COLAR: open-label clinical study of IL-6 blockade with tocilizumab for the treatment of immune checkpoint inhibitor-induced colitis and arthritis

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ABSTRACT

Background Immune-related adverse events due to immune checkpoint inhibitors (ICIs) are not always effectively treated using glucocorticoids and it may negatively affect the antitumor efficacy of ICIs. Interventional studies of alternatives to glucocorticoids are lacking. We examined whether interleukin-6 blockade by tocilizumab reduced ICI-induced colitis and arthritis.

Methods and patients Patients with solid cancer experiencing Common Terminology Criteria for Adverse Events (CTCAE v5.0) grade ≥1 ICI-induced colitis/diarrhea (n=9), arthritis (n=9), or both (n=2) were recruited and treated with tocilizumab (8 mg/kg) every 4 weeks until worsening or unacceptable toxicity. Patients were not allowed to receive systemic glucocorticoids and other immunosuppressive drugs within the 14-day screening period. The primary endpoint was clinical improvement of colitis and arthritis, defined as ≥1 grade CTCAE reduction within 8 weeks. Secondary endpoints were improvements in glucocorticoid-free remission at week 24; safety; radiologic, endoscopic, and histological changes; and changes in plasma concentrations of C reactive protein, cytokines (IL-6, IL-8, and IL-17), and YKL-40.

Results Nineteen patients were available for efficacy analysis; one patient was excluded due to pancreatic insufficiency-induced diarrhea. Patients received treatment with pembrolizumab (n=10) or nivolumab (n=4) as monotherapy or ipilimumab and nivolumab (n=5) combined. Seven patients had been initially treated with glucocorticoids, and two of them also received infliximab. Ten patients continued ICI therapy during tocilizumab treatment. The primary endpoint was achieved in 15 of 19 (79%) patients. Additional one patient had ≥1 grade reduction at week 10, and another patient had stabilized symptoms. At week 24, ongoing improvement without glucocorticoids (n=12), including complete remission (n=10), was noted. Five patients had grades 3–4 treatment-related adverse events, which were manageable and reversible.

Conclusions Tocilizumab showed promising clinical efficacy and a manageable safety profile in the treatment of ICI-induced colitis and arthritis. Our findings support the feasibility of randomized trials of immune-related adverse events.

WHAT IS ALREADY KNOWN ON THE TOPIC

⇒ Treatment with glucocorticoids is not always effectively treating immune-related adverse events and may negatively affect the antitumor efficacy. Tocilizumab, an anti-interleukin-6 (IL-6) receptor monoclonal antibody, may interfere with the immune system to decrease immune-related toxicities. We hypothesized that tocilizumab would result in reduced immune checkpoint inhibitor (ICI)-induced colitis and arthritis.

WHAT THIS STUDY ADDS

⇒ The results of this study demonstrate that tocilizumab has promising efficacy for management of ICI-induced colitis and/or arthritis (84% clinical benefit rate) and manageable safety profile.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Further studies are required to confirm these results and to eventually compare efficacy of tocilizumab with currently standard approaches in the treatment of ICI-induced toxicities.

BACKGROUND

Immune checkpoint inhibitors (ICIs) targeting the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death protein 1 (PD-1) pathway have shown exceptional efficacy and durable responses in a wide range of solid tumors. However, ICIs may induce potentially severe and even lethal immune-related adverse events (irAEs) involving any organ. Conversely, several studies have
reported a favorable relationship between irAEs and antitumoral response.4–7 Although irAEs are usually mild and manageable, ICI discontinuation and initiation of glucocorticoids for moderate to severe irAEs are indicated. Yet, if the severity of irAEs does not decrease during initial glucocorticoids, an immunosuppressive drug should be initiated.23 8–10

The impact of glucocorticoids and other immunosuppressive drugs on the antitumoral effects of ICIs remains controversial and needs to be explored further. The exact pathophysiology underlying irAEs has not been fully elucidated; however, it is considered to be linked to disturbances of the immune checkpoints that generally maintain immunologic homeostasis.3 In addition, an increase in T cell activation and proliferation, impaired regulatory T cell survival and increased counts of 17 T-helper (Th17) cells, proinflammatory cytokines, cross-reactivity, autoantibodies, and microbiome are speculated to be involved in irAEs, such as colitis and rheumatic disorders.2 Especially, Th17 cells that induce interleukin-17 (IL-17) production are involved in several immune diseases, including inflammatory bowel diseases, rheumatoid arthritis, and ICI-induced colitis.211 Interleukin-6 (IL-6) is a proinflammatory cytokine and a major player in inflammation and cancer progression.12–14 IL-6 stimulates the differentiation of naïve CD4+ cells into Th17 cells, and the inhibition hereof may alter the Th17–regulatory T cell balance without supporting cancer cell attacks.11 13 Tocilizumab, an IL-6 receptor monoclonal antibody, has been approved for the management of rheumatic diseases (including rheumatoid arthritis, giant cell arteritis, systemic sclerosis), chimeric antigen receptor T cell therapy (CAR T) related cytokine release syndrome (CRS), and COVID-19.15–18 In addition, a threefold increase of IL-17 and IL-6 parallel with the threefold increase of IL-17 and IL-6 parallel with the severity of irAEs does not decrease during initial glucocorticoids, an immunosuppressive drug should be initiated.23 8–10

Assessments

Oncologists evaluated all patients with assistance from gastroenterologists or rheumatologists for the assessment of colitis/diarrhea and arthritis. Gastrointestinal assessment was scheduled at tocilizumab initiation and repeated after 1 month, including the following: history, physical examination, fecal analysis (pathogenic viral and bacterial species including Clostridioides difficile and calprotectin), and computed tomography (CT) or combined positron emission tomography CT scans. All patients with colitis/diarrhea underwent colonoscopy with biopsies at treatment initiation, including: histopathology, physicians’ global assessment, and a colitis activity score (Mayo Score, online supplemental methods). Colonoscopies were repeated after 1–3 months. Rheumatological evaluation included history, physical examination,
Table 1 Characteristics of patients with colitis treated with tocilizumab

| Patient ID | Sex, Age | Cancer, stage | Treatment (doses) | BOR | ICI-status | Other irAEs than colitis (CTCAE) | Duration: 1 CTC AE grade before inclusion | CTC AE grade, week 0 | CTC AE grade, week 8 | CTC AE grade, week 24 | Supportive, "as needed" | Systemic GCs within 24 weeks | Response to TCZ |
|------------|----------|---------------|------------------|-----|------------|--------------------------------|---------------------------------|-------------------|-------------------|-------------------|-----------------------|------------------------|------------------|
| C1         | M 70y    | CCA, IV lpi 1mg/kg+Nivo 3mg/kg (3+1) SD | Ongoing | None | New-onset, 4 days | No | 2 | 3 | 2 | J | J | T | NE | NE | NE | Loperamide | Yes, in Week 20, due to transition to palliative care |
| C2         | M 67y    | NSCLC, IV Pembrol 2mg/kg (15) PR | Interrupted | Rash (1) | New-onset, 3 days | No | 2 | 1 | 0 | NE | NE | NE | NE | NE | NE | Loperamide | Yes, shifted to prednisolone on Day 12 due to worsening |
| C9         | M 66y    | Melanoma, III Nivo 400mg, (2) | NE | Interrupted | None | New-onset, 33 days | No | 2 | 3 | 1 | J | J | J | J | J | Loperamide | No |
| C14        | F 55y    | Melanoma, IV Nivo 6mg/kg (1) NE | Permanently discontinued | Hyperthyroidism (2) | Chronic, 101 days | Yes, steroid-refractory | 2 | 2 | 1 | J | J | J | J | J | J | Loperamide | Yes |
| C15        | M 63y    | RCC, IV lpi 1mg/kg+nivo 3mg/kg (2) NE | Restarted | Arthralgia (1) | New-onset, 16 days | No | 2 | 2 | 1 | J | J | J | J | NE | NE | NE | None | Yes, relapse of colitis during ICI reintroduction |
| C17        | F 56y    | CCA, IV lpi 1mg/kg+nivo 3mg/kg (4) SD | Interrupted | Hyperthyroidism (1), rash (1) | New-onset, 17 days | No | 1 | 3 | 0 | ++ | J | J | 0 | NE | NE | NE | Psyllium | Yes, switch to budesonide with response |
| C18        | M 55y    | Melanoma, IV lpi 3mg/kg+nivo 1mg/kg (4) NE | Interrupted | None | New-onset, 26 days | No | 1 | 2 | 0 | J | J | J | J | NE | NE | NE | Loperamide | Yes, single dose methylprednisolone due to a treatment-related reaction |
| C19        | F 71y    | Bladder cancer, IV Pembrol 2mg/kg (23) NE | Interrupted | None | Chronic, 97 days | No | 2 | 1 | 1 | J | J | J | J | J | NE | Loperamide, Prolamine | No |
| AC12       | M 72y    | NSCLC, IV Pembrol 2mg/kg (23) PR | Permanently discontinued | Rash (1) | Chronic, 33 days | Yes, steroid-dependent | 1 | 1 | 0 | J | J | J | J | 0 | Loperamide | No |
| AC20       | F 60y    | Ocular melanoma, IV Pembrol 2mg/kg (10) SD | Restarted | Hypophysitis (2), pneumonitis (2) | Chronic, 787 days | Yes, steroid-dependent | 2 | 1 | 1 | J | J | J | J | ++ | J | J | Loperamide | No |

The arrows indicate the following: =, stable/no change; ↑, ↑, increase or decrease of CTC AE grade ≥1; and ↓, complete remission of symptoms. Some patients were not evaluable owing to initiation of non-ICI therapy or treatment with systemic glucocorticoids for colitis or arthritis. Definition of new-onset irAEs, debut of irAEs within <90 days; chronic irAEs, debut for >90 days ago. Colitis was classified as grade 1, asymptomatic; grade 2, abdominal-pain, mucus or blood in stool, grade 3, severe abdominal-pain, profound fatigue, grade 4, life-threatening, agent intervention is indicated. Diarrhea as grade 1, increase ≥4 stools/day over baseline; grade 2, increase ≥5 stools/day over baseline; grade 3, ≥10 stools/day over baseline; grade 4, life-threatening. Abdominal-pain as grade 1, mild pain; grade 2, moderate pain, limiting instrumental activities of daily living; grade 3, severe pain limiting self-care activities of daily living; grade 4, life-threatening. Agent intervention is indicated. Arthritis as grade 1, increase or decrease of CTCAE grade ≥1; and ↓, complete remission of symptoms. Some patients were not evaluable owing to initiation of non-ICI therapy or treatment with systemic glucocorticoids for colitis or arthritis. Definition of new-onset irAEs, debut of irAEs within <90 days; chronic irAEs, debut for >90 days ago. Colitis was classified as grade 1, asymptomatic; grade 2, abdominal-pain, mucus or blood in stool, grade 3, severe abdominal-pain, profound fatigue, grade 4, life-threatening, agent intervention is indicated. Diarrhea as grade 1, increase ≥4 stools/day over baseline; grade 2, increase ≥5 stools/day over baseline; grade 3, ≥10 stools/day over baseline; grade 4, life-threatening. Abdominal-pain as grade 1, mild pain; grade 2, moderate pain, limiting instrumental activities of daily living; grade 3, severe pain limiting self-care activities of daily living; grade 4, life-threatening. Agent intervention is indicated. Arthritis as grade 1, increase or decrease of CTCAE grade ≥1; and ↓, complete remission of symptoms. Some patients were not evaluable owing to initiation of non-ICI therapy or treatment with systemic glucocorticoids for colitis or arthritis. Definition of new-onset irAEs, debut of irAEs within <90 days; chronic irAEs, debut for >90 days ago. Colitis was classified as grade 1, asymptomatic; grade 2, abdominal-pain, mucus or blood in stool, grade 3, severe abdominal-pain, profound fatigue, grade 4, life-threatening, agent intervention is indicated. Diarrhea as grade 1, increase ≥4 stools/day over baseline; grade 2, increase ≥5 stools/day over baseline; grade 3, ≥10 stools/day over baseline; grade 4, life-threatening. Abdominal-pain as grade 1, mild pain; grade 2, moderate pain, limiting instrumental activities of daily living; grade 3, severe pain limiting self-care activities of daily living; grade 4, life-threatening. Agent intervention is indicated. Arthritis as grade 1, increase or decrease of CTCAE grade ≥1; and ↓, complete remission of symptoms. Some patients were not evaluable owing to initiation of non-ICI therapy or treatment with systemic glucocorticoids for colitis or arthritis. Definition of new-onset irAEs, debut of irAEs within <90 days; chronic irAEs, debut for >90 days ago. Colitis was classified as grade 1, asymptomatic; grade 2, abdominal-pain, mucus or blood in stool, grade 3, severe abdominal-pain, profound fatigue, grade 4, life-threatening, agent intervention is indicated. Diarrhea as grade 1, increase ≥4 stools/day over baseline; grade 2, increase ≥5 stools/day over baseline; grade 3, ≥10 stools/day over baseline; grade 4, life-threatening. Abdominal-pain as grade 1, mild pain; grade 2, moderate pain, limiting instrumental activities of daily living; grade 3, severe pain limiting self-care activities of daily living; grade 4, life-threatening. Agent intervention is indicated.

*Cancer related pain, requiring increased doses of morphine.
†Management of irAEs prior to screening: C14 received prednisolone 5-100mg (192 days for colitis) and infliximab (5 doses for colitis, 4 doses for arthritis, 1 dose for hypophysitis) and lum放进inax (5 days for hypophysitis, 5 days for rash, 10 days for pneumonitis). C19 received prednisolone 5-100 mg (912 days for colitis) and infliximab (6 mg/kg, 2 doses for colitis, last dose 45 days prior to inclusion). AC22 received prednisolone 20-250 mg 890 days for colitis, hydrocortisone 30 mg (62 days for hypophysitis), lum放进inax (6 mg/kg for rash, 30 mg for pneumonia) and infliximab (5 mg/kg for colitis, 5 mg/kg for hypophysitis). AC20 received prednisolone 25-250 mg 890 days for colitis, hydrocortisone 30 mg (62 days for hypophysitis), lum放进inax (5 mg/kg for rash). AC20 received pembrolizumab 2 mg/kg (23) and pembrolizumab 2 mg/kg for hypophysitis, melpanonas (2 mg/kg for pneumonia).
### Table 2  Characteristics of patients with arthritis treated with tocilizumab

| Baseline patient characteristics (arthritis) | Characteristics of the patients' arthritis treated with tocilizumab |
|--------------------------------------------|-----------------------------------------------------------------|
| Patient ID | Sex, Age | Cancer, stage and treatment (doses) | BOR | ICI-status | Other irAEs (CTCAE grade) | Duration:1 CTCAE grade before inclusion | Shifted from GCs | CTCAE grade, week 0 | CTCAE grade, week 8 | CTCAE grade, week 24 | Supportive, “as needed” | Systemic GCs in within 24 weeks | Response to TCZ |
|-----------|----------|-----------------------------------|-----|-----------|--------------------------|--------------------------------------|-------------------|-----------------|-----------------|-----------------|-------------------|------------------------|----------------|
| A1        | M 76 years | NSCLC, IV Pembro 2 mg/kg (15) | SD  | Ongoing  | None | New-onset, 3 days | No | 2 | 3 | 3 | TNE | TNE | NE | NE | NE | NE | Arthralgia, GVs and lidoicaine IA in both knees, 2 times in Week 1-3, paracetamol, tramadol | Yes | Worthing of arthritis during ICIs on Day 24, started prednisolone | No |
| A2        | M 77 years | Cutaneous SCC, IV Pembro 2 mg/kg (9) | CR  | Permanently discontinued | Collitis (1), hypothyroidism (2) | Chronic, 90 days | 3 | 2 | 2 | 2 | ++2 | ++2 | ++2 | ++2 | ++2 | 0 | 0 | 0 | Paracetamol, ibuprofen | No | Yes |
| A3        | M 62 years | NSCLC, III ptx 1 mg/kg+No 3 mg/kg (4+10) | SD  | Ongoing  | None | New-onset, 12 days | No | 3 | 3 | 0 | ↓↓ | ↓↓ | 0 | ↓↓ | ↓↓ | 0 | Ibuoprofen, local intra-articular injection in one knee between in week 3 | Yes | ICI-induced hypophysitis | Yes |
| A4        | F 60 years | NSCLC, IV Pembro 2 mg/kg (29) | SD  | Ongoing  | Psoriasis (2) | New-onset, 12 days | 2 | 2 | 0 | ↓↓ | 0 | 0 | 0 | 0 | ↓↓ | ↓↓ | 0 | Paracetamol, tramadol | No | Yes |
| A5        | M 62 years | Cutaneous SCC, IV Pembro 2 mg/kg (12) | PR  | Ongoing  | Hypothyroidism (2), rash (1) | Chronic, 12 days | 0 | 2 | 2 | 1 | ↓↓ | ↓↓ | 0 | ↓↓ | ↓↓ | 0 | Paracetamol | No | Yes |
| A6        | M 72 years | NSCLC, III Pembro 2 mg/kg (10) | PR  | Ongoing  | Hepatitis (1) | New-onset, 15 days | 2 | 2 | 0 | ↓↓ | 0 | 0 | 0 | 0 | ↓↓ | ↓↓ | 0 | GCs IA in both knees in Week 2, paracetamol | No | Yes |
| A7        | F 30 years | Melanoma, III ptx 60 mg/kg, ad (6) | PR  | Ongoing  | None | New-onset, 71 days | Yes | 2 | 2 | 1 | ↓↓ | ↓↓ | 0 | ↓↓ | ↓↓ | 0 | Diclofenac, tramadol | Yes | ICI-induced hypophysitis and non-specific irAEs | Yes |
| A8        | F 65 years | Melanoma, IV Nivo 480 mg (33) | CR  | Ongoing  | Diarrhea (1) | New-onset, 85 days | No | 2 | 2 | 0 | ↓↓ | 0 | 0 | NE | NE | NE | Paracetamol | Yes | Switch to prednisolone due to colds and risk factors for COVID-19 | No |
| A9        | M 55 years | Melanoma, IV Nivo 480 mg (33) | PR  | Permanently discontinued | Diarrhea (1) | Chronic, 752 days | Yes, steroid-dependent | 2 | 2 | 1 | ↓↓ | 0 | ++1 | ↓↓ | 0 | None | Continued regular GCs IA | No | Yes |
| A10       | M 72 years | NSCLC, IV Pembro 2 mg/kg (33) | PR  | Permanently discontinued | Rash (1) | Chronic, 922 days | Yes, steroid-dependent | 2 | 2 | 1 | ↓↓ | 1 | 1 | 1 | 1 | None | Paracetamol | No | Yes |
| A11       | F 60 years | Cutaneous melanoma, IV Pembro 2 mg/kg (33) | SD  | Reversed | Hypothyroidism (2), pneumonitis (1) | Chronic, 506 days | No | 2 | 2 | 0 | ↓↓ | 0 | 0 | NE | NE | NE | Paracetamol | Yes | Switch to prednisolone due to colds and risk factors for COVID-19 | No |
| A12       | M 72 years | NSCLC, IV Pembro 2 mg/kg (33) | PR  | Permanently discontinued | Rash (1) | Chronic, 922 days | Yes, steroid-dependent | 2 | 2 | 1 | ↓↓ | 1 | 1 | 1 | 1 | None | Continued regular antihistamines and GCs IA to Week 9, stopped due to response to tocilizumab, ibuprofen, and tramadol | No | Yes |

The arrows indicate the following: ↔, stable; no change; ↑↑, increase or decrease of CTCAE grade ≥3; and ↓↓, complete resolution of symptoms. Some patients were not evaluable owing to initiation of non-ICI therapy or treatment with systemic glucocorticoids for colitis or arthritis. Definition of new-onset irAEs; debut of irAEs within <90 days; chronic irAEs; debut for more than 90 days ago. Arthralgia and myalgia are graded from 1 to 3 on CTCAE V.5.0 (grade 1, mild pain; grade 2, moderate pain; grade 3, severe pain). Definition of arthritis and colitis: arthritis, limitation of self-care activities of daily living; colitis, severe abdominal pain. Arthralgia and myalgia are graded from 1 to 3 on CTCAE V.5.0 (grade 1, mild pain; grade 2, moderate pain; grade 3, severe pain). Definition of arthritis and colitis: arthritis, limitation of self-care activities of daily living; colitis, severe abdominal pain. Arthralgia and myalgia are graded from 1 to 3 on CTCAE V.5.0 (grade 1, mild pain; grade 2, moderate pain; grade 3, severe pain). Definition of arthritis and colitis: arthritis, limitation of self-care activities of daily living; colitis, severe abdominal pain. Arthralgia and myalgia are graded from 1 to 3 on CTCAE V.5.0 (grade 1, mild pain; grade 2, moderate pain; grade 3, severe pain). Definition of arthritis and colitis: arthritis, limitation of self-care activities of daily living; colitis, severe abdominal pain. Arthralgia and myalgia are graded from 1 to 3 on CTCAE V.5.0 (grade 1, mild pain; grade 2, moderate pain; grade 3, severe pain). Definition of arthritis and colitis: arthritis, limitation of self-care activities of daily living; colitis, severe abdominal pain.

*Previous treatment with ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg).

†Management of irAE prior to screening: A4 received prednisolone 25 mg for diarrhea and levothyroxine for hypothyroidism. A10 received prednisolone 25 mg (12 days) for arthritis. A13 received prednisolone 25 mg (12 days) for arthritis. A16 received prednisolone 5-25 mg for diarrhea. AC12 received prednisolone 5-25 mg (922 days) for arthritis. All others received no treatment for irAE.

AC, arthritis and colitis; BOR, best overall response; C, colitis; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; F, female; GCs, glucocorticoids; IA, intra-articular; ICI, immune checkpoint inhibitor; NE, not evaluable; Nivo, nivolumab; NSCLC, non-small cell lung cancer; Pembro, pembrolizumab; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease; TCZ, tocilizumab.
## Table 3  Radiologic, endoscopic, and histological features in patients with ICI-induced colitis

| Treatment assessment | Evaluation assessment |
|----------------------|-----------------------|
| **Patient ID** | **Radiologic findings** | **Endoscopic findings** | **Physicians global assessment** | **Total mayo score** | **Histologic** | **Radiologic findings** | **Endoscopic findings** | **Physicians global assessment** | **Total mayo score** | **Histologic** | **Response to TCZ** |
| C1 | Bowel wall thickening (ascending, transverse, descending colon, and sigmoid) | Normal findings | Mild | 4 | Severe intraepithelial lymphocytosis; mild cryptitis; apoptosis; moderate chronic inflammation in lamina propria; increased subepithelial collagenous band | Unchanged in ascending and transverse colon; slightly increased in the descending colon and sigmoid | Mild irritation | Mild | 3 | Mild intraepithelial lymphocytosis ↓; mild cryptitis; apoptosis; mild chronic inflammation in lamina propria ↓; normal subepithelial collagenous band ↓ | Yes |
| C2 | Bowel wall thickening (rectum) | Edema, redness, pus, erosions from coecum to anal | Severe | 10 | Ulcerations; diffuse cryptitis and crypt abscesses; severe acute and chronic inflammation in lamina propria; crypt destructions; altered crypt architecture | Reduced bowel wall thickening (rectum) | Decreased redness and edema (rectosigmoid junction and rectum) | Mild | 2 | No ulcerations; focal cryptitis and crypt abscesses ↓; mild acute and chronic inflammation in lamina propria ↓; altered crypt architecture ↔ | No, glucocorticoids indicated before evaluation |
| C9 | Bowel wall thickening (pancolitis) | Edema and minor blood extractions, | Mild | 4 | Cryptitis, crypt abscesses; intraepithelial lymphocytosis; apoptosis; increased amount of plasma cells and eosinophils in lamina propria | No signs of inflammation | Entire colon with edema and vulnerable mucosa | Mild | 2 | No cryptitis ↓; no crypt abscesses; no intraepithelial lymphocytosis ↓; apoptosis ↓; increased amount of plasma cells and eosinophils in lamina propria ↑ | Yes |
| AC12 | NE | Normal | Normal | 1 | Edema; intraepithelial lymphocytosis; increased amount of plasma cells and eosinophils in lamina propria | NE | Normal | Normal | 0 | No edema; focal intraepithelial lymphocytosis ↓; mild chronic inflammation in lamina propria ↓ | Yes* |
| C14 | Bowel wall thickening (pancolitis) | Edema (general) | Mild | 4 | Erosions; cryptitis, crypt abscesses; apoptosis; moderate chronic inflammation with eosinophils in lamina propria | No signs of colitis | Normal | Normal | 0 | No erosions; no cryptitis or crypt abscesses; no apoptosis; mild chronic inflammation in lamina propria ↓ | Yes* |
| C15 | Bowel wall thickening (rectosigmoid colon) | Edema rectosigmoid colon | Moderate | 6 | Ulceration; cryptitis, crypt abscesses; moderate chronic inflammation with eosinophils in lamina propria | Reduced bowel wall thickening (rectum) | Normal | Mild | 3 | No ulceration; no cryptitis or crypt abscesses; mild chronic inflammation with eosinophils in lamina propria ↓ | Yest, but experienced relapse during ICIs. Control after initiation of glucocorticoids |
| C17 | Bowel wall thickening (pyloric partly gastric ventricle, duodenum, jejenum, and rectum) | Normal | Normal | 3 | Intraepithelial lymphocytosis; chronic inflammation in lamina propria | Increased wall thickening (pyloric part of the gastric ventricle, small intestine, and rectum) | Normal | Normal | 3 | Normal mucosa; no intraepithelial lymphocytosis; no inflammation | No, stable symptoms. Control during budesonide |
and measurement of circulating levels of autoantibodies (antinuclear antibodies, rheumatoid factor, and anticyclic citrullinated peptide antibodies). Imaging tests were performed if indicated. We examined the patients twice in week 1, followed by every 2–3 weeks according to the investigator’s judgment and irAE severity. Patients were followed up for at least 30 days (±5 days) for CTCAE assessment and then every 8–12 weeks for 6 months after the last tocilizumab dose. Plasma concentrations of C reactive protein (CRP) as part of routine analyses, cytokines (IL-6, IL-8, and IL-17), and YKL-40 were measured before initiation and every 2–3 weeks until the end of the treatment (online supplemental methods).

Outcomes

The primary endpoint was clinical benefit, defined as ≥1 grade reduction of ICI-induced colitis/diarrhea and/or arthritis using CTCAE V.5.0 within 8 weeks after tocilizumab initiation. The secondary endpoints were safety, ≥1 grade reduction without glucocorticoids within 8 weeks of treatment initiation, and sustained glucocorticoid-free remission at week 24. The exploratory endpoints were radiologic, endoscopic, and histological changes and changes in plasma concentrations of CRP, cytokines (IL-6, IL-8, and IL-17), and YKL-40 during tocilizumab.

Statistical analysis

A sample size of 20 was required according to Simon’s 2-stage optimal design to obtain a significance level of 5% and a power of 80% in the one-sided test of the null hypothesis (<50% clinical benefit rate) against the alternative hypothesis (≥80% clinical benefit rate). In the first stage, seven patients were treated, and in the case of ≤4 patients with reduction of symptoms, accrual would be terminated. Otherwise, the trial would include an additional 13 patients in the second stage. The null hypothesis would be rejected if ≥14 of 20 patients with clinical benefit were observed.

All patients with ICI-induced colitis/arthritis who met the inclusion criteria and received ≥1 cycle of tocilizumab were analyzed for treatment efficacy (evaluable populations). Time to symptom reduction was defined as the time from treatment initiation (tocilizumab) to the date of ≥1 CTCAE grade reduction of symptom. Complete remission of symptoms was defined as the time from tocilizumab initiation to CTCAE grade 0 of colitis/diarrhea and arthritis.

Descriptive statistics were used to summarize the characteristics of the cohort and to report adverse events (AEs). Continuous outcome measures were presented as medians and ranges. CIs were estimated by using binomial tests. Statistical analyses were performed by using Microsoft Excel v2002 and R Studio V.1.2.5001.
RESULTS

Patient characteristics

Of 27 patients screened, 20 patients with arthritis (n=9), colitis/diarrhea (n=9), or both (n=2) induced by ICIs were enrolled. Seven patients were excluded: four declined to participate, two did not meet the inclusion criteria (non-ICI-related arthralgia), and one patient failed the glucocorticoid tapering. One patient with diarrhea was subsequently excluded from the efficacy analysis due to diarrhea caused by pancreatic insufficiency with no relation to ICIs (online supplemental figure S2). None had a history of autoimmune diseases. Before initiating tocilizumab treatment, the median duration of colitis/diarrhea and arthritis symptoms was 26 days (3–787) and 71 days (3–922). Seven patients had initially received systemic glucocorticoids for colitis and/or arthritis, and two of them also received treatment with infliximab for colitis (tables 1 and 2). All patients stopped receiving glucocorticoid therapy or other immunosuppressive drugs within the 14-day screening period; however, those with hypophysitis continued regular hydrocortisone substitution.

Eight of 10 patients with confirmed ICI-induced colitis/diarrhea had CT-verified bowel wall thickening; five (50%) had endoscopic changes with edema of either the entire colon or left colonic segments. The median Mayo Score was 4 (1–10). All 10 patients had biopsy-proven colitis in the absence of enteritis. Fecal calprotectin levels available in five patients ranged from 109 to >1800 µg/mg. Five of the 11 patients with arthritis were positive for antinuclear antibodies, and two for a low-level rheumatoid factor.

Efficacy outcomes

At week 8, 15 of 19 patients (79%, 95% CI 54% to 94%) had ≥1 grade reduction of symptoms without using glucocorticoids. The median time from tocilizumab initiation to reduction was 14 days for both colitis (3–28)

Figure 1  Treatment overview. All 20 patients are illustrated. Patient C8 was excluded from efficacy analysis due to pancreatic insufficiency-induced diarrhea. Treatment for ICIs and tocilizumab are shown from the time point of tocilizumab initiation. Nine of 20 patients received systemic therapy with systemic glucocorticoids. Six patients experienced cancer progression within the study period (24 weeks), including C18 with melanoma, who had new melanoma moles which were surgically resected and followed by a durable complete response. At the cut-off for disease status in October 2021, three additional patients experienced cancer progression; two were rechallenged with a PD-1 inhibitor. ICI, immune checkpoint inhibitor; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; TCZ, tocilizumab.
and arthritis (5–72). One of the two patients with stable symptoms who continued treatment responded at week 10. Two patients experienced worsening symptoms after a single infusion and started glucocorticoids after 12 and 24 days, respectively. All six patients with persistent colitis or arthritis (duration of ≥90 days) responded to tocilizumab treatment. Within 24 weeks, 16 of 19 patients (84%, 95% CI 60% to 96%) achieved ≥1 grade reduction following treatment with tocilizumab. At week 24, 12 patients had ongoing reduction of symptoms, 10 of which achieved durable complete remission of symptoms; however, one patient treated with concomitant ICIs and tocilizumab did not achieve any clinical benefit from tocilizumab and shifted to systemic glucocorticoids on day 24. In total, 10 of 11 patients had reduced symptoms of arthritis (table 2).

### Treatment exposure

All patients received ≥1 dose of tocilizumab. The median number of infusions and treatment duration were 5 (1–10) and 24 weeks (2–36), respectively. Three patients discontinued tocilizumab after one infusion (worsening symptoms (n=2) or an infusion-related reaction (n=1)). One patient was readministered with tocilizumab owning arthritis relapse. Within 24 weeks, 10 patients received concomitant ICI and tocilizumab therapy with a median duration of 10 weeks (3–65) (figure 1).

### Safety

Sixteen of 20 (80%) patients had AEs of any grade related to tocilizumab, none of which were fatal. Five patients (25%) experienced grades 3–4 treatment-related AEs (TRAEs): Neutropenia (n=2, one of them developed new-onset hypophysitis and severe infection/septic shock); thrombocytopenia (n=1); colitis with ulcerations (n=1), and allergic reaction (n=1) requiring glucocorticoids and observation at the hospital (table 4).

### Inflammatory markers

An increase in IL-6 level was observed in all patients regardless of response as expected. Plasma levels of IL-8, IL-17, CRP, and YKL-40 decreased mainly in patients who responded to treatment. One patient with glucocorticoid-refractory colitis had a notable decrease in IL-17 levels, correlating with clinical response (figure 2, online supplemental figures S5,S6).

### Cancer status

From tocilizumab initiation and during the study period of 24 weeks, six of 20 (30%) patients experienced cancer progression (data are shown in figure 1, for further description, see online supplemental results and online supplemental figures S7A–B and S8A–B).

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**Table 4** Safety table

| Safety population (n=20) | Any grade | Grade 3–4 |
|-------------------------|-----------|-----------|
|                         | N (%)     | N (%)     |
| Any AE                  | 20 (100)  | 8 (40)    |
| TRAE                    | 16 (80)   | 5 (25)    |
| Neutrophil count decreased | 4 (20)  | 2 (10)    |
| Platelet count decreased | 4 (20)   | 1 (5)     |
| Alanine transaminase increased | 4 (20)  | 0         |
| Aspartate transaminase increased | 4 (20)  | 0         |
| Anorexia                | 2 (10)    | 0         |
| Fatigue                 | 2 (10)    | 0         |
| Cold symptoms           | 2 (10)    | 0         |
| Colitis                 | 1 (5)     | 1 (5)     |
| Infusion-related reaction | 1 (5)   | 1 (5)     |
| Septic shock            | 1 (5)     | 1 (5)     |
| Abdominal pain          | 1 (5)     | 0         |
| Dry eyes                | 1 (5)     | 0         |
| Dry mouth               | 1 (5)     | 0         |
| Eczema                  | 1 (5)     | 0         |
| Headache                | 1 (5)     | 0         |
| Hoarseness              | 1 (5)     | 0         |
| Nausea                  | 1 (5)     | 0         |
| Pruritus                | 1 (5)     | 0         |
| Rhinitis                | 1 (5)     | 0         |
| Urinary tract infection | 1 (5)     | 0         |
| Vomiting                | 1 (5)     | 0         |

AE, adverse event; TRAE, treatment-related AE.
DISCUSSION
To the best of our knowledge, this is the first study to demonstrate that tocilizumab, an IL-6-receptor inhibitor, can be safely used to treat ICI-induced colitis/diarrhea and arthritis. The majority (15/19, 79%) of evaluable patients had a reduction of CTCAE grade by ≥1 within 8 weeks and additional one had ≥1 grade reduction at 10 weeks. Thus, the threshold for primary efficacy was met. At week 24, symptom reduction was experienced by 16 (84%) patients and durable responses by 12 patients, including complete remission of symptoms in 10 patients. During this treatment, half of the patients were able to continue ICIs.

Importantly, we observed acceptable toxicity during ICIs and tocilizumab combination therapy; however, colon ulceration and an increased risk of infection should be considered, especially in patients with cancer. In this study, only patients previously treated with chemotherapy developed neutropenia and thrombopenia, both well-known TRAEs. Nevertheless, we cannot exclude these two severe above-mentioned events could be influenced by ICI exposure or combination with tocilizumab. One patient achieving clinical benefit permanently discontinued tocilizumab due to an infusion-related reaction after the first infusion. Hypersensitivity reactions related to tocilizumab have been reported in <1% of patients.28 It is unknown if ICI-treated patients are more prone to develop hypersensitive drug reactions compared with ICI-naive patients; however, ICIs might activate drug-responsive T-cells, which are effectors of hypersensitivity.29

The use of tocilizumab to manage irAEs has been previously investigated in retrospective studies and case series with promising results. Stroud et al reported clinical improvements in 27 of 34 patients treated with tocilizumab and glucocorticoids for severe pneumonitis, serum sickness, and cerebritis.21 The benefit of tocilizumab for ICI-induced arthritis, polymyalgia rheumatica, myositis, myocarditis, CRS, and hemophagocytic syndrome has been reported.22 24 30 Recently, tocilizumab was successful in treating multiple irAEs and preventing flare of pre-existing autoinflammatory diseases in 21 of 22 patients with melanoma.23 In our study, two patients experienced worsening of colitis and arthritis after one tocilizumab infusion (on day 12 and day 24, respectively). We cannot exclude the possibility that a more prolonged treatment exposure to tocilizumab is required due to increased tocilizumab clearance. In patients with inflammatory signatures of CAR T-cell induced CRS, tocilizumab infusion is usually repeated if symptoms do not improve within 48 hours.20 31 One patient with stable symptoms was diagnosed with microscopic colitis, a histopathological subgroup of ICI-induced colitis, and did not respond to tocilizumab treatment. The patient was then effectively treated with budesonide, as reported by Hughes et al.32

Although the antitumoral efficacy of ICIs has been extensively studied, crucial concerns regarding resumption of ICIs following moderate to severe irAEs, concomitant immunosuppressive therapies (especially in patients with pre-existing autoimmune diseases), and management of glucocorticoid-refractory irAEs are arising. However, no controlled trials have thus far defined the strategies for the effective management of specific irAE, and international guidelines are primarily based on retrospective cohorts, case series, and case reports; especially guidelines for treating glucocorticoid-dependent or -refractory cases are mainly based on expert opinions.89 33 In our study, increasing levels...
of IL-6 were observed in all patients due to blockade of the IL-6 receptors while levels of IL-8, IL-17, CRP, and YKL-40 decreased in responding patients. We noticed a patient with glucocorticoid-refractory colitis, treated with infliximab twice with minimal efficacy, achieved complete remission of symptoms after tocilizumab treatment. This response was paralleled by a decrease of a high circulating level of IL-17 before treatment, suggesting that cytokine levels are potential biomarkers in patients with irAEs refractory to standard treatment options. Early intervention with an immunosuppressive agent is reported to lead to more favorable outcomes. Furthermore, adding a glucocorticoid-sparing therapy, especially in long-term irAEs, may dampen the risk of glucocorticoid-induced AE. Currently, infliximab and vedolizumab are the preferred second-line and third-line treatment options for ICI-induced colitis. However, ustekinumab (anti-IL-23/12), tofacitinib (a JAK inhibitor), and fecal microbiota transplantation may be effective for the treatment of refractory colitis. Loperamide ‘as needed’ was allowed in this study; however, it is debated if loperamide should be withdrawn in severe colitis to prevent a potential risk of toxic colon dilatation. In addition, CMV infection should be excluded in glucocorticoid-refractory cases, as we did in this study.

Glucocorticoids are the first choice of therapy for rheumatologic AE triggered by ICIs and usually long-term administration is required. No specific biological disease-modifying antirheumatic drugs have shown superiority, and treatment with TNF-inhibitors may require repeated administration with unknown influence on the antitumor response. However, concomitant treatment with ICIs and TNF-inhibitors is being studied (NCT03293784). The antitumor effect of tocilizumab was not an endpoint in this study. However, we observed cancer disease control in majority of included patients at 24 weeks. Thus, despite the small population size, tocilizumab did not seem to affect negatively the anticancer responses induced by ICIs; similar to previous reports. Clinical trials of tocilizumab (NCT04940299, NCT04258150, NCT04375228, and NCT04691817) on anticancer responses and irAEs are ongoing.

The limitations of this study were the lack of a control group and the small population size. Thus, we cannot exclude that the observed reduction of symptoms was related to the natural course of irAEs, delayed biological effect of ICI treatment, or intra-articular glucocorticoids and other supportive agents being used. However, few data on these subjects are available making this study important as a first starter. We may also have selected patients with favorable outcomes because patients had to go through a 14-day long screening period if shifted from glucocorticoids. Also, low statistical power may increase the risk of spurious findings. We included a broad spectrum of ICI regimens and cancer types, which may have skewed outcomes. The variable duration of symptoms up to inclusion suggested a heterogeneous cohort, limiting the generalizability of results. Moreover, irAEs may be caused by several relatively unknown mechanisms, and some may like to respond better to treatment than others. The strengths of this study were its prospective study design and extensive multidisciplinary workup. In addition, we supplied measurements of circulating cytokines and YKL-40. Larger comprehensive cohorts, including controls testing tocilizumab or alternative strategies for irAEs are needed. Still, a central concern is the sparsity of data related to safety and efficacy of treating irAEs with glucocorticoids and immunosuppressive drugs, including their effects on anticancer responses. However, whether immunosuppression related to tocilizumab is more acceptable than glucocorticoids is unknown. The CTC grading of irAEs should also be more specific and include imaging, endoscopy, and histopathology results. In addition, many patients treated with ICIs experience multiorgan toxicity. Therefore, a guide to multidisciplinary team building and management would be an oncological imperative of essential value. Future studies incorporating blood-based biomarkers in irAEs, as well as selecting other steroid-sparing agents are warranted. Finally, moving anti-IL-6 agents to first-line therapy for the management of the new-onset irAEs should be studied from a cost-effective perspective as it would have significant implications.

### CONCLUSIONS

Tocilizumab showed promising clinical efficacy and a manageable safety profile in 16 of 19 (84%, 95% CI 60 to 97%) patients experiencing ICI-induced colitis and/or arthritis. Half of the patients successfully continued ICIs concomitant with tocilizumab. Future prospective studies of organ-specific irAEs managed with glucocorticoids as a standard approach and experimental therapies, including randomization, are warranted to refine treatment guidelines.

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checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 2021;39:4073–126.
4. Hussaini S, Chehade R, Boldt RG, et al. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors - A systematic review and meta-analysis. Cancer Treat Rev 2021;92:102134.
5. Eggermont AMM, Kicosinski M, Blank CU, et al. Association between immune-related adverse events and recurrence-free survival among patients with stage III melanoma randomized to receive pembrolizumab or placebo: a secondary analysis of a randomized clinical trial. JAMA Oncol 2020;6:519–27.
6. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer 2019;7:306.
7. Shankar B, Zhang J, Naqash AR, et al. Multisystem immune-related adverse events associated with immune checkpoint inhibitors for treatment of non-small cell lung cancer. JAMA Oncol 2020;6:1952–6.
8. Reid PD, Cifu AS, Bass AR. Management of Immunotherapy-Related toxicities in patients treated with immune checkpoint inhibitor therapy. JAMA 2021;325:485–9.
9. Brahmer JR, Abu-Sheh H, Ascierto PA, et al. Society for immunotherapy of cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435.
10. National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. In: NCCN guidelines. Version 1.2022, 2022.
11. Noack M, Miossec P. Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. Autoimmun Rev 2014;13:668–77.
12. Keegan A, Ricciuti B, Garden P, et al. Plasma IL-6 changes correlate to PD-1 inhibitor responses in NSCLC. J Immunother Cancer 2020;8:e000678.
13. Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat Rev Immunol 2018;18:773–89.
14. Wang M, Zhai X, Li J, et al. The role of cytokines in predicting the response and adverse events related to immune checkpoint inhibitors. Front Immunol 2021;12:670391.
15. Le RG, LL, Yuan W, et al. Fda approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. Oncologist 2018;23:943–7.
16. Gabay C, Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541–50.
17. van Rhee F, Voorhees P, Dispensieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018;132:2115–24.
18. Gordon AC, Mounsey PR, et al. REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 2021;384:1491–502.
19. Bjoern J, Iversen TZ, Nitschke NJ, et al. Safety, immune and clinical responses in metastatic melanoma patients vaccinated with a long peptide derived from indoleamine 2,3-dioxigenase in combination with ipilimumab. Cytotherapy 2016;18:1043–55.
20. Kotch C, Barrett DT, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. Expert Rev Clin Immunol 2019;15:813–22.
21. Stroud CR, Hegde A, Cherry C, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. J Oncll Pharm Pract 2019;25:551–7.
22. Kim ST, Tayar J, Trinh VA, et al. Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. Ann Rheum Dis 2017;76:2061–4.
23. Dimitriou F, Hogan S, Menzies AM, et al. Interleukin-6 blockade for prophylaxis and management of immune-related adverse events in cancer immunotherapy. Eur J Cancer 2021;157:214–24.
24. Campochiaro C, Farina N, Tonelli A. Tocilizumab for the treatment of immune-related adverse events: a systematic literature review and a multicentre case series. Eur J Intern Med 2021.
25. Cappelli LC, Gutierrez AK, Bingham CO, et al. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care Res 2017;69:1751–63.
26. Arnaud-Coffin P, Maillet D, Gan HK, et al. A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. Int J Cancer 2019;145:659–68.
27. Common Terminology Criteria for Adverse Events (CTCAE), v5.0. National Institutes and health, National cancer Institute 2017, 2017.

REFERENCES
1. Postow MA, Sidlow R, Hellmann MD. Immune-Related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68.
2. Ramos-Casals M, Brahmer JR, Callahan MK, et al. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers 2020;6:38.
3. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune

Holmstroem RB, et al. J Immunother Cancer 2022;10:e005111. doi:10.1136/jitc-2022-005111
Checkpoints inhibition reduces the threshold for drug-specific T-cell priming and increases the incidence of sulfasalazine hypersensitivity. Toxicol Sci 2022;186:58–69.

30 Olivares-Hernández A, Figuero-Pérez L, Amores Martín MA, et al. Response to treatment with an anti-interleukin-6 receptor antibody (tocilizumab) in a patient with hemophagocytic syndrome secondary to immune checkpoint inhibitors. Case Rep Oncol Med 2021:2021:1–5.

31 Neelapu SS, Tummala S, Kebrisaii P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47–62.

32 Hughes MS, Molina GE, Chen ST, et al. Budesonide treatment for microscopic colitis from immune checkpoint inhibitors. J Immunother Cancer 2019;7:292.

33 Alexander JL, Ibraheem H, Sheth B, et al. Clinical outcomes of patients with corticosteroid refractory immune checkpoint inhibitor-induced enterocolitis treated with infliximab. J Immunother Cancer 2021;9:e002742.

34 Abu-Sheh H, Ali FS, Wang X, et al. Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor-induced colitis. J Immunother Cancer 2019;7:93.

35 Bergqvist V, Hertvig E, Gedeon P, et al. Vedolizumab treatment for immune checkpoint inhibitor-induced enterocolitis. Cancer Immunol Immunother 2017;66:581–92.

36 Ibraheem H, Baillie S, Samaan MA, et al. Systematic review with meta-analysis: effectiveness of anti-inflammatory therapy in immune checkpoint inhibitor-induced enterocolitis. Aliment Pharmacol Ther 2020;52:1432–52.

37 Bushu S, Melia J, Sharman W, et al. Efficacy and outcome of tofacitinib in immune checkpoint inhibitor colitis. Gastroenterology 2021;160:e933:932–4.

38 Wang Y, Wiesnoski DH, Helmink BA, et al. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. Nat Med 2018;24:1804–8.

39 Thomas AS, Ma W, Wang Y. Ustekinumab for refractory colitis associated with immune checkpoint inhibitors. N Engl J Med 2021;384:581–3.

40 Walley T, Milson D. Loperamide related toxic megacolon in Clostridium difficile colitis. Postgrad Med J 1990;66:582.

41 Samaan MA, Pavlidis P, Papa S, et al. Gastrointestinal toxicity of immune checkpoint inhibitors: from mechanisms to management. Nat Rev Gastroenterol Hepatol 2018;15:222–34.

42 Franklin C, Rooms I, Fiedler M, et al. Cytomegalovirus reactivation in patients with refractory checkpoint inhibitor-induced colitis. Eur J Gastroenterol Hepatol 2018;30:998–1004.

43 Kostine M, Finckh A, Bingham CO, et al. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. Ann Rheum Dis 2021;80:36–48.

44 Montfort A, Filleron T, Virazels M, et al. Combining nivolumab and ipilimumab with infliximab or Certolizumab in patients with advanced melanoma: first results of a phase Ib clinical trial. Clin Cancer Res 2021;27:1037–47.

45 Brammer JE, Braunstein Z, Katapadi A, et al. Early toxicity and clinical outcomes after chimeric antigen receptor T-cell (CAR-T) therapy for lymphoma. J Immunother Cancer 2021;9:e002303.