BSG endorsed guidance of the management of immune checkpoint inhibitor induced enterocolitis

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Abstract

Immune checkpoint inhibitors (ICPis) are a novel class of cancer treatment that have improved outcomes for a subset of cancer patients. They work by antagonizing important inhibitory immune pathways, thereby augmenting immune mediated anti-tumour responses. However, immune activation is not cancer specific and often results in activation of immune cells in non-cancer tissues resulting in off-target immune-mediated injury and organ dysfunction. Diarrhoea and gastrointestinal tract inflammation are common and sometimes serious side effects of ICPi therapy. Prompt recognition of gastrointestinal toxicity and in many cases rapid institution of anti-inflammatory and/or biological therapy is required to reverse these complications. Optimal management of organ specific complications frequently requires engagement with gastroenterologists to deliver improved outcomes for patients developing ICPi-induced enterocolitis. In this British Society of Gastroenterology (BSG) endorsed guidance document we have developed a consensus framework for the investigation and management of ICPi-induced enterocolitis.

Summary of recommendations

Statement 1

A diagnosis of ICPi- enterocolitis should be considered in all patients presenting with gastrointestinal symptoms, and who have received at least one dose of an ICPi, even following ICPi cessation (*OE Level 1, 100% agreement*).

Statement 2

Gastroenterologists should be aware of the CTCAE tool, which is the standard way of reporting diarrhoea/colitis severity in the oncology community and in ICPi clinical trials. However, it should not be used exclusively to triage investigation and treatment decisions (*OE Level 3, 88% agreement*).

Statement 3

We recommend urgent flexible sigmoidoscopy and biopsy (even in the presence of macroscopically normal mucosa) as first line investigation (*OE Level 2, 100% agreement*).

Statement 4

Ileocolonoscopy should be considered in patients with treatment refractory or persistent diarrhoea, especially in patients with normal sigmoidoscopy (including histology) (*OE Level 3, 94% agreement*).

Statement 5

OGD (and biopsy) should be considered in patients with upper GI symptoms, or persistent diarrhoea, especially in patients with normal ileocolonoscopy (including histology) (*OE Level 4, 100% agreement*).

Statement 6

In patients presenting with GI symptoms, initial investigations should also include stool cultures (and C.difficile toxin testing) and blood tests (full blood count, renal function and electrolytes, CRP, liver profile and thyroid function) (*OE Level 3, 100% agreement*).

Statement 7

In patients with ICPi-enterocolitis, we recommend early administration of oral corticosteroids (40mg prednisolone or equivalent), or in moderate to severe disease, IV corticosteroids (methylprednisolone 1mg/kg or equivalent) (*OE Level 3, 93% agreement*).

Statement 8

In the absence of response to oral corticosteroids within 3-5 days, we recommend escalation to IV corticosteroids (methylprednisolone 1mg/kg or equivalent) (*OE Level 3, 81% agreement*).

Statement 9

We recommend that patients receiving IV corticosteroids or those with high risk endoscopic features (mucosal ulceration, extensive colitis), should undergo pre-biologic screening in anticipation of treatment escalation to infliximab. This should not delay treatment initiation (*OE Level 4, 100% agreement*).

Statement 10

Early escalation to infliximab should be considered in patients with mucosal ulceration or extensive colitis (*OE Level 3*, *100% agreement*).

Statement 11

In the absence of response to high dose intravenous corticosteroids (within 3 days) we recommend immediate switch to infliximab (*OE Level 3, 94% agreement*).

Statement 12

Treatment options for patients not responding to infliximab (up to 3 doses), include vedolizumab, calcineurin inhibitors and mycophenolate mofetil (*OE level 4, 100% agreement*).

Statement 13

Pre-existing IBD should not be considered a contraindication to ICPi therapy. We suggest prompt assessment of disease activity prior to starting ICPi and regular monitoring, with rapid investigation and treatment escalation in the event of relapse (*OE Level 4, 100% agreement*).

Background and methodology

This (BSG) endorsed guidance document was commissioned to provide direction on the management of immune check point inhibitor (ICPi) -induced enterocolitis. Currently, there is insufficient evidence for a formal BSG guideline, although as additional clinical data emerges, we anticipate replacing this guidance document with more comprehensive guidelines in due course.

The group comprised a multi-disciplinary working group, which included representation from experts in gastroenterology (NP, TR, RS, JL, BH, OB, PI, MS, PP, HI) oncology (MG, SP, ST, JL, NY, LS) histopathology (MG), dietetics (LE), and nursing (NH) and also included patient representation. The topics for review were agreed via electronic correspondence, and allocated to the writing group (NP, RS, OB, MS, BH, TR, PP, HI, SP, LS, MG, LE), who were then responsible for conducting a literature search to identify original research papers, conference abstracts and existing guidelines, through to August 2018. The evidence was appraised for quality of evidence and was summarised. The working group had a face to face meeting to evaluate the evidence and agree on a set of provisional guidance statements that would then enter the anonymised electronic voting round. In important areas where a substantial gap in evidence was identified, research questions were proposed; these are included at the end of the manuscript. Sixteen voting members (individuals from the working group who felt qualified to vote on guidance statements) voted on their level of agreement with each statement using a five-point likert scale (one=strongly agree, five=strongly disagree). Free text spaces were provided alongside each statement, to allow for comments or suggestions, which were particularly encouraged from voters who disagreed. Statements were only included if there was ≥80% agreement, otherwise there was an opportunity to review and modify the statement and enter into another round of electronic voting. If after two rounds there was continuing disagreement, if 50% of the group agreed and <20% disagreed, statements were accepted. The level of supporting evidence for each statement was assessed using the approach of the Oxford Centre for Evidence-Based Medicine[1]. This process took place over the course of 13 months.

Introduction

Immune checkpoint inhibitors (ICPi) have transformed therapeutic paradigms in oncology. These monoclonal antibodies (mAbs) selectively antagonize checkpoint molecules, such as CTLA-4 or PD-1, thereby preventing their inhibitory signals to the immune system, which results in sustained immune activation and augmented anti-tumour immunity. Their benefit was first demonstrated in advanced melanoma, where patients treated with ipilimumab (anti-CTLA-4 mAb) and chemotherapy had a significant overall survival benefit compared to patients treated with chemotherapy alone[2]. Subsequently, landmark studies reporting favourable outcomes for additional mAbs targeting PD-1 (nivolumab and pembrolizumab) or its ligand PD-L1 (atezolizumab, durvalumab, avelumab) have led to approval for use in a wide variety of advanced cancers, including melanoma, non-small cell lung cancer (NSCLC), renal cell and urothelial cancers, as well as for adjuvant therapy (i.e. treatment after surgical resection of all disease) in melanoma (Table 1)[3-10]. Survival rates in key trials are detailed in Table 2. ICPi therapy offers durable clinical benefit beyond cessation of treatment[11]. However, the novel mechanism of action of immune activation has led to recognition of a new repertoire of immune-related adverse-events (irAEs) with potential to affect any organ system. Common sites of toxicity include the skin, gut, liver and endocrine system[12]. Consequently, oncology engagement with different specialists has become commonplace to achieve optimal, organ-specific management of irAEs.

Gastrointestinal manifestations of ICPi treatment

To standardise reporting of treatment related adverse events in cancer patients, the US National Cancer Institute developed a symptom-based classification system called the Common Terminology Criteria for Adverse Events (CTCAE)[13]. This instrument defines adverse events and includes a severity grading score for different symptom complexes across different organ systems. The CTCAE grading system is the most commonly used tool to identify and grade irAEs and includes a severity scoring framework for diarrhoea (defined as a “disorder characterized by frequent and watery bowel

movements") and colitis (defined as a "disorder characterized by inflammation of the colon"). Some limitations of the CTCAE grading system will be discussed in detail below, but challenges include overlap, redundancy and interchangeability of these definitions. For instance, many patients with diarrhoea are diagnosed with ICPi-induced colitis without objective confirmation (macroscopic, histologic or biochemical) of colonic inflammation. In this document we have used an operational definition of ICPi- induced enterocolitis to denote inflammation of the gastrointestinal tract, that is typically associated with gastrointestinal symptoms, most notably diarrhoea.

Gastrointestinal toxicities following treatment with ICPi are common and include nausea, vomiting, diarrhoea, abdominal pain and rectal bleeding[14-18]. Systemic features, such as fever, pyrexia, fatigue and anorexia are also common[19-21], which may be independent of GI inflammation. Accordingly, it is uncertain whether enterocolitis concomitantly presenting with significant systemic features, such as pyrexia and tachycardia is necessarily linked to more severe intestinal inflammation, as would be inferred in patients with acute severe ulcerative colitis (UC).

Incidence

Diarrhoea is the second most common irAE (after skin manifestations) but is most common reason for ICPi interruption and permanent discontinuation[22,23]. Risk is influenced by the immunotherapy regimen with diarrhoea occurring most frequently in patients prescribed anti-CTLA-4- containing regimens, and is more common in anti-CTLA-4/anti-PD-1 combination therapy, compared to anti-PD-1 monotherapy (**Figure 1**). Colonic perforation reportedly occurs in 1-3% of patients, most commonly in anti-CTLA-4 containing regimens[14,24-27]. There is some evidence that risk of ICPi-enterocolitis may be linked to tumour type, with higher rates reported in melanoma patients[28,29].

Time to onset and resolution

The kinetics of diarrhoea presentation are regimen- dependent with slightly accelerated presentation observed in anti-CTLA-4 containing regimens [20,30] as compared with anti-PD-1 treatments (**Figure 2**).

The median time to onset of diarrhoea is around four to seven weeks after starting treatment (**Figure 2**), however, there is a broad range, with some patients experiencing symptoms as early as one week post ICPi exposure, and others developing symptoms months or even years after cessation of therapy[31-33]. Accordingly, the diagnosis of ICPi-enterocolitis should be considered in all patients presenting with gastrointestinal symptoms who have received at least one dose of ICPi, even following long periods after drug cessation.

There is also a large variation in the time to resolution, which is contributed by factors including ICPi regimen, whether ICPi was interrupted after development of diarrhoea/colitis, and how quickly anti-inflammatory treatment was instigated[33-35]. Pooled trial data demonstrates resolution of ICPi-induced diarrhoea within one to five weeks on average, although many patients experience protracted symptoms for many months[19,22,30], with case reports even describing resolution after years[36].

Statement 1
A diagnosis of ICPi- enterocolitis should be considered in all patients presenting with gastrointestinal symptoms, and who have received at least one dose of an ICPi, even following ICPi cessation (*OE Level 1, 100% agreement*).

Assessing disease severity and the Common Terminology Criteria for Adverse Events

Whilst the CTCAE has been helpful for standardising the recognition and reporting of drug- induced adverse events, it has important limitations. Diarrhoea and colitis are considered completely separate entities and definitions are crude. Within clinical trials, and in current clinical practice, patients with ICPi-enterocolitis do not always undergo diagnostic tests to confirm or exclude intestinal inflammation and, accordingly “colitis”, “enterocolitis” and “diarrhoea” are often used interchangeably. Current management algorithms recommend treatment with corticosteroids irrespective of whether endoscopic, histologic or biomarker-defined evidence of inflammation is available[37]. A comparison of the CTCAE grade for diarrhoea with IBD severity scoring tools (**Table 3**), demonstrates that CTCAE

grading may underestimate colitis severity. For example, a patient with a stool frequency of six times a day above baseline would only be graded at the mild end of the CTCAE scoring scale (grade two) yet would be graded at the severe end of the spectrum for an equivalent UC presentation using the stool frequency sub-component of the Mayo score[38]. In addition, the severity of endoscopic appearances, including the presence of deep ulceration or extensive colitis has no impact on the CTCAE grading for colitis or diarrhoea. Recent data indicates that diarrhoea frequency is a poor indicator of endoscopic severity of disease and treatment response[14,15]. In a retrospective case series by Foppen et al. (n=92), the proportion of patients with either grade two or grade three diarrhoea that required treatment escalation with anti-TNF was almost identical (68% vs 67%) [14]. In immunotherapy clinical trials and within oncology clinical practice, the CTCAE grading system is widely adopted for recording and communicating adverse events. Familiarity with the CTCAE grades will be advantageous for gastroenterologists engaging with the oncology community, but an understanding of its limitations in risk stratifying ICPi-enterocolitis is important.

Statement 2
Gastroenterologists should be aware of the CTCAE tool, which is the standard way of reporting diarrhoea/colitis severity in the oncology community and in ICPi clinical trials. However, it should not be used exclusively to triage investigation and treatment decisions (*OE Level 3, 88% agreement*).

Diagnostic Tests

Many patients with ICPi-induced diarrhoea, and especially those with perceived milder disease (e.g. CTCAE grade one or two), are treated without diagnostic tests. Furthermore, the value of diagnostic tests, including endoscopy, histology and non-invasive markers of inflammation has not been prospectively established.

Lower Gastrointestinal Endoscopy

Patients with ICPi-induced diarrhoea exhibit a range of endoscopic findings including normal looking mucosa, erythema, oedema, loss of vascular pattern, inflammatory exudate, friability, erosions and

ulcers[14,15,18,39,40]. ICPi-induced enterocolitis typically affects the left colon with 3-8% of patients having isolated right sided disease[14,15] (**Figure 3**). The first major endoscopy study reported findings from 88 endoscopies (62 colonoscopies and 26 flexible sigmoidoscopies). In this study 84% of patients had macroscopic evidence of colitis and 68% had extensive colitis. Normal endoscopic appearances were present in 16%[14]. The largest study to date from Abu-Sbeih et al. reported endoscopic findings in 182 patients presenting with ICPi-induced diarrhoea, the majority of whom were investigated by colonoscopy (n=135). Extensive colitis was present in fewer patients (31%), with isolated right sided disease again uncommonly seen. Macroscopically normal colonic mucosa was observed in 37%[15]. Although these two important endoscopy studies report broadly similar results, discrepancies between them could be accounted for by the relatively low numbers of patients studied, different thresholds for endoscopy referral between centres, or differences in the patient population studied. For instance, in the Foppen et al. study[14], where endoscopic changes were more severe (e.g. more extensive colitis and fewer patients with normal appearances), a greater number of patients were exposed to anti-CTLA-4- containing regimens in comparison with the Abu-Sbeih et al. study (78% vs 63%) [15].

Abu-Sbeih et al additionally classified endoscopic findings as “Crohn’s disease(CD)-like” (deep serpiginous ulceration with normal looking surrounding mucosa) or “UC-like” (continuous erythema with loss of vascular pattern and mucosal bleeding). Most patients were categorized as UC-like (76/115, 66%). The Foppen study additionally calculated Mayo endoscopy sub-scores and the van der Heide score (an uncommonly used endoscopic scoring system for UC). Mayo endoscopic subscores indicated that most patients had mild/moderate disease (Mayo 0: 16%, 1: 52%, 2: 29% and 3: 3%). Importantly, both studies reported a similar frequency of ulceration (around 30%) which was associated with corticosteroid refractoriness. Both studies reported a poor correlation between frequency of diarrhoea and endoscopic findings, while rectal bleeding correlated with both endoscopic severity and ulceration. Accordingly, rectal bleeding in this population could be considered a potential important marker for more severe disease. Some studies have only reported findings in

patients with overt evidence of macroscopic mucosal inflammation[39,41], which makes the true prevalence of particular features difficult to calculate. Furthermore, there are inherent biases associated with retrospective studies including variation in endoscopic assessment (flexible sigmoidoscopy vs colonoscopy vs ileocolonosocpy). A recent systematic review of 226 patients with ICPi-induced colitis diagnosed at lower GI endoscopy, found that nearly all patients had left sided colonic involvement (>98%), and that isolated right sided disease was uncommon[42]. Although the data comprised 61 studies, the majority were low sample size case series (fewer than ten patients). Furthermore, the two largest and highest quality endoscopy studies performed to date (Foppen et al. and Abu-Sbeih et al.) were not included in the analysis. Taken altogether, current data indicates that sigmoidoscopy should be adequate to capture diagnosis in most patients.

From a pragmatic perspective there are other advantages to recommending flexible sigmoidoscopy as a first line diagnostic test. Flexible sigmoidoscopy is lower cost, doesn't require oral bowel preparation and is less time consuming, so is likely to be more accessible as a rapid access option. Although isolated right sided disease is uncommon, a potential limitation of flexible sigmoidoscopy as a first line investigation is underestimation of disease severity. In the Foppen et al. study 24% of patients with extensive colitis had more severe signs of inflammation in the right hemicolon[14]. Accordingly, subsequent investigation with ileocolonoscopy and/or upper GI endoscopy (see below) may be required in patients with unexplained, refractory symptoms or in treatment resistance.

There is a significant subset of patients with ICPi-induced diarrhoea with a normal macroscopic appearance of the colon, but with microscopic features of inflammation detected during histological evaluation. This has been reported to occur in up to 37% of patients[14,21,39,43]. It is uncertain if this represents a less aggressive phenotype, partially treated disease, or whether macroscopic changes have recently resolved or are about to emerge in these patients. Although histological findings reminiscent of conventional collagenous or lymphocytic colitis are recognised[44-46], it is also common to see hallmark features of ICPi-induced colitis, such as neutrophilic inflammation and crypt abscess formation, even in the presence of a macroscopically normal colon[45,47].

The incidence and distribution of small intestinal inflammation and how this relates to GI symptoms caused by ICPi is uncertain. In the Abu-Sbeih et al. study, ileal involvement was reported in 6% of patients with colitis, although this may be an underestimate of the incidence of small bowel disease given it was unclear what proportion of patients underwent ileal intubation. Also, this study did not report whether isolated ileitis occurred in any of the cohort, or whether this occurred concomitantly with colitis[15]. A study from the same group reporting endoscopy findings in 53 patients found isolated ileal involvement in only one case, consistent with the notion that small bowel involvement may be relatively common in patients with concomitant colitis, but less common as an isolated manifestation[48]. One of the first detailed descriptions of patients with endoscopically confirmed macroscopic intestinal inflammation in patients treated with anti-CTLA-4 monotherapy (n=25), reported terminal ileal involvement in 20% of patients undergoing colonoscopy[39].

There are currently no evidence based thresholds for triggering endoscopic evaluation in patients with ICPi-induced diarrhoea, however, given the poor correlation between symptoms and severity of mucosal injury (see below), flexible sigmoidoscopy should be considered in all patients with persistent diarrhoea irrespective of CTCAE grade. Patients presenting with more severe symptoms should be promptly investigated, especially when high dose systemic corticosteroids are being contemplated.

Prognostic value of endoscopy

As well as confirming diagnosis, endoscopy is a useful tool for risk-stratification and guiding therapeutic strategy. Endoscopic features of colonic ulceration and extensive colitis are associated with corticosteroid- refractory disease and should reduce the threshold for treatment escalation[14,15]. However, these data should be interpreted with some caution. The retrospective nature of the endoscopy studies identifying these prognostic features are inherently prone to bias (and type I error), since clinicians may have made treatment decisions (e.g. escalation to infliximab) based on endoscopic findings, such as mucosal ulceration. In other words, the prognostic features identified were in fact decision drivers, rather than independent predictors. Nevertheless, with currently available evidence

the presence of severe inflammation observed during endoscopy, particularly ulceration, should prompt a low threshold for escalation to infliximab (IFX) in patients not responding to first line treatment (**see management algorithm**).

Statement 3
We recommend urgent flexible sigmoidoscopy and biopsy (even in the presence of macroscopically normal mucosa) as first line investigation (*OE Level 2, 100% agreement*).

Statement 4
Ileocolonoscopy should be considered in patients with treatment refractory or persistent diarrhoea, especially in patients with normal sigmoidoscopy (including histology) *(OE Level 3, 94% agreement*).

Oesophagogastroduodenoscopy (OGD)

The value of OGD in patients with ICPi-enterocolitis is less well understood. In the largest study evaluating 60 ICPi- treated patients with upper GI symptoms (most commonly nausea, vomiting and epigastric pain) 68% had abnormal findings. Non-ulcerative inflammation was the most common finding at OGD (56.7%). Mucosal ulceration was present in 12% and normal appearances were observed in 31.7%[49]. In patients that had both OGD and colonoscopy, just over half had inflammation involving both the upper and lower GI tract[49], echoing findings from an earlier study[14]. In another series, inflammatory changes in the upper GI tract were common in 40 patients with ICPi-induced diarrhoea who underwent OGD and included gastritis (40%) and duodenitis (17.5%). Importantly, even in the absence of macroscopically visible disease, there was a significant burden of microscopic inflammation especially in the duodenum (28%)[50], which most commonly comprised chronic lymphocytic inflammation and/or increased intraepithelial lymphocytes (86%) with villous atrophy present in 71%[50]. The high yield of inflammatory disease observed in the upper GI tract of patients with upper GI symptoms justifies investigation with OGD and biopsy. Although the data are less comprehensive, the high rate of duodenal inflammation and architectural disruption, including villous atrophy may also justify consideration of OGD in patients with persistent diarrhoea, especially in

treatment refractory patients, and individuals with a macroscopically and microscopically normal colon.

Statement 5
OGD (and biopsy) should be considered in patients with upper GI symptoms, or persistent diarrhoea, especially in patients with normal ileocolonoscopy (including histology) (*OE Level 4, 100% agreement*).

Histopathology

The main pathological features seen in ICPi-enterocolitis are summarised in **Table 4** and appear to be similar for both anti-CTLA-4 and anti-PD-1/PD-L1-containing regimens, although appropriately powered studies are lacking [51]. Chronic inflammation in the lamina propria is the most common finding in the colon of patients with ICPi-induced colitis, characterised by a mixed infiltrate of lymphocytes, eosinophils and plasma cells[14,40,41,48,52] (**Figure 4**). Acute inflammation is the next most common feature, which includes ulceration, superficial epithelial or crypt infiltration by neutrophils or neutrophilic crypt abscess formation[14,40,41,48,52]. Increased apoptotic activity within crypt epithelium occurs in up to half of cases. Crypt atrophy and dropout is also reported[52]. A pattern of lymphocytic colitis-like morphology with increased intra-epithelial lymphocytes (IELs) has also been reported in around 10% of cases. It tends to have a reduced acute inflammatory component compared to the more usual pattern of 'active colitis'[52]. Features of chronicity such as prominent basal plasmacytosis and crypt distortion are less common[14]. Discrete, well-formed granulomas are unusual, unless associated with crypt rupture[52]. Collagenous colitis-like morphology has also been reported[40,44,46]. Resection specimens have only rarely been examined, because colectomy is a rare event, but changes include extensive acute severe colitis with transmural inflammation and necrosis, with abrupt transitions between ulcers and normal mucosa [39,53]. Biopsies should be examined for cytomegalovirus (CMV) infection, especially in patients exposed to immunosuppression or with corticosteroid

refractory colitis[52,54]. We recommend that all samples taken in the context of potential ICPi-enterocolitis are marked as 'urgent' and we suggest at least four biopsies are taken.

Cross sectional Imaging

Three retrospective single centre studies have reported the diagnostic value of cross-sectional imaging in ICPi-induced enterocolitis with differing results. Garcia-Neuer *et al.* reported CT findings in 34 patients with metastatic melanoma who had additionally undergone colonoscopy with histologically proven ICPi-induced colitis following treatment with ipilimumab[55]. The most common finding on CT scan was diffuse, pan-colonic circumferential wall thickening, although segmental disease was noted in some patients. CT scan had a sensitivity of 85%, specificity of 75%, positive predictive value of 96% and a negative predictive value of 43% for diagnosis of ICPi-colitis. In another study of 53 patients with ICPi-induced diarrhoea, CT scans performed in the subset of 36 patients with endoscopically confirmed ICPi-induced colitis were only abnormal in 53%. Furthermore, in the ten patients with macroscopically normal endoscopic appearances of the colon, CT scans were reported as showing features of colitis in 10%, with a sensitivity on 53% and a specificity of 78%[48]. A smaller study looking at the utility of radiological diagnosis of irAEs, included eight patients with colitis developing following anti-PD-1 treatment[56]. CT abnormalities were identified in all eight patients, with the most common feature being diffuse bowel wall thickening with contrast enhancement and peritoneal fat infiltration in six out of eight patients, with the remaining two patients exhibiting segmental changes[56]. Although 18F-FDG PET was only performed in two patients with anti-PD-1 induced colitis, both patients showed striking radiotracer uptake in the colon. Taken together these limited data probably indicate that when features of colitis are present on a CT scan then there is a good probability that colitis is present, but that "normal" scans might not necessarily exclude disease. Endoscopy and biopsy should be considered the gold standard investigation for diagnosis. Because this population of patients is likely to undergo relatively frequent cross-sectional imaging as part of their cancer management, any interval imaging should include assessment for features of colitis. CT scanning is also valuable in patients presenting with abdominal pain, or non-specific deterioration (especially if

high-dose corticosteroids are being administered) to exclude intestinal perforation. The value of other imaging modalities, including small intestinal MRI and ultrasound has not been reported. There are no data regarding the diagnostic value of video capsule endoscopy.

Faecal calprotectin and lactoferrin

The use of faecal calprotectin (fcal) in ICPi-induced enterocolitis has been assessed in a number of studies. In a prospective study Brennan et al. found elevated fcal levels during anti-CTLA-4 treatment, associated with loose stool, as early as two weeks after the first dose. Unfortunately, methodological limitations of the study (small sample size and lack of gold standard investigation in a large proportion of included patients) did not allow for the assessment of the prognostic value of early fcal testing [57]. Another study from the MD Anderson Cancer Center investigated faecal lactoferrin concentration in 71 patients with ICPi-induced diarrhoea. A positive faecal lactoferrin result had a sensitivity for detecting macroscopic colitis of 70% and a sensitivity for detecting histological colitis of 90%. A subset of 39 patients was additionally investigated with fcal. In patients with colonic ulceration the mean fcal was 465mcg/g of stool, whereas it was 152mcg/g stool in patients with normal endoscopic features[15]. Mirroring the faecal lactoferrin data, an elevated fcal concentration (>150mcg/g stool) had a sensitivity of 68% for detection of macroscopic evidence of colitis and a sensitivity of 86% for detecting microscopic evidence of inflammation. More data is needed to determine whether fcal can be used to stratify patients according to initial treatment strategy, or as a tool to triage which patients need endoscopic evaluation.

Excluding gastrointestinal infection

Differential diagnoses, including infection, should be considered in the diagnostic work-up of patients with diarrhoea, even when a close temporal relationship to ICPi exposure exists. The incidence of infectious diarrhoea in ICPi-treated patients is low[14,41,58], and even in cases where GI infection has been identified, anti-inflammatory therapy has been needed in addition to anti-microbial therapy to induce symptomatic improvement[14,41,58,59]. *Clostridium difficile* (C.difficile) infection should be

excluded[59], especially in patients who have recently received antibiotics. CMV- associated colitis has been reported following ICPi-therapy, although in most patients this appears to be associated with corticosteroid- resistance and persistent/relapsing symptoms[52,54]. Although there are too few cases to inform evidence-based practice, repeat lower GI endoscopy and biopsy to exclude superadded CMV infection (as well as to re-assess disease severity), should be considered in patients with corticosteroid- resistant disease.

Other investigations

Thyroid function tests may be useful to exclude immune-mediated thyroiditis as a cause for diarrhoea which occurs in up to 8% of ICPi-treated patients[60]. Although the outcome of almost all ICPi-induced thyroid disease is permanent hypothyroidism, patients may initially present with thyrotoxicosis. It is also important to remember that these patients may have received other therapies for their malignancy, prior to receiving immunotherapy which may also lead to GI complications (e.g. radiation colitis, drug- induced colitis). Investigations to exclude other causes of GI symptoms, including bile salt malabsorption and small intestine bacterial overgrowth (SIBO) should probably be reserved for patients with recalcitrant symptoms in the absence of objective evidence of inflammation. Faecal elastase measurement should be considered in patients with steatorrhoea to exclude pancreatic insufficiency resulting from immune-mediated pancreatitis[61,62].

Statement 6
In patients presenting with GI symptoms, initial investigations should also include stool cultures (and C.difficile toxin testing) and blood tests (full blood count, renal function and electrolytes, CRP, liver profile and thyroid function) (*OE Level 3, 100% agreement*).

Management

Treatment goals are rapid reversal of symptoms, restoration of quality of life, avoidance of complications, and where possible and/or appropriate, to enable continuation or re-introduction of immunotherapy. Current management algorithms stratify treatment according to CTCAE grading of

diarrhoea. In patients with low grade diarrhoea, European oncology guidance (ESMO) recommend the use of anti-motility/diarrhoeal agents such as loperamide for symptomatic relief[37]. However, there is a paucity of data on the effectiveness and safety of this approach, or how often patients will subsequently require anti-inflammatory therapy. A retrospective study reported that resolution of symptoms occurred spontaneously in two out of seven patients with CTCAE grade one diarrhoea, or following loperamide or codeine treatment in the remaining five patients[63]. In IBD, anti-motility agents are not recommended and are avoided in severe disease due to the risk of promoting toxic megacolon[64,65]. There are other concerns about solely using symptomatic therapy in patients with CTCAE diarrhoea grade one to two diarrhoea. There is poor concordance between CTCAE diarrhoea grade and the severity of mucosal inflammation observed during endoscopy in ICPi-enterocolitis[14,66], and therefore, there is a potential risk of undertreating some patients with a significant burden of intestinal inflammation or delayed institution of appropriate anti-inflammatory treatment. In this group of patients, anti-motility agents could theoretically mask deteriorating symptoms and/or precipitate toxic megacolon. These concerns again highlight the potential value of definitive diagnostic tests, such as endoscopy. Anti-motility agents could be used with a greater degree of confidence in patients with diarrhoea following exclusion of macroscopic or microscopic inflammation of the GI tract, or in patients with very mild symptoms (e.g. CTCAE grade I diarrhoea of short duration). In patients with persistent and/or deteriorating diarrhoea anti-motility agents should be discouraged unless significant GI inflammation has been objectively excluded.

Corticosteroids

Early initiation of systemic corticosteroids (CS) is the cornerstone of management of ICPi-induced enterocolitis. The rationale for early treatment is that rapid institution of CS (within five days) is likely to lead to a faster resolution of symptoms compared to delayed treatment[35]. The majority of ICPi-treated patients presenting with diarrhoea will require CS. In a real-world dataset from the MD Anderson Cancer Center (n=117 with diarrhoea), 67.5% of patients required CS treatment [16]. In

another real-world cohort study of melanoma patients treated with ipilimumab at the Sloan Memorial Kettering Cancer Center (n=87 with diarrhoea), 57% required CS[67]. ESMO guidance recommend that the CS regimen is determined according to CTCAE grade, although no studies to date have investigated the optimal dose of oral CS in this context. In patients with persistent grade one (>two weeks), or grade two (>3 three days) diarrhoea, oral CS at a starting dose of 0.5mg-1mg/kg of oral prednisolone is used and tapered over at least four weeks [37,68-70]. In historical IBD literature, there is no additional clinical benefit gained in patients with active colitis treated in the out-patient setting in with 60 mg/day of prednisolone, as compared with patients prescribed 40 mg/day. However, CS-related adverse events were significantly more common at the higher dose[71]. Accordingly, it would be reasonable to start prednisolone 0.5mg/kg once daily in all patients with ICPi-induced enterocolitis. Current ESMO guidance suggests escalation to IV CS therapy in patients not responding to oral CS within 72 hours[72]. The definition of steroid refractoriness in this context has not been formally determined and the expectation of rapid resolution of symptoms during initial institution of CS therapy unverified. Although early clinical response to oral prednisolone 40mg OD was observed in historical UC studies[73-76], clinical outcomes were typically reported at later time points. Response rates exceeding 75% have been reported in UC patients treated with CS, including robust end points such as mucosal healing, although the earliest time points at which patients have been evaluated is typically at two weeks post initiation of CS[73-76]. In one of these studies clinical remission was observed in 25% of UC patients following one week of treatment with oral prednisolone 40mg OD[76]. Additional capture of clinical response/clinical remission in UC patients was observed with continued oral CS treatment between week one and two, indicating that there could be merit in persevering with oral CS beyond three days before escalating to IV regimens. As well as switching to IV CS regimens in patients resistant to oral prednisolone, it may also be reasonable to consider immediate institution of high-dose IV CS in patients presenting with severe disease (e.g. CTCAE grade three to four diarrhoea). The optimal IV CS regimen has not been determined, although current oncology management guidelines suggest intravenous methylprednisolone (1mg-2mg/kg)[37], for which there is some published evidence[17,72,77,78].

Other studies have also described the successful use of IV hydrocortisone[79] and dexamethasone [21]. Advantages of methylprednisolone over other CS's include its once daily dosing and low mineralocorticoid activity. There is no evidence regarding whether 1mg/kg or 2mg/kg is more effective or associated with altered risk of side effects. The average UK man now weighs over 80kg, and 2mg/kg dosing of methylprednisolone (160mg) would administer twice the amount of daily corticosteroid used in acute severe ulcerative colitis, which is the most severe form of UC (400mg IV hydrocortisone is equivalent to 80mg IV methylprednisolone- see **Table 5**.) Accordingly, there seems little rationale for using doses in excess of 1mg/kg of methylprednisolone and failure to respond to this regimen should prompt consideration of escalation to alternative therapies. Pre-biologics screening for TB, varicella zoster (VZV) status as well as serology for HIV, hepatitis B/C should be considered in all patients requiring IV CS and could even be justified in all patients starting combination anti-CTLA-4/anti-PD-1 therapy given the high risk of requiring high dose systemic CS or biologic therapy in this subgroup of patients. The results of pre-biologic screening tests should not delay escalation of therapy. Likewise, although there would be insufficient time to institute pre-emptive vaccination in patients unexposed to VZV, knowledge of exposure/immunity status would facilitate prompt recognition of de novo infection and institution of appropriate therapy.

Most patients respond to CS, with a systematic review based on 26 studies spanning a range of immune check point therapies, reporting that CS induced short term remission in 62% of ICPi-diarrhoea patients[80]. Factors predicting CS resistance have not been prospectively identified, but two observational studies indicate that the presence of colonic ulcers, or extensive colitis on endoscopy predict a steroid refractory course and the need to institute biological therapy [14,81]. Patients responding to IV CS within three to five days should be switched to oral CS and tapered over four to eight weeks [17,69,70,72,78], bearing in mind some patients may need an even slower wean[14,15]. Abrupt discontinuation of CS therapy can result in recurrence or worsening of symptoms [82] and/ or Addisonian crises.

Therapy should be escalated in patients not responding to intravenous CS within three days. Currently, the first line escalation option with the most data is the anti-TNF monoclonal antibody IFX [14,18,58,63,83-87], which is associated with faster symptom resolution compared to CS alone[85]. Real world data (n=75) suggests that up to 48% of patients may need IFX[85]. If not already established, flexible sigmoidoscopy should be requested to confirm the diagnosis, establish disease severity and exclude complications (e.g. CMV associated colitis). As discussed above, high risk features identified during endoscopy could be used as a stratification tool to identify patients in whom it would be appropriate to reduce the threshold for escalation to IFX[14,15] (**see managementalgorithm**).

Statement 7
In patients with ICPi-enterocolitis, we recommend early administration of oral corticosteroids (40mg prednisolone or equivalent), or in moderate to severe disease, IV corticosteroids (methylprednisolone 1mg/kg or equivalent) (*OE Level 3, 93% agreement*).

Statement 8
In the absence of response to oral corticosteroids within 3-5 days, we recommend escalation to IV corticosteroids (methylprednisolone 1mg/kg or equivalent) (*OE Level 3, 81% agreement*).

Statement 9
We recommend that patients receiving IV corticosteroids or those with high risk endoscopic features (mucosal ulceration, extensive colitis), should undergo pre-biologic screening in anticipation of treatment escalation to infliximab. This should not delay treatment initiation (*OE Level 4, 100% agreement*).

Infliximab

A systematic review of IFX efficacy in patients with CS- refractory, ICPi-induced diarrhoea reported response rates in excess of 80%[80], notwithstanding the inherent risk of reporting bias in systematic reviews. A single dose of IFX (5mg/kg) is often sufficient to allow full resolution of symptoms, although up to 35% of patients may need a second dose due to symptomatic relapse or incomplete response [63,84,88,89], which should be administered within two weeks. Some patients require additional doses with the decision to administer further doses usually based on the presence of ongoing symptoms [41,90,91]. The value of repeat dosing, or completion of standard induction regimens in patients with rapid

symptom resolution has not been established. This may be a particularly important issue in patients with high risk endoscopic features, and especially in those with deep mucosal ulceration. Patients not responding to three infusions of IFX should be regarded as IFX- refractory and other therapeutic options should be considered. Other anti-TNF agents have not been extensively studied, although successful use of adalimumab has also been reported [92].

In the management of acute severe UC, there is growing interest in the role of therapeutic drug monitoring and accelerated IFX induction regimens (with higher doses of up to 10mg/kg and/or administration of more than two infusions within two weeks). These approaches offer the theoretical advantage of delivering sufficient drug to overcome high tissue concentration of TNF, where drug is rapidly "mopped up" ("inflammatory sink")[93], loss of drug in faeces when the colon is very inflamed [94], and poor drug "carriage" in the periphery in patients with low albumin levels[95]. Data suggesting a benefit in IBD are currently limited to observational series [96], although there is at least one randomised trial in this area ongoing (ClinicalTrials.gov Identifier: NCT02770040). There are no data available regarding accelerated IFX dosing in ICPi-induced enterocolitis, and the decision to adopt this strategy should be based on clinical judgement and might be favoured in patients with severe disease, high-risk endoscopic features and/or low serum albumin levels.

If extended exposure to combinations of immunosuppressive agents is planned, prophylaxis against *pneumocystis jirovechii* (PCP) infection should be considered. For patients receiving ICPi, European oncology guidance suggests that prophylaxis should be 'considered for patients receiving long-term (> six weeks) treatment with immunosuppressive drugs[37]. Extrapolating from the IBD experience, the risk of PCP was 0.3 cases or fewer per 100 patient-year of exposure in patients receiving either CS, immunomodulators, or biologics which increased to 0.6 per 100 patient-years of exposure on double therapy. Whilst there were no cases while on triple therapy, there were fewer than 19 patient-years of exposure studied[97]. The risk of PCP in ICPi-treated patients has not been formally defined, however, there have been a few reports of PCP after IFX and CS use[58,98] including two out of 17 patients in one study[98]. As discussed earlier, there has also been a tendency for higher CS dosing in ICPi-induced

enterocolitis than in UC (2mg/kg methylprednisolone in some patients), often in combination with IFX, therefore the risk might be higher than in the IBD community, which may also be demographically different (younger and without concomitant advanced cancer). Taken altogether we suggest that PCP prophylaxis should be considered when the combination of high dose CS and IFX is planned (**see management algorithm**).

Statement 10
Early escalation to infliximab should be considered in patients with mucosal ulceration or extensive colitis (*OE Level 3*, *100% agreement*).

Statement 11
In the absence of response to high dose intravenous corticosteroids (within 3 days) we recommend immediate switch to infliximab (*OE Level 3, 94% agreement*).

Vedolizumab

Vedolizumab, a gut selective monoclonal antibody targeting leukocyte integrin α4β7, is efficacious in induction and maintenance of remission of both CD and UC[99,100], and may have a promising role in the management of ICPi-induced enterocolitis. The largest study to date is a retrospective multi-centre case series of 28 patients with biopsy proven ICPi-enterocolitis who had CS and/or IFX refractory disease[101]. Using a standard IBD induction regimen, 24/28 achieved sustained clinical remission after a median of three infusions (interquartile range 1–4). At six months follow up, 54% achieved endoscopic remission. Mirroring the IBD experience, IFX naïve patients were more likely to achieve clinical remission with vedolizumab than IFX experienced patients (95% vs 67% respectively). Other case reports and case series describe favourable outcomes of vedolizumab treatment in CS refractory ICPi-enterocolitis [102-104].

Other therapeutic options

Alternative immunosuppressive agents used to treat refractory ICPi-induced enterocolitis include calcineurin inhibitors (usually tacrolimus) and mycophenolate mofetil (MMF)[72,90,105-109]. In acute,

severe colitis there are safety concerns about sequential use of powerful immunosuppressive agents immediately after IFX failure [110]. However, case series have reported resolution of ICPi-enterocolitis in patients failing CS and IFX treatment following treatment with oral tacrolimus (0.01mg/kg or 0.06mg/kg)[106]. In this case series, tacrolimus was effective in treating two out of three CS and/or IFX refractory patients. Interestingly, one patient relapsed after cessation of CS and tacrolimus (294 days after the last ICPi dose) and needed long term tacrolimus maintenance. A recent case series of 11 melanoma patients with CTCAE grade three diarrhoea following combination anti-CTLA-4/anti-PD1 therapy described first line treatment with MMF (1g BD) in combination with high-dose CS. Seven patients were successfully weaned from CS without flare. However, relapse occurred in four out of 11 patients who required IFX therapy[107].

More recently, faecal microbiota transplant (FMT) has been explored as a potential therapeutic strategy in ICPi-enterocolitis. Wang et al. described the first case series of two patients with CS, IFX and vedolizumab- refractory disease who received compassionate use FMT. Following therapy with either one or two treatments, both patients had complete resolution of clinical symptoms and improvement in endoscopic findings[111]. Further work is needed to investigate the efficacy of this strategy, and perhaps more pertinently, evaluate the impact of inducing a less colitogenic microbiome on the anti-cancer response to ICPi given emerging evidence that the composition of the intestinal microbiota can significantly influence the anti-cancer efficacy of ICPi[112,113].

Statement 12
Treatment options for patients not responding to infliximab (up to 3 doses), include vedolizumab, calcineurin inhibitors and mycophenolate mofetil (*OE level 4, 100% agreement*).

Corticosteroid withdrawal in patients requiring biological therapy

The optimal strategy for CS withdrawal in patients requiring treatment with biologics has yet to be defined. Factors, such as the length and dose of prior CS exposure should be considered. In patients completely refractory to CS who are commenced on alternative immunosuppressive therapies there

is a strong rationale for rapid CS withdrawal. In patients prescribed prolonged courses of CS it is prudent to ensure effective resumption of adrenocortical function prior to discontinuation. Options inlcude measurement of 9am plasma cortisol concentration or performing a short synacthen test once prednisolone is tapered to 5-10mg/day.

Surgery for ICPi-induced colitis

In patients with treatment refractory ICPi-induced severe enterocolitis, or following intestinal perforation, surgical management may be required. Perforation occurs more commonly in anti-CTLA-4 containing regimes at a rate of 1-3% [114,115], although a recent systematic review suggested this could be as high as 5.1% [116]. When surgery is required for treatment refractory extensive colitis, sub-total colectomy and formation of an end ileostomy should be performed[114,117]. There are no data to inform the potential for ileostomy reversal in these patients, however, in theory, once inflammation has fully resolved reversal including ileorectal anastomosis or ileoanal pouch formation should be possible. Additional considerations, such as response to immunotherapy, cancer prognosis, life expectancy and performance status should influence the decision-making process.

Management of microscopic inflammation

Up to one third of patients have a macroscopically normal colon[14,15], many of whom will have microscopic evidence of inflammation ranging from typical histological features of ICPi-induced disease to more classical forms of microscopic colitis (lymphocytic or collagenous colitis). There is some evidence to suggest patients with ICPi-induced microscopic colitis follow a more aggressive disease course than conventional microscopic colitis. A retrospective study reported the clinical course in 65 patients with microscopic colitis, including 15 ICPi treated patients (13 with lymphocytic colitis and two with collagenous colitis), 39 cancer patients with no exposure to ICPi, and 11 with no cancer. They found that ICPi-associated microscopic colitis required increased hospitalisation and

treatment with oral and IV CS and infliximab[44] although it is worth considering that this may also represent different thresholds for management of ICPi treated patients .

Other options for patients with microscopic inflammation include topical CS, such as budesonide or beclomethasone dipropionate . In a case series of two patients with diarrhoea and microscopic colitis, both patients achieved clinical and histological remission following a four week course of topical beclomethasone dipropionate (Clipper)[47]. Further work is needed to evaluate the role for topical steroid preparations, including budesonide, in managing microscopic inflammation or even milder forms of macroscopically evident disease.

Safety of immunosuppression in ICPi-treated patients

CS use is associated with an increased rate of infection in patients treated with ICPi[66]. In a retrospective, single centre case-series of 740 ICPi-treated melanoma patients, the risk of serious infection, defined as requiring hospitalization and/or intravenous antibiotics, was 14% in patients treated with CS (at least 10mg/day dose equivalent of prednisolone for at least ten days)[118]. The median CS exposure was 40mg prednisolone equivalent/day with a median duration of CS treatment of 60 days. This study also identified infection risk in patients treated with IFX. Serious infection occurred in 24% of patients treated with IFX, although 53/54 patients treated with IFX were concomitantly treated with CS [118]. In this cohort, bacterial pneumonia and bacteraemia were the most commonly reported infections in ICPi-treated patients. Fungal (including *Pneumocystis jirovecii* pneumonia and invasive pulmonary *Aspergillosis*), viral (Herpes zoster) and parasitic (Strongyloides) infections were also observed[118].

Data are needed to inform whether immunosuppressive treatments, including CS and anti-TNF, impact on the anti-cancer efficacy of ICPi's (which depend on immune activation). Most reports indicate that CS and/or anti-TNF administration do not adversely affect response to therapy or overall survival in patients treated with immune check point blockade[22,67,88,91,119,120]. However, reduced overall

survival has been reported in melanoma patients treated with high-dose steroids compared to those treated with low dose steroids[121], although in this study CS were prescribed for autoimmune hypophysitis developing after anti-CTLA-4 therapy. Cancer outcome data has also been reported in 640 non-small cell lung cancer patients treated with PD-1/L1 inhibitors, among whom 90 were taking CS (equivalent dose of prednisolone ;:: 10mg/day) at the point of ICPi initiation[122]. The subset of patients exposed to CS at baseline had reduced progression-free survival and overall survival in comparison with unexposed patients[122].

In keeping with the gut- selective mechanism of action of vedolizumab the safety data available to date in conventional IBD is reassuring, with no excessive risk of cancer or serious infection detected[123-126]. Vaccination studies have demonstrated, as anticipated, that whilst vedolizumab suppresses gut immune responses to orally delivered vaccines, systemic immunization is preserved [127]. The safety of vedolizumab and the lack of impact on systemic immune responses is a highly attractive concept in immunotherapy treated cancer patients requiring intervention for colitis. If the positive preliminary clinical experiences with vedolizumab are replicated in other ICPi-induced enterocolitis patient cohorts, then a compelling case for 1st line treatment could be convincingly made.

Nutritional support

Nutritional disturbance is a frequent complication of conventional IBD [128,129], and is also likely to be a significant issue in ICPi-enterocolitis, especially in some patients with metastatic cancer. Nutritional support with assistance from the dietetics team (ideally a dietitian with expertise in oncology and/or IBD) should be considered, especially in patients requiring hospital admission. The aim should be to meet energy and protein needs as defined by the ESPEN guidelines on nutrition in cancer [130]. Where oral intake cannot be maintained consideration must be made for enteral or parenteral nutrition. Dietary adjustments, including a bland diet, low fibre diet and lactose avoidance have been advocated by some groups [72,105]. However, there is a paucity of evidence to support this approach, so patients are advised to continue to eat a varied diet including fibre as per the ESPEN IBD guidance[131]. Patients

should be counselled on the importance of maintaining oral hydration. Some management algorithms incorporate considerations of bowel rest and total parenteral nutrition (TPN) in severe disease [72,132], but there is no evidence for this approach. Historical studies of TPN in acute, severe colitis failed to show benefit over enteral nutrition [133], and increased rates of adverse events including infection were observed [134,135]. Moreover, TPN adds significant costs and length to hospital admissions, especially when septic, metabolic or venous access complications occur [136,137]. The role for exclusive enteral nutrition has also not been evaluated in this context.

Prophylaxis

To date there are no effective therapeutic options to prevent the onset of diarrhoea in ICPi-treated patients. Two randomised placebo-controlled trials failed to show a benefit of topical budesonide in preventing ipilimumab-induced diarrhoea [57,138].

Management of symptomatic relapse

Data regarding rates of relapse during CS withdrawal are limited. A systematic review comprising almost a thousand patients with ICPi -induced colitis/diarrhoea reported successful outcomes from CS treatment of 60%[80]. Overall relapse rates after an initial response in a retrospective study of 72 patients with ICPi colitis (on single or dual ICPi therapy) appear to be in the region of 20-25%. Relapse during CS taper was observed in 17-43%, and was more common in patients on dual ICPI therapy[139] . Following relapse on CS withdrawal, options include increasing back to the last effective dose and tapering more slowly, or escalating to IV CS or IFX. Relapses in patients with prolonged exposure to CS, or other immunosuppressive therapy warrant re-evaluation, including repeat sigmoidoscopy with biopsy to exclude complications, such as superimposed CMV infection.

Management of patients with pre-existing IBD

With increasing deployment of ICPi, it is inevitable that cancer patients with pre-existing IBD will be considered for ICPi therapy. There is little high-quality evidence to inform decision making in this setting and in many of the landmark clinical trials, patients with pre-existing immune mediated inflammatory diseases or those taking immunosuppressive treatments were excluded [140-146]. Several retrospective case series[147-150] and case reports[151-153] of IBD patients with cancer treated with CTLA-4 or PD-1 inhibitors have been published with varying outcomes. Although case reports and case series are prone to reporting bias, treatment with ICPi has frequently resulted in IBD exacerbations, even in patients with documented clinical and endoscopic remission. Consequences inlcude mild symptomatic relapse to induction of perforating disease and requirement for surgical intervention [152] [151]. The ICPi regimen selected may have some bearing on risk of IBD relapse. In a retrospective case series of six patients with clinically quiescent/mild IBD treated with ipilimumab, two patients presented with diarrhoea, which responded to either IV CS or IFX[148] . Another case series reported favourable outcomes of five IBD patients and another with coeliac disease treated with anti-PD-1, with no documented exacerbations[149], consistent with anti-PD-1 therapy being a less potent driver of diarrhoea/colitis in this patient subgroup. Our interpretation of these limited data is that IBD should not be considered a contraindication to potentially life-saving immunotherapy. A pragmatic approach would include baseline assessment of disease activity, vigilant monitoring for relapse (e.g. regular faecal calprotectin measurement) and rapid re-investigation in the event of relapse with rapid institution of appropriate treatment.

Statement 13
Preexisting IBD should not be considered a contraindication to ICPi therapy. We suggest prompt as sessment of disease activity prior to starting ICPi with regular monitoring, rapid investigation and treatment escalation in the event of relapse *(OE Level 4, 100% agreement*).

Considerations in patients with multiple organ involvement

ICPi-enterocolitis can occur concurrently with other immune related adverse events[20,154,155]. In a retrospective safety review of three clinical trials from patients on combination anti-CTLA-4/anti-PD-1 treatment (n=448), 30.1% developed irAEs in more than one organ category[20]. In another retrospective review of 80 patients who discontinued ICPi combination therapy because of irAEs, 10% had more than one concurrent toxicity[155]. There are no data on how best to manage patients with simultaneous irAEs in different organ systems, however, pragmatic approaches using therapeutic agents with evidence of efficacy in both situations is a logical approach, and in most circumstances systemic CS are a sensible first line option. In patients with concomitant enterocolitis and hepatitis, MMF 1g BD is an obvious second line option, since there are reports that it is effective for both conditions[37,107].

Research areas

ICPi-induced enterocolitis is a relatively new clinical problem and research insights across different aspects of disease are urgently needed. Perhaps most pressingly, prospective clinical trial data is needed to provide an evidence base for new and existing treatment strategies, with both efficacy and safety end points. There is also merit in understanding immune mechanisms of ICPi-induced enterocolitis to guide the development of targeted therapies. It is anticipated that these efforts will additionally provide new insights into the fundamental biology of mucosal homeostasis, and how different checkpoint molecules contribute to this finely tuned balance in individual patients. Key areas identified by the committee requiring research attention include:

- Development and validation of risk stratification instruments and biomarkers to gauge disease severity and to guide therapy
- Determine markers that predict patients at high risk of developing ICPi-enterocolitis and develop effective prophylactic strategies.
- Determine the optimal dose, regimen and withdrawal strategy of oral and intravenous CS

- Direct comparisons of the safety and efficacy of CS and IFX (preferably in a head to head clinical trial).
- Determine the role of 5-ASA in induction and maintenance of remission
- Determine role of topical steroids in induction and maintenance of remission
- Service development studies to evaluate best care models, including endoscopy provision/capacity for urgent 72-hour flexible sigmoidoscopy in an era of anticipated ICPi expansion.
- The therapeutic implications of dietary interventions including pre and probiotics, bowel rest, and use of modified diets including elemental and low FODMAP diets, or manipulation of dietary fibre intake.
- Role of intestinal microbiota manipulation using FMT, probiotics and prebiotics on colitis and cancer outcomes in ICPi-treated poatients.
- Determine the efficacy of accelerated IFX dosing has an impact on rate of remission and relapse
- Understand the role of therapeutic drug monitoring (IFX and vedolizumab)
- Define the immunobiology of ICPi-induced enterocolitis to develop targeted therapy
- Understand the role of MMF, tacrolimus and ciclosporin in inducing and maintaining remission
- Prospective evaluation of the impact of immunosuppressive therapy on anti-cancer ICPi-efficacy

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Figure 1: Incidence of ICPi-induced diarrhoea according to regimen

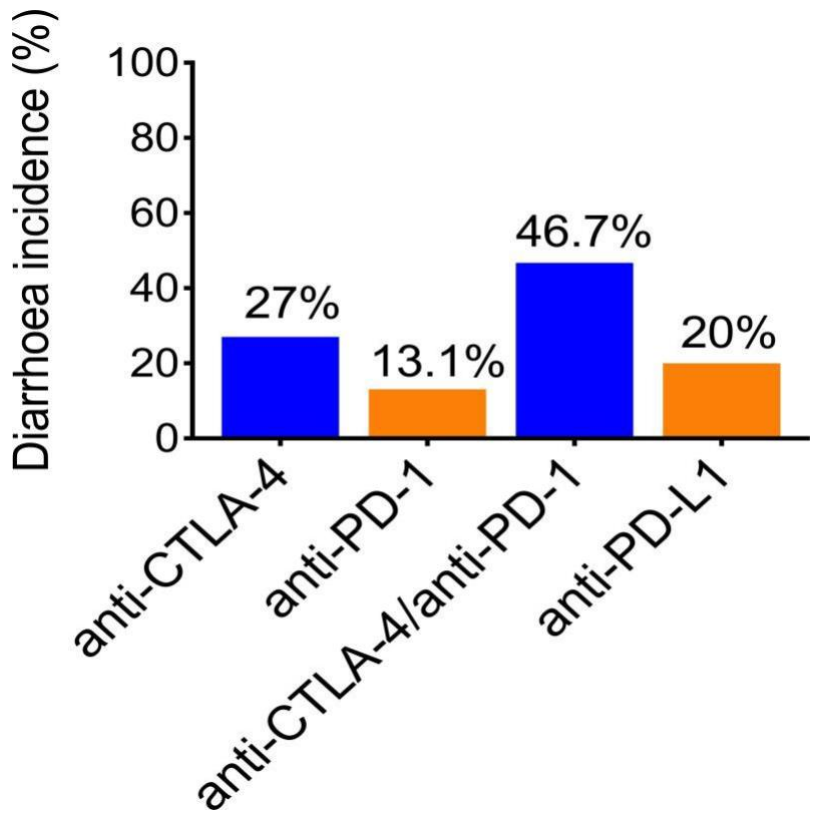


Figure 1: Incidence of all-CTCAE grade ICPi-induced diarrhoea according to regimen. Data are based on the summary of Product Characteristics from the electronic Medicines Compendium (eMC)[33], where anti-CTLA-4 treated melanoma patients received Ipilimumab (3mg/kg) in clinical trials (n=767). Anti-PD-1 monotherapy treated patients were pooled across numerous tumour types and treated with nivolumab (3 mg/kg) (n=2578). In the anti-CTLA-4/anti-PD-1 group, melanoma patients were pooled from a cohort of nivolumab (1 mg/kg) plus ipilimumab (3mg/kg) (n=448) treated patients. In the anti-PD-L1 group, patients across different tumour types were pooled from an atezolizumab treated cohort (n=3178).

Figure 2: Time of onset of all grade-diarrhoea/colitis

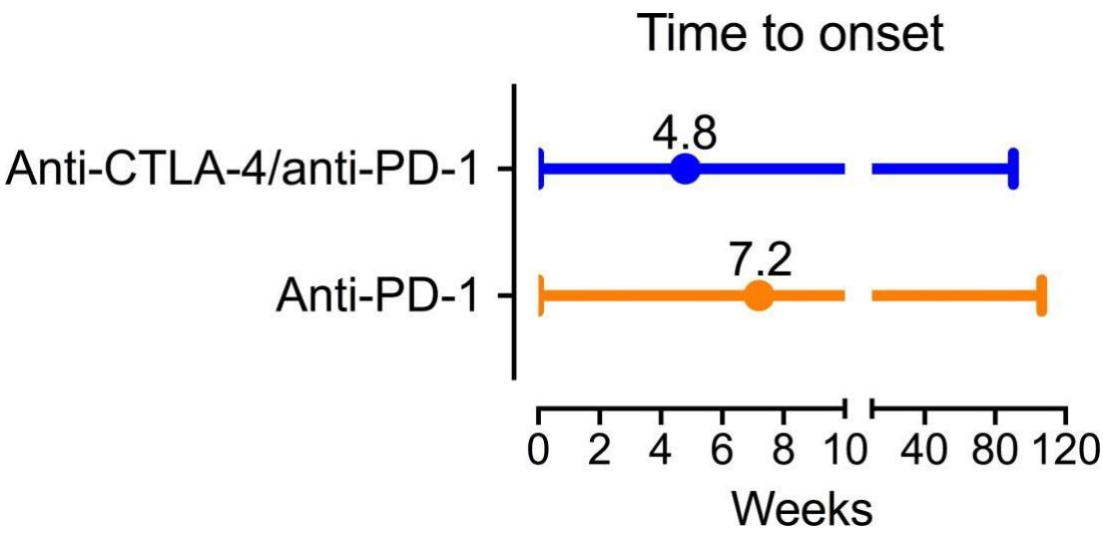
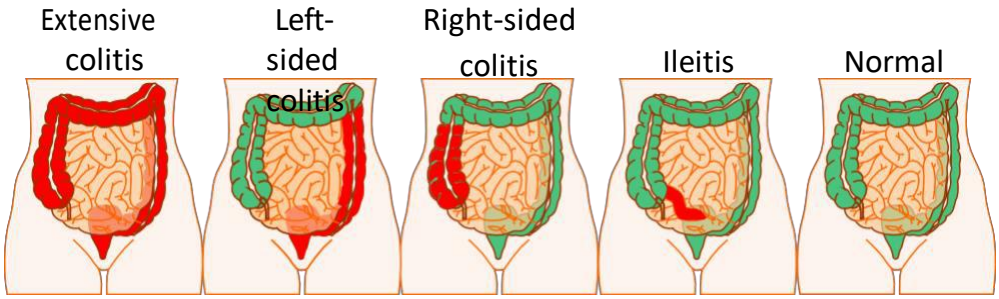


Figure 2: Time of onset of all grade-diarrhoea/colitis. Data are based on the summary of Product Characteristics from the electronic Medicines Compendium (eMC)[33] depicting time to onset to diarrhoea/colitis where anti-CTLA-4/anti-PD-1 melanoma patients were pooled from a cohort of nivolumab (1 mg/kg) plus ipilimumab (3mg/kg) (n=448) treated patients. The anti-PD-1 (nivolumab 3mg/kg) monotherapy treated cohort were pooled across patients with numerous tumour types (n=2578). Line depicts range. Median is depicted by circle.

Figure 3: Distribution of intestinal inflammation in ICPi-enterocolitis



Abu-Sbeih (n=182)	23%	31%	3%	6%	37%
Foppen (n=97)	68%	NR	8%	NR	16%

Figure 3: Distribution of intestinal inflammation in patients with ICPi-induced diarrhoea assessed by lower GI endoscopy. Data are from 2 real world endoscopy studies, in cancer patients presenting with diarrhoea following treatment with different anti-CTLA-4, anti-PD-1 and anti-PD-L1 regimens, including combination therapies, underwent endoscopy. NR = not reported.

Figure 4: Histological features of ICPi-induced colitis

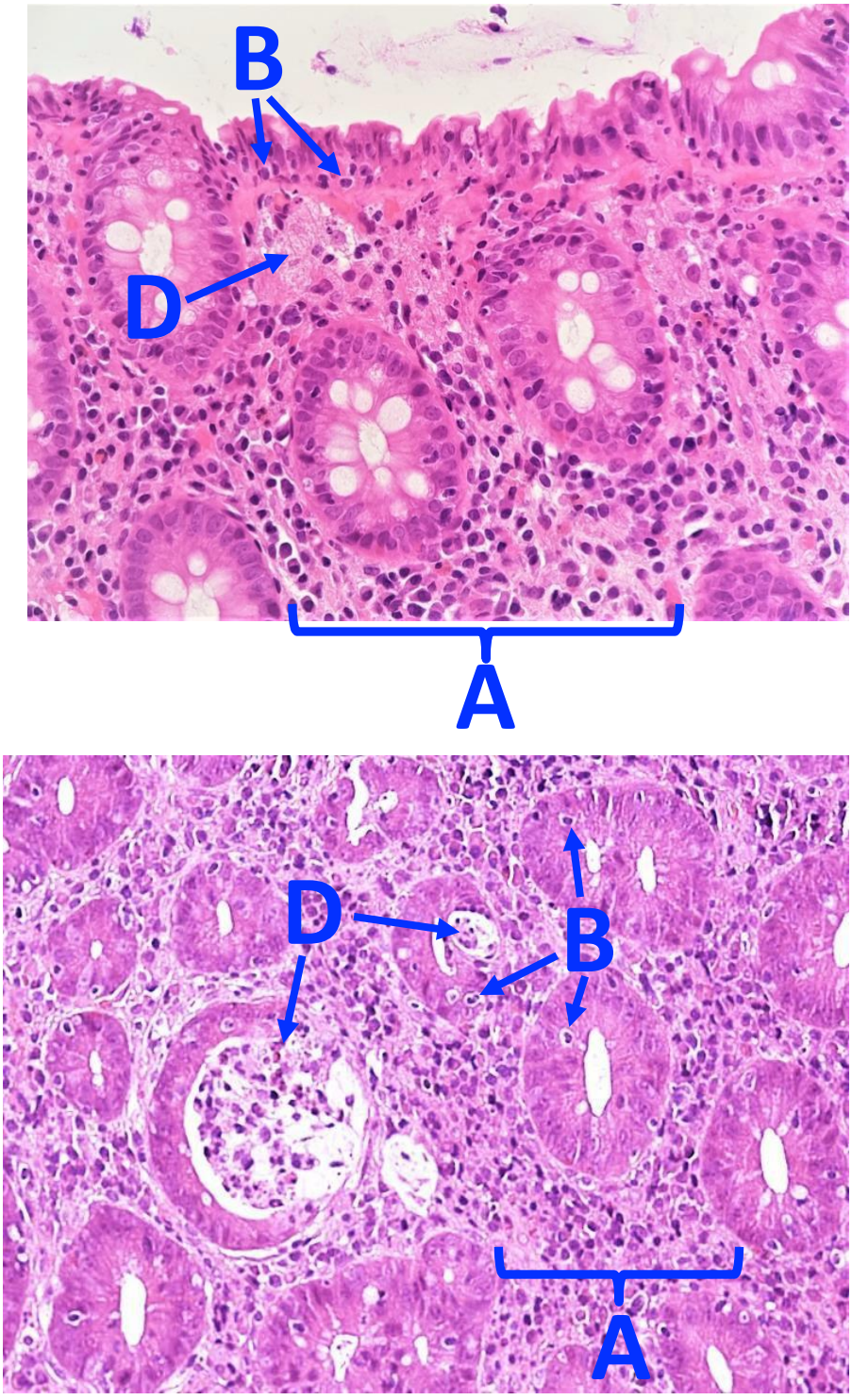


Figure 4: Histology (H&E) section from colonic biopsies sampled from the sigmoid colon from a patient with ICPi-enterocolitis. Section shows increased lamina propria cell infiltrate (A), increased intraepithelial lymphocytes (IELs) (B), crypt abscesses (C) and apoptotic debris (D).

Table 1: European Medicine Agency (EMA) approved ICPi's for treatment of cancer

Anti-PD-1	**Anti-PD-L1**	**Anti-CTLA-4**	**Anti-PD-1 & anti-CTLA-4**
• Pembrolizumab • Nivolumab • Cemiplimab	• Atezolizumab • Avelumab • Durvalumab	• Ipilimumab	• Ipilimumab & Nivolumab
Melanoma Non-small cell lung cancer Renal cell cancer Urothelial cancers Squamous head & Neck cancers Hodgkins' lymphoma Mismatch-repair deficiency tumours Cutaneous squamous cell cancer	Non-small cell and small cell lung cancer Urothelial cancers Merkel cell cancer	Melanoma	Melanoma Renal cell carcinoma

Table 2: Landmark survival rates from Phase III studies of first-line metastatic treatment with ICPi's in melanoma, non-small cell lung cancer (NSCLC) and renal cell cancer (RCC)

	Anti-PD-1 (%)	Anti-PD-L1 (%)	Anti-CTLA-4 (%)	Combination anti-CTLA-4 & anti-PD-1 (%)
Melanoma				
3-year OS*	52%**	-	34%✣	58%**
NSCLC				
2-year OS	51%♦	66%♦♦	-	data immature
RCC				
18-month OS	82%†	-	-	75%††

*OS- overall survival
**CM-067 – nivolumab cf ipilimumab (Wolchok et al. NEJM 2017)
♦KN024 – pembrolizumab vs chemotherapy (Reck et al. NEJM 2016)
♦♦ PACIFIC study-durvalumab after chemoradiotherapy (Antonia et al. NEJM 2018)
† Pembrolizumab +axitinib (Rini et al.NEJM 2019)
††CM-214- ipilimumab+nivolumab cf sunitinib (Motzer et al. NEJM 2018)

Table 3: A comparison of CTCAE for diarrhoea and colitis

	CTCAE diarrhoea	CTCAE colitis	Mayo score	MTWSI
Grade 0	N/A	N/A	Normal number of stools per day	0-2
Grade 1	Increase of <4 stools/day over baseline	Asymptomatic; clinical or diagnostic observations only	1-2 stools more than normal	<4
Grade 2	Increase of 4-6 stools/day over baseline	Abdominal pain; mucous or blood in stool	3-4 stools more than normal	>6
Grade 3	Increase of ≥7 stools/day over baseline, incontinence	Severe abdominal pain; peritoneal signs	≥5 or more stools	>10
Grade 4	Life threatening consequences	Life threatening consequences		
Grade 5	Death	Death		

Table 4: Histological findings in ICPi-enterocolitis

Study	Number (n)	Chronic inflammation	Acute inflammation	Increased apoptosis	Increased IELs*	Crypt distortion
Foppen et al.2018	90	83%	79%	42%	10%	10%
Wang et al.2018	53	60%	23%	23%	8%	n/a#
Vershuren et al. 2016	27	n/a	92%	n/a	n/a	40%
Gonzalez et al.2017	17	76%	71%	47%	0%	53%
Foppen et al.2018	90	83%	79%	42%	10%	10%

Table 4: Summary of the main histological findings in ICPi-enterocolitis. Data derived from colonic biopsies from 4 real world studies in a total of 187 patients with ICPi-enterocolitis. *IELS- intra- epithelial lymphocytes.

Table 5: Equivalent anti-inflammatory doses of corticosteroids (adapted from the British National formulary)

5mg prednisolone =	Methylprednisolone 4 mg
	Hydrocortisone 20mg
	Dexamethasone 0.75mg

ICPi-associated diarrhoea

Investigations

Stool cultures (M,C&S, C.difficile)
Faecal calprotectin
Bloods (full blood count, renal profile, electrolytes, liver profile, CRP, thyroid function)

Flexible sigmoidoscopy (or colonoscopy)
-Acquire at least 4 biopsies
-Test for CMV*

Inflamed mucosa?

No

Assess histology for microscopic inflammation

Histology normal?

Yes

Consider investigating remainder of GI tract with ileocolonoscopy and OGD
-Consider alternative diagnoses and investigations (bile salt malabsorption, SIBO, PI)*

No

Initiate therapy or continue to monitor response if therapy already initiated

Yes

Presence of high risk endoscopic features?
-Ulceration
-Extensive inflammation (beyond splenic flexure)

No

Initiate therapy or continue to monitor response if therapy already initiated

Yes

Low threshold for early escalation to infliximab

Management

(can be initiated in tandem with investigations)

Early administration of oral CS* (40mg prednisolone or equivalent),
-In moderate to severedisease consider IV CS (methylprednisolone 1mg/kg or equivalent)**

Response within 3-5 days?

Yes

Continue to monitor during CS taper

Relapse on steroid taper

Increase CS backto lowest effective dose, and increase duration of taper

Further relapse on CS taper or CS dependant

Escalate to IV CS (methylprednisolone 1mg/kg or equivalent)
-Request pre-biologic screen***
-Escalate to infliximab if already on IV CS

Response within 3 days?

Yes

Start oral CS and taper regimen

Further relapse on CS taper or CS dependant

Escalate to 5mg/kg infliximab
-Maximum 3 infusions

Inadequate response

Consider second line escalation therapy:
-Vedolizumab
-Mycophenolate mofetil
-Calcineurin inhibitors

No

Considerations during hospitalisation

-Nutritional review

-Regular abdominal X-ray; cross sectional imaging

-DVT prophylaxis

*CS- corticosteroids; CMV- cytomegalovirus; SIBO- small intestinal bowel overgrowth; PI- pancreatic insufficiency
**Mild disease includes CTCAE grade 1, or 2 of short duration, however other clinical features such as endoscopic findings, presence of rectal bleeding and systemic inflammatory features should contribute to determining disease severity.
*** Pre-biologic screen includes chest imaging within 6 months, TB IGRA, VZV status, Hep B/C and HIV serology