Immunotherapy-Induced Diarrhea Evaluation Table 2023: Multiple Interventions

A total of 10 references were reviewed for the update of this topic. Multiple interventions were reported on, including the use of biologics vedolizumab and infliximab, corticosteroids, and budesonide prophylaxis, and antidiarrheal use for immunotherapy-induced diarrhea. Prospective data on this topic are limited. Systematically reviewed observational studies and clinical practice guidelines informed effectiveness recommendations for multiple interventions.

Systematic Review

Citation	Design/Method Sample/Setting	Variables and Intervention	Outcome Measures	Results/Analysis	Limitations	Quality and Nursing Implications
Nielsen, D.L., Juhl, C.B., Chen, I.M., Kellermann, L., & Nielsen, O.H. (2022). Immune checkpoint inhibitor–induced diarrhea and colitis: Incidence and management. A systematic review and meta-analysis. *Cancer Treatment Reviews, 109,* 102440. https://doi.org/10.1016/j.ctrv.2022.102440	**Design:** Systematic review and meta-analysis **Method:** PRISMA. Database search: MEDLINE®, Embase®, and CENTRAL from 2010 to 2021. Dual screening and data extraction. Risk of Bias using McMaster Quality Assessment Scale for Harms and Newcastle-Ottawa Quality Assessment Inclusion criteria: • Phase I–IV studies of adult patients with cancer who experienced immune checkpoint inhibitor (ICI)-induced diarrhea/colitis with monotherapy or combination with chemotherapy or tyrosine kinase inhibitors • Patients with ICI-induced colitis with histology or endoscopy data • Phase I–IV or retrospective studies with 5 or more patients who received biologic treatment for ICI-induced colitis	**Independent Variable(s):** Biologic use: Infliximab and/or vedolizumab **Dependent Variable(s):** ICI-induced diarrhea/colitis symptoms	Incidence of diarrhea and colitis CTCAE in majority of studies (N = 397) Adverse event monitoring	Primary findings on management reported here: Infliximab and vedolizumab were both effective in treatment of ICI-induced colitis (20 publications including 613 patients). Remission of symptoms for infliximab was 87% (95% confidence interval [CI] [79%, 94%] in 502 patients) and for vedolizumab was 88% (95% CI [62%, 100%] in 111 patients). Differences were not significant (p = 0.96). Incidence of diarrhea/colitis was compared across programmed cell death protein 1 (PD-1) versus programmed cell death-ligand 1 (PD-L1) versus cytotoxic T-lymphocyte antigen 4 (CTLA-4) versus combination therapy. Incidence of diarrhea and colitis was higher with CTLA-4 inhibitor ipilimumab and with ICI combined with chemotherapy or tyrosine kinase inhibitor use, and with combination ICI use. Authors suggest an individualized approach to treatment of patients with low-grade diarrhea that includes conservative measures like loperamide, hydration, and monitoring prior to escalation to corticosteroid use.	Limited details about glucocorticoid use High heterogeneity in studies describing endoscopic findings and/or biologic treatment for ICI-induced colitis Because of retrospective search for enterocolitis, some references may have been missed Small sample sizes for some studies Diarrhea/colitis was not consistently confirmed with endoscopy. Heterogeneity in measurement of AEs; some studies did not use CTCAE grading	Findings were valid and reliable and applicable to the population of interest. Consistency in grading of diarrhea and gastrointestinal (GI) symptoms is needed. Patients receiving ICIs require education about diarrhea reporting and management prior to initiation. Accurate assessment of patients' GI symptoms when receiving ICIs by nursing staff would be crucial for successful modification of prophylaxis without steroids. More prospective trials are needed in this area. Vedolizumab and infliximab are effective agents in treating ICI-induced colitis.

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Tran, A.N., Wang, M., Hundt, M., Chugh, R., Ohm, J., Grimshaw, A., . . . Al-Bawardy, B. (2021). Immune checkpoint inhibitor–associated diarrhea and colitis: A systematic review and meta-analysis of observational studies. *Journal of Immunotherapy, 44*(8), 325–334. https://doi.org/10.1097/CJI.0000000000000383	**Design:** Systematic review and meta-analysis of observational studies **Methods:** Database search: Embase, MEDLINE/PubMed®, Scopus®, and Web of Science Core Inclusion criteria: Observational studies about immune-related adverse events diarrhea and colitis in patients receiving ICIs. Retrospective or prospective observational studies of adult patients were included. Dual reviewers for screening and data extraction. Newcastle-Ottawa Scale was used. Quality of studies was determined by a point system. **Sample:** 9,015 citations retrieved, 25 articles, 12,661 patients most commonly on immunotherapy for melanoma (23 of 25 studies) followed by lung, hematologic, and genitourinary cancers, renal cell carcinoma, and colon cancer	**Independent Variable(s):** ICI use (CTLA-4, PD-1, and PD-L1 alone or in combination) **Dependent Variable(s):** Primary outcomes of interest: Incidence of ICI-related diarrhea/colitis, severity of events, endoscopic /histologic findings Secondary outcomes: Management strategies including drug therapy, surgery, and treatment interruption or discontinuation. Corticosteroid monotherapy versus corticosteroid with biologic therapy for immune-related adverse events	All-grade incidence of diarrhea measured using CTCAE, discontinuation of treatment, interruption of treatment, management strategies, and effectiveness in reduction of symptoms	Management results: In patients treated with corticosteroids plus biologics (infliximab, vedolizumab, or adalimumab), the reduction of ICI-induced diarrhea was greater than in corticosteroids alone (88.4%, 95% CI [79.4, 93.8]) versus (58.3%, 95% CI [49.3, 66.7]) ($p < 0.001$). Infliximab was the most commonly used biologic.	Review is limited by the observational nature of studies, heterogeneity between studies, high risk of bias.	The study methodology was sound and rigorous. Patients who experience the immune-related adverse event diarrhea/colitis need careful nursing monitoring for responsiveness of corticosteroid therapy, including frequent reinforcement of teaching of patient monitoring and reporting of refractory symptoms. Corticosteroid and biologic interventions are most frequently used for steroid-refractory immune-related adverse event diarrhea/colitis or high-grade diarrhea/colitis.

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Ding, M., Zhang, X., Wang, J., Gao, F., Zheng, X., Yuan, J., & Qi, X. (2023). Treatment and outcomes of immune checkpoint inhibitors-associated colitis/diarrhea: A systematic review and meta-analysis. *Digestive and Liver Disease, 55*(12), 1621–1631. https://doi.org/10.1016/j.dld.2023.02.016	**Design:** Systematic review and meta-analysis **Method:** PRISMA. Database search: PubMed, Embase, and Cochrane Library. Newcastle-Ottawa Scale was used to assess study quality. Two researchers conducted data extraction. **Sample:** 27 included studies with melanoma and other mixed cancer sites. Date on results ranged from 2015 to 2021. **Setting:** Included studies were conducted in multiple countries: the United States, the Netherlands, the United Kingdom, Germany, Switzerland, China, France, Australia, and Japan, with the United States being the most common site.	**Independent Variable(s):** ICI exposure, corticosteroid, or biologic use **Dependent Variable(s):** Incidence of diarrhea/colitis, overall response, response to corticosteroids, response to biologics, short-term mortality, ICI discontinuation, and ICI restart	CTCAE diarrhea/colitis grading	Pooled responses for ICI-associated colitis and diarrhea: Corticosteroid treatment: Rate of response was 50% (95% CI [35%, 65%]) with significant heterogeneity ($p < 0.01$). Biologic treatment: Rate of response was 96% (95% CI [87%, 100%]) with significant heterogeneity ($p < 0.01$). The pooled rate of steroid-refractory colitis/diarrhea was 42% (95% CI [28%, 56%]) with significant heterogeneity ($p < 0.01$). The pooled incidence of any grade of colitis and diarrhea was 17% (95% CI [11%, 23%]) with significant heterogeneity ($p < 0.01$). The pooled incidence of high-grade colitis was 17% (95% CI [9%, 26%]) with significant heterogeneity ($p < 0.01$). The pooled incidence of low-grade colitis was 3% (95% CI [2%, 5%]) with significant heterogeneity ($p = 0.01$). The pooled incidence of low-grade diarrhea was 13% (95% CI [7%, 22%]) with significant heterogeneity ($p < 0.01$). The pooled incidence of high-grade diarrhea was 15% (95% CI [6%, 28%]) with significant heterogeneity ($p < 0.01$).	The main limitation of this review and meta-analysis was the heavy reliance on retrospective cohort studies. Consideration for prospective randomized controlled trial in the future to allow for longitudinal assessment may be warranted. Use of classification scales for severity of immune-related adverse events and dosage/duration of ICIs varied among studies. Publication bias noted	Overall, the review and meta-analysis were rigorous, and the methodologic approach was clear. Based on selected evidence, the authors attempted to mitigate the influence of publication bias/poor quality by examining the differences between the poor- and high-quality studies. These findings are applicable to patients with cancer and add to the body of evidence on ICI-associated complications and treatments. Nurses can apply findings in clinical practice for early identification of diarrhea in patients with cancer receiving ICIs. Early intervention may minimize treatment-related complications. Nurse knowledge of management recommendations (e.g., corticosteroids) and signs of worsening diarrhea/colitis/additional adverse events can assist in advocacy for interventions likely to be effective.

General Evidence

Citation	Design/Method Sample/Setting	Variables and Intervention	Outcome Measures	Results/Analysis	Limitations	Quality and Nursing Implications
Zou, F., Faleck, D., Thomas, A., Harris, J., Satish, D., Wang, X., . . . Wang, Y. (2021). Efficacy and safety of vedolizumab and infliximab treatment for immune-mediated diarrhea and colitis in patients with cancer: A two-center observational study. *Journal for ImmunoTherapy of Cancer*, *9*(11), e003277. https://doi.org/10.1136/jitc-2021-003277	**Design:** Observational **Method:** Retrospective chart review **Sample**: N = 184, aged older than 18 years, with a median age of 64 years; inclusive of patients with solid malignancies, primarily with stage IV disease admitted for immune-mediated diarrhea and colitis 64% male, 36% female **Setting**: Multisite	**Independent Variable(s):** Vedolizumab, infliximab, steroid use, combination treatment **Dependent Variable(s)**: Immune-mediated diarrhea and colitis, recurrence, duration of hospital course, intensive care unit transfer, clinical remission, admission for immune-mediated diarrhea and colitis, immune-mediated diarrhea and colitis recurrence and cancer outcome, response time, exposure to steroids, attempts at steroid tapers	CTCAE, version 5.0, was used for severity ratings extracted from medical records.	Patients with cancer who were treated with vedolizumab for refractory immune-mediated diarrhea and colitis were comparable (89% versus 88%, p = 0.79) to those who were treated with infliximab. Specifically, patients with cancer who were treated with vedolizumab had lower immune-mediated diarrhea and colitis recurrence (14% versus 29%, p = 0.008), somewhat longer time to vedolizumab response (18 days versus 13 days, p = 0.012), fewer hospitalizations (p = 0.005), shorter length of hospitalization (p = 0.043), shorter exposure to steroids (35 days versus 50 days, p < 0.001), and fewer attempts to taper steroid regimens (p = 0.016).	The main limitation is that research design did not use a controlled trial design. Limitations specific to retrospective analysis: 1. Limited generalization of study findings despite large cohort sample 2. Missing data because of medical chart review and lack of documentation 3. Clinician discretion related to management of immune-mediated diarrhea and colitis, particularly the use of steroids Other limitations: 1. Limited inclusion of historically marginalized groups 2. Use of two well-resourced cancer centers; the experiences and cancer care of patients at centers that may not have similar resources may be different.	Despite the constraints of the research design, the findings are highly informative and could be generalized with caution in interpretation. The findings of this study are most meaningful for White male patients with advanced solid malignancies who are undergoing treatment for steroid-refractory immune-mediated diarrhea and colitis. Although the efficacy of vedolizumab and infliximab are similar for treatment of steroid-refractory immune-mediated diarrhea and colitis, those who receive vedolizumab are more likely to fair well as it relates to steroid use, hospital course, and recurrence of their refractory immune-mediated diarrhea and colitis. Patients were seen to have better survival outcomes with less steroid exposure and higher doses of selective immunosuppressive therapy. Concerted efforts to confirm these results with randomized controlled trials are warranted.

Clinical Practice Guidelines/Expert Opinion

Guideline Citation	Purpose	Sample/Setting	Significant Recommendations	Limitations	Quality and Nursing Implications
Schneider, B.J., Naidoo, J., Santomasso, B.D., Lacchetti, C., Adkins, S., Anadkat, M., . . . Bollin, K. (2021). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *Journal of Clinical Oncology*, *39*(36), 4073–4126. https://doi.org/10.1200/JCO.21.01440	Provided guidance recommendations on the management of immune-related adverse events in patients receiving immune checkpoint inhibitors	175 studies were reviewed in forming this recommendation. Expert consensus was used because of lack of high-quality evidence.	Recommendations included here are specific to ICI-induced diarrhea/colitis management. Grade 1 diarrhea–conservative management: loperamide, dietary changes, rehydration/electrolyte replacement The recommendation for Grade 2 or higher diarrhea associated with ICIs is corticosteroids at 1–2mg/kg/day. Steroid tapers over 4–6 weeks when symptoms improve to grade 1 or less. If using a biologic agent, the taper can be shortened. In patients refractory to corticosteroids (no improvement in 72 hours), consider infliximab or vedolizumab. Endoscopic evaluation for severity assessment can be considered. Budesonide and immunosuppressants are not indicated for mild diarrhea.	Expert consensus used because of lack of high-quality evidence	This clinical practice guideline offers a comprehensive guide to immune-mediated adverse events with inclusion of management strategies broken down by grade of symptom severity. Recommendations are made to guide all members of the healthcare team in management of immune-related adverse events during treatment with immune checkpoint blockade for cancer. Nurses can apply these findings to a large population of patients receiving ICI therapy for the purpose of early recognition of symptoms, knowledge about diagnostic workup and management strategies, and providing anticipatory guidance to patients and caregivers during treatment.

Guideline Citation	Purpose	Sample/Setting	Significant Recommendations	Limitations	Quality and Nursing Implications
Dougan, M., Blidner, A.G., Choi, J., Cooksley, T., Glezerman, I., Ginex, P., . . . Rapoport, B.L. (2020). Multinational Association of Supportive Care in Cancer (MASCC) 2020 clinical practice recommendations for the management of severe gastrointestinal and hepatic toxicities from checkpoint inhibitors. *Supportive Care in Cancer, 28*(12), 6129–6143. https://doi.org/10.1007/s00520-020-05707-3	The purpose of these practice recommendations is to provide an overview of the gastrointestinal and hepatic complications of immune checkpoint blockade, including recommendations for diagnosis and for treatment. This review provides guidance to GI specialists.	Patients with cancer receiving treatment with ICIs with GI immune-related adverse events that may not respond to initial treatment strategies	Recommendations include laboratory testing, imaging, endoscopy to confirm diagnosis of GI immune-related adverse events, initial treatment, and management of first-line treatment failure with immunosuppressive therapies. Most patients with checkpoint inhibitor (entero)colitis, enteritis, or gastritis respond to high-dose corticosteroids and steroid taper over 4–6 weeks. About 1/3 of patients will require advancing to further treatment with immune suppression. Infliximab and vedolizumab have been effective in the treatment of ICI-induced enterocolitis. Standard doses used for irritable bowel disease are used, and typically 1–3 infusions are sufficient, with limited need for maintenance therapy. Experts recommend that patients refractory to corticosteroid treatment and infliximab or vedolizumab have repeated stool cultures, *Clostridium difficile* testing, and ova and parasite testing. Limited evidence suggests that switching from one biologic to the other may be appropriate after failure. Additional recommendations were made for ICI-induced hepatitis management.	Consensus-based guideline based on an expert panel from the Multinational Association of Supportive Care in Cancer with supporting evidence Recommendations focused specifically on advanced complications refractory to initial treatment. Authors acknowledge the limited data available beyond retrospective data and expert opinion.	Well-cited expert opinion resource from a professional organization focused on escalating/refractory GI immune-related adverse events associated with ICI and the GI specialist considerations Some cited studies were missing details. These recommendations can be applied to an adult population receiving ICIs. Nurses caring for patients receiving ICIs can use these findings to understand advanced measures for refractory initial treatment of ICI-induced diarrhea/colitis.

Guideline Citation	Purpose	Sample/Setting	Significant Recommendations	Limitations	Quality and Nursing Implications
Brahmer, J.R., Abu-Sbeih, H., Ascierto, P.A., Brufsky, J., Cappelli, L.C., Cortazar, F.B., . . . Ernstoff, M.S. (2021). Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *Journal for Immunotherapy of Cancer, 9*(6), e002435. https://doi.org/10.1136/jitc-2021-002435	To update recommendations and guidance to assist clinicians to manage adverse events related to ICIs	Patients with cancer receiving ICIs	Management recommendations included here: For patients experiencing diarrhea/colitis of greater than or equal to grade 2, corticosteroids should be started. IV corticosteroids are indicated for grade 4. Steroid taper over 4 weeks after improvement to less than or equal to grade 1. If there is no improvement with corticosteroid therapy within 3–5 days, or recurrence after tapering, then 3 doses of infliximab should be administered at weeks 0, 2, and 6. If symptoms persist after second dose of infliximab, hold the third dose, and administer 3 doses of vedolizumab at weeks 0, 2, and 6. .	Consensus-based recommendations, based on available evidence Inherent subjectivity and bias based on clinical experience	Description of recommendations with in-depth review of each ICI agent, potential side effect profile, and recommendations showed rigor. Consensus threshold was 75% approval of voting members. There was a period of public comment prior to publishing. Evidence rating by way of the Oxford Centre for Evidence-Based Medicine was used to determine agreement among expert panel members. An interprofessional expert panel was also used to review evidence that informed the recommendations, which added additional rigor. Findings are applicable to the care of patients with cancer, given the evolving and expanding research landscape of immunotherapy. Early identification and management of ICI-related adverse events may reduce burden of toxicities associated with ICI, which then improves clinical outcomes for patients with cancer receiving this specific immunotherapy. Oncology nurses' ability to identify and initiate interprofessional discussion with the clinical care team about grading and subsequent early management of specific ICI-related adverse events not only improves individual-level care, but also informs refinement of ICI treatment protocols long-term. Given the current nursing workforce landscape and limited resources, using ICI-specific protocols or tools in real-life fast-paced practice settings to identify adverse effects may be difficult.

Guideline Citation	Purpose	Sample/Setting	Significant Recommendations	Limitations	Quality and Nursing Implications
Bossi, P., Antonuzzo, A., Cherny, N.I., Rosengarten, O., Pernot, S., Trippa, F., . . . Ripamonti, C.I. (2018). Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. *Annals of Oncology,, 29*(Suppl. 4), iv126–iv142. https://doi.org/10.1093/annonc/mdy145	To provide guidance related to the identification, assessment considerations, and treatment options for adult patients with cancer experiencing diarrhea.	Adult patients receiving cancer therapy	Thorough assessment of symptoms and severity of symptoms combined with nutritional counseling, and diagnostic testing is recommended for diarrhea related to chemotherapy, immunotherapy, and/or radiation therapy. Immunotherapy-induced diarrhea management in this guideline: Rapid treatment within 5 days of symptoms Grade 1 treatment recommendations include the administration of oral antidiarrheal agents Grade 2 recommendations include stopping the immunotherapy agents and initiation of budesonide for nonbloody diarrhea. Oral corticosteroids can be started at 0.5–1mg/kg/day prednisone equivalent for ulceration and bleeding seen on endoscopy or for persistent symptoms after 3 days. Grade 3 and 4 IV corticosteroid, avoidance of loperamide and opioids and infliximab for persistent symptoms with vedolizumab as a reasonable alternative. Prolonged immunosuppressive therapies require pneumocystosis antibiotic prophylaxis. Addition of empirical antibiotics should be considered for patients with leukocytosis or fevers.	Consensus-based guideline The guideline does not include information related to the search strategy or criteria used to determine the references included; however, it does include in-text citation with level and grade of recommendation. References include articles published as early as 1991.	The recommendations included within the guideline could be applied to the adult population of patients receiving cancer therapy. Future studies are needed to determine the effectiveness of proposed interventions. This clinical practice guideline adds to the growing body of evidence on the management of treatment-related diarrhea/colitis due to immune checkpoint blockade. Nurses can use the information to identify and intervene early when GI symptoms are present in patients receiving ICIs.

Expert Opinion Citation	Purpose	Sample/Setting	Significant Recommendations	Limitations	Quality of Evidence/Worth to Practice
Desmedt, V., Jauregui-Amezaga, A., Fierens, L., Aspeslagh, S., Dekervel, J., Wauters, E., . . . Lobatón, T. (2023). Position statement on the management of the immune checkpoint inhibitor-induced colitis via multidisciplinary modified Delphi consensus. *European Journal of Cancer, 187,* 36–57. https://doi.org/10.1016/j.ejca.2023.03.025	To provide updated practice advice to gastroenterologists and oncologists on the diagnosis and management of ICI-induced GI in Belgian hospitals using a Delphi consensus method	**Sample**: Management of patients with or at risk for ICI-induced colitis **Setting:** Position statement from Belgian stakeholder groups intended as guidance for oncologists in Belgian hospitals	Management of ICI-induced colitis consensus recommendations: Consensus was reached on treatment interruption if ICI-induced colitis is suspected in the setting of grade 2 or greater diarrhea and use of early systemic corticosteroids as first-line therapy with early assessment of response. Steroids can be tapered over 4–6 weeks if there is improvement to less than or equal to grade 1 diarrhea. Prophylactic budesonide is not recommended for mild ICI-induced colitis with no benefit reported in two randomized controlled trials. Biologic agents can be used as escalation therapy after corticosteroids in patients nonresponsive to treatment and in cases of high-risk endoscopic findings (ulcerations and extensive inflammation). Infliximab can be considered as a first-line biologic agent for steroid-refractory patients with high-risk endoscopic features. Consensus was not reached on use of vedolizumab in patients with mild colitis without high-risk endoscopic features. Consensus was reached on switching from 1 biologic to another (i.e., infliximab to vedolizumab or vedolizumab to infliximab) in the cases of nonresponse to 1 biologic.	Consensus-based position statement using supportive evidence and expert consensus; level and strength of evidence was not reported. Quality assessment of evidence was not reported. A study comparing vedolizumab and infliximab was not available at the time of this Delphi process, which may have further influenced decisions surrounding use of vedolizumab. Guidance is for Belgian hospitals.	Comprehensive position statement on the management of ICI-induced colitis with supporting evidence; recommendations for early identification and management of ICI-induced colitis were provided in this Belgian position statement. Nurses can apply this knowledge when caring for patients at risk for ICI-induced colitis.

Expert Opinion Citation	Purpose	Sample/Setting	Significant Recommendations	Limitations	Quality of Evidence/Worth to Practice
Dougan, M., Wang, Y., Rubio-Tapia, A., & Lim, J.K. (2021). AGA Clinical Practice Update on diagnosis and management of immune checkpoint inhibitor colitis and hepatitis: Expert review. *Gastroenterology, 160*(4), 1384–1393. https://doi.org/10.1053/j.gastro.2020.08.063	To provide expert review and best practice advice for treatment of patients with ICI GI effects	Patients receiving ICIs and experiencing gastrointestinal and hepatic adverse effects	Recommendations for ICI-related colitis treatment: ICI colitis can have rapid onset and usually responds to high-dose corticosteroids (0.5–2 mg/kg prednisone equivalent daily) with a taper of 4–6 weeks. Budesonide is recommended for microscopic colitis but not indicated as prophylaxis for ICI enterocolitis. For failure on first-line steroids within 72 hours, second-line immunosuppressants infliximab or vedolizumab can be used. For patients who do not respond to the initial choice of immunosuppressant, treatment can be switched to the other. Other recommendations are radiology imaging, ruling out infectious causes, and endoscopic biopsy confirmation if possible, to rule in colitis.	This is an expert opinion review that references lower-level evidence guiding recommendations because of lack of prospective data.	This guideline is worthwhile to practice. Experts in the field of gastroenterology collaborated to form this expert opinion piece. A helpful algorithm was provided to guide action and testing in cases of suspected immune-mediated diarrhea/colitis. GI adverse reactions are commonly experienced in patients receiving ICI therapy. It is important for nurses to be knowledgeable about symptoms of GI toxicity from ICIs. These toxicities must be identified quickly and escalated by nurses so appropriate diagnosis can be made and treatment can be started. The information contained in the review is helpful to nurses for educating patients and families about symptoms to monitor and report, diagnostic tests and laboratory values to expect, treatment options, and how ICI treatment may proceed post–adverse reaction.