Colitis After Cancer Immunotherapy: Considerations for a Prevalent Immune-Related Adverse Event

Colitis after Cancer Immunotherapy
Considerations for a Prevalent Immune-Related Adverse Event

by

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I have reviewed this thesis. It represents work done by the author under my supervision and guidance.

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Abstract

Background:

Immune checkpoint inhibitors (CPIs) have revolutionized oncologic therapy but can lead to immune-related adverse events (irAEs). Corticosteroids are first-line treatment with escalation to biologic immunosuppression in refractory cases. CPI-related gastroenterocolitis (GEC) affects 20-50% of patients receiving CPIs and carries significant morbidity and mortality. The severe form of disease is not well-described. In addition, patients with a histopathologically defined subset of CPI-related GEC, which we term CPI-related microscopic colitis (MC), may benefit from first-line budesonide administration. We present the retrospective clinical characterization of CPI-related GEC requiring admission at a single institution (inpatient GEC cohort) and a retrospective preliminary evaluation of a pilot cohort of CPI-related MC treated with budesonide (MC cohort).

Methods:

For the inpatient GEC cohort, clinical, laboratory, radiographic, and endoscopic data were extracted from charts of all melanoma patients ≥18 years of age admitted to one institution for CPI-related GEC, from 2/05/2011 to 12/13/2016. Patients were followed until 12/31/2017 for further admissions. Survival, outcomes, and pharmaceutical-use analyses were performed.

For the MC cohort, clinical, laboratory, and endoscopic data were extracted from charts of all patients ≥18 years of age with prior CPI exposure and prior flexible sigmoidoscopy performed from 3/1/2017 to 12/31/18 for evaluation of possible colitis. CPI-related MC was defined as clinical and histopathologic evidence of colitis without endoscopic evidence of inflammation (Mayo Endoscopic Score 0). Diagnoses were confirmed by two reviewers, one with expertise in CPI complications. Survival and outcomes analyses were performed.

Results:

Median time-to-admission from initial CPI exposure for the overall cohort was 73.5 days. Median length of stay was 4.5 days. 50.0% required second-line immunosuppression. Readmission for recrudescence occurred in 33.3%. Common Terminology Criteria for Adverse Events (CTCAE) grade was not significantly associated with outcomes. Hypoalbuminemia (p=0.005), relative lymphopenia (p=0.027), and decreased lactate dehydrogenase (p=0.026) were associated with second-line immunosuppression. There was no difference in PFS or OS (p=0.367, 0.400) for second-line immunosuppression. Subgroup analysis showed that early corticosteroid administration (p=0.045) was associated with decreased PFS.

There was no significant difference in average age or sex distribution between patients with MC and patients with non-MC GEC. Exposure to potential MC triggers tended to occur more often in the MC than non-MC cohort. Symptoms tended to start a median of 84 days later in the MC cohort, with borderline significance (p=0.064). Budesonide administration tended to result in faster symptom resolution (p=0.070). 10/12 (83.3%) patients with MC received additional cycles of immunotherapy after budesonide. Univariate Cox regressions showed that budesonide administration was significantly protective against treatment failure (HR 0.33, 95% CI 0.14-0.81) and borderline protective against progressive disease (HR 0.27, 95% CI 0.04-0.91).

Conclusions:

Severe CPI-related GEC typically manifests within 3 months of immunotherapy exposure. Rates of second-line immunosuppression and readmission for recrudescence were high. CTCAE grade did not capture heterogeneous degree of severity in our cohort. Second-line immunosuppression was not associated with poorer oncologic outcomes; however, early corticosteroid exposure was associated with decreased PFS.

CPI-related MC, defined as clinical and histopathologic evidence of colitis with Mayo Endoscopic Score 0, is a clinical subset of CPI-related GEC that tends to present later in the course of immunotherapy. Budesonide is an effective treatment for CPI-related MC that controls symptoms and prolongs time on immunotherapy.

Further prospective investigation is warranted in both cohorts.

Glossary of Terms

Analysis of variance	ANOVA
Common Terminology Criteria for Adverse Events	CTCAE
Confidence interval	CI
Cytotoxic T-lymphocyte antigen 4	CTLA-4
Gastroenterocolitis	GEC
Hazard ratio	HR
Immune-related adverse event	irAE
Immune checkpoint inhibitor	CPI
Microscopic colitis	MC
Overall survival	OS
Programmed cell death receptor (ligand) 1	PD-1/PD-L1
Progression-free survival	PFS
Tumor necrosis factor alpha inhibition	TNFαi

Introduction

Overview

Immune checkpoint inhibitors (CPIs) have revolutionized cancer therapy over the past decade.[1,2] CPIs are clinically associated with durable responses in many subsets of cancer patients, including those with melanoma, non-small-cell lung cancer[3], urologic cancers[4], hematologic malignancies[5,6], and microsatellite instability or mismatch-repair deficiencies, and are rapidly growing in use.[7-11] These novel agents are felt to enhance the body's adaptive immune response to cancer and thus achieve clinical effect: inhibition of major T-lymphocyte coinhibitory pathways blocks tumor "immune escape" mechanisms and allows for immune-mediated antitumor activity.[2]

Current CPIs target two distinct pathways of T cell co-inhibition: cytotoxic T-lymphocyte antigen-4 (CTLA-4), or programmed cell death-1 (PD-1) receptor and its ligand (PD-L1). CTLA-4 is an activation-induced mature T-cell surface protein that is recruited to the immune synapse several days after T-cell receptor signaling begins. CTLA-4 binds to CD80 and CD86, competing with the co-stimulatory protein CD28, attenuating T cell signaling in response to antigen recognition.[12] Its crucial influence on development of immune self-tolerance was documented first in CTLA-4 knockout mice: rapid T-cell mediated multiorgan inflammation occurred almost immediately and resulted in death within four weeks of birth.[13,14] The exact mechanisms of action by which CTLA-4 achieves immune inhibition have not yet been fully elucidated. However, given the clinical success of soluble CTLA-4-immunoglobulin fusion proteins in treating not only CTLA-4 deficiency but also other autoimmune disease, it is felt that the receptor primarily exerts its effects by outcompeting CD28 and thus preventing costimulation; CTLA-4 may additionally act to downregulate CD80/86 on dendritic cells.[2,15,16] Antitumoral effect via CTLA-4 blockade was noted first in 1996.[17] In murine models, mechanistic evidence for such benefit points to depletion of intratumoral regulatory T-cells that express high levels of CTLA-4 via Fc-mediated

destruction, but the exact mechanism of antitumor effect is still unclear in humans.[17-20] Ipilimumab is the anti-CTLA-4 monoclonal antibody approved for use in the United States.

The PD-1 protein is a T-cell transmembrane receptor that, in conjunction with its ligand, signals through SHP phosphatase and regulates peripheral T-cell activation, exhaustion, and tolerance.[2,21-23] Though the PD-1 protein holds a place of importance in antitumor immune activity, its deficiency clinically results in relatively mild autoimmune toxicities.[2] The PD-1 pathway, when activated, results in direct and downstream attenuation of T-cell receptor signaling; decreased T-cell motility as well as reduced T-cell interaction with antigen-presenting cells; and induction of the regulatory T-cell phenotype.[2,24] It is felt that PD-1 pathway blockade results in the rejuvenation of intratumoral T-cells and thus an antitumor effect.[25] The following anti-PD-1 monoclonal antibodies have been approved for use: nivolumab and pembrolizumab. The following anti-PD-L1 monoclonal antibodies have been approved for use: avelumab, atezolizumab, and durvalumab.

In sum, blockade of the CTLA-4 and/or PD-1 pathways and the consequent loss of peripheral T-cell tolerance allows for an “unleashing” of the adaptive immune system against cancer. However, such a sacrifice of major T-cell self-tolerance pathways necessarily increases the risk of autoimmune attack. Clinical practice corroborates this: as indications for CPI administration expand, immune-mediated adverse events (irAEs) are becoming increasingly common.[1,11,26-30] In general, the self-targeting seen in irAEs is felt to result from an underlying predisposition to autoimmunity, with or without shared tumor-tissue antigenicity, triggered by T-cells that no longer can achieve adequate self-tolerance.[30,31] Multiple potential mechanisms can explain the symptoms of autoimmune disease that arise in patients treated with CPIs. Clinically, direct tissue infiltration is seen in vitiligo and myocarditis[31,32]; indirect autoantibody generation is seen in myasthenia gravis and meningoencephalitis[33,34]; and indirect inflammatory factor production is seen in CPI-induced cytokine release syndrome.[35]

Although any organ system can be affected, irAEs typically involve the skin, gastrointestinal tract, and lungs. The severity and spectrum of irAEs is related to the specific pathway targeted, with inhibition of CTLA-4 having more frequent and more severe irAEs compared to inhibitors of PD-1 or PD-L1.[1] Combination CPI therapy generally leads to more significant irAEs than either therapy alone.[30] Globally speaking, high-dose corticosteroids are first-line immunosuppression, with escalation to biologics as needed.[11]

Prognostic Implications and Prediction of irAE Development

While it is biologically plausible that irAEs might be correlated with stronger antitumor immune responses, there are still relatively few data by which such immune activation has been invariably linked to anti-tumor effect. Cutaneous irAEs can be positively correlated with improved survival in melanoma patients, likely at least in part due to shared antigens.[36,37] Studies have also suggested that development of any irAE might correlate with clinical benefit.[38,39] Little evidence currently exists for irAEs affecting other organ systems, however, and the picture may be confounded by the immunosuppressive treatments patients receive for severe irAEs.

For prognostic and therapeutic reasons, the identification of predictors of irAEs remains a key challenge facing oncologists today.[8,40] Several recent investigations have suggested possible risk factors for the development of irAEs.[41] Select single-nucleotide polymorphisms in genes associated with autoimmunity have been implicated.[42] Particular baseline autoantibody profiles enriched in antinuclear targets have also been associated with general immunotherapy-related toxicities.[43] With respect to clinically available testing, lower lactate dehydrogenase levels have been correlated with better outcomes in melanoma but have not been correlated with toxicity development[44-47]; pre-toxicity absolute and relative eosinophil counts as well as lymphocyte counts have been associated with eventual irAE development as well.[48,49] To date, prediction of response to irAE treatment is not possible.

Statement of Purpose

CPI-related (gastroentero)colitis is a relatively prevalent and often severe irAE that is not well-characterized. My aim in the following piece is to explore this topic in depth, drawing on both previously published literature and original clinical research. In Section 1, I provide a broad overview of the clinical entity and present the findings of a comprehensive single-center retrospective investigation regarding the disease. In Section 2, I briefly review sporadic microscopic colitis, a disease that shows significant overlap with a specific subset of CPI-related (gastroentero)colitis, and present the preliminary findings of a small single-center retrospective study.

Section 1

CPI-related (Gastroentero)colitis

Background

(Gastroentero)colitis (GEC) is among the most common and severe irAEs associated with CPIs.[1,30,50,51] 25% of patients receiving anti-CTLA-4 therapy develop low-grade GEC, while 11% experience severe GEC; 10-20% of patients exposed to anti-PD-1/PD-L1 develop a low-grade GEC, while 2% develop high-grade symptoms.[1,26-28,52] As expected, combination therapy seems to have at least an additive, if not synergistic, effect on toxicity: 46-51% of exposed patients develop CPI-related GEC, with 8-18% developing a severe form.[27,28]

Empiric evidence in CPI-related GEC suggests that gastrointestinal immune homeostasis is often significantly disrupted in the setting of CPI therapy[1], but specific pathogenesis is not fully understood. From previously published data, CPI-related GEC typically presents with diarrhea, abdominal pain, and evidence of gastrointestinal tract ulceration, similar to inflammatory bowel disease.[1,30] Symptom onset ranges from six weeks to several months after initial CPI administration; symptoms are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) classification system. Inflammation most often affects the colon and can be concomitantly seen in stomach or small intestine; however, isolated gastritis or enteritis can also occur.[53] Diagnostic approaches include radiography and endoscopy with further histopathologic examination. Endoscopy is typically characterized by significant ulceration in severe CPI-related GEC.[1,30,51]

CPI-related GEC often requires acute intervention and forces oncologists to make difficult choices regarding further immunotherapy. Management of CPI-related GEC relies on high-dose corticosteroids with escalation to infliximab, though alternative second-line therapies are emerging[11,54-56]; the particular steroid administered does not seem to impact clinical course.[11,57] There has been relatively little investigation of risk factors for CPI-related GEC, but particular endoscopic findings[40] have been linked to severe disease. Another study suggested that elevated baseline circulating interleukin-17 at two weeks

was associated with later development of severe CPI-related GEC.[58] There are relatively few data on prediction of CPI-related GEC using readily available laboratory testing.

Severe disease can result in bowel perforation and death, more usually associated with anti-CTLA-4 therapy but occurring regardless of specific receptor blockade.[50,59,60] CPI-related GEC is anecdotally accompanied by significant morbidity and intuitively substantial cost, as expected given the condition's similarity to inflammatory bowel diseases.[61] There are few published studies, however, describing a consolidated patient cohort hospitalized for the condition. We thus aimed to clinically characterize CPI-related GEC requiring hospitalization.

Methods

Ethics

This study was approved by the Partners Human Research Committee, the Institutional Review Board of the Massachusetts General Hospital (MGH).

Patients

We identified all patients ≥18 years of age with stage III/IV melanoma hospitalized for expert-confirmed CPI-related GEC from 2/05/2011 to 12/13/2016; patients were followed for further admissions until 12/31/2017 (MGH Research Patient Data Registry). CPI-related GEC was defined as clinical and/or histopathologic evidence of gastrointestinal inflammation best explained by prior CPI exposure. Diagnoses were confirmed by two reviewers with expertise in CPI complications (Figure 1-1).

Data Collection

We extracted clinical, laboratory, radiographic, and endoscopic data from electronic medical records (Table S1). The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, was used for adverse event classification. Two independent database audits confirmed high accuracy.

Endpoints

Primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints were length of stay (LOS), rate of readmission, and time to GEC resolution (grade 1 symptoms or better).

Statistical Analysis

Descriptive statistics were displayed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, Washington, USA). Statistical analysis was performed using SAS Studio (version 9.4M6, SAS Institute, Cary, NC, USA). Data are expressed as "mean +/- standard deviation," "mean +/- standard error," or "median (range)" where appropriate. P-values are two-sided, with $\alpha = 0.05$.

The chi-square test or Fisher's exact test and the ANOVA method or the Student's *t*-test were employed where appropriate. Survival curves were generated using Kaplan-Meier analysis. Log-rank and Wilcoxon testing are reported where appropriate. Survival was measured from CPI exposure date to date of death, date of transition to hospice, or censored date. Date of death or transition to hospice was determined by electronic medical record review. Date of oncologic progression was defined as the date imaging was performed showing progressive disease. Median follow-up time was 28.0 months. 28 patients transitioned to hospice care and/or died during the study interval. With a sample size of 30 in each subgroup, a follow-up time of 60 months, and a median PFS of 10.5 months in those who did not receive second-line immunosuppression and 30.5 months in those who did receive second-line immunosuppression, we retrospectively calculated that our severe CPI-related GEC study has over 80% power to detect a survival difference between populations using a two-sided log-rank test at a significance level of 0.05.

Results

Characteristics and Typical Hospital Course

Baseline characteristics are summarized in Table 1-1. 60 patients with advanced melanoma, totaling 88 admissions, were hospitalized for CPI-related GEC from 6/1/11 to 12/31/17. Average age on admission was 65 years; 38/60 (63%) patients were male and 52/60 (86.7%) had stage IV melanoma. Hepatic (21/60, 35.0%) and gastrointestinal (13/60, 21.7%) metastases were relatively frequent. Median Eastern Cooperative Oncology Group (ECOG) performance status was 0 at the time of CPI initiation.

28/60 patients (47%) received ipilimumab monotherapy; 24/60 (40%) received combination CPI. Seven patients (12%) received pembrolizumab alone, one received nivolumab alone (2%), and two (3%) received alternative combinations. Median number of prior therapies was two. Previous treatment with CPIs was uncommon (8/60, 13.3%) and no patients had had prior admissions for irAEs.

Admissions occurred a median of 73.5 days (range: 18.0-1075.0) after first CPI dose. Presenting symptoms included diarrhea (83/88, 94%), nausea and/or vomiting (32/88, 36%), abdominal pain (37/88, 42%), melena/hematochezia (18/88, 20%), and fecal incontinence (5/88, 6%). In 49/88 admissions (55.7%), corticosteroids had been prescribed prior to admission. Admission chemistries and blood counts were typically within or near the normal range. Patients showed a mild lymphopenia (average 14.6%, 1120 cells/mL), mild anemia (average hemoglobin 12.8 g/dL), and hypoalbuminemia (average 3.6 g/dL). ESR (31.1 mm/h) and CRP (3.3 mg/L) were slightly elevated. One patient tested positive for *Clostridioides difficile* toxin, but the presentation was not consistent with isolated *Clostridioides difficile* colitis.

Cross-sectional imaging was abnormal in 20/38 patients (52.6%). Diagnostic endoscopy was performed during 79/88 admissions (89.8%; 69 admissions with either an upper or lower endoscopy, 10 with both). Luminal inflammation was found in 57/79 endoscopies (72.2%). Nearly all admitted patients

received corticosteroids (57/60, 95.0%), with most instances of admission (77/88, 87.5%) involving at least 1 mg/kg prednisone or equivalent; 70/88 (79.5%) received intravenous high-dose corticosteroid. 3/60 (5.0%) experienced spontaneous symptom resolution without immunosuppression.

30/60 patients (50.0%) ultimately required second-line immunosuppression. Most received infliximab (28/30, 93.3%). Emergent bowel resection occurred in 2 admissions (2.3%), and exploratory laparotomy in 1 (1.1%). Table 1-2 displays the differential associations between selected variables and second-line immunosuppression. Ipilimumab monotherapy ($p = 0.010$), stage III disease post-resection ($p = 0.011$), and the absence of gastrointestinal metastases ($p = 0.028$) were associated with second-line immunosuppression. Patients who received second-line immunosuppression had lower serum albumin ($p = 0.005$), lactate dehydrogenase (LDH) ($p = 0.026$), and relative lymphocyte counts ($p = 0.027$) (Table 1-2). They also tended to be younger with a higher median number of prior oncologic therapies and more weight loss (Table S2).

Second-line immunosuppression was not associated with CTCAE grade, type of CPI treatment, ECOG performance status, corticosteroid use prior to admission, or the presence/absence of radiographic or endoscopic abnormalities (Table 1-2). Presence of melena or hematochezia on admission was associated with CTCAE grade ≥2 (Table 1-3).

Endpoint Assessment

Primary endpoints

We characterized oncologic outcomes and associations with second-line immunosuppression (Table 1-4, Figure 1-2). Overall mean PFS and OS were 23.8 and 36.1 months, respectively (medians 14.5 and 54.6 months). Mean PFS and OS for patients without second-line immunosuppression were 12.2 and 24.2 months (medians 10.8 and 35.6 months). Mean PFS and OS for those who received second-line immunosuppression were 26.4 and 39.4 months (medians 30.6 and 54.6 months). No significant

differences in second-line immunosuppression were observed in PFS (p = 0.367 log-rank, 0.174 Wilcoxon) or OS (p = 0.400 log-rank, 0.298 Wilcoxon).

We also examined oncologic outcomes with respect to the timing of corticosteroid exposure in patients with stage IV melanoma who received at least two cycles of ipilimumab: "early" steroid exposure, defined as corticosteroids within 64 days after CPI administration; and "late" steroid exposure, defined as corticosteroids at least 64 days after CPI administration. Decreased PFS was significantly associated with early steroid exposure (p = 0.045 log-rank, 0.025 Wilcoxon) with a trend toward decreased OS (Figure 1-3b). Similar analyses for different types of corticosteroid exposures on our overall cohort revealed significant differences in two major stratifications (Figure S1) and several borderline differences (data not shown). Similar analyses for the time interval between symptoms and corticosteroid exposures revealed no significant differences in PFS or OS (data not shown). By the same token, "early" admission was associated with poorer PFS at borderline significance (p = 0.133 log-rank, 0.046 Wilcoxon) but showed no significant difference in OS. Timings of analyzed corticosteroid exposures were significantly collinear with time to admission (Figure S2).

Secondary endpoints

Average LOS was 5.8 +/- 4.2 days; median LOS was 4.5 days. Readmission for GEC recrudescence was 33.3% (20/60); 30.0% of the cohort (18/60) were readmitted within 30 days. 10.0% (6/60) required multiple readmissions. Maximum number of readmissions was three. GEC resolution rate was 87.5% (49/56) at one month post-discharge and 98.0% (50/51) at three months post-discharge (Figure 1-4); the same pattern was observed regardless of second-line immunosuppression use. No differences in LOS or rate of readmission for GEC recrudescence between patients who received second-line immunosuppression and those who did not were observed. CTCAE grade was overall not significantly associated with short-term outcomes, but grade 4 severity was associated with LOS approximately one week longer than that of other grades (12.7 days vs. 5.5 days, p = 0.033) and grade 2 cases tended to

worsen within one month of discharge (Table 1-3). The small number of grade 4 cases precluded meaningful long-term survival analysis. Patients who received second-line immunosuppression tended to be readmitted more often ($p = 0.091$) and to require multiple readmissions ($p = 0.055$).

Early IV steroid exposure was associated with lower likelihood of readmission for recrudescence ($p = 0.019$). Any early steroid exposure trended toward lower likelihood of readmission for recrudescence but did not reach significance ($p = 0.060$). No differences were observed in LOS.

Additional Analysis

Melanoma and irAE treatment strategies changed over our study period. We accordingly characterized patterns of second-line immunosuppression use and time from admission to infliximab administration over 2011-2017 in patients receiving ipilimumab-containing regimens. Infliximab use did not vary significantly over the six years studied (Table 1-5a). Likewise, no significant variation was noted in time to infliximab administration (Table 1-5b). Mean time from initial admission to infliximab exposure intervals ranged from 11.3 days in 1/2016-12/2017 to 51.2 days in 1/2014-12/2015; median interval range was small, between 19 days in 1/2016-12/2017 and 20.5 days prior to 1/2014 ($p = 0.188$).

Discussion

We describe the typical disease course of CPI-related GEC requiring hospitalization in patients with advanced melanoma, including post-discharge outcomes, and we identify factors associated with second-line immunosuppression use for symptom control. Survival analysis suggests that while second-line immunosuppression is not associated with worse PFS or OS, increased time from initial CPI to corticosteroid administration is significantly associated with increased PFS and is collinear with time to admission.

From our analysis, we conclude that patients with severe CPI-related GEC generally develop symptoms approximately nine weeks post-initial CPI, one week more than the median time to

presentation for any-severity CPI-related GEC reported previously[62], and are admitted at a median of 10 weeks from initial CPI administration. Our reported age is noticeably higher than a recent study's but corroborates other reported results from mixed inpatient/outpatient cohorts; our time to presentation is aligned with prior studies'.[51,63,64] Common clinical features include diarrhea, abdominal pain, and nausea and vomiting. A smaller proportion also manifested with melena or hematochezia. Compared with the reported presentation of non-severe CPI-related GEC, the severe form of the condition is associated with a higher incidence of melena and hematochezia.[51,64] Intriguingly, we report a lower prevalence of abdominal pain.[51,64]

Diagnostic workup in the overall cohort was notable for the difference between radiography and endoscopy in revealing inflammation. The substantially lower rate at which imaging was performed may reflect adaptation of clinical practice to the fact that radiography was often unremarkable, whereas endoscopy was abnormal in most of the cases in which it was performed. Indeed, several recent investigations have suggested markers for CPI-related GEC development, of which "high-risk" endoscopic findings are the most promising.[40,65-67] In our cohort, second-line immunosuppression was administered at a 50.0% frequency. As expected, this was substantially higher than the 22.5% rate reported in prior studies on any-severity CPI-related GEC.[64] Our rate of surgical therapeutic intervention (5.0%) was comparable to that of prior investigations (6%); we thus stress the need for providers to monitor their patients with severe CPI-related GEC carefully.[64]

Regardless of second-line immunosuppression, however, patients with severe CPI-related GEC are high short-term utilizers of healthcare services. The average LOS for severe CPI-related GEC was nearly two days longer than that of the general cancer patient admission at a comparable institution.[68] Rate of readmission for recrudescence was 33.3%, which is lower than reported overall rates of cancer patient readmission (43%).[68] Our thirty-day rate of readmission for recrudescence (30.0%), however, was substantially higher than reported values for thirty-day unplanned readmission rates in cancer patients

(14.9%).[69] Nevertheless, if patients were not readmitted within the first three months post-discharge, symptoms almost invariably resolved (98.0%) during the same timeframe. Average PFS was comparable to published estimates for standard CPI regimens in advanced melanoma.[27,70]

In our study, more severe relative lymphopenia, lower serum albumin, and lower LDH are significantly correlated with higher chance of second-line immunosuppression use. The absolute differences are small; however, they may indicate underlying mechanisms of disease. Hypoalbuminemia may result from enteric ulcerations that are associated with more severe GEC.[65-67] The difference in relative lymphopenia we observed, without significant difference in absolute lymphopenia, may indicate increased neutrophilic production, driven perhaps in part by elevated interleukin-17 levels due to immunotherapy[58] but more likely by multiple cytokines generated in response to gastrointestinal stromal compromise and subsequent immune activation by microbial products. Lower LDH may suggest that CPI-related GEC which requires hospitalization and second-line immunosuppression is actually a positive prognostic factor for oncologic response.[44] The significant differences in second-line immunosuppression for age, tumor stage, and absence of non-hepatic gastrointestinal tract metastases are most likely due to a heterogeneous population and dose-dependent ipilimumab toxicity: during 2011-2017, a small number of patients with high-risk non-metastatic melanoma were treated with adjuvant ipilimumab at an increased dose. High-dose adjuvant CTLA-4 inhibition has been shown in stage III melanoma to both prolong survival and increase risk of irAE.[71]

We were unable to detect a significant difference in several variables between those who received second-line immunosuppression and those who did not. Though a recent study suggests that sarcopenia and other body composition parameters are associated with ipilimumab-related irAEs[72], relative weight change does not appear to correlate with administration of second-line immunosuppression. Additionally, we found that the CTCAE grading system did not show a statistically significant difference in second-line immunosuppression use or rate of readmission for CTCAE grade. Such findings

demonstrate that substantial heterogeneity in severe CPI-related GEC is not adequately captured by CTCAE alone: a more nuanced classification system with stronger correlation to second-line immunosuppression use and readmission is needed. CTCAE grade 4 cases do present more frequently with melena or hematochezia. CTCAE grade 4 cases also stay approximately one week more in the hospital; however, this is most likely due to a distribution of CTCAE grades very skewed towards 3.

Our survival analyses indicate that second-line immunosuppression in severe CPI-related GEC does not negatively impact oncologic outcomes and does not affect LOS or readmission frequency. Intriguingly, our findings suggest that, in a subset of patients, decreased time from CPI administration to corticosteroids at any dose is linked to poorer PFS. In the same group of patients, decreased time from CPI administration to admission tended toward poorer outcomes as well but did not reach significance by log-rank testing. The two variables were also shown to be highly collinear. Significant differences were noted at a 64 day threshold; other exposure parameters showed borderline significance (Figure S1).

This is compatible with a model of cancer immunotherapy-related autoimmune disease in which corticosteroids impact the antitumor response. Such a model has been previously proposed, though not without controversy.[73] A significant association between long-term corticosteroid administration and poorer oncologic outcomes in patients with non-small-cell lung cancer has been reported[74], and a recent study of ipilimumab-induced hypophysitis in patients with advanced melanoma suggested that higher corticosteroid doses resulted in reduced OS.[75] An alternative model must be kept in mind: patients who were admitted later for CPI-related GEC generally received more immunotherapy, potentially accounting for the observed difference in PFS. While early corticosteroid exposure may indeed lead to poorer survival outcomes and further investigation is needed, we stress that high-dose corticosteroids in acute irAEs constitute lifesaving first-line treatment for many patients.[11]

In addition, our study provides a historical analysis on patterns of ipilimumab use and TNFαi use. Ipilimumab-containing regimens without second-line immunosuppression use peaked in 1/2014-12/2015, and on the whole trended toward more use of second-line immunosuppression. Time from CPI or admission to TNFαi seem to have peaked prior to 1/2014 and in 1/2014-12/2015, respectively; median times to TNFαi administration have stayed essentially constant over the past six years.

Section 2

CPI-related Microscopic Colitis

Background

Correlation of histopathologic examination with endoscopic findings in CPI-related GEC suggests a subset of CPI-related GEC characterized by normal appearing mucosa on endoscopy, but with pathologic findings reminiscent of sporadic microscopic colitis (MC): CPI-related MC.[1] Sporadic MC has a reported incidence of 1-25/100,000 individuals in European and North American studies.[76] MC tends to manifest as a chronic watery diarrhea in older adults, affecting women more frequently than men. Sporadic MC is classified as one of two types based on histopathologic features: lymphocytic colitis and collagenous colitis.[76,77] The pathophysiology of the disease is poorly understood, but the disease is ultimately felt to develop after an aberrant immune response to a specific, unknown antigen in individuals with a baseline genetic risk and particular environmental exposures.[77-81] Potential pharmaceutical triggers include proton pump inhibitors and serotonin modulators.[77]

Diagnosis is confirmed by normal or mildly abnormal endoscopy combined with histopathologic findings of intraepithelial lymphocytosis and lamina propria expansion with a mixed infiltrate of acute and chronic inflammatory cells; in collagenous colitis, a thickened subepithelial collagen band is observed.[76] Standard treatment consists of first-line budesonide; response is generally quite good, with one-third of patients able to achieve lasting disease remission after eight weeks of immunosuppression.[82] Reported outcomes, however, do vary: one recent study suggested that up to 90% of patients with sporadic MC require long-term immunosuppressive maintenance therapy.[83]

Despite multiple similarities between CPI-related and sporadic MC, CPI-related MC may have a more aggressive clinical course and require more intensive immunosuppression.[77] Nevertheless, there are empiric retrospective and clinical data suggesting that this subset of CPI-related GEC patients may respond particularly well to budesonide in the first-line setting.

A single study has evaluated the ability of prophylactic budesonide to reduce the incidence of CPI-related GEC in unselected patients on immunotherapy, and no studies have evaluated the impact of

therapeutic budesonide in CPI-related microscopic colitis.[57] As CPI-related microscopic colitis exhibits significant overlap with sporadic microscopic colitis and given empiric treatment success in individual cases, we felt that there might be significant benefit to therapeutic budesonide administration in this condition. In a small, retrospective pilot cohort of patients with CPI-related MC who received budesonide in their course of immunosuppressive treatment, we aimed to clinically characterize the disease and examine our patients' outcomes.

Methods

Ethics

This retrospective analysis was approved by the Partners Human Research Committee, the Institutional Review Board of the Massachusetts General Hospital (MGH).

Patients

We identified all patients ≥18 years of age who had prior CPI exposure and underwent flexible sigmoidoscopy from 3/1/2017 to 12/31/18 for evaluation of possible colitis. CPI-related MC was defined as clinical and histopathologic evidence of colitis without endoscopic evidence of inflammation (Mayo Endoscopic Score of 0). Diagnoses were confirmed by two reviewers, one with clinical expertise in CPI complications.

Data Collection

We extracted clinical, laboratory, radiographic, and endoscopic data from electronic medical records. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, was used for adverse event classification.

Endpoints

Primary endpoints were time to treatment failure (TTTF), PFS, and OS. Secondary endpoints were description of rate of admission for GEC symptoms; time from symptom onset to resolution; absence of

symptoms at 3 months after initial resolution; discontinuation of CPI due to toxicity; and incidence of new irAE development.

Statistical Analysis

The same software and parameters used in the CPI-related GEC study described in Section 1 were employed here as well.

Results

Characteristics and Clinical Course

Baseline characteristics of patients are summarized in Tables 2-1 and S3 with univariate analyses stratified by GEC subset and budesonide administration, respectively. 28 patients with CPI-related GEC were identified on endoscopy from 3/01/2017 to 12/31/18. 13/28 (46.4%) had CPI-related MC. Cancers represented included primarily advanced-stage hematologic and solid malignancies. 15/28 (53.6%) had standard CPI-related GEC, with the distribution approximately evenly split from Mayo Endoscopic Scores 1-3. Average age on admission for the MC cohort was 62 years; 7/13 (53.8%) were male. We observed no difference in average age or sex distribution of the two cohorts. Patients in both cohorts were treated primarily with PD-1/PD-L1 therapies (MC: 11/13, 84.6%; non-MC: 10/15, 66.7%), frequently in conjunction with traditional chemotherapeutic regimens or other non-immune targeted inhibitors. Metastases to abdominal organs were relatively common; hepatic metastases were less common, as were luminal metastases (Table 2-1). Patients with MC tended to have higher proportions of recent exposure to proton-pump inhibitors (7/13, 53.9%), serotonin modulators (4/13, 30.8%), and hormone exposure (2/13, 15.4%). The majority of the MC (10/13, 76.9%) and non-MC cohorts (9/15, 60.0%) used non-immunosuppressive antidiarrheal medications to help control symptoms: atropine-diphenoxylate, loperamide, and cholestyramine were the three most common medications used.

The overall clinical course of each patient with MC is summarized in Figure 2-1. We assumed that the patient's most recent immunotherapeutic regimen was responsible for the development of MC, and we defined the patient's initial CPI exposure by the first cycle of this treatment regimen. 12/13 (92.3%) patients with MC were treated with budesonide; 2/14 (14.3%) patients with non-MC CPI-related GEC were treated with budesonide in addition to other corticosteroids. Time to symptom onset from initial CPI exposure, then, occurred a median of 88 days later in the MC cohort (Table 2-2), with borderline significance. Median time to symptom onset from the most recent CPI cycle was 5.0 days and 6.0 days for the MC cohort and non-MC cohort, respectively ($p = 0.298$). Time from symptom onset to medical evaluation did not differ significantly between the two groups. Common presenting symptoms included diarrhea (MC: 13/13, 100.0%; non-MC: 14/15, 93.3%). Abdominal pain (38.5% vs. 53.3%) tended to be slightly more prevalent in non-MC GEC ($p = 0.431$), whereas urgency (46.2% vs. 26.7%) tended to be more prevalent in MC ($p = 0.433$). Average CTCAE grade was 2 for both cohorts and its distribution did not show a significant difference between the groups ($p = 0.893$). Initial chemistries and blood counts were typically within or near normal ranges. Slight lymphopenia with corresponding neutrophilia was noted in both cohorts.

Endpoint Assessment

Primary endpoint assessment

We characterized oncologic outcomes associated with budesonide administration (Figure 2-2). The timeframe of our study precluded the presentation of meaningful OS data; our small sample size precluded analysis stratified by tumor type. Univariate Cox regression for the effect of budesonide administration on TTTF showed a hazard ratio of 0.33 (95% CI 0.14-0.81); similar Cox regression analysis for effect on PFS showed a hazard ratio of 0.27 (95% CI 0.07-1.04).

Secondary endpoint assessment

Consistent with earlier onset of symptoms, median time from first CPI exposure to first corticosteroid exposure at any dose was 182.0 days for the MC cohort but 81.0 days for the non-MC cohort ($p = 0.044$). Median time from symptom onset to first corticosteroid exposure at any dose did not differ significantly between cohorts, though MC tended to be treated later (MC: 28.0 days; non-MC: 15.0 days; $p = 0.446$). Less than half of each cohort was admitted for GEC symptoms (MC: 2/13, 15.4%; non-MC: 7/15, 46.7%; $p = 0.695$), though patients with non-MC CPI-related GEC tended to be admitted more often. Median LOS was approximately one week in both cohorts. Median time from symptom onset to resolution did not differ between cohorts (MC: 52.0 days; non-MC: 42.0 days; $p = 0.806$). Median time from treatment to symptom resolution was 14.0 days for the MC cohort and 22.0 days for the non-MC cohort ($p = 0.070$). More than 80% of MC patients were GEC symptom-free at 3 months after initial resolution; more than 90% of non-MC patients were GEC-symptom-free at 3 months ($p = 0.565$). The majority of patients in both cohorts were discontinued from their CPI regimens (MC: 8/13, 61.5%; non-MC: 10/14, 71.4%), primarily due to toxicity (MC: 6/8, 75.0%; non-MC: 10/10, 100.0%). 10/12 (83.3%) patients with MC who received budesonide received further immunotherapy after budesonide had been initiated (Figure 2-1). New irAEs developed at a rate of 23.1% in the MC cohort and 35.7% in the non-MC cohort. Table S5 presents outcome data by budesonide administration.

Additional Analysis

4/13 (30.8%) patients with MC received TNFαi administration for refractory symptoms. Of the four patients, only one received TNFαi after further immunotherapy (Patient 8, Figure 2-1).

Discussion

We defined CPI-related MC as an entity affecting patients with previous exposure to immunotherapy and with clinical as well as histopathologic evidence of colitic inflammation, but without

endoscopic signs of inflammation (Mayo Endoscopic Score 0). This is in contrast to a recent prior study, which allowed for abnormal findings on endoscopy.[77] In this preliminary retrospective analysis, we describe key features of the typical disease course of CPI-related MC and compare them to CPI-related non-MC GEC. We also present a retrospective evaluation of budesonide as first-line treatment for CPI-related MC. Our findings suggest that: (1) CPI-related MC is similar to sporadic MC but more intense in symptoms and requiring more intensive immunosuppression; and (2) budesonide is an effective treatment that prolongs time on immunotherapy.

CPI-related MC occurs across cancer types, suggesting a central drug-related component to its development; we feel that our relatively large proportions of melanoma and non-small cell lung cancer are due to the relatively larger-scale use of immunotherapy for those tumor types. We did not find a female preponderance in our study. In our analysis of the prevalence of selected known risk factors for sporadic MC in CPI-related MC, we found no predictors of disease.[78,84] However, we note that proton pump inhibitor use and hormonal exposure in particular tended to have higher proportions in our MC cohort. Further prospective investigation into these candidate risk factors for CPI-related MC development in the context of current guideline-based management is warranted. We also report a lack of clinical features or laboratory values that were significantly associated with the diagnosis of CPI-related MC as opposed to other non-MC CPI-related GEC. Such a finding highlights the critical role endoscopy plays in the initial workup of CPI-related GEC.

We show that the time interval between CPI exposure and symptom onset tends to be longer by far in CPI-related MC (median 150.0 days) than non-MC GEC (median 66.0 days), and time to immunosuppressive treatment was significantly longer (182 days vs. 81 days, $p = 0.044$). Antidiarrheal medications were used at a somewhat higher rate in patients with MC (76.9% vs. 60.0%). This may suggest that CPI-related MC is a milder, mechanistically distinct form of disease that can be controlled with non-immunosuppressive antidiarrheals alone for a longer period of time. We note that the patients

who received budesonide for MC were able to receive further immunotherapy (Figure 2-1); the majority (9/10) did so without need for second-line immunosuppression.

Even so, budesonide, despite its being a highly effective treatment for long-term sporadic MC control[82], did not prevent an ultimately high rate of second-line TNFαi administration for refractory symptom control in the MC cohort: TNFαi use was 30.8%, compared with reports of TNFαi use at <5% in sporadic MC.[85] Unexpectedly, only one patient who received further immunotherapy after budesonide initiation ultimately required TNFαi for persistent colitis, suggesting that CPI dose-dependence does not necessarily drive MC recurrence. The patient had stage IV melanoma with evidence of hypermutation; the patient's clinical course was notable for concomitant dermatologic irAE at time of initial GEC symptoms and continued Mayo Endoscopic Score 0 on repeated flexible sigmoidoscopy. The rate of admission was 32.1% in our study, and our median LOS was longer than that of severe CPI-related GEC (Section 1) by approximately 3 days. This is most likely due to institutional practice: we prioritize outpatient endoscopies with rapid assessment and intervention in cases of potential CPI-related GEC.

CPI-related MC and non-MC CPI-related GEC alike do lead to an eventual discontinuation of CPI regimen, primarily due to toxicity; these findings are in line with prior literature.[1] Absence of recrudescence after initial symptom control was achieved in over 80% of the MC cohort, at a rate lower of that for severe CPI-related GEC within 3 months (Section 1). It is possible that the patients with MC continue to receive immunotherapy for longer than those patients with severe CPI-related GEC, thus potentiating any dose-dependent adverse effects. The incidence of novel irAE development (23.7%) corroborates prior studies on overall CPI-related GEC rechallenged with immunotherapy[64], but interpretation must be weighed against our findings above suggesting that dose-dependence does not fully explain symptom recrudescence.

Our survival analyses of TTTF and PFS are intriguing and warrant further investigation. Our findings that receiving budesonide is protective in a statistically significant manner against treatment failure (HR

0.331) and is borderline protective against disease progression fit with several models of autoimmune disease triggered by cancer immunotherapy. They may indeed indicate that systemic corticosteroids have a relatively large impact on the antitumor response when compared with budesonide.[1,74,75] Given the known high correlation between having MC and receiving budesonide and given our demonstration that patients with MC experience a longer time interval between CPI and corticosteroid exposure, these findings may instead indicate that increased time between CPI and corticosteroids is beneficial, as previously discussed (Section 1). Alternatively, the increased time on immunotherapy afforded to patients with MC may naturally result in increased TTTF and PFS. Regardless of disease model, however, we show that budesonide is an effective treatment that may result in better oncologic outcomes.

Conclusions and Future Directions

The CPI-related GEC study presented in Section 1 was based upon univariate survival analyses performed in a subset of patients. The findings presented may thus be confounded by multiple factors, including codependence. The cohort's heterogeneous CPI exposure is another potential confounding variable. Other limitations include a retrospective study design, which does not allow for causality inference and is inherently confounded by survival bias. Small sample size limited our power to make statistical observations. The six-year study period encompassed substantial changes in standard-of-care therapy for melanoma.[86,87] Of note, though many patients received ipilimumab monotherapy and few patients received PD-1 targeted monotherapies, combination CPI regimens are well-represented, allowing for limited generalizability but indicating a need for further study.

The CPI-related MC study presented in Section 2 has similar limitations. Its retrospective perspective precluded causal inference and introduced inherent survival bias. Small sample size precluded multivariate regression; we performed univariate Cox regression modeling to ensure that we did not overfit our data. Our short time frame precluded the performance of long-term survival analysis. Several of our variables were highly correlated, limiting our ability to parse out their individual effects and introducing potential codependence into our findings. Most patients studied received PD-1 or PD-L1 inhibitors, reflecting current practice but also potentially reflecting differences risk for this syndrome according to immunotherapeutic agent; our sample size precluded analysis stratified by CPI regimen. Our sample size also precluded analysis by tumor type for our heterogeneous population. Our findings are consequently limited in generalizability, indicating a need for further study.

Typical CPI-related GEC requiring hospitalization manifests within three months of initial CPI with a distinct constellation of clinical features. Diagnostic workup shows multiple abnormalities, several of which may be associated with second-line immunosuppression use. Overall, 50% of patients receive

second-line immunosuppression. Readmission for recrudescence is high. If patients are not readmitted for symptom recrudescence, however, their GEC will most likely substantially improve within three months post-discharge. Second-line immunosuppression has no detrimental effect on oncologic outcomes, but corticosteroid timing may.

CPI-related MC, a subset of CPI-related GEC, is a clinical entity that seems to be distinct from sporadic MC. Known risk factors for sporadic MC may play a role in the development of the CPI-related form of disease. Budesonide is an effective first-line treatment for CPI-related MC and prolongs time on immunotherapy. The rate of subsequent TNFαi use was significantly higher than that in sporadic MC. Univariate Cox regression analysis suggests that budesonide administration is protective against treatment failure and may result in better PFS.

Further studies in CPI-related GEC requiring hospitalization are needed to: (1) add nuance to the "classic" clinical description presented; (2) construct a granular grading system that accounts for inpatient disease severity; (3) corroborate the survival analysis findings presented; and (4) prospectively parse the survival impact of time from initial CPI exposure to corticosteroid administration apart from that of time on immunotherapy. Further investigation into CPI-related MC is also needed: in particular, our findings suggest that a randomized trial for first-line budesonide in this subset of disease may be warranted.

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Tables and Figures

Table 1-1
Selected typical characteristics of patients with CPI-related GEC requiring admission. Univariate analysis displayed.

Table 1-1: Characteristics of the Patients at Baseline				
	Overall	No use of second-line immunosuppression	Use of second line immunosuppression	p-value
Number of patients	60	30/60 (50.0%)	30/60 (50.0%)	1.000
Number of admissions	88	35/88 (39.8%)	53/88 (60.3%)	0.288
Age in years (mean +/- SD)	65.1 +/- 12.2	67.9 +/- 12.3	62.4 +/- 11.6	0.080
Sex (M:F)	38:22	18:12	20:10	0.592
CPI regimen				
Ipilimumab	28/60 (46.7%)	9/30 (30.0%)	19/30 (63.3%)	0.010**
Pembrolizumab	7/60 (11.7%)	6/30 (20.0%)	1/30 (3.3%)	0.103
Nivolumab	1/60 (1.7%)	1/30 (3.3%)	0/30 (0.0%)	1.000
Combination	24/60 (40.0%)	14/30 (46.7%)	10/30 (33.3%)	0.292
Other	2/60 (3.3%)	1/30 (3.3%)	1/30 (3.3%)	1.000
Tumor stage				
II	1/60 (1.7%)	1/30 (3.3%)	0/30 (0.0%)	0.011**
III	7/60 (11.7%)	0/30 (0.0%)	7/30 (23.3%)	
IV	52/60 (86.7%)	29/30 (96.7%)	23/30 (76.7%)	
Prior therapies				
Median number of prior therapies (IQR)	2 (1-3)	1 (1-2)	2 (1-3)	0.076
Resection	46/60 (76.7%)	22/30 (73.3%)	24/30 (80.0%)	0.542
Radiation	25/60 (41.7%)	11/30 (36.7%)	14/30 (46.7%)	0.432
Pegylated interferon	12/60 (20.0%)	4/30 (13.3%)	8/30 (26.7%)	0.197
Targeted inhibitor	15/60 (25.0%)	7/30 (23.3%)	8/30 (26.7%)	0.766
Chemotherapy	2/60 (3.3%)	2/30 (6.7%)	0/30 (0.0%)	0.492
CPI	8/60 (13.3%)	3/30 (10.0%)	5/30 (16.7%)	0.706
Gastrointestinal metastases				
Liver	21/60 (35.0%)	11/30 (36.7%)	10/30 (33.3%)	0.787
Other	13/60 (21.7%)	10/30 (33.3%)	3/30 (10.0%)	0.028**
Median ECOG Performance Status at initial CPI administration (IQR)	0 (0-1)	0 (0-1)	1 (0-1)	0.358

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate. The p-value for survival analysis was determined with log-rank testing.
SD: standard deviation
IQR: interquartile range
ECOG: Eastern cooperative oncology group
CPI: immune checkpoint inhibitor
CTCAE: common terminology criteria for adverse events
**Statistically significant at $\alpha<0.05$

Table 1-2

Selected presenting features of CPI-related GEC requiring hospitalization, together with components and results of initial diagnostic approach. Inadequate bowel preparations obscuring visual examination occurred at a negligible rate. Univariate analysis displayed.

Table 1-2: Selected Features of CPI-related GEC presentation and initial diagnostic approach				
	Overall	No use of second-line immunosuppression	Use of second-line immunosuppression	p-value
Time to presentation, days				
Mean +/- SD	133.1 +/- 199.9	119.8 +/- 138.8	141.8 +/- 232.5	0.616
Median	73.5	93.0	70.0	
Presenting signs and symptoms				
Diarrhea	83/88 (94.3%)	33/35 (94.3%)	50/53 (94.3%)	1.000
Nausea and/or vomiting	32/88 (36.4%)	10/35 (28.6%)	22/53 (41.51%)	0.217
Abdominal pain	37/88 (42.1%)	13/35 (37.1%)	24/53 (45.3%)	0.449
Melena/hematochezia	18/88 (20.5%)	6/35 (17.1%)	12/53 (22.6%)	0.531
Fecal incontinence	5/88 (5.7%)	3/35 (8.6%)	2/53 (3.8%)	0.383
Other	32/88 (36.4%)	14/35 (40.0%)	18/53 (34.0%)	0.564
Percent weight change from baseline	-6% +/- 7%	-5% +/- 5%	-6% +/- 8%	0.275
Median CTCAE symptom grade (IQR)	3 (3-3)	3 (2-3)	3 (3-3)	0.198
Median ECOG Performance Status at admission (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.897
Laboratory results at admission: mean +/- SD				
Routine chemistries	No significant abnormalities	No significant abnormalities	No significant abnormalities	>0.05
Albumin (g/dL)	3.6 +/- 0.6	3.8 +/- 0.6	3.5 +/- 0.6	0.005**
Lactate dehydrogenase (U/L)	251.7 +/- 28.4	309.5 +/- 273.1	189.9 +/- 69.7	0.026**
Erythrocyte sedimentation rate (mm/hr)	31.1 +/- 28.4	31.4 +/- 26.8	30.9 +/- 31.2	0.976
C-reactive protein (mg/L)	3.3 +/- 2.3	4.2 +/- 2.7	2.9 +/- 2.0	0.294
Complete Blood Count (CBC)	No significant abnormalities	No significant abnormalities	No significant abnormalities	>0.05
Lymphocytes, relative (%)	14.6 +/- 2.1	17.2% +/- 10.0%	12.9% +/- 8.0%	0.027**
Lymphocytes, absolute (K cells/mL)	1.12 +/- 0.71	1.31+/- 0.64	1.11 +/- 0.74	0.193
Corticosteroid use at admission	49/88 (55.7%)	17/35 (48.6%)	32/53 (60.4%)	0.275
Diagnostic studies on admission				
Radiographic signs of gastrointestinal inflammation	20/38 (52.6%)	3/10 (30.0%)	17/28 (60.7%)	0.144
Endoscopic signs of gastrointestinal inflammation	54/69 (78.2%)	23/31 (74.2%)	31/38 (81.6%)	0.459

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
Routine chemistries include the following: serum sodium (mmol/L), serum potassium (mmol/L), serum chloride (mmol/L), blood urea nitrogen (mg/dL), serum creatinine (mg/dL), lactate (mmol/L).
Complete blood count includes the following: white blood cells (K cells/mL), hematocrit (%), hemoglobin (g/dL), platelets (K cells/mL).
Other symptoms included fatigue, night sweats, abdominal bloating, chills, dysphagia, and hypotension.
SD: standard deviation
IQR: interquartile range
CTCAE: common terminology criteria for adverse events

ECOG: Eastern cooperative oncology group
Endoscopy includes: esophagogastroduodenoscopy, flexible sigmoidoscopy, and colonoscopy
**Statistically significant at $\alpha<0.05$

Table 1-3
Selected variables regarding patients with CPI-related GEC, stratified by CTCAE grade upon presentation. Univariate analysis displayed.

Table 1-3: Selected Admission-Specific Variables by CTCAE Grade					
	CTCAE 1	CTCAE 2	CTCAE 3	CTCAE 4	p-value
Number of cases	1	13	70	3	0.253
Clinical Features					
Diarrhea	1/1 (100.0%)	12/13 (92.3%)	67/70 (95.7%)	2/3 (66.7%)	0.160
Nausea/vomiting	0/1 (0.0%)	5/13 (38.5%)	26/70 (37.1%)	1/3 (33.3%)	1.000
Abdominal pain	1/1 (100.0%)	5/13 (38.5%)	30/70 (42.9%)	2/3 (66.7%)	0.889
Melena/hematochezia	1/1 (100.0%)	0/13 (0.0%)	15/70 (21.4%)	2/3 (66.7%)	0.042**
Fecal incontinence	1/1 (100.0%)	0/13 (0.0%)	5/70 (7.1%)	0/3 (0.0%)	1.000
Other	0/1 (100.0%)	7/13 (53.9%)	24/70 (34.3%)	1/3 (33.3%)	0.525
Endoscopy abnormalities	N/A	7/10 (70.0%)	44/56 (78.6%)	2/2 (100.0%)	0.808
Time to admission in days					
Mean +/- SD	59 +/- N/A	133.4 +/- 198.2	137.8 +/- 207.7	85 +/- 16.8	
Median	59	74	76.5	91	0.954
Length of stay in days per admission					
Mean +/- SD	6 +/- N/A	5.5 +/- 4.3	5.5 +/- 4.0	12.7 +/- 2.9	
Median	6	4	4	11	0.033**
GEC symptom return to grade 1 or baseline after first admission					
At 1 month post-discharge	1/1 (100.0%)	6/7 (85.7%)	42/46 (91.3%)	0/1 (0.0%)	0.098
At 3 months post-discharge	0/0 (N/A)	5/5 (100.0%)	40/41 (97.6%)	2/2 (100.0%)	1.000

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
CTCAE: Common Terminology Criteria for Adverse Events
GEC: gastroenterocolitis
SD: standard deviation
NE: not estimable
**Statistically significant at $\alpha<0.05$

Table 1-4

Characteristics of later hospital course and post-discharge course as primary and secondary endpoints of the study. GEC symptoms were inquired after at standard oncologic follow-up visits. Of note, the total number of patients decreased over time, yielding decreasing denominators in "GEC symptom resolution after first admission." Univariate analysis displayed.

Table 1-4: Characteristics of Hospital and Post-Discharge Course				
	Overall	No use of second-line immunosuppression	Use of second-line immunosuppression	p-value
Length of stay in days per admission				
Mean +/- SD	5.8 +/- 4.2	5.2 +/- 3.7	6.3 +/- 4.5	0.226
Median	4.5	4.0	5.0	
Readmissions for recrudescence				
Number of patients requiring >1 readmission	20/60 (33.3%)	5/30 (16.7%)	15/30 (50.0%)	0.091
Number of patients requiring ≥1 readmission	6/60 (10.0%)	0/30 (0.0%)	6/30 (20.0%)	0.055
GEC symptom return to grade 1 or baseline after first admission				
At 1 month post-discharge	49/56 (87.5%)	24/28 (85.7%)	25/28 (89.3%)	0.669
At 3 months post-discharge	50/51 (98.0%)	22/23 (95.7%)	28/28 (100.0%)	0.451
Progression-free Survival				
Mean +/- SE	23.8 +/- 2.5	12.2 +/- 1.6	26.4 +/- 3.6	0.367
Median (CI)	14.5 (6.6-NE)	10.8 (4.8-NE)	30.6 (6.5-NE)	
Overall Survival				
Mean +/- SE	36.1 +/- 2.9	24.2 +/- 2.6	39.4 +/- 4.2	0.400
Median (CI)	54.6 (30.8-NE)	35.6 (12.2-NE)	54.6 (13.7-NE)	

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
GEC: gastroenterocolitis
SD: standard deviation
SE: standard error
NE: not estimable

Table 1-5

Univariate analysis of change in selected variables over study's timespan. **(a)** Analysis of ipilimumab use over time. Statistically significant differences not observed. **(b)** Analysis of change in time interval from first admission to TNFαi administration, as surrogate for need for second-line immunosuppression, over study's timespan. No statistically significant differences seen, including in results by individual year (not shown).

Table 1-5a: Univariate Analysis of Ipilimumab Administration by Use of Second-Line Immunosuppression over Study Timespan

		Use of second-line immunosuppression (%)	p-value
	Number of patients with anti-CTLA-4 containing regimen, 2011-2017	29/52 (55.8%)	0.694
	Prior to 1/2013	13/18 (72.2%)	0.564
	1/2014-12/2015	7/23 (30.4%)	
	1/2016-12/2017	9/11 (81.8%)	

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
CTLA-4: cytotoxic T-lymphocyte antigen-4
**Statistically significant at α<0.05

Table 1-5b: Univariate Analysis of Time from First Admission to TNFαi Administration over Study Timespan

			Time to TNFαi (days)	p-value
	Prior to 1/2014	Mean +/- SD	18.1 +/- 12.2	0.188
		Median	20.5	
	1/2014-12/2015	Mean +/- SD	51.2 +/- 68.5	
		Median	19.5	
	1/2016-12/2017	Mean +/- SD	11.3 +/- 46.9	
		Median	19	

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
TNFαi: tumor necrosis factor alpha inhibitor
SD: standard deviation
**Statistically significant at α<0.05

Table 2-1
Selected typical characteristics of patients with confirmed CPI-related GEC on flexible sigmoidoscopy. Univariate analysis by microscopic colitis displayed.

Table 2-1: Characteristics of the Patients at Baseline, with Colitis Subset Stratification				
	Overall	Microscopic colitis	Non-microscopic colitis	p-value
Number of patients	28	13	15	1.000
Age in years				
Mean +/- SD	62.6 +/- 9.2	62.4 +/- 8.6	62.9 +/- 10.0	
Median	62.5	62	64	0.893
Sex (M:F)	16:12	7:6	9:6	0.743
CPI regimen				
Ipilimumab monotherapy	3/28 (10.7%)	1/13 (7.7%)	2/15 (13.3%)	
PD-1 monotherapy	19/28 (67.9%)	10/13 (76.9%)	9/15 (60.0%)	
PD-L1 therapy	2/28 (7.1%)	1/13 (7.7%)	1/15 (6.7%)	0.839
Ipilimumab-PD-1 combination therapy	4/28 (14.3%)	1/13 (7.7%)	3/15 (20.0%)	
Tumor type				
Melanoma	15/28 (53.6%)	6/13 (46.2%)	9/15 (60.0%)	0.464
Non-small cell lung cancer	7/28 (25.0%)	3/13 (23.1%)	4/15 (26.7%)	0.686
Cutaneous squamous cell carcinoma	2/28 (7.1%)	0/13 (0.0%)	2/15 (13.3%)	0.484
Colorectal cancer	1/28 (3.6%)	1/13 (7.7%)	0/13 (0.0%)	0.464
Diffuse large B-cell lymphoma	1/28 (3.6%)	1/13 (7.7%)	0/13 (0.0%)	0.464
Ovarian adenocarcinoma	1/28 (3.6%)	1/13 (7.7%)	0/13 (0.0%)	0.464
Renal cell carcinoma	1/28 (3.6%)	1/13 (7.7%)	0/13 (0.0%)	0.464
Gastrointestinal metastases				
Abdominal viscera	13/28 (46.4%)	8/13 (61.5%)	5/15 (33.3%)	0.136
Liver	4/28 (14.3%)	0/13 (0.0%)	4/15 (26.7%)	0.102
Gastrointestinal lumen	4/28 (14.3%)	1/13 (7.7%)	3/15 (20.0%)	0.600
Antibiotic use w/in 1 month	4/28 (14.3%)	2/13 (15.4%)	3/15 (20.0%)	1.000
Antibiotic use w/in 3 months	5/28 (17.9%)	2/13 (15.4%)	3/15 (20.0%)	1.000
PPI use history	10/28 (35.7%)	7/13 (53.9%)	3/15 (20.0%)	0.114
Serotonin modulator use history	7/28 (25.0%)	4/13 (30.8%)	3/15 (20.0%)	0.670
Hormonal exposure	2/28 (7.1%)	2/13 (15.4%)	0/15 (0.0%)	0.206
Use of other antidiarrheal medications	19/28 (67.9%)	10/13 (76.9%)	9/15 (60.0%)	0.435

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
SD: standard deviation
CPI: immune checkpoint inhibitor
PD-1: programmed cell death receptor-1
PD-L1: programmed cell death receptor-1 ligand
PPI: proton pump inhibitor

Table 2-2
Selected presenting features, together with components and results of diagnostic approaches. Inadequate bowel preparations obscuring visual examination occurred at a negligible rate. Univariate analysis by colitis subset displayed.

Table 2-2: Selected Features of Presentation and Diagnostic Approaches by Colitis Subset					
		Overall	Microscopic colitis	Non-microscopic colitis	p-value
Time from symptom onset to first medical contact (days)					
	Mean +/- SD	8.6 +/- 10.7	6.6 +/- 5.9	10.3 +/- 13.6	
	Median (range)	5	5	8	0.368
Time from first CPI exposure to symptom onset (days)					
	Mean +/- SD	160.3 +/- 172.8	225.0 +/- 214.9	104.1 +/- 103.5	
	Median (range)	72.5	150	66	0.064
Time from most recent CPI exposure to symptom onset (days)					
	Mean +/- SD	10.6 +/- 15.5	7.2 +/- 6.6	13.5 +/- 20.2	
	Median (range)	5	5	6	0.298
Presenting signs and symptoms					
	Diarrhea	27/28 (96.4%)	13/13 (100.0%)	14/15 (93.3%)	1.000
	Nausea and/or vomiting	4/28 (14.3%)	2/13 (15.4%)	2/15 (13.3%)	1.000
	Abdominal pain	13/28 (46.4%)	5/13 (38.5%)	8/15 (53.3%)	0.431
	Urgency	10/28 (35.7%)	6/13 (46.2%)	4/15 (26.7%)	0.433
	Fecal incontinence	5/28 (17.9%)	2/13 (15.4%)	3/15 (20.0%)	1.000
	Melena and/or hematochezia	1/28 (3.6%)	0/13 (0.0%)	1/15 (6.7%)	1.000
	Bloating	3/28 (10.7%)	1/13 (7.7%)	2/15 (13.3%)	1.000
	Weight loss	2/28 (7.1%)	1/13 (7.7%)	2/15 (13.3%)	1.000
	Epigastric burning	1/28 (3.6%)	0/13 (0.0%)	1/15 (6.7%)	1.000
CTCAE symptom grade: median (IQR)		2 (1-3)	2 (1-3)	2 (1-3)	0.893
Laboratory results at symptom evaluation					
	Routine chemistries	No significant abnormalities	No significant abnormalities	No significant abnormalities	>0.05
	Albumin (g/dL)	4.2 +/- 0.7	4.4 +/- 0.9	3.9 +/- 0.4	0.075
	Lactate dehydrogenase (U/L)	218.7 +/- 86.1	229.2 +/- 103.9	211.7 +/- 78.1	0.715
	Complete blood count	No significant abnormalities	No significant abnormalities	No significant abnormalities	>0.05
	Neutrophils, relative	69.0% +/- 11.0%	68.0% +/- 7.3%	69.9% +/- 13.6%	0.662
	Neutrophils, absolute (k cells/mL)	5.95 +/- 5.59	4.79 +/- 1.59	6.96 +/- 7.46	0.314
	Lymphocytes, relative	19.3% +/- 6.2%	19.6% +/- 5.5%	18.9% +/- 7.0%	0.777
	Lymphocytes, absolute (k cells/mL)	1.75 +/- 2.17	1.31 +/- 0.35	2.15 +/- 2.99	0.324
	Eosinophils, relative	2.4% +/- 2.1%	2.2% +/- 1.7%	2.6% +/- 2.5%	0.707
	Eosinophils, absolute (k cells/mL)	0.16 +/- 0.15	0.16 +/- 0.15	0.17 +/- 0.15	0.943
	Elevated TTG IgA titer	1/13 (7.7%)	0/9 (9.0%)	1/4 (25.0%)	0.308
Endoscopic abnormalities					
	Mayo score 0	13	-	-	-

	Mayo score 1	5	-	-	-
	Mayo score 2	6	-	-	-
	Mayo score 3	3	-	-	-

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
SD: standard deviation
CTCAE: Common Terminology Criteria for Adverse Events
IQR: interquartile range
TTG IgA: tissue transglutaminase immunoglobulin A

Table 2-3

Characteristics of short-term and long-term outcomes as endpoints of the study. GEC symptoms were inquired after at standard oncologic follow-up visits. Of note, the total number of patients decreased over time, yielding decreasing denominators in "Absence of symptom recrudescence." Univariate analysis by colitis subset displayed.

Table 2-3: Short-term and Long-term Outcomes Stratified by Colitis Subset				
	Overall	Microscopic colitis	Non-microscopic colitis	p-value
Interventions				
Corticosteroids < 1 mg/kg/d, non-budesonide	10/18 (35.7%)	2/13 (15.4%)	8/15 (53.3%)	0.055
Corticosteroids ≥ 1 mg/kg/d	6/28 (21.4%)	1/13 (7.7%)	5/15 (33.3%)	0.173
TNFαi administered	11/28 (38.3%)	4/13 (30.8%)	7/15 (46.7%)	0.390
Time from first CPI to first corticosteroid exposure (days)				
Mean +/- SD	187.8 +/- 176.9	258.2 +/- 212.3	122.4 +/- 106.9	
Median (range)	116	182	81	0.044**
Time from symptom onset to first corticosteroid exposure (days)				
Mean +/- SD	29.1 +/- 26.2	33.2 +/- 26.0	25.3 +/- 26.8	
Median (range)	18	28	15	0.446
Admissions	9/28 (32.1%)	2/13 (15.4%)	7/15 (46.7%)	0.695
Length of stay (days)				
Mean +/- SD	8.8 +/- 3.8	7.5 +/- 2.1	9.1 +/- 4.2	
Median	7	7.5	7	0.620
Time from symptom onset to GEC symptom resolution (days)				
Mean +/- SD	48.8 +/- 25.2	50.1 +/- 21.2	47.7 +/- 29.0	
Median	50.5	52	42	0.806
Time from treatment to GEC symptom resolution (days)				
Mean +/- SD	24.4 +/- 20.4	16.9 +/- 11.8	30.9 +/- 24.2	
Median	17	14	22	0.070
Absence of symptom recrudescence				
At 1 month after initial resolution	21/27 (77.8%)	10/12 (83.3%)	11/15 (73.3%)	0.662
At 2 months after initial resolution	20/25 (80.0%)	8/11 (72.7%)	12/14 (85.7%)	0.623
At 3 months after initial resolution	22/25 (88.0%)	9/11 (81.8%)	13/14 (92.9%)	0.565
At 6 months after initial resolution	16/20 (80.0%)	6/8 (75.0%)	10/12 (83.3%)	1.000
At 12 months after initial resolution	11/14 (78.6%)	4/6 (66.7%)	7/8 (87.5%)	0.538
Discontinuation of CPI	18/27 (66.7%)	8/13 (61.5%)	10/14 (71.4%)	0.695
Due to toxicity	16/18 (88.9%)	6/8 (75.0%)	10/10 (100.0%)	
Due to progression of disease	2/18 (11.1%)	2/8 (25.0%)	0/10 (0.0%)	0.183
Incidence of novel irAEs	8/27 (29.6%)	3/13 (23.1%)	5/14 (35.7%)	0.678

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
TNFαi: Tumor necrosis factor α inhibition
CPI: immune checkpoint inhibitor
SD: standard deviation
GEC: gastroenterocolitis

irAE: immune-related adverse event

Figure 1-1
Process diagram depicting the generation of the patient cohort upon which descriptive and analytic statistics were performed. Patients were excluded at the initial screening for the following reasons: under 18 years of age; admitted for primary hospital problems unlikely to be secondary to irAEs. Patients were excluded at the second screening for the following reasons: complete absence of diarrhea, nausea/vomiting, or abdominal pain; otherwise admitted for primary hospital problems definitively not secondary to CPI-related GEC. Patients were excluded at the audits stage by expert opinion after careful electronic medical record review.

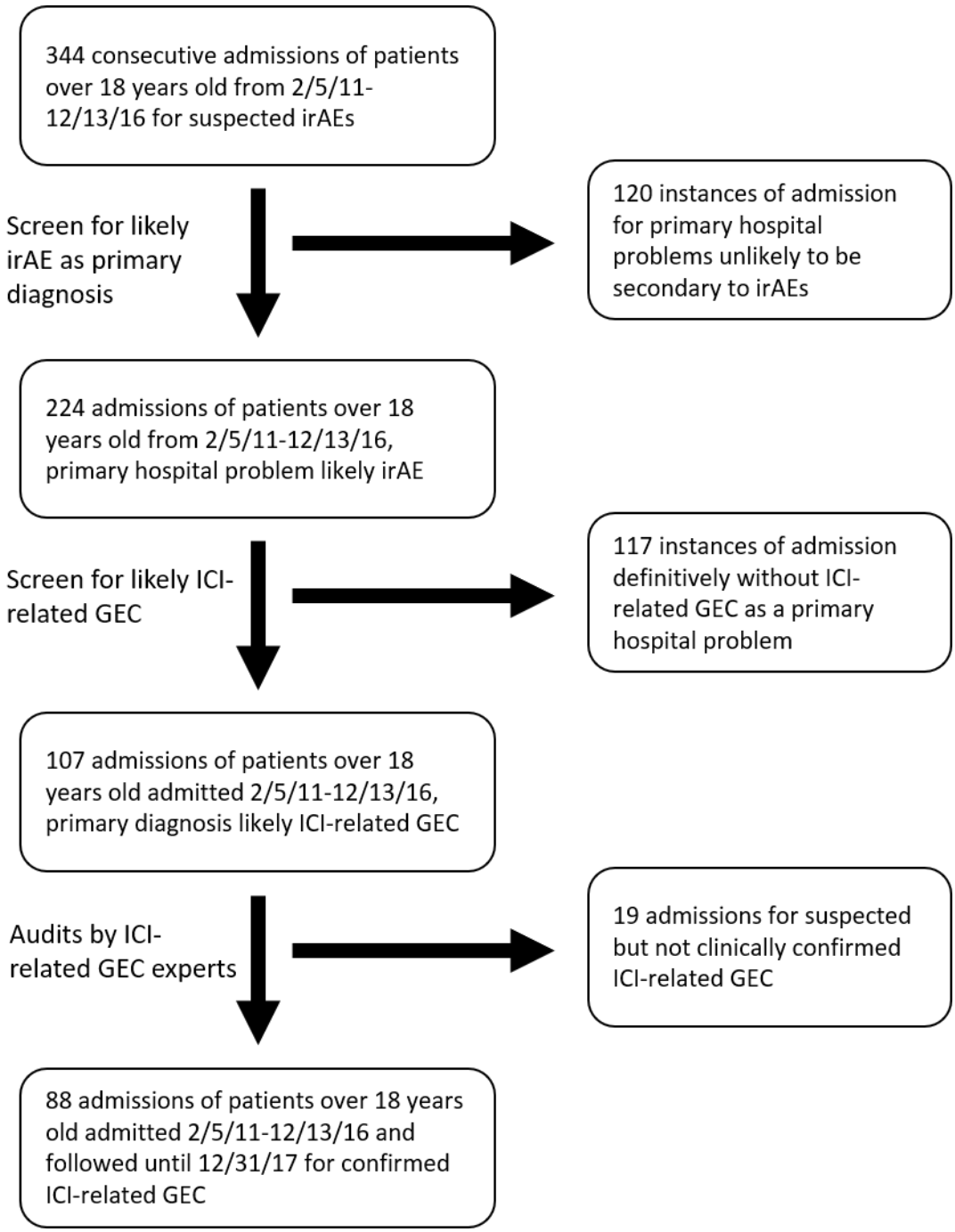
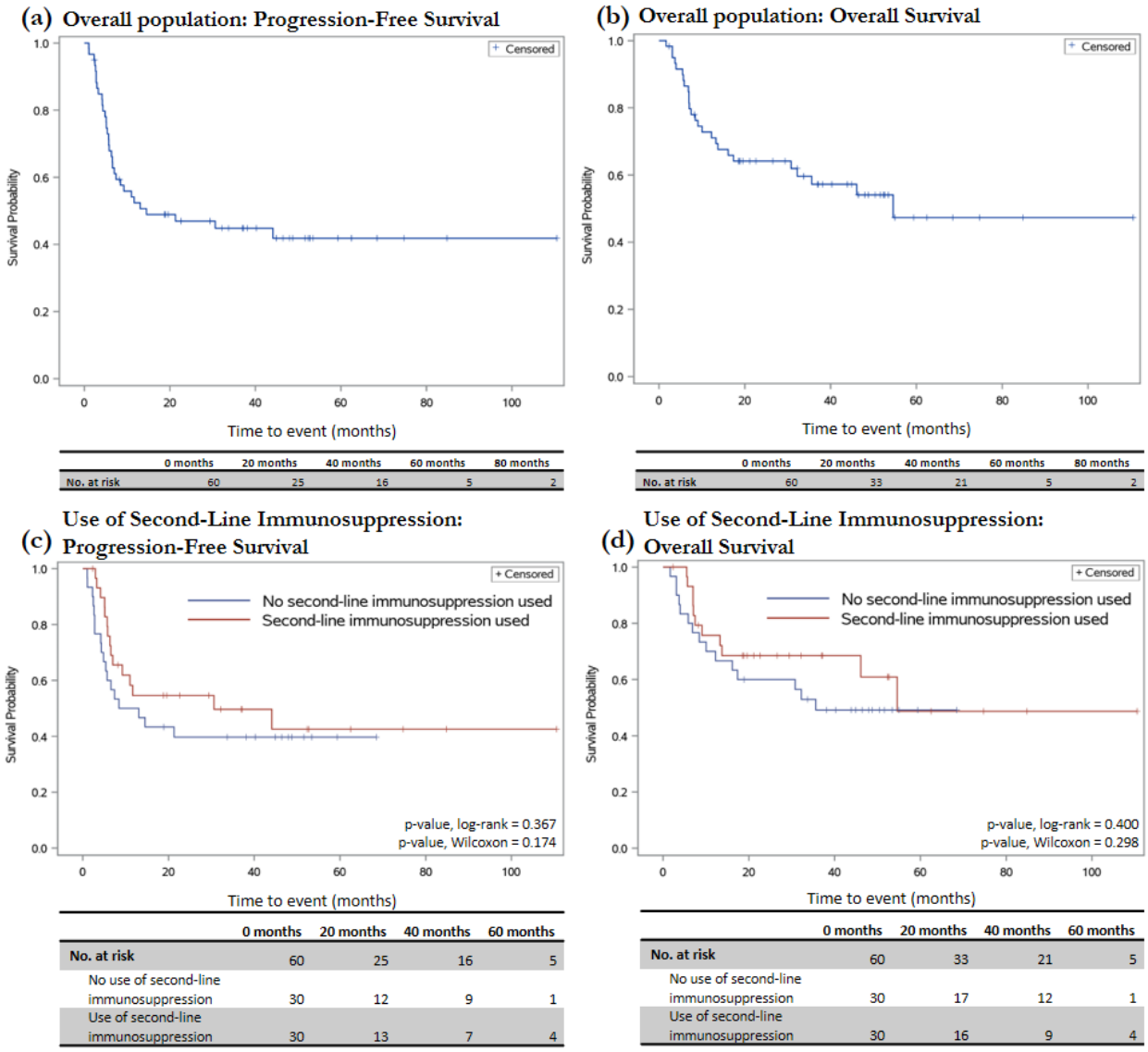


Figure 1-2
Kaplan-Meier survival graphs depicting oncologic outcomes. PFS: progression-free survival. OS: overall survival. CI: confidence interval. **(a)** PFS, overall population. **(b)** OS, overall population. **(c)** PFS, stratified by use of second-line immunosuppression. **(d)** OS, stratified by use of second-line immunosuppression.



	0 months	20 months	40 months	60 months	80 months
No. at risk	60	25	16	5	2

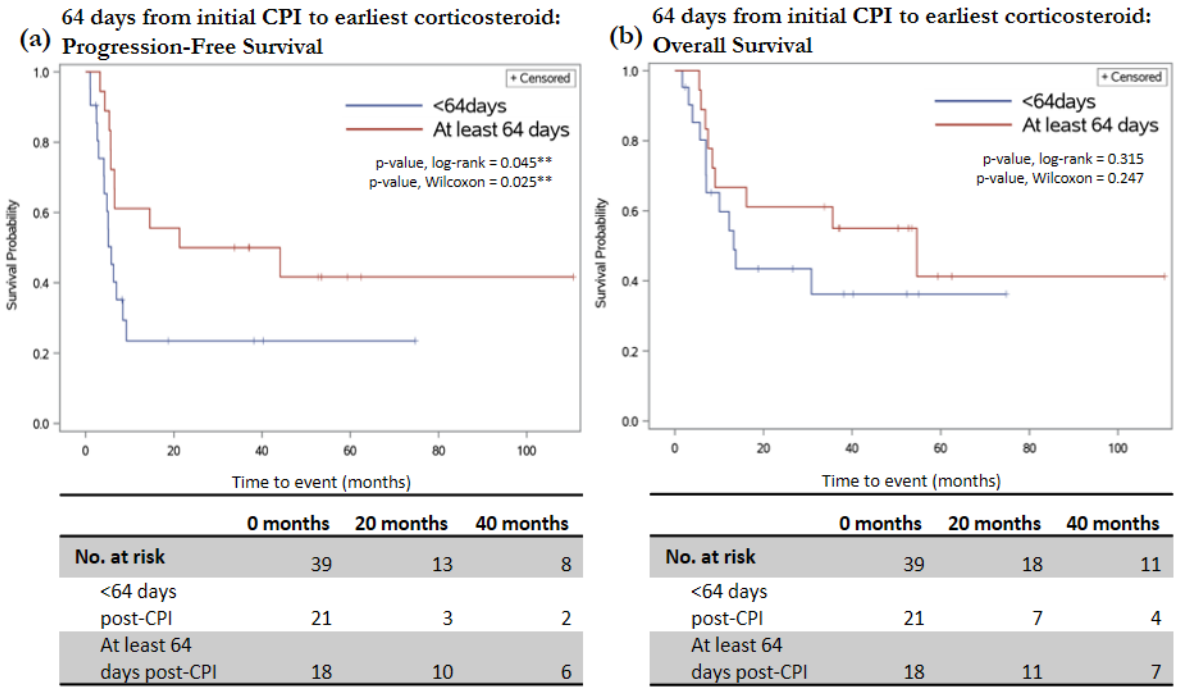
	0 months	20 months	40 months	60 months	80 months
No. at risk	60	33	21	5	2

	0 months	20 months	40 months	60 months
No. at risk	60	25	16	5
No use of second-line immunosuppression	30	12	9	1
Use of second-line immunosuppression	30	13	7	4

	0 months	20 months	40 months	60 months
No. at risk	60	33	21	5
No use of second-line immunosuppression	30	17	12	1
Use of second-line immunosuppression	30	16	9	4

Figure 1-3

Kaplan-Meier survival curves for oncologic outcomes in patients with stage IV melanoma who received at least two cycles of ipilimumab, stratified by corticosteroid exposure. Time threshold: 64 days. One patient had unclear corticosteroid dosing timing and was therefore not included in this analysis. ** denotes significance at $\alpha<0.05$. **(a)** PFS, stratified by time from initial CPI administration to earliest corticosteroid exposure at any dose. **(b)** OS, stratified by time from initial CPI administration to earliest corticosteroid exposure at any dose.



	0 months	20 months	40 months
No. at risk	39	13	8
<64 days post-CPI	21	3	2
At least 64 days post-CPI	18	10	6

	0 months	20 months	40 months
No. at risk	39	18	11
<64 days post-CPI	21	7	4
At least 64 days post-CPI	18	11	7

Figure 1-4
Proportions of patients with GEC symptom resolution to grade 1 or baseline, stratified by second-line immunosuppression. $p > 0.05$ by ANOVA.

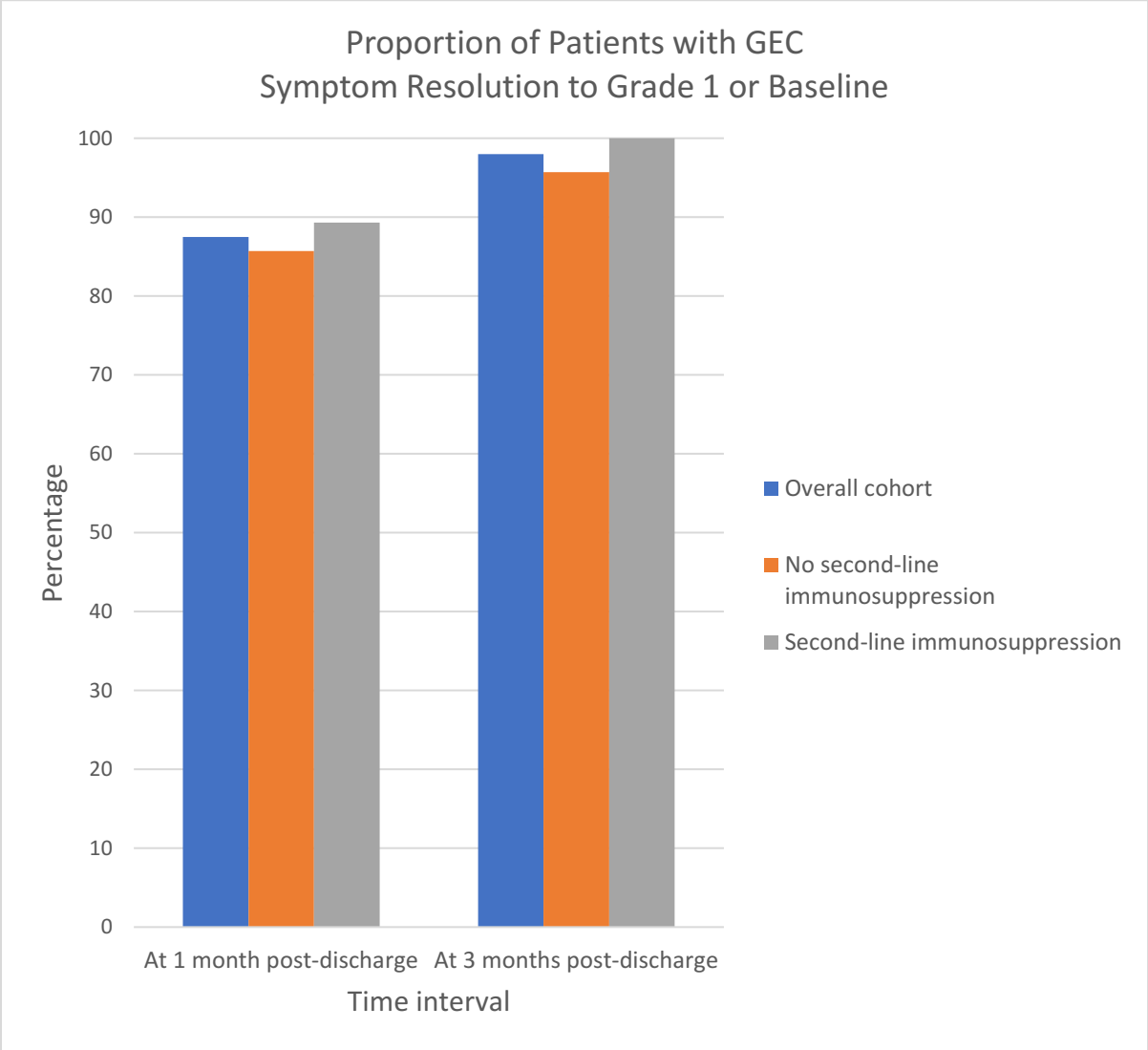
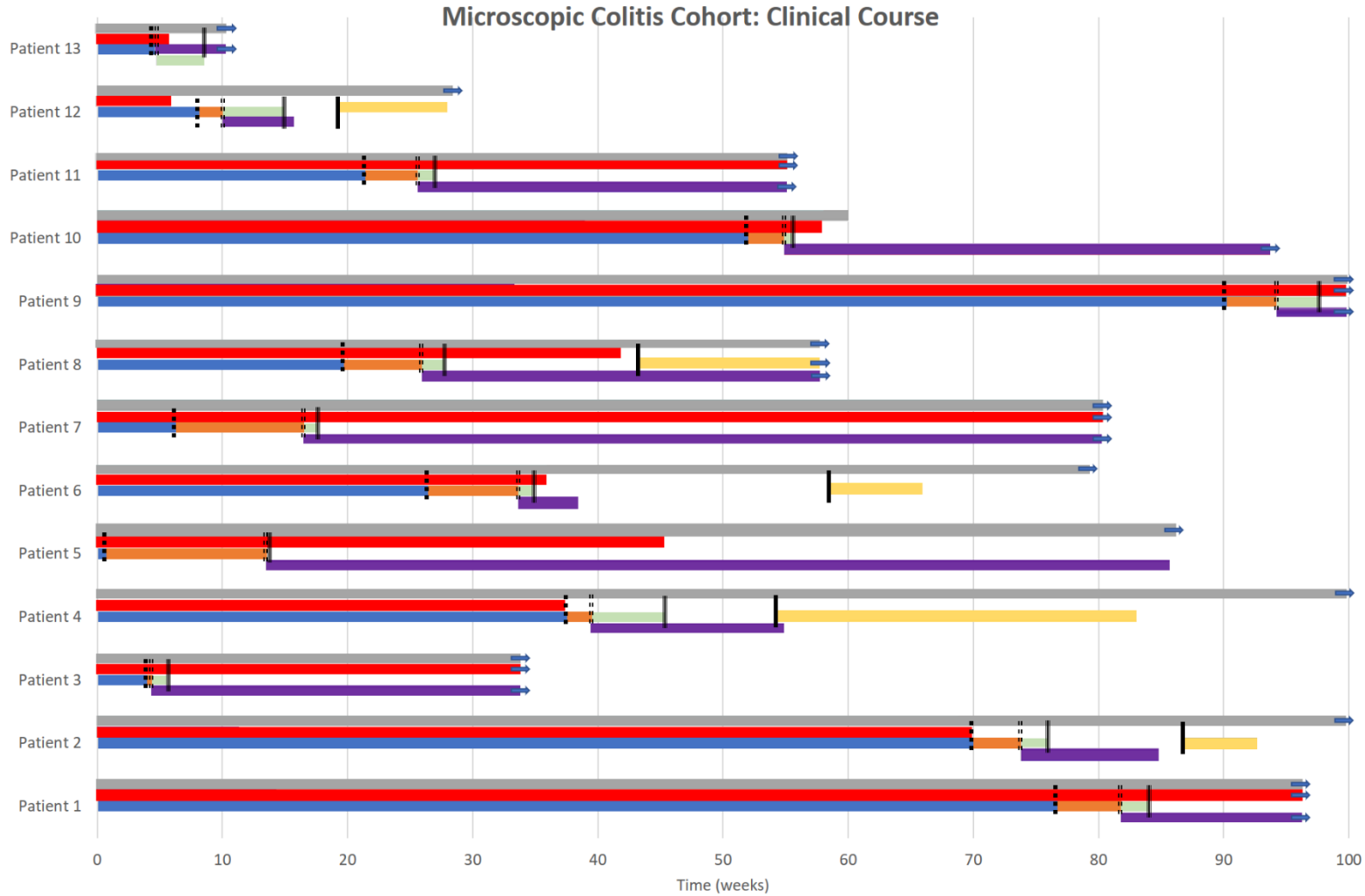


Figure 2-1

Complete clinical course for all patients with CPI-related MC, with legend below. Symptom recurrences shown if at least one week in duration. Of note, Patient 12 did not receive budesonide and received guideline-dose corticosteroids, represented in purple below. Arrows indicate extension of specified time interval through last recorded healthcare contact.



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12*	Patient 13
Duration of CPI regimen	>96	69	>34	37	45	36	>80	42	>128	58	>55	6	>6
Time since first CPI cycle to symptom onset	77	70	4	38	1	26	6	20	90	52	21	8	5
Time from symptoms to budesonide	5	4	0	2	13	7	10	6	4	3	4	2	0
Duration of budesonide	>14	11	>29	16	72	5	>64	>32	>34	>39	>29	7	7
Time to initial symptom resolution	2	2	1	6	0	1	1	2	3	1	1	5	4
Duration of symptom recurrence	None	6	None	29	None	8	None	15	None	None	None	9	None
Time to progression	CR	PR	Mixed	CR	86	PR	PR	NED (baseline)	PR	60	PR	Mixed	No eval yet

Symptom onset

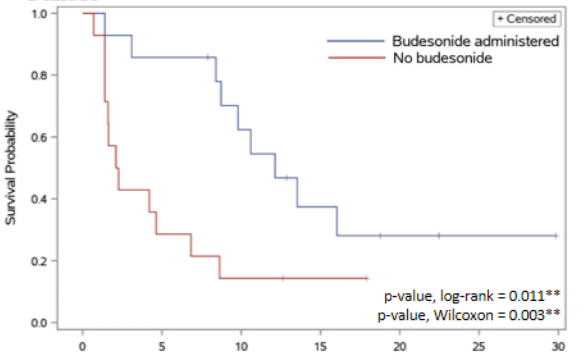
Budesonide initiation

Symptom resolution

Symptom recurrence

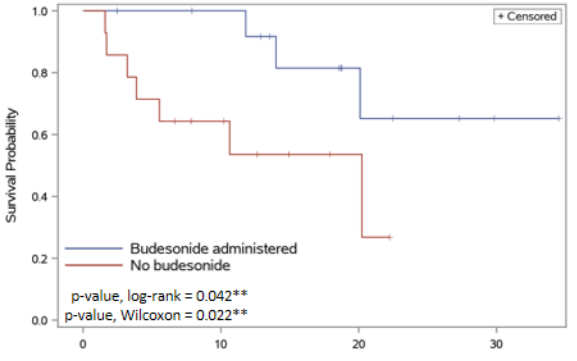
Figure 2-2
Kaplan-Meier survival curves for TTTF and PFS. ** denotes significance at α<0.05. **(a)** TTTF, stratified by budesonide exposure. **(b)** PFS, stratified by budesonide exposure.

(a) Budesonide Exposure: Time to Treatment Failure



	0 months	5 months	10 months	15 months
No. at risk	28	16	10	5
Budesonide administered	14	12	8	4
No budesonide administered	14	4	2	1

(b) Budesonide Exposure : Progression-Free Survival



	0 months	5 months	10 months	15 months
No. at risk	28	16	19	11
Budesonide administered	14	13	12	8
No budesonide administered	14	10	7	3

Supplemental Table 1
Full listing of data collection variables determined *a priori* from clinical experience, sorted alphabetically.

Table S1: Full List of Variables Specified prior to Data Collection
Age of patient at time of admission
Age of patient at time of initial CPI administration
Antibiotics within one month of admission
Antibiotics within three months of admission
CTCAE grade at admission
Date of admission
Date of birth
Date of condition worsening while inpatient, if any
Date of discharge
Date of infliximab administration
Date of last known MGH healthcare contact
Date of symptom onset
Deceased vs. alive
Destination of discharge
DFJV Disease Group
Dose of alternative second-line immunosuppressive agent
Dose of corticosteroids patient was taking upon admission
Duration of alternative second-line immunosuppressive agent
Duration of inpatient methylprednisolone regimen
Duration of prednisolone regimen started inpatient
ECOG performance status: at admission
ECOG performance status: at initial CPI administration
Endoscopy, lower: findings
Endoscopy, lower: locations examined
Endoscopy, upper: findings
Endoscopy, upper: locations examined
Fecal studies: calprotectin
Fecal studies: fecal leukocyte count
Fecal studies: osmolar gap
Fecal studies: stool culture
Further oncologic outcomes, if rechallenged with CPI
Hepatitis B serology screening
Histopathologic results from lower endoscopy
Histopathologic results from upper endoscopy
HLA typing, if applicable
CPI rechallenge status
CPI regimen
CPI-related GEC outcomes, 1 month post-discharge: CT findings
CPI-related GEC outcomes, 1 month post-discharge: endoscopic findings
CPI-related GEC outcomes, 1 month post-discharge: subjective findings
CPI-related GEC outcomes, 12 months post-discharge: CT findings
CPI-related GEC outcomes, 12 months post-discharge: endoscopic findings
CPI-related GEC outcomes, 12 months post-discharge; subjective findings
CPI-related GEC outcomes, 18 months post-discharge: CT findings
CPI-related GEC outcomes, 18 months post-discharge: endoscopic findings
CPI-related GEC outcomes, 18 months post-discharge: subjective findings

CPI-related GEC outcomes, 24 months post-discharge: CT findings
CPI-related GEC outcomes, 24 months post-discharge: endoscopic findings
CPI-related GEC outcomes, 24 months post-discharge: subjective findings
CPI-related GEC outcomes, 3 months post-discharge: CT findings
CPI-related GEC outcomes, 3 months post-discharge: endoscopic findings
CPI-related GEC outcomes, 3 months post-discharge: subjective findings
CPI-related GEC outcomes, 6 months post-discharge: CT findings
CPI-related GEC outcomes, 6 months post-discharge: endoscopic findings
CPI-related GEC outcomes, 6 months post-discharge: subjective findings
CPI-related GEC outcomes, 9 months post-discharge: CT findings
CPI-related GEC outcomes, 9 months post-discharge: endoscopic findings
CPI-related GEC outcomes, 9 months post-discharge: subjective findings
Infectious disease studies: Adenovirus
Infectious disease studies: Clostridium difficile assay
Infectious disease studies: Cryptosporidium
Infectious disease studies: Cytomegalovirus
Infectious disease studies: Giardia
Infectious disease studies: Helicobacter pylori stool antigen/breath test
Infectious disease studies: Microsporidium
Infectious disease studies: other testing
Infectious disease studies: Rotavirus
Infectious disease studies: stool ova and parasites examination
Initial CPI exposure
Laboratory testing: Albumin (upon admission and additionally if required critical care)
Laboratory testing: Blood urea nitrogen (upon admission and additionally if required critical care)
Laboratory testing: C-reactive protein (upon admission and additionally if required critical care)
Laboratory testing: Erythrocyte sedimentation rate (upon admission and additionally if required critical care)
Laboratory testing: Hematocrit (upon admission and additionally if required critical care)
Laboratory testing: Hemoglobin (upon admission and additionally if required critical care)
Laboratory testing: Lactate (upon admission and additionally if required critical care)
Laboratory testing: Lactate dehydrogenase (upon admission and additionally if required critical care)
Laboratory testing: Leukocyte count (upon admission and additionally if required critical care)
Laboratory testing: Relative lymphocyte count (upon admission and additionally if required critical care)
Laboratory testing: Serum chloride (upon admission and additionally if required critical care)
Laboratory testing: Serum creatinine (upon admission and additionally if required critical care)
Laboratory testing: Serum ferritin (upon admission and additionally if required critical care)
Laboratory testing: Serum iron (upon admission and additionally if required critical care)
Laboratory testing: Serum platelets (upon admission and additionally if required critical care)
Laboratory testing: Serum potassium (upon admission and additionally if required critical care)
Laboratory testing: Serum sodium (upon admission and additionally if required critical care)
Laboratory testing: Tissue transglutaminase IgA (upon admission and additionally if required critical care)
Laboratory testing: Total protein (upon admission and additionally if required critical care)
Laboratory testing: Vitamin B12
Length of stay
Lower endoscopy modality
Maximum dose of inpatient methylprednisolone
Maximum dose of inpatient prednisolone
Maximum dose of TNFαi
Maximum irAE severity grade
Medical Record Number

Most intensive treatment location: general ward vs intensive care
New GEC recurrence, if rechallenged with CPI
New irAE occurrence, if rechallenged with CPI
New irAE severity, if rechallenged with CPI
Number of prior therapies
Oncologic outcomes at 18 months post-discharge, 18mo
Oncologic outcomes at 24 months post-discharge
Oncologic outcomes at nine months post-discharge
Oncologic outcomes at one month post-discharge
Oncologic outcomes at one year post-discharge
Oncologic outcomes at six months post-discharge
Oncologic outcomes at three months post-discharge
Outcome of new irAE, if rechallenged with CPI
Pneumocystis jirovecii pneumonia prophylaxis
Presence and location of gastrointestinal metastases at time of admission
Prior oncologic regimens
Purified protein derivative testing/other tuberculosis screening test result
Putative location of inflammation at admission
Radiographic imaging: bowel wall thickening
Radiographic imaging: diffuse inflammation
Radiographic imaging: fluid-filled distention
Radiographic imaging: mesenteric vessel engorgement
Radiographic imaging: perf (worst)
Radiographic imaging: segmental inflammation a/w diverticulosis
Redosing of TNFαi
Requirement for critical care at admission
Sex
Significant tumor cytogenetic abnormalities
Status of oncologic response at time of discharge
Study identifier
Symptoms and signs that prompted application of critical care
Symptoms/signs at presentation
Time from initial CPI administration to admission
Time from initial CPI administration to hepatitis B serology testing
Time from initial CPI administration to symptom onset
Time from initial CPI administration to tuberculosis screening
Time from symptom onset to admission
Time to corticosteroid administration or other GEC-related intervention from admission
Time to earliest methylprednisolone dose from admission
Time to CPI rechallenge from last CPI dose prior to most recent admission
Treatment regimen for new irAE, if rechallenged with CPI
Tuberculosis screening
Tumor stage
Type of irAE
Upper endoscopy modality
Use of alternative second-line immunosuppression, and if so agent used
Use of corticosteroids upon admission
Use of inpatient antacid regimen
Use of inpatient ciprofloxacin or metronidazole
Use of methylprednisolone prior to TNFαi

Use of oral corticosteroids prior to methylprednisolone
Use of oral corticosteroids prior to TNFαi
Use of other immunosuppression prior to alternative agent
Use of pre-CPI antacid
Weight at initial CPI administration
Weight change
Weight upon admission

Supplemental Table 2

Additional presentation features of CPI-related GEC and results from diagnostic testing, including full routine chemistries and full complete blood count.

Table S2: Additional features of CPI-related GEC presentation and initial diagnostic approach				
	Overall	No use of second-line immunosuppression	Use of second-line immunosuppression	p-value
Laboratory results at admission: mean +/- SD				
Serum sodium (mmol/L)	135 +/- 4	136.1 +/- 2.7	134.9 +/- 4.4	0.133
Serum potassium (mmol/L)	3.9 +/- 0.6	4.0 +/- 0.6	3.8 +/- 0.6	0.273
Serum chloride (mmol/L)	99 +/- 5	100 +/- 3	99 +/- 5	0.354
Blood urea nitrogen (mg/dL)	21.7 +/- 15.1	21.4 +/- 16.2	22.0 +/- 14.4	0.850
Serum creatinine (mg/dL)	1.2 +/- 1.0	1.2 +/- 1.2	1.3 +/- 1.0	0.717
Lactate (mmol/L)	1.7 +/- 1.1	1.8 +/- 1.0	1.6 +/- 1.1	0.766
Leukocytes (K cells/mL)	9.04 +/- 3.81	8.95 +/- 4.37	9.11 +/- 3.42	0.850
Hgb (g/dL)	12.8 +/- 2.0	12.5 +/- 1.6	13.0 +/- 2.2	0.247
Hct (%)	38.3 +/- 5.1	37.6 +/- 4.1	38.7 +/- 5.7	0.300
Plt (K cells/mL)	273 +/- 90	263 +/- 87	280 +/- 92	0.389
Diagnostic studies on admission				
EGD signs of GI inflammation	8/12 (66.7%)	4/4 (100.0%)	4/8 (50.0%)	0.208
Lower endoscopy signs of GI inflammation	49/67 (73.1%)	20/29 (69.0%)	29/38 (76.3%)	0.501

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
SD: standard deviation
IQR: interquartile range
ECOG: Eastern cooperative oncology group
CTCAE: common terminology criteria for adverse events
LDH: lactate dehydrogenase
GI: gastrointestinal
EGD: esophagogastroduodenoscopic

Supplemental Table 3:
Selected typical characteristics of patients with confirmed CPI-related GEC on flexible sigmoidoscopy. Univariate analysis by budesonide administration displayed.

Table S3: Characteristics of the Patients at Baseline, Stratified by Budesonide Administration				
	Overall	Budesonide received	No budesonide	p-value
Number of patients	28	14	14	1.000
Age in years				
Mean +/- SD	62.6 +/- 9.2	63.4 +/- 9.5	61.9 +/- 9.2	
Median	62.5	62.5	62	0.660
Sex (M:F)	16:12	8:6	8:6	1.000
CPI regimen				
Ipilimumab monotherapy	3/28 (10.7%)	0/14 (0.0%)	3/14 (21.4%)	0.164
PD-1 monotherapy	19/28 (67.9%)	12/14 (85.7%)	7/14 (50.0%)	
PD-L1 therapy	2/28 (7.1%)	1/14 (7.1%)	1/14 (7.1%)	
Ipilimumab-PD-1 combination therapy	4/28 (14.3%)	1/14 (7.1%)	3/14 (21.4%)	
Gastrointestinal metastases				
Abdominal viscera	13/28 (46.4%)	8/14 (57.1%)	5/14 (35.7%)	0.256
Liver	6/28 (21.4%)	2/14 (14.3%)	4/14 (28.6%)	0.648
Gastrointestinal tract	4/28 (14.3%)	0/14 (0.0%)	4/14 (28.6%)	0.098
Antibiotic use w/in 1 month	4/28 (14.3%)	1/14 (7.1%)	3/14 (21.4%)	0.596
Antibiotic use w/in 3 months	5/28 (17.9%)	1/14 (7.1%)	4/14 (28.6%)	0.326
PPI use history	10/28 (35.7%)	6/14 (42.9%)	4/14 (28.6%)	0.430
Serotonin modulator use history	7/28 (25.0%)	4/14 (28.6%)	3/14 (21.4%)	1.000
Hormonal exposure	2/28 (7.1%)	1/14 (7.1%)	1/14 (7.1%)	1.000
Use of other antidiarrheal medications	19/28 (67.9%)	9/14 (64.3%)	10/14 (71.4%)	1.000

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
SD: standard deviation
CPI: immune checkpoint inhibitor
PD-1: programmed cell death receptor 1
PD-L1: programmed cell death receptor 1 ligand
PPI: proton pump inhibitor

Supplemental Table 4
Selected presenting features with diagnostic approaches in patients with confirmed CPI-related GEC upon flexible sigmoidoscopy, stratified by budesonide administration. ** denotes significance at $\alpha<0.05$.

Table S4: Selected Features of Presentation and Diagnostic Approaches by Budesonide Administration					
		Overall	Microscopic colitis	Non-microscopic colitis	p-value
Time from symptom onset to first medical contact (days)					
	Mean +/- SD	8.6 +/- 10.7	6.6 +/- 5.7	10.6 +/- 14.0	
	Median (range)	5	5	5.5	0.340
Time from first CPI exposure to symptom onset (days)					
	Mean +/- SD	160.3 +/- 172.8	235.9 +/- 209.6	84.6 +/- 75.7	
	Median (range)	72.5	167.5	61.5	0.017**
Time from most recent CPI exposure to symptom onset (days)					
	Mean +/- SD	10.6 +/- 15.5	6.1 +/- 6.1	15.0 +/- 20.5	
	Median (range)	5	4.5	8	0.134
Presenting signs and symptoms					
	Diarrhea	27/28 (96.4%)	14/14 (100.0%)	13/14 (92.9%)	1.000
	Nausea and/or vomiting	4/28 (14.3%)	2/14 (14.3%)	2/14 (14.3%)	1.000
	Abdominal pain	13/28 (46.4%)	4/14 (28.6%)	9/14 (64.3%)	0.058
	Urgency	10/28 (35.7%)	5/14 (35.7%)	5/14 (35.7%)	1.000
	Fecal incontinence	5/28 (17.9%)	3/14 (21.4%)	2/14 (14.3%)	1.000
	Melena and/or hematochezia	1/28 (3.6%)	0/14 (0.0%)	1/14 (7.1%)	1.000
	Bloating	3/28 (10.7%)	1/14 (7.1%)	2/14 (14.3%)	1.000
	Weight loss	2/28 (7.1%)	1/14 (7.1%)	1/14 (7.1%)	1.000
	Epigastric burning	1/28 (3.6%)	0/14 (0.0%)	1/14 (7.1%)	1.000
CTCAE symptom grade: median (IQR)		2 (1-3)	2 (1-3)	2 (1-3)	0.801
Laboratory results at symptom evaluation					
	Routine chemistries	No significant abnormalities	No significant abnormalities	No significant abnormalities	>0.05
	Albumin (g/dL)	4.2 +/- 0.7	4.3 +/- 0.9	4.0 +/- 0.4	0.191
	Lactate dehydrogenase (U/L)	218.7 +/- 86.1	214.9 +/- 100.2	222.0 +/- 78.7	0.880
	Complete blood count	No significant abnormalities	No significant abnormalities	No significant abnormalities	>0.05
	Neutrophils, relative	69.0% +/- 11.0%	67.2% +/- 7.7%	70.9% +/- 13.5%	0.376
	Neutrophils, absolute (k cells/mL)	5.95 +/- 5.59	4.66 +/- 1.60	7.24 +/- 7.66	0.228
	Lymphocytes, relative	19.3% +/- 6.2%	19.7% +/- 5.3%	18.8% _/- 7.3%	0.707
	Lymphocytes, absolute (k cells/mL)	1.75 +/- 2.17	2.10 +/- 2.99	1.37 +/- 0.52	0.399
	Eosinophils, relative	2.4% +/- 2.1%	2.5% +/- 1.8%	2.3% +/- 2.4%	0.748
	Eosinophils, absolute (k cells/mL)	0.16 +/- 0.15	0.18 +/- 0.15	0.15 +/- 0.15	0.671
	Elevated TTG IgA titer	1/13 (7.7%)	0/9 (0.0%)	1/4 (25.0%)	0.308
Endoscopic abnormalities					
	Mayo score 0	13	-	-	-

	Mayo score 1	5	-	-	-
	Mayo score 2	6	-	-	-
	Mayo score 3	3	-	-	-

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
SD: standard deviation
CTCAE: Common Terminology Criteria for Adverse Events
IQR: interquartile range
TTG IgA: tissue transglutaminase immunoglobulin A

Supplemental Table 5

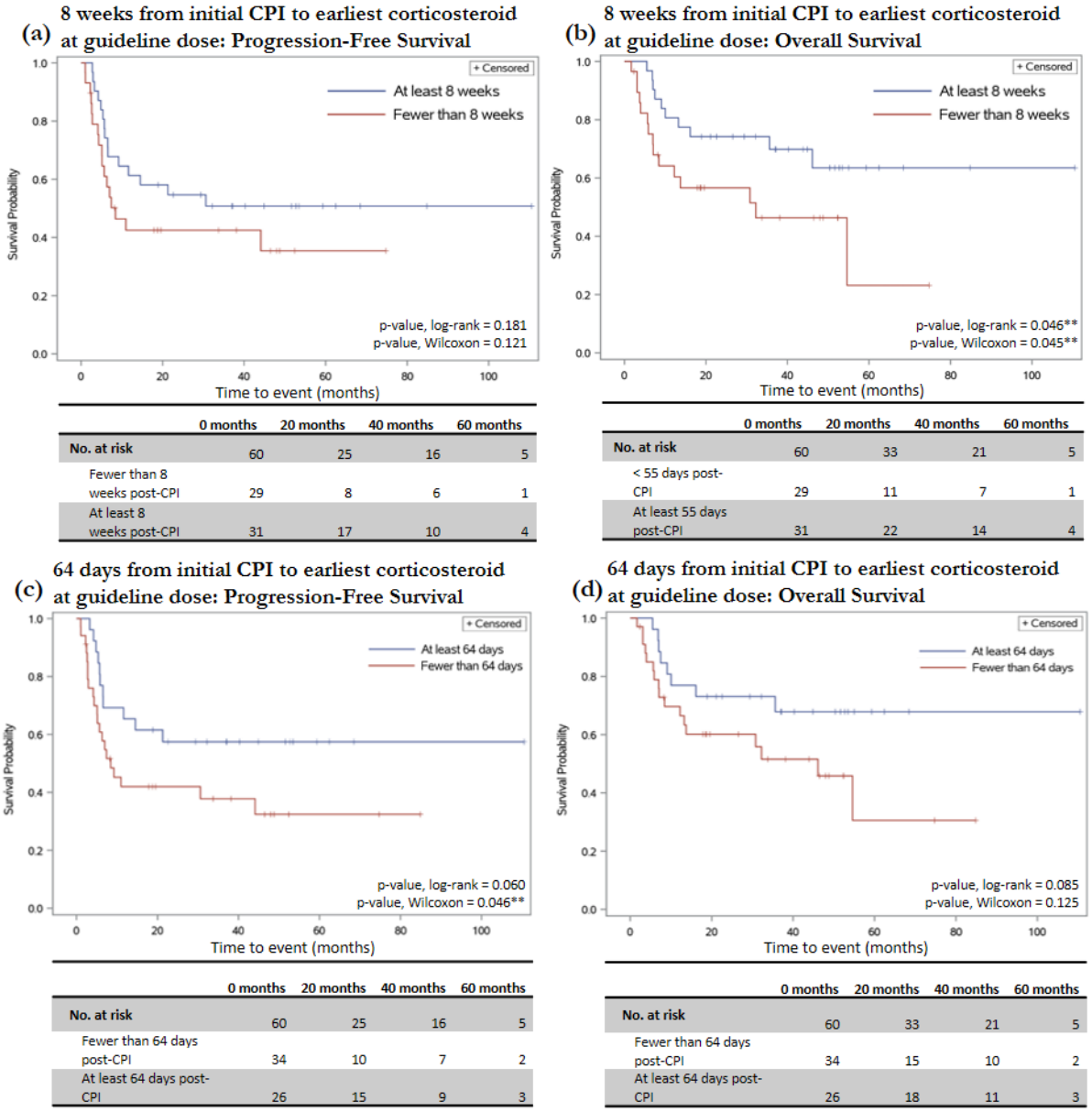
Characteristics of short-term and long-term outcomes as endpoints of the study. GEC symptoms were inquired after at standard oncologic follow-up visits. Univariate analysis by budesonide administration displayed. ** denotes significance at $\alpha<0.05$.

Table S5: Short-term and Long-term Outcomes Stratified by Budesonide Administration				
	Overall	Microscopic colitis	Non-microscopic colitis	p-value
Interventions				
Corticosteroids < 1 mg/kg/d, non-budesonide	10/18 (35.7%)	2/14 (14.3%)	8/14 (57.1%)	0.018**
Corticosteroids ≥ 1 mg/kg/d	6/28 (21.4%)	1/14 (7.1%)	5/14 (35.7%)	0.165
TNFαi administered	11/28 (38.3%)	4/14 (28.6%)	7/14 (50.0%)	0.426
Time from first CPI to first corticosteroid exposure (days)				
Mean +/- SD	187.8 +/- 176.9	258.2 +/- 212.3	122.4 +/- 106.9	
Median (range)	116	182	81	0.044**
Time from symptom onset to first corticosteroid exposure (days)				
Mean +/- SD	29.1 +/- 26.2	33.2 +/- 26.0	25.3 +/- 26.8	
Median (range)	18	28	15	0.446
Admissions	9/28 (32.1%)	4/14 (28.6%)	5/14 (35.7%)	1.000
LOS (days)				
Mean +/- SD	8.8 +/- 3.8	9.3 +/- 4.0	8.4 +/- 4.0	0.761
Median	7	8	7	
Time from symptom onset to GEC symptom resolution (days)				
Mean +/- SD	48.8 +/- 25.2	54.7 +/- 23.6	42.9 +/- 26.3	0.220
Median	50.5	54	41.5	
Time from treatment to GEC symptom resolution (days)				
Mean +/- SD	24.4 +/- 20.4	23.9 +/- 24.2	24.9 +/- 16.6	0.892
Median	17	14.5	21.5	
Absence of symptom recrudescence				
At 1 month after initial resolution	21/27 (77.8%)	12/13 (92.3%)	9/14 (64.3%)	0.695
At 2 months after initial resolution	20/25 (80.0%)	10/12 (83.3%)	10/13 (76.9%)	1.000
At 3 months after initial resolution	22/25 (88.0%)	10/12 (83.3%)	12/13 (92.3%)	0.593
At 6 months after initial resolution	16/20 (80.0%)	7/9 (77.8%)	9/11 (81.8%)	1.000
At 12 months after initial resolution	11/14 (78.6%)	5/7 (71.4%)	6/7 (85.7%)	1.000
Discontinuation of CPI	18/27 (66.7%)	8/13 (61.5%)	10/14 (71.4%)	0.695
Due to toxicity	16/18 (88.9%)	6/8 (75.0%)	10/10 (100.0%)	
Due to progression of disease	2/18 (11.1%)	2/8 (25.0%)	0/10 (0.0%)	0.183
Incidence of novel irAEs	8/27 (29.6%)	2/14 (14.3%)	6/13 (46.2%)	0.103

The p-value was calculated by ANOVA for numerical covariates and chi-square test or Fisher's exact for categorical covariates, where appropriate.
TNFαi: Tumor necrosis factor α inhibition
CPI: immune checkpoint inhibitor
SD: standard deviation
GEC: gastroenterocolitis
irAE: immune-related adverse event

Supplemental Figure 1

Selected Kaplan-Meier survival curves for oncologic outcomes in all patients, stratified by corticosteroid exposure, for which significant differences were noted between groups. Of note, all corticosteroid doses for which we accounted were at least equivalent to prednisolone 7.5 mg/day. Time threshold is specified per graph. Guideline dosing: at least 1 mg/kg/day. ** denotes significance at $\alpha<0.05$. **(a)** PFS, stratified by time from initial CPI administration to earliest corticosteroid exposure at guideline dosing. Time threshold: 8 weeks. **(b)** OS, stratified by time from initial CPI administration to earliest corticosteroid exposure at guideline dosing. Time threshold: 8 weeks. **(c)** PFS, stratified by time from initial CPI administration to earliest corticosteroid exposure at guideline dose. Time threshold: 64 days. **(d)** OS, stratified by time from initial CPI administration to earliest corticosteroid exposure at guideline dose. Time threshold: 64 days.



	0 months	20 months	40 months	60 months
No. at risk	60	25	16	5
Fewer than 8 weeks post-CPI	29	8	6	1
At least 8 weeks post-CPI	31	17	10	4

	0 months	20 months	40 months	60 months
No. at risk	60	33	21	5
< 55 days post-CPI	29	11	7	1
At least 55 days post-CPI	31	22	14	4

	0 months	20 months	40 months	60 months
No. at risk	60	25	16	5
Fewer than 64 days post-CPI	34	10	7	2
At least 64 days post-CPI	26	15	9	3

	0 months	20 months	40 months	60 months
No. at risk	60	33	21	5
Fewer than 64 days post-CPI	34	15	10	2
At least 64 days post-CPI	26	18	11	3

Supplemental Figure 2

Representative scatter plot with 95% ellipse prediction demonstrating collinearity between time to admission and time to first corticosteroid exposure from initial CPI administration. Time measured in days. Collinearity with other variables not shown.