ICI-related microscopic colitis has been found to require more aggressive treatment and result in increased morbidity and mortality in comparison to non-ICI-related microscopic colitis, highlighting the importance of this diagnosis.<sup>20</sup>

There are several limitations to acknowledge. First, this was a retrospective study with a small sample size with bias inherent to historical decision-making and accuracy of documentation. Second, while 85% of our patients were not involved in clinical trials, they received specialist cancer centre management potentially limiting applicability of our findings to all settings. The cohort captured reflects management practice prior to the wide availability of consensus guidelines for management and this may account for some apparent inconsistencies with current guidelines in the use of steroids and timing of infliximab. Third, use of FS does not cover the whole bowel and there was heterogeneity in practitioners and their reports. Nonetheless, this study provides useful information as a basis for comparison and real-world data that may help inform prospective trials of management for ir-D/C.

## CONCLUSION

Our study highlights that rates of grade 3 ir-D/C for anti-PD1 and combination ipi+nivo are higher than those reported in clinical trials and that the rate of steroid-refractory cases is significant, especially for ipi+nivo-treated patients. A 58-day median duration of CS for grade 3 ir-D/C places a significant number of patients at risk of iatrogenic complications, especially infection and mood changes, reinforcing the need for steroid-specific supportive care. We also demonstrate that microscopic colitis is an important subgroup, advocating biopsies even with macroscopically normal bowel in patients with ir-D/C (this has the added benefit of excluding CMV-related diarrhoea as well). The management of ir-D/C has a significant impact on health services due to high rates of inpatient admission and thus further research to predict susceptibility to ir-D/C and to refine and triage our approach to management is paramount.

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