BOTENSILIMAB and BALSTILIMAB

MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

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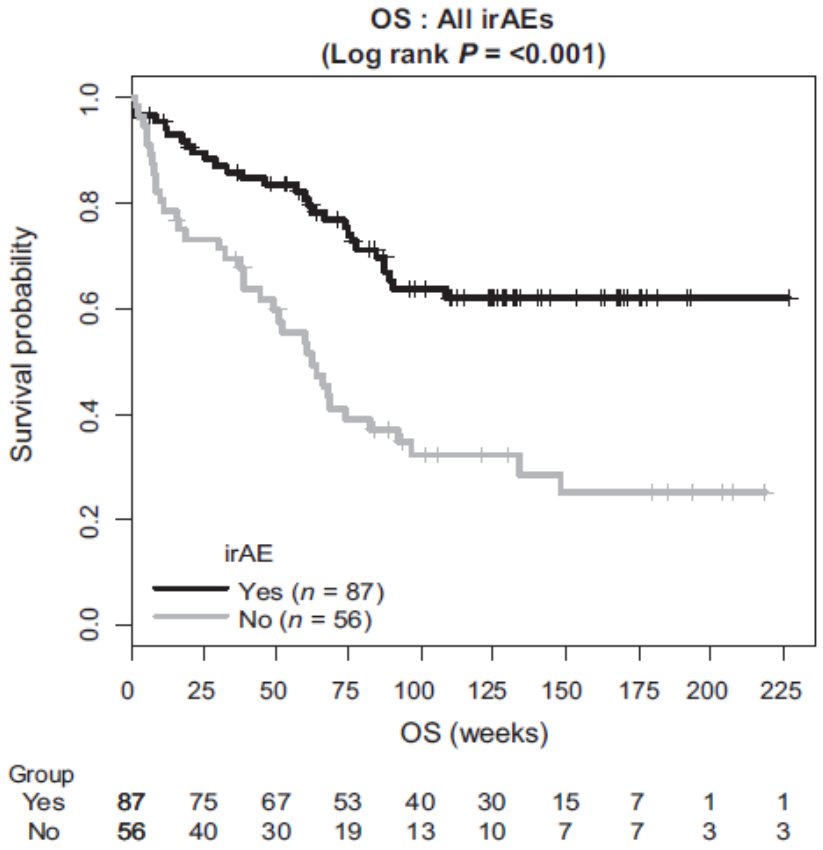
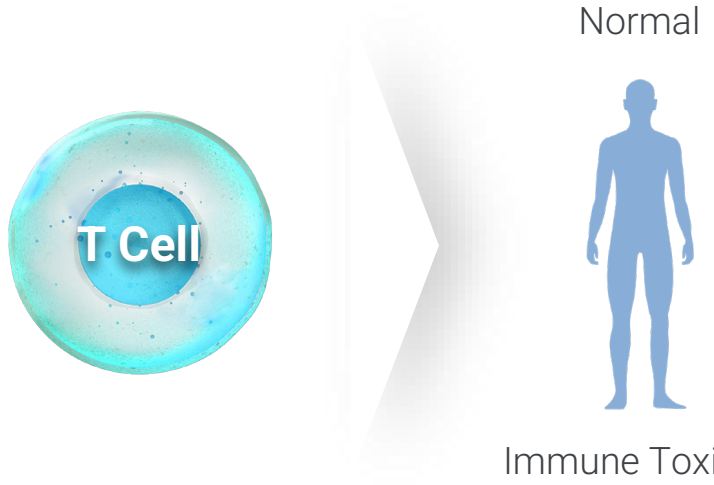
Immune-mediated Diarrhea / Colitis

Early Onset Symptoms

Other Adverse Events

IMMUNE CHECKPOINT INHIBITORS & IMMUNE SYSTEM RESPONSE





Checkpoint Inhibition is a Double-edged Sword

"Releasing the brakes" off safety checkpoints can also allow the body's immune system to inadvertently attack normal cells in our body.

Freeman-Keller, M., Kim, Y., Cronin, H., et al. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin. Cancer Res., vol. 22, no. 4, 2016, pp. 886-894. DOI: 10.1158/1078-0432.CCR-15-1136

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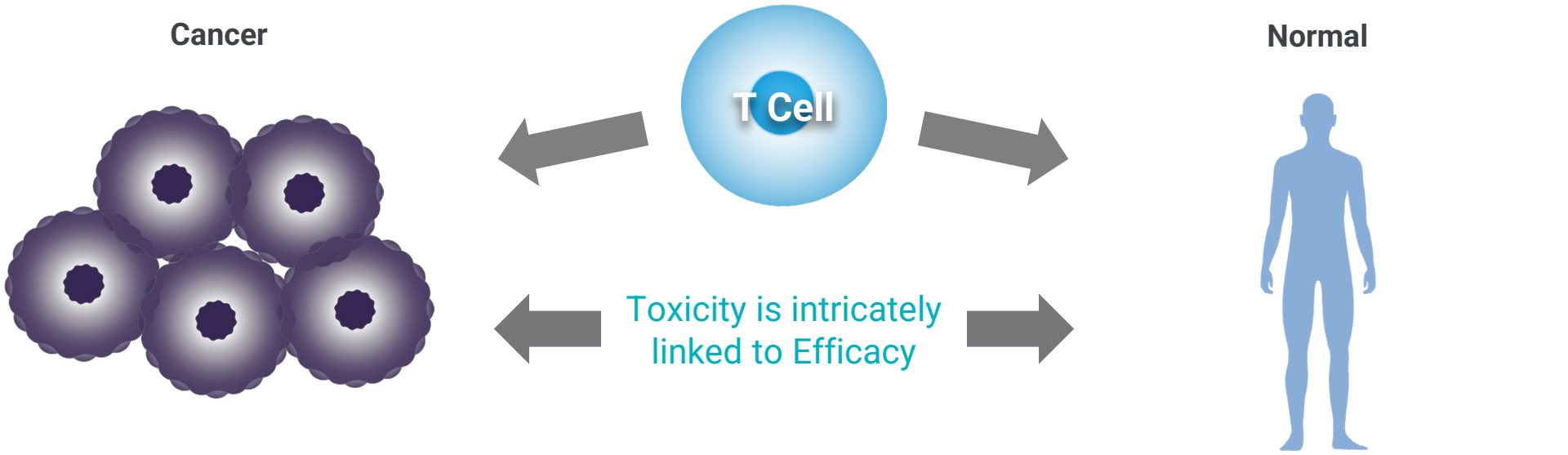
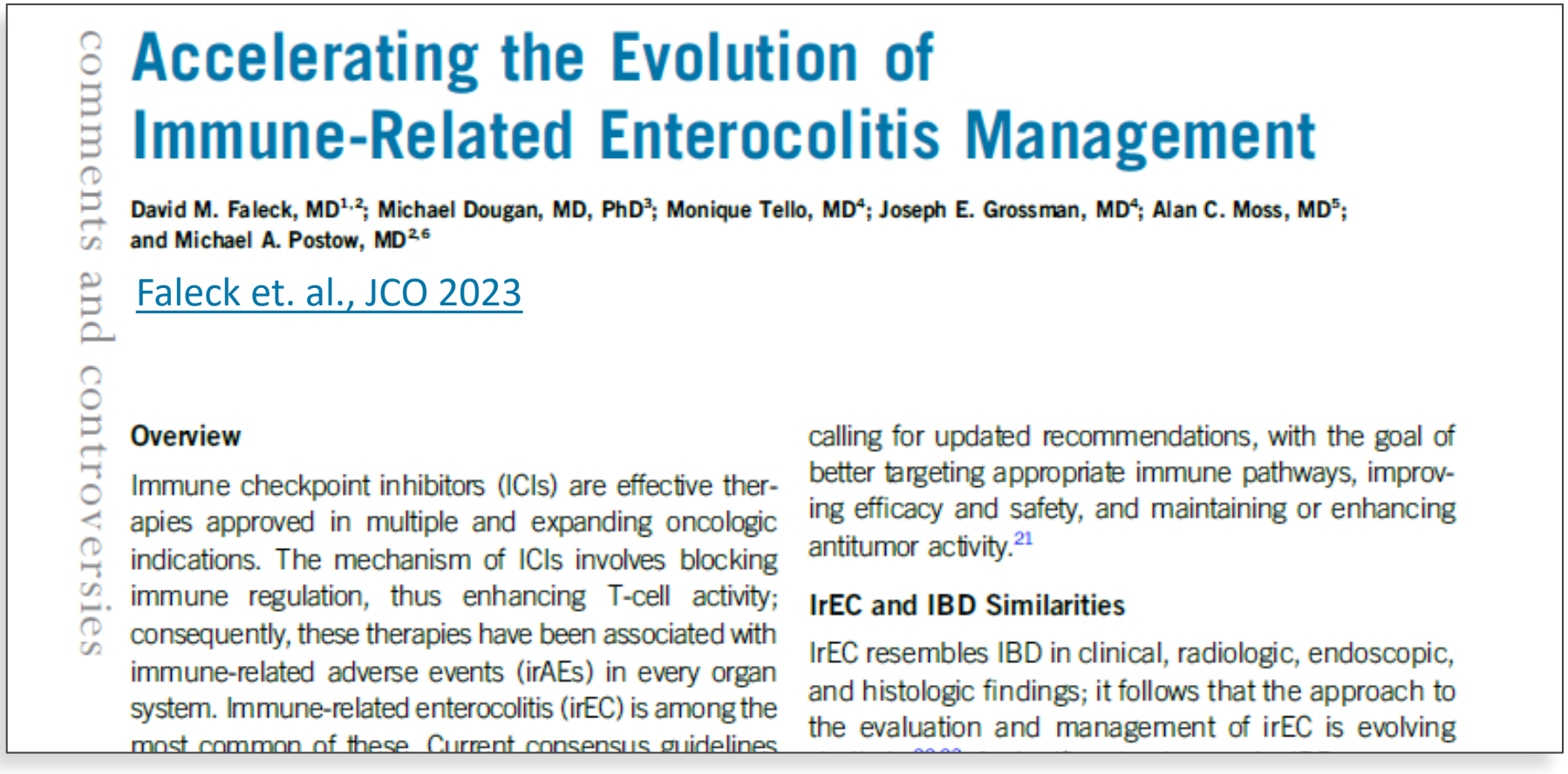
IMMUNE CHECKPOINT INHIBITORS & IMMUNE SYSTEM RESPONSE



Patient Education | **Early Recognition** | **Early Intervention**

Critical to maximizing patient benefit and experience

THE CASE FOR EARLIER INTERVENTION IN IrEC MANAGEMENT:



comments and controversies

Accelerating the Evolution of Immune-Related Enterocolitis Management

David M. Faleck, MD[1,2]; Michael Dougan, MD, PhD[3]; Monique Tello, MD[4]; Joseph E. Grossman, MD[4]; Alan C. Moss, MD[5]; and Michael A. Postow, MD[2,6]

Faleck et. al., JCO 2023

Overview

Immune checkpoint inhibitors (ICIs) are effective therapies approved in multiple and expanding oncologic indications. The mechanism of ICIs involves blocking immune regulation, thus enhancing T-cell activity; consequently, these therapies have been associated with immune-related adverse events (irAEs) in every organ system. Immune-related enterocolitis (irEC) is among the most common of these. Current consensus guidelines calling for updated recommendations, with the goal of better targeting appropriate immune pathways, improving efficacy and safety, and maintaining or enhancing antitumor activity.[21]

IrEC and IBD Similarities

IrEC resembles IBD in clinical, radiologic, endoscopic, and histologic findings; it follows that the approach to the evaluation and management of irEC is evolving

IrEC= Immune – Related Enterocolitis

Faleck, D. M., Dougan, M., & Tello, M., et al. (2023). Accelerating the Evolution of Immune-Related Enterocolitis Management. *Journal of Clinical Oncology, 41*(12), 3110-3115. https://doi.org/10.1200/JCO.22.02914

MANAGEMENT OF IMMUNE-MEDIATED DIARRHEA/COLITIS (IMDC)

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MANAGEMENT OF IMMUNE-MEDIATED DIARRHEA / COLITIS

Agenus recommendations based on clinical studies and society guidelines

3 KEYS TO EFFECTIVE MANAGEMENT OF IMDC

Patient Education

Understanding symptoms to look out for in the context of a change from baseline bowel movements, the importance of early recognition and treatment, the impact of treatment delay, knowing how to reach the medical team

Early Recognition

Through **patient education and rapid communication** with medical team is key for effective management of IMDC

Early Intervention

With steroids and anti-TNFs can be highly effective for IMDC, in conjunction with supportive care[1, 2, 3]

Johnston RL, Lutzky J, Chodhry A, et al. Cytotoxic T-lymphocyte-associated antigen 4 antibody-induced colitis and its management with infliximab. Dig Dis Sci. 2009;54:2538-2540. doi:10.1007/s10620-009-0937-4
Wang Y, Abu-Sbeih H, Mao E, et al. Immune-checkpoint inhibitor-induced diarrhea and colitis in patients with advanced malignancies: retrospective review at MD Anderson. J Immunother Cancer. 2018;6(1):37. doi:10.1186/s40425-018-0411-1
Abu-Sbeih H, Ali FS, Wang X, et al. Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor-induced colitis. J Immunother Cancer. 2019;7(1):93. doi:10.1186/s40425-019-0577-1
Zoghbi, M., Burk, K.J., Haroun, E. et al. Immune checkpoint inhibitor-induced diarrhea and colitis: an overview. Support Care Cancer 32, 680 (2024). https://doi.org/10.1007/s00520-024-08889-2

MANAGEMENT OF IMMUNE-MEDIATED DIARRHEA / COLITIS

Agenus recommendations based on clinical studies and society guidelines

PRESENTATION OF IMDC

Abrupt onset of frequent watery stools, minimal abdominal cramps, worse in the morning

Typical onset is **4-6 weeks after treatment with botensilimab**

- But can be as soon as 1 week after treatment, specially if the patient has had prior irAEs, or has predisposing factors

Can escalate rapidly from grade 1 to 4 in as little as 3-5 days if left untreated

Alarm symptoms:

Rarely presents with fever, blood or mucus in the stool, or significant abdominal pain

- These alarm symptoms may indicate a serious underlying process that requires emergent intervention
- The patient should have an emergency evaluation

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BASELINE HISTORY AND PATIENT EDUCATION CHECKLIST

Baseline History / Exam

- Establishing baseline daily bowel movement history is critically important
- Baseline QuantiFERON-TB Gold (QFT) or T-Spot blood test (which is required)

Pre-Treatment

- Preemptive prescription for oral prednisone can facilitate early treatment
- Availability of infliximab onsite before patient is dosed

Patient Education

- Instruct instruction to avoid antibiotics and probiotics in weeks prior to treatment[1,2]
- Provide patient with direct contact information for MD & on call answering service number for after hours and weekends

Eng, L., Sutradhar, R., & Niu, Y., et al. (2023). Impact of antibiotic therapy on the effectiveness of immune checkpoint inhibitors. J. Clin. Oncol., 41(12), 3122-3128. https://doi.org/10.1200/JCO.23.00049
Pinato, D. J., Howlett, S., & Ottaviani, D., et al. (2023). Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. J. Clin. Oncol., 41(12), 3130-3136. https://doi.org/10.1200/JCO.23.00050

MANAGEMENT OF IMMUNE-MEDIATED DIARRHEA / COLITIS

Agenus recommendations based on clinical studies and society guidelines

INITIAL ASSESMENT

- Patient should be assessed in person, ideally, within 24h of onset of symptoms and no more than 2 days after onset of symptoms
- Evaluate clinical presentation:
  - ✓ **consistent with IMDC?**
    - small volume frequent watery bowel movements, with or without mild cramps, with or without nausea/vomiting
    - no fever, blood, mucous or significant abdominal pain → alarm symptoms
  - ✓ check for **non-immune causes of diarrhea**
  - ✓ check for **infectious causes of diarrhea** (stool bacterial cultures, stool clostridium difficile (C. diff) toxin, stool CMV, stool ova and parasites)
  - ✓ determine if any recent antibiotic use, infectious exposure, travel, culprit food
- Grade diarrheal episodes vs. baseline stool number **(CTCAE Grade 1-4)**
- Make sure that:
  - ✓ any stool softeners/laxatives are discontinued
  - ✓ oral fluid intake, especially electrolyte-rich fluids, and switch to a bland diet
  - ✓ note that anti-motility agents are ineffective in the setting of IMDC
- If patient cannot get into clinic within 24h, high grade or symptoms onset >24h → consider **starting oral prednisone immediately**
  - ✓ Having a filled prescription on hand at home facilitates early treatment

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MANAGEMENT OF IMMUNE-MEDIATED DIARRHEA / COLITIS

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IF IMDC REMAINS THE PRIMARY CONCERN

Recommended Treatment

- ✓ **Start corticosteroids (CS)**
  - Gr 1-2: 0,5-1 mg/kg/day prednisone
  - Gr 3-4: 1-2 mg/kg/day prednisone
- ✓ **Treatment with infliximab 5 mg/kg**
  - regardless of response to CS or grade
  - if TB testing positive* → vedolizumab
  - consider 10 mg/kg IFX for grade 4 or hypoalbuminemia (<2,5)

*If TB testing (ie, Quantiferon Gold) is positive, then infliximab should not be given unless deemed acceptable by treating provider based on further workup and intervention, if the risk of anti-TNF is considered unacceptable, consider vedolizumab as an alternative

If improvement is rapid (symptoms to grade 1 or less within 48h post-IFX)

- ✓ **Rapid steroid taper** (<1 week)
  - if plan to resume BOT: administer 3 doses of IFX (0, 2, 6 weeks)
  - if no plan to resume BOT: additional IFX up to you

If improvement is slow (clear improvement but not to grade 1 or less within 48h post-IFX)

- ✓ Slower steroid taper (2-4 weeks)
- ✓ Administer 3 doses of IFX (0, 2, 6 weeks)

If there is no improvement (symptoms do not improve within 48h post-IFX)

- ✓ Re-evaluation of non-immune causes of diarrhea/colitis and/or GI consult for consideration of endoscopy
- ✓ If immune-mediated etiology still suspected, increase CS dosing to 1-2 mg/kg/day prednisone
- ✓ Consider IFX-redosing at higher dose[1]
- ✓ Consider vedolizumab treatment or additional immunosuppressive therapy

~ KEY TARGETS ~

Time to steroids from onset:
<24 hours

Time to anti-TNF from onset:
<72 hours

Only patients who meet the following criteria will be considered eligible to restart BOT:

- **diarrhea was not immune-mediated OR**
- **didn't exceed Gr2, responded to treatment and received at least 1 dose of IFX and will receive a total of 3 (0, 2, 6 weeks)**

All patients may be eligible to restart BAL (even if grade 3 or higher) if diarrhea/colitis was not attributed to BAL

Harris JP, Abu-Sbeih H, Wang Y, et al. Management of immune-mediated diarrhea and colitis in patients treated with immune checkpoint inhibitors. Oncologist. 2022;27(4):e350-e359. doi:10.1093/oncolo/oyac019
See also C-800-01 study protocol as referenced in Bullock AJ, Schlechter BL, Fakih MG, et al. Botensilimab plus balstilimab in relapsed/refractory microsatellite stable metastatic colorectal cancer: a phase 1 trial. Nat Med. 2024;30(6):830-837. doi:10.1038/s41591-024-03083-7

MANAGEMENT OF EARLY ONSET SYMPTOMS

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MANAGEMENT OF EARLY ONSET SYMPTOMS

Agenus recommendations based on clinical studies and society guidelines

Botensilimab may cause early-onset, usually self-limited signs /symptoms*

**C-800-01: 148 patients MSS mCRC treated with 1 or 2 mg/kg BOT*

Presentation

- From hours to 14 days post infusion

  Signs and symptoms:
  - Intermittent, low-grade fever
  - Chills, rigors
  - Fatigue, malaise
  - Myalgias
  - Mild self-limited nausea, anorexia, vomiting or diarrhea
- Resolves within a few days
- May recur with subsequent infusions
- If it didn't occur with the 1st dose, it is unlikely to occur with subsequent doses → consider alternate etiologies

Workup

- If persistent, infectious workup may be indicated
- Consider evaluating inflammatory markers

Management

- Acetaminophen
- NSAIDs
- Anti-motility agents (if ineffective, consider alternative diagnosis)
- Recommend careful monitoring of any patient who appears to have this syndrome to ensure resolution
- **If doesn't resolve within a few days, consider alternative etiologies**

Bullock AJ, Schlechter BL, Fakih MG, et al. Botensilimab plus balstilimab in relapsed/refractory microsatellite stable metastatic colorectal cancer: a phase 1 trial. Nat Med. 2024;30(6):830-837. doi:10.1038/s41591-024-03083-7

MANAGEMENT OF EARLY ONSET SYMPTOMS

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MANAGMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Infusion Reactions:

May develop during or shortly after drug infusion and generally resolves within 24 hours of infusion completion. **The patient must be monitored for 60 (±10) minutes total after infusion**
Bullock AJ. Nat Med (2024): C-800-01, 148 patients MSS mCRC treated with 1 or 2 mg/kg BOT Q6W + 3 mg/kg BAL Q2W → 3 patients had infusion reactions, 2 grade 1 and 1 grade 2

Grading (NCI CTCAE v5.0)	Treatment	Premedication
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the treating physician.	**None**
Grade 2 Requires therapy or infusion interruption, but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hr.	**Stop infusion** Additional appropriate medical therapy may include, but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen (paracetamol) • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hr of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose.	**Patient may be premedicated** 1.5 hr (± 30 minutes) prior to infusion of botensilimab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500 1000 mg PO (or equivalent dose of analgesic).
Grade 3 Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates).	**Stop infusion** Additional appropriate medical therapy may include, but is not limited to: • epinephrine (In cases of anaphylaxis, epinephrine should be used immediately) • other vasopressors • iv fluids • antihistamines • NSAIDs • acetaminophen (paracetamol) • narcotics • oxygen • corticosteroids	**No subsequent dosing**
Grade 4 Life-threatening; vasopressor or ventilatory support indicated.	**Stop infusion** Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated.	**No subsequent dosing**

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Thompson JA, Schneider BJ, Brahmer J, et al. Management of immunotherapy-related toxicities, version 1.2020. JNCCN Journal of the National Comprehensive Cancer Network. 2020;18(3):231-241. doi:10.6004/jnccn.2020.0012
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Haanen JBAG, Obeid M, Spain L, et al. Tumor-infiltrating lymphocytes improve progression-free survival compared with ipilimumab in advanced melanoma: results from a phase III trial. Presented at the ESMO Congress 2022; Paris, France
Naidoo J, Murphy C, Atkins MB, et al. Society for Immunotherapy of Cancer (SITC) consensus definitions for immune checkpoint inhibitor-associated immune-related adverse events (irAEs) terminology. J Immunother Cancer. 2023;11:e006398. doi:10.1136/jitc-2022-006398

MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

AST/ALT Elevation or Increased Bilirubin or Hepatitis:

Transient elevations seen within 2 weeks of initial dosing may fall under treatment related (early-onset symptoms)

b	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1 Asymptomatic (AST or ALT > ULN to 3 × ULN and/or total bilirubin > ULN to 1.5 × ULN).	**Continue with close monitoring**	None	• Consider alternate etiologies. • Consider monitoring labs 1-2 times weekly. • Manage with supportive care for symptom control.
Grade 2 Asymptomatic (AST or ALT > 3.0 to ≤ 5 × ULN and/or total bilirubin > 1.5 to ≤ 3 × ULN).	**Hold**	• If no improvement seen in 3-5 days, administer steroid (0.5-1 mg/kg/day prednisone) or equivalent. • If inadequate improvement after 3 days of steroids, consider adding mycophenolate mofetil.	• Increase frequency of monitoring to every 3 days. • Consider hepatology consultation. • Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs. Temporarily hold other potentially hepatotoxic oncologic agents.
Grade 3 AST or ALT 5-20 × ULN and/or total bilirubin 3-10 × ULN, OR symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; and reactivation of chronic hepatitis.	**Permanently discontinue**	• Immediately start steroid 1-2 mg/kg methylprednisolone or equivalent. • If no improvement is achieved with steroid refer to hepatologist for further pathologic evaluation of hepatitis. • If steroid refractory, consider adding azathioprine or mycophenolate. • In the case of Grade 3/4 AE refractory to steroids, infliximab should not be used without Sponsor approval (due to potential hepatotoxicity).	• Labs daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 × ULN and/or elevated total bilirubin > 3 × ULN. • If steroid refractory, consider liver biopsy to rule out NASH, tumor, cholestatic variants, other drug-related hepatic inflammation, infection, or other autoimmune entity. • Consider transfer to specialty care facility if necessary.
Grade 4 AST or ALT > 20 × ULN and/or total bilirubin 10 × ULN OR decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, and coma).	**Permanently discontinue**	Follow Grade 3 recommendations as listed, with the following addition for Grade 4: • Administer 2 mg/kg/day methylprednisolone equivalents.	

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Elevation in Amylase/Lipase; Pancreatitis:

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
All Grades	**Not required to hold treatment for evaluation unless symptomatic.**	• Per guidelines, the role of systemic corticosteroids is not defined but could be considered if non-immune etiologies are ruled out.	• Routine monitoring of amylase or lipase in asymptomatic patients is not recommended. Symptomatic pancreatitis due to immune checkpoint inhibitors is very rare. If patient develops symptomatic pancreatitis, recommend standard evaluation to rule out other etiologies. This includes abdominal CT with contrast and MRCP.

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Maculopapular Rash or Inflammatory Dermatitis:

For additional treatment guidelines of bullous dermatoses and severe cutaneous adverse reactions, please refer to local guidelines.

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1 to 2	**Continue treatment;** ho,wever **if persistent, consider withholding** and monitoring for improvement.	• Treat with anti-histamines and topical corticosteroids for Grade 1 or 2 per guidelines. For persistent symptoms, can consider systemic corticosteroids. • For Grade 3 or 4, administer systemic corticosteroids.	• Ensure adequate evaluation to confirm etiology or exclude other causes • Perform total body skin exam. • Consider dermatologic consultation if persistent or Grade 3 or higher autoimmune skin disease is suspected/ consider skin biopsy.
Grade 3 to 4	**Withhold,** consider restarting treatments once resolved to Grade 1. Must discuss with sponsor before restarting.		

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Peripheral/Central Neuropathy:

(for diagnosis specific guidance such as Guillain-Barré syndrome (GBS), aseptic meningitis, encephalitis, autonomic dysfunction, myasthenia gravis, and demyelinating diseases follow SoC society guidelines (e.g., Table 7 in Schneider 2021)

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1	Consider **holding treatment** depending on nature and trajectory of symptoms (except for GBS and myasthenia gravis, which require permanent discontinuation).	Monitor.	• Patients presenting with any neurological symptoms should be referred to a neurologist and ICI should be held until the grade of symptoms is confirmed. • For neuropathic pain, consider nonopioid management with gabapentin, pregabalin, or duloxetine. • For Grade 3-4, admit patient and obtain neurology consultation. For guidance on work up, monitoring, and management, please see reference. This includes peripheral neuropathy, GBS, aseptic meningitis, encephalitis, autonomic dysfunction, myasthenia gravis, and demyelinating diseases.
Grade 2	**Withhold** (except for GBS and myasthenia gravis, which require permanent discontinuation). Discuss with sponsor before re-starting.	General steroid guidance (please see diagnosis-specific recommendation in appendix) • Grade 2: Consider methylprednisone 0.5-1 mg/kg/day • Grade 3-4: Initiate IV methylprednisolone 2-4 mg/kg/day For GBS, early intervention is critical, please see "reference" for guidance on, steroids, IVIG, or plasma exchange. Note: Immune-mediated GBS is notable for benefit from steroids in comparison with idiopathic GBS. For myasthenia gravis please see reference regarding steroid dosing, use of pyridostigmine, rituximab, IVIG, and plasma exchange. For aseptic meningitis, encephalitis, and other neuropathies please see reference regarding prophylactic use of antivirals and antibiotics while diagnosis is being established.	
Grade 3 or 4	**Permanently discontinue** (except for certain peripheral neuropathies that limited functional impact, must discuss with sponsor before restarting).		

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Nephritis and Renal Dysfunction:

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1	**Continue.**	• Monitor	• Work-up and evaluation should include: renal labs, hydration status, medication review for nephrotoxic exposures and urine electrolytes + renal ultrasound to help differentiate pre-renal, intrinsic and post-renal/obstructive etiologies. • Consider nephrology consult.
Grade 2	**Hold** until clinical improvement noted.	• Administer corticosteroids. May start with 0.5 mg/kg/day of prednisone. If worsening or no improvement after 1 week consider 1-2 mg/kg/day prednisone followed by taper.	
Grade 3 or 4	**Permanently discontinue.**		

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Adrenal Insufficiency:

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1-2	Consider **holding** until patient is stabilized on replacement hormone.	• Initiate replacement therapy with hydrocortisone (Grade 1: 15-20 mg, Grade 2: 30-50 mg, Grade 3: 50-100 mg in divided doses). • Most patients will also require fludrocortisone. See local guidelines for further details on dosing and monitoring.	• Please consult endocrinology for Grade 2 and above; consider same for Grade 1. • Workup and evaluation should include hydration status, basic metabolic panel, renin and aldosterone, ACTH stimulation test, precipitating cause of crisis such as infection, and adrenal CT for metastasis or hemorrhage.
Grade 3 or 4	**Hold** until patient is stabilized on replacement hormone. Only resume treatment after discussion with sponsor.		

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Hyperthyroidism / Hypothyroidism:

(Hyperthyroidism generally resolves in weeks with supportive care and often precedes primary hypothyroidism)

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1	**Continue.**	• Monitor.	• Monitor for signs and symptoms of thyroid disorders. • Consider endocrine consultation for unusual presentations, difficulties titrating hormone therapy or Grade 3-4.
Grade 2	**Continue.**	• Hyperthyroidism: If appropriate, treat with nonselective beta-blockers (e.g., propranolol) or thioamides. • Hypothyroidism: Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per SoC.	
Grade 3 or 4	**Withhold;** consider restarting treatments once adequate control achieved.		

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Hyperglycemia or Diabetes (DM):

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1	**Continue** with close clinical follow-up.	• Monitor.	• Obtain routine laboratory panel for autoimmune DM evaluation. • For any patient with new onset DM or worsening of existing diabetes to Grade 3+, please obtain endocrine consultation.
Grade 2	**May hold** until glucose control is obtained.	• Initiate insulin replacement therapy for patients with T1DM. • Administer appropriate therapy for diabetic ketoacidosis, as indicated.	
Grade 3 to 4	**Hold** until glucose control is obtained.		

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Hypophysitis:

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1- 2	**Withhold** until patient is stabilized on replacement hormones.	• CRITICAL to collect labs (am cortisol/ACTH, TSH/free T4, and electrolytes) before initiating replacement therapy. Note: Variation in axes impacted may provide clarity on drug attribution. • Initiate replacement therapy with hydrocortisone (Grade 1: 15-20 mg, Grade 2: 30-50 mg, Grade 3: 50-100 mg in divided doses). • Consider oral pulse prednisone or equivalent therapy for abnormal MRI brain findings suggestive of edema. For Grade 2: 1 mg/kg/day and for Grade 3+: 1-2mg/kg/day. • Other hormone replacement therapy is not initiated until after adrenal corticosteroid, i.e., thyroid, mineralocorticoid, and/or testosterone/estrogen) • See local guidelines for further details on dosing and monitoring.	• Please consult endocrinology for Grade 2 and above; consider same for Grade 1. • Work-up and evaluation should include: evaluation of adrenal axis, thyroid axis, testosterone/estrogen axis, visual field assessment, and brain MRI for pituitary evaluation. • Patients will need education on stress dosing for sick days, use of emergency steroid injectables and when to seek medical attention for adrenal crisis.
Grade 3-4	**Hold** until patient is stabilized on replacement hormones.		

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Pneumonitis

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1	Consider **holding** until workup performed.	• Monitor.	• Workup should include pulse oximetry, CT chest with contrast; for Grade 2 and higher include infectious workup and consider COVID-19 evaluation as per local guidance. • Consider pulmonary function test including DLCO if clinically indicated. • Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered.
Grade 2	**Hold** until clinical diagnosis established and clinical improvement noted. Discuss with sponsor prior to resuming treatment.	• Administer corticosteroids (initial dose of prednisone 1-2 mg/kg or equivalent) followed by taper. • Consider infliximab (5 mg/kg) if symptom improvement is not noted after 3 days on high-dose IV corticosteroids.	
Grade 3 or 4	**Permanently discontinue.**		

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Gastritis/ Upper GI inflammation

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1	**Continue.**	• Monitor.	
Grade 2	Consider **hold,** discuss with sponsor.	• Recommend symptomatic management including but not limited to agents such as PPIs and antiemetics. • For treatment, please refer to diarrhea/colitis recommendations on early intervention with steroids and steroid-sparing agents such as infliximab. Note: Consider IV steroids in place of oral steroids due to risk of reduced absorption.	• Recommend GI workup including H. pylori testing, CMV and EGD ± biopsy for symptomatic and/or persistent disease.
Grade 3	**Hold,** may restart following discussion with Sponsor.		
Grade 4	**Permanently discontinue.**		

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

Cardiovascular Toxicities:

(e.g., myocarditis, pericarditis, arrythmias, and impaired ventricular function). For additional guidance on management of myocarditis, refer to Table 9.1 in ASCO guidelines (Schneider 2021).

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Grade 1	**Withhold** and discuss with sponsor before re-starting treatment.	• For patients with Grade ≥ 2, early (i.e., within 24 hours) initiation of high-dose corticosteroids (1-2 mg/kg/day of prednisone, oral or IV depending on symptoms) should be considered as it is likely to be beneficial without adverse effects. • In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin. May also consider abatacept (costimulatory molecule blockade) or alemtuzumab (CD52 blockade) as additional immunosuppression in life-threatening cases.	• All grades warrant work up and evaluation using cardiac enzymes (CPK/troponin) and EKG, and echocardiogram • Cardiac consultation recommended for all grades.
Grade 2-4	**Permanently discontinue.**		

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MANAGEMENT OF OTHER ADVERSE EVENTS

Agenus recommendations based on clinical studies and society guidelines

All other immune-mediated AEs:

(Please refer to local guidelines for management)

Grading (NCI CTCAE V5.0)	Action Taken with Botensilimab and Balstilimab	imAE Management with Corticosteroid and/or Other Therapies	Monitor And Follow-Up
Intolerable/ persistent Grade 2	**Withhold.**		
Grade 3 or 4	**Withhold or permanently discontinue** based on the type of event. Discussion with the Sponsor required prior to resuming therapy.	• Management per society guidelines and best SoC.	• Ensure adequate evaluation to confirm etiology or exclude other causes.

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SUMMARY BOT / BAL: ADVERSE EVENT MANAGEMENT

- BOT and BAL are investigational agents and are not currently approved for use by any regulatory authority.
- Botensilimab may cause early-onset, usually self-limiting, signs /symptoms
- Management of Diarrhea and Colitis - Three Keys to Effective management
  - Patient Education - Understanding symptoms to look out for
  - Early Recognition – through education and rapid communication
  - Early Intervention - with steroids and anti-TNGs can be highly effective
- Proactive patient management is critical and includes a comprehensive baseline history and patient education checklist

Key Points:

Educate Patient:

IMDC caught early ***can be easier to manage.*** This is why symptoms ***must be reported quickly (<24 hours)***

We have ***effective treatments for IMDC*** and other side effects

Early action is very important in the treatment of IMDC

Delays can result in ***more severe side effects*** and ***having to stop investigational drugs***