Canadian Association of Nurses in Oncology
Association canadienne des infirmières en oncologie

This program meets Canadian Association of Nurses in Oncology (CANO) guidelines and is expected to support nurses in their understanding of immune-mediated adverse events in bladder cancer. Endorsement is provided by CANO for a time period of one year, ending September 2019.

Nursing standard: Best practices for counselling and managing adverse events in patients with bladder cancer treated with immuno-oncology agents

Part 1: Overview of immuno-oncology therapies indicated for treatment of advanced bladder cancer

- Immuno-oncology (IO) is type of cancer therapy that involves improving the body's immune response to target and attack tumours[1].
- The use of IO therapy in bladder cancer offers an effective alternative for patients for whom previously there were few options for durable response, including those who are ineligible for cisplatin-based regimens or who are at risk of significant toxicity[2].
- As of September 2018, four IO agents have been approved for use in locally advanced and metastatic urothelial (bladder) carcinoma by Health Canada[3-6] (Table 1).
  - These IO agents are administered via IV infusion over 30-60 min every 2-3 weeks, until no further clinical benefit or unmanageable toxicity.

Table 1: Immuno-oncology agents in bladder cancer

Agent	Dose	Route/ Schedule	Infusion time	Health Canada indication
TECENTRIQ® (Atezolizumab)[3]	1200 mg	IV infusion every 3 weeks	60 min first dose, 30 min subsequent doses (if initial dose is well-tolerated)	NOC/c locally advanced or metastatic urothelial carcinoma*
BAVENCIO™ (Avelumab)[4]	10 mg/kg	IV infusion every 2 weeks	60 min	NOC/c locally advanced or metastatic urothelial carcinoma*
IMFINZI® (Durvalumab)[5]	10 mg/kg	IV infusion every 2 weeks	60 min	NOC/c locally advanced or metastatic urothelial carcinoma*
KEYTRUDA® (Pembrolizumab)[6]	200 mg	IV infusion every 3 weeks	30 min	NOC without conditions locally advanced or metastatic urothelial carcinoma*†

*with disease progression during/following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Duration of treatment is until loss of clinical benefit or unmanageable toxicity.

†or up to 24 months without disease progression.

ACRONYMS AND ABBREVIATIONS: NOC, notice of compliance; NOC/c, notice of compliance with conditions.

Part 2: Best practices for counselling patients starting immuno-oncology therapy

QUESTION

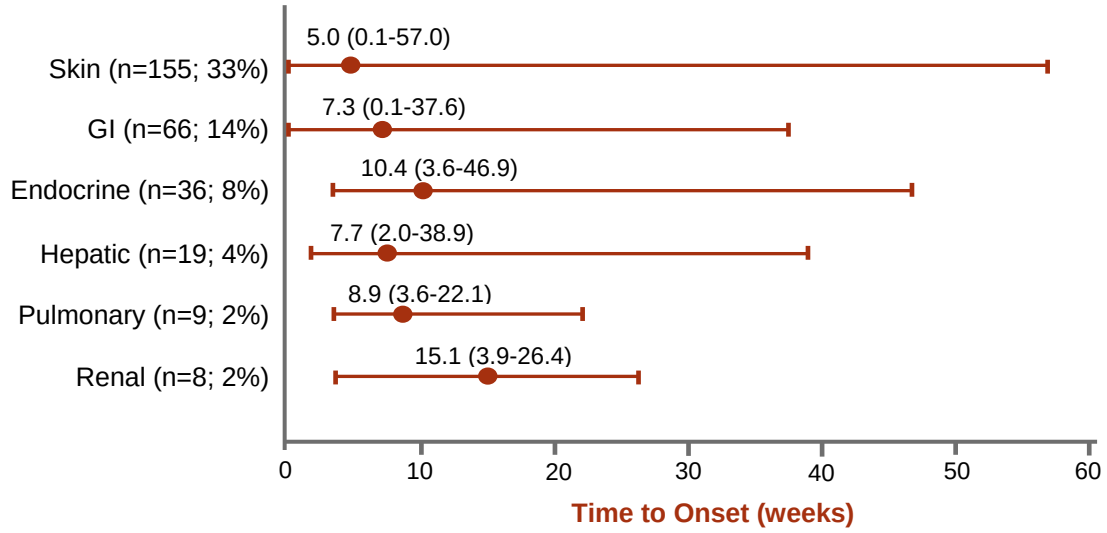
What counselling can nurses provide to successfully prepare patients to start immuno-oncology therapy?

Patient counselling can be divided into four main themes: informed consent, schedule and administration, support, and follow-up

INFORMED CONSENT:

- Prior to initiating patient education, assess the patient's existing level of knowledge and use the information in this section as a guide to reinforce and build upon any baseline knowledge.
- Explain the goals and potential risks of immuno-oncology therapy:
  - Provide basic information on the immune system and immunotherapy.
  - Explain how IO agents support the immune system to recognize and attack tumours.
  - Set up appropriate expectations for response.
    - Setting patient expectations ahead of treatment may reduce patient anxiety[7].
      - Inform patients as to what to expect prior to the first infusion and at every point of contact[7].
      - Inform patients that despite apparent disease progression (enlarging lesions) after starting IO therapy, they may ultimately respond to and benefit from treatment as it may take time for an effective anti-tumour immune response to build[7].
  - Review any potential contraindications (eg, patients who have experienced a severe hypersensitivity reaction to the agent or any ingredients in the formulation[3-6]).
  - Review risk factors for emergence of immune-mediated adverse events (imAEs), including personal and family history of autoimmune disease and toxicities to previous immuno-therapies[8].
    - Where diagnosis of family members is uncertain, investigate conditions such as long-term follow-up for a chronic disease, long-term prescription of steroids, chronic rheumatological conditions, inflammatory bowel disease, cutaneous disease or thyroid conditions running in the family[8].
    - The immune response induced by IO agents could enhance peritumoural inflammation and be responsible for **different patterns of toxicity** depending on the location of the tumour[8].
      - For example, the immune response may become symptomatic presenting as shortness of breath or headache when the lung or central nervous system are involved, respectively.
    - Review patients' medication lists for immune-modulating potential (eg, steroids, NSAIDs), and exposure to certain chemical products/mineral dusts (eg, silica), which can increase risk of autoimmune disease[8].

- Review common adverse events and strategies for management:
  - Explain that toxicity related to IO agent-use includes imAEs that results from immunologic causes. imAEs likely result from impaired self-tolerance leading to immune reactions against healthy organs and tissues[9].
  - Explain that imAEs are often unpredictable and can cause inflammation of any organ, with dermatologic, gastrointestinal, hepatic and endocrine toxicities typically predominating[9].
  - The most common imAEs are rash/pruritus, diarrhea/colitis, transaminitis, and sometimes pneumonitis or endocrine toxicity[9].
  - Most imAEs do not occur before the first 4 weeks of therapy[10], and several imAEs exhibit a characteristic pattern in the timing of their occurrence; while skin and gastrointestinal toxicities tend to occur the earliest, liver and endocrine toxicities tend to occur later[11,12] (Figure 1).
  - Ensure patients are aware that toxicity can worsen without appropriate management, even after treatment discontinuation.
    - Neglecting these toxicities or delaying care can lead to a worse prognosis or even death[8].
    - The management of imAEs is specific and sometimes urgent. It absolutely requires co-ordination with the health care team that has prescribed the treatment[8].
- Explain the initial assessment before initiation of IO therapy, which may include all or some of the following: physical examination, electrocardiograms, bloodwork, and radiological imaging[8,13] (Table 2).



Adapted from Weber, J et al. J Clin Oncol. 2017;35(7):785-795.

Figure 1: Timing of imAEs with the immuno-oncology agent, nivolumab*,[12]

*Note: Data on the timing of imAEs with other IO agents in this drug class (ie, atezolizumab, avelumab, durvalumab, pembrolizumab) are limited.

Table 2: Recommended baseline assessments

HISTORY AND PHYSICAL EXAMINATION[8]	LABORATORY TESTS[8]	IMAGING AND OTHER TESTS[8,13]
• Performance status • Weight, height, body mass index • Heart rate, blood pressure • General symptoms • Pre-existing symptoms (eg, bowel movements, dyspnea, rash, headaches) • History of fever/recent infection • Medication list • Current/ongoing treatments	• Complete blood count • Electrolytes • Glucose • Total bilirubin, liver enzymes • TSH, T4* • Cortisol and ACTH* • LH*, FSH*, estradiol*, testosterone* • Urinalysis* • Virology (HIV, HCV, HBV) • Antibody* (ANA, TPO Ab, Tg Ab)	• Baseline electrocardiogram • Chest x-ray • CT of chest, abdomen/pelvis • Brain MRI

*If clinically indicated.

ACRONYMS AND ABBREVIATIONS: Ab, antibody; ACTH, adrenocorticotropic hormone; ANA, antinuclear antibody; CT, computed tomography; FSH, follicle-stimulating hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LH, luteinizing hormone; MRI, magnetic resonance imaging; T4, thyroxine; Tg, thyroglobulin; TPO, thyroperoxidase; TSH, thyroid-stimulating hormone.

- Explain the need for continued treatment, and that a dosing delay or discontinuation of treatment may be required based on individual safety and tolerability.
- Set expectations for patient responsibilities, including attending all laboratory tests (including blood work and urinalysis) at every cycle before IO therapy administration, continual tracking and reporting any AEs.
  - Stress the importance that patients and their family members are their own advocates in the reporting of imAEs. Although most imAEs are relatively infrequent, the threshold for concern should be higher than with conventional chemotherapy because of the potential of imAEs to evolve quickly to life-threatening conditions such as neurological disorders and myocarditis[8,9].
- Provide handouts or other resources (eg, websites, support groups) that summarize the key information about immunotherapy so that the patient can review them later at his or her own pace[8,9].

SCHEDULE AND ADMINISTRATION:

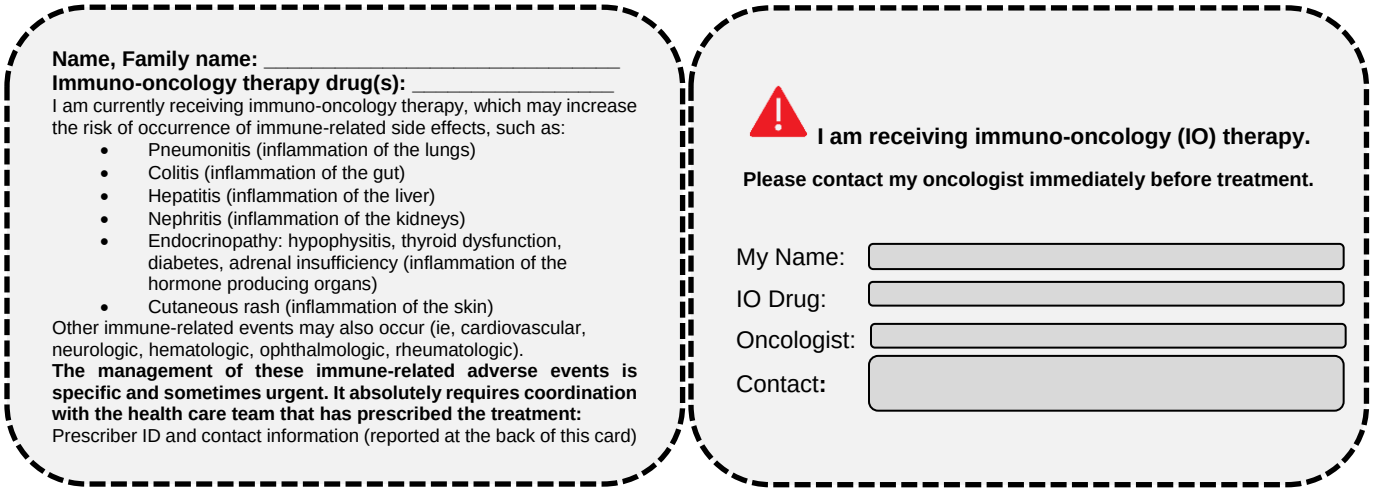
- Review the patient's treatment regimen (see Table 1) and scheduled appointments, including infusions, blood work and other laboratory tests or imaging.
  - At every cycle before administration of IO therapy, check laboratory tests, including complete blood count, serum electrolytes and creatinine, glucose, liver function tests and thyroid function tests. Compare these tests to baseline values to detect gradual changes over time[8].
  - Review new symptoms or increase of pre-existing imAE symptoms. Explain that if imAEs occur, visits may need to become more frequent and follow-up with sub-specialists may be necessary to manage symptoms[8].
- Help the patient set appropriate expectations about each appointment, its duration, and the possibility of needing more time based on laboratory results and any symptoms reported.
  - Monitoring new and/or worsening symptoms may need further evaluation to determine if discontinuation of the IO agent is warranted[8,9].
  - Management of imAEs may require coordination with specialists such as dermatologists, hematologists etc.[8.9]
- After treatment termination, the patient should be evaluated every 3 months for the first year, then every 6 months thereafter. Any suspicious symptoms should lead to proper investigation, which may include imaging and/or laboratory investigations, if clinically indicated[8].

SUPPORT:

- Outline the support available from nurses and other members of the health care team.
  - If possible, provide contact information for a primary nurse who the patient can call with follow-up questions[9]. Also ensure patients know who to contact after hours in emergency situations.
  - Provide printed materials with other key phone numbers and sources of information about support options[9].
- Ask the patient about support resources at home – are there people to help with driving, chores etc., as needed? Refer to other resources (social worker, meals on wheels) if needed.
- Discuss the distance the patient travels for each visit. Consider this in planning each treatment cycle. Are there options for laboratory checks closer to home?
- Tell patients that it is important for them to inform any doctor who cares for them (eg, emergency room physician, family practitioner) that they are receiving IO therapy since it may influence treatment decisions.
  - Provide patients with an immuno-oncology letter. This letter can help properly notify other health care professionals about the management and monitoring requirements for imAEs. The letter includes information about the patient's IO treatment, common imAEs, and the need for urgent management in coordination with the prescribing health care team.
  - Encourage patients to use medical ID bracelets and/or wallet cards that include contact information of the treating physician, the name of the IO agent and treatment dates (Figure 2)[8,9].

A number of tools are available to support patients and healthcare professionals in optimizing IO therapy. The CIOSK (Community Immuno-Oncology Support Kit) found at https://ciosktraining.net/ciosk-resources is a Canadian website that provides various resources, including:

- **Immune-related adverse events clinic posters and handouts**
- **IO therapy call-back questionnaire (for nurses/pharmacists conducting telephone follow-ups)**
- **Patient diary (symptom tracker)**
- **IO therapy letter (for patients to share with healthcare professionals in the community when care is required outside the oncology setting)**



Adapted from from Champiat S, et al. Ann Oncol. 2016;27(4):559-574.

Figure 2: Example of a patient wallet card

FOLLOW-UP:

- Patients should be contacted on a regular basis through a call-back protocol to assess occurrence of imAEs, especially during the first 3 months of therapy when they are most likely to occur[9].
  - Develop a call-back questionnaire and use it to monitor the patient's general health, as well as signs and symptoms associated with organ toxicities (see https://ciosktraining.net/ciosk-resources).
    - Such a questionnaire can be used as a screening tool to identify areas requiring further assessment.
  - The questionnaire should include organ-specific information, such as:
    - Skin: Do you have a rash? Where? Does your skin itch? Do you have skin blisters or peeling?
    - Gastrointestinal: How many times do you have a bowel movement each day? Is this different than normal? Do you have watery or foul-smelling stools? Are your stools dark, tarry, or sticky? Have you experienced pain in your belly?
    - Hepatic: Has your urine been darker than normal? Do you notice your skin or whites of your eyes turning yellow? Do you have pain on the right side of your belly? Do you bleed or bruise easily?
    - Pulmonary: Have you had any shortness of breath or trouble breathing? Do you have a new or worsening cough?
    - Renal: Have you had: persistent or unusual headaches? Dizziness or fainting? Unusual weight loss/gain? Changes in your eyesight? Have you felt: hotter or colder than usual? Tired/sluggish? Your heart racing? Have you had a change in hunger/thirst?
    - Other: Have you had: fever or chills? Additional swelling? Change in pain frequency/severity? Mouth sores or dry mouth? Any other troublesome symptoms?
  - Consult the patient's oncologist before administering further IO treatment if reportable symptoms are discovered.
- Educate patients about common AEs – what to watch for, when to seek urgent care, how and when to report them to the healthcare team, and how to manage them (Table 3).
- Instruct patients to avoid self-management of symptoms without discussing with their oncologist or general practitioner[8].
- As with many cancer therapies, IO agents may also affect a patient's reproductive health or sexuality. Be prepared to initiate discussions surrounding sexual health issues with sensitivity and use a non-judgemental approach.

Table 3: Patient education on symptom management*

		SYMPTOMS	
Patient should:	Go to ER if:	• Blood in stool (dark, tarry); mucous; abdominal pain • Dark/tea-coloured urine • Yellowing in whites of eyes	• Sudden shortness of breath • Chest pain, heart irregularities
	Contact Cancer Centre if:	• Skin is itchy with no improvement after using cream for 24 hours • 4 or more bowel movements above normal	• Right-sided abdominal pain • New cough • Increased fatigue
	Record and discuss at next appointment if:	• Redness or flushing of skin	• 2-3 bowel movements above normal

*Based on feedback from 12 oncology nurses attending National Nursing Advisory Board Meeting/Focus Group in conjunction with 2017 CANO Conference.

- Encourage patients to use a diary to record and discuss changes in symptoms at their next appointment. These changes may include skin appearance/colour, frequency and appearance of bowel movements, appearance of urine, breathing, pain and tiredness[8].
  - Monitor any variation in symptoms or laboratory results from baseline. If the symptom is non-severe or non-specific, continue to monitor it closely to evaluate its evolution and repeat laboratory and imaging tests, if necessary[8].
  - Be aware that neglecting immune-related toxicities or delaying adequate care can lead to a worse prognosis and may also be fatal. Conversely, focusing mainly on imAEs and ignoring potential incidental events (eg, infection, thrombosis) may also have negative consequences. Most frequent AEs are those related to disease progression; therefore, any new symptom should prompt a tumour evaluation seeking disease progression[8].
- Give the patient written material that they can consult at their leisure.
- For patients interested in additional information, suggest online and community sources that are reliable and mention that not all sources can be trusted.

Part 3: Best practices for reducing imAEs from immuno-oncology therapy

COMMON imAEs

- In general, when an imAE is suspected, IO therapy may be delayed in order to monitor the evolution of symptoms during diagnosis[8].
- Temporary suspension or termination of IO agent is determined based on nature and severity of a confirmed imAE[8].
- Grade 2 toxicities are generally managed with a treatment break until symptoms recover or toxicity returns to grade 1 or less[8].
- Recall that imAEs are often unpredictable and can cause inflammation of any organ, with dermatologic, gastrointestinal, hepatic and endocrine toxicities typically predominating[9]. See Table 4 for management of common imAEs and individual product monographs for more detailed information.
- Instruct patients to avoid self-management and report all symptoms to their oncology team as early as possible.
- Notify the physicians of all nursing assessments. The physician should collaborate in symptom management of imAEs[8].
- Early identification and treatment of imAEs are essential to limit their severity and duration.
- While some low grade imAEs can be easily managed, most other toxicities (especially if grade >1) require specialist referrals for proper monitoring and management.
  - Ensure patients are aware that toxicity can self-perpetuate without appropriate management, even after treatment discontinuation, and that neglecting these toxicities or delaying care can lead to a worse prognosis or even death[7].
  - Monitor patients for resolution of symptoms and for relapse and recurrence of imAEs[8].
  - With all imAEs, plan a nursing follow-up call for the next business day and/or create a care plan if unable to follow-up.
- In case of grade 1 or 2 infusion-related reactions, consider pre-medication with antipyretic (eg, acetaminophen) and antihistamine for prophylaxis of subsequent infusion reactions[4].
- After IO therapy suspension, resuming therapy can typically be considered[8]:
  - If the side-effect is stabilized ≤ grade 1 (returned to baseline); and
  - If the steroid dose is reduced to ≤10 mg/day prednisone or equivalent; and
  - In the absence of other immunosuppressive drugs.
- In general, IO therapy should be permanently discontinued in the case of adverse immune dysfunction, that is[8]:
  - Life-threatening (grade 4);
  - Severe (grade 3) and recurring; or
  - Moderate (grade 2) but not resolved despite appropriate treatment.

Table 4: Common immune-mediated adverse events

SKIN imAEs				
ADVERSE EVENT	**FREQUENCY**			
	ATEZOLIZUMAB[3]	**AVELUMAB[4]**	**DURVALUMAB[5]**	**PEMBROLIZUMAB[6]**
RASH/DERMATITIS	NR	NR	1.0%	NR

PATIENT EDUCATION	MANAGEMENT
• Set appropriate expectations about incidence, timing and severity of skin imAEs • The characteristic rash is faintly erythematous and maculopapular, involves the trunk and extremities, and may be pruritic[14] • Counsel patients on sun safety, avoiding skin irritants, skin care (moisturizers, soaps), topical corticosteroids and antihistamines (oral or topical)[13,15-18] • Educate patients on steroid use where relevant[15-18]	• Exclude other causes (eg, viral, illness, infection, other drug rash)[13] Grade 1-2 imAEs affecting ≤30% of skin surface[13,15-18] • Continue IO therapy and treat symptoms with topical agents • Check weekly for improvement in symptoms • If symptoms persist for more than 1-2 weeks, recur, or cover >30% BSA, withhold IO agent and initiate corticosteroids (1 to 2 mg/kg/day prednisone PO or equivalent) Grades 3-4 imAEs[13,15-18]: • Interrupt or discontinue IO therapy immediately and initiate corticosteroids (1 to 2 mg/kg/day prednisone PO or equivalent) • Consult dermatologist • Punch biopsy may be required

GASTROINTESTINAL imAEs				
ADVERSE EVENT	**FREQUENCY**			
	ATEZOLIZUMAB[3]	**AVELUMAB[4]**	**DURVALUMAB[5]**	**PEMBROLIZUMAB[6]**
DIARRHEA	18.5%	NR	2.1%	NR
COLITIS	1.1%	0.4%	0.5%	1.7%*

PATIENT EDUCATION	MANAGEMENT
• Set appropriate expectations about incidence, severity and timing of gastrointestinal imAEs • Counsel patients on diet and avoidance of high fibre/lactose diet[13] • Educate patient on steroid use and/or immunosuppressive agents where relevant[13,15-19]	• Order lab tests (including stool, urine, and blood), endoscopy, and/or abdominal CT/X-ray[13] Grade 1 (Diarrhea <4 stools/day over baseline)[15-19]: • Treat with anti-diarrheal agents and continue IO treatment Grade 2 (4 to 6 stools/day over baseline)[13,15-19]: • Withhold IO agent • If diarrhea persists beyond 3-5 days or recurs, administer corticosteroids (0.5 to 1 mg/kg/day prednisone PO or equivalent) • Consider prophylactic antibiotics Grade 3 or 4[13,15-19]: • Discontinue IO agent and consult gastroenterologist in case of grade 4 or persistent grade 3 imAEs • Rule out bowel perforation prior to steroid therapy (endoscopic evaluation may be required) • Continually evaluate for GI perforation or peritonitis • Administer corticosteroids (1 to 2 mg/kg/day prednisone PO or IV equivalent) • May initiate prophylactic antibiotics • Consider immunosuppressive agents if no response or recurring (infliximab or MMF)

*Frequency reported from Reference Safety Data Set (includes melanoma and non-small cell lung cancer patients only)[6]

ACRONYMS AND ABBREVIATIONS: BSA, body surface area; MMF, Mycophenolate mofetil; NR, not reported; PO, orally.

Table 4 (Continued): Common immune-mediated adverse events

HEPATIC imAEs				
ADVERSE EVENT	**FREQUENCY**			
	ATEZOLIZUMAB*[3]	**AVELUMAB[4]**	**DURVALUMAB[5]**	**PEMBROLIZUMAB[6]**
HEPATITIS	0.3%	0.8%	2.1%	0.7%†
Grade 3-4 increase in:				
AST	1.3%	NR	NR	NR
ALT	1.2%	NR	NR	NR
BILIRUBIN	0.4%	NR	NR	NR

PATIENT EDUCATION	MANAGEMENT
• Set appropriate expectations about incidence, severity and timing of hepatitic imAEs • Patient education on laboratory tests, and, where relevant, steroid use and immunosuppressive agents[15-19]	For all grades of imAEs[15-19]: • Rule out infectious or malignant causes or obstruction • Increase LFT monitoring until resolution Grade 2: (AST/ALT >3-5x ULN, or total bilirubin >1.5-3x ULN)[15-19] • Withhold IO therapy • Monitor LFTs every 3 days until resolved • Initiate corticosteroids (0.5 to 1 mg/kg prednisone PO or equivalent) if elevation persists for more than 5-7 days or worsens Grade 3 or 4: (AST/ALT >5xULN or bilirubin >3xULN or AST/ALT increases 50% baseline and lasts ≥1 week in patients with liver metastasis who begin treatment with grade 2 elevation of AST/ALT)[15-19] • Permanently discontinue IO therapy • Administer corticosteroids (1 to 2mg/kg/day prednisone PO or equivalent) • Initiate prophylactic antibiotics for opportunistic infections. • Monitor LFTs every 1-2 days • Consider non-steroid immunosuppressive agents (MMF) if persistent, worsening or recurring

ENDOCRINE imAEs				
ADVERSE EVENT	**FREQUENCY**			
	ATEZOLIZUMAB*[3]	**AVELUMAB[4]**	**DURVALUMAB[5]**	**PEMBROLIZUMAB[6]**
HYPOTHYROIDISM	4.7%	4.0%	5.2%	8.5%†
HYPERTHYROIDISM	1.7%	0.8%	1.0%	3.4%†

PATIENT EDUCATION	MANAGEMENT
• Set appropriate expectations about incidence, severity and timing of endocrine imAEs (hypophysitis is very rare)[13] • Patient education on laboratory tests, endocrine disorders and steroid use (where relevant)[13] • Review symptoms of endocrine disorders, including: persistent or unusual headaches, extreme tiredness, weight gain or loss, mood/behaviour changes, dizziness/fainting, hair loss, feeling cold, constipation, and/or deeper voice[15-19]	Asymptomatic TSH elevation[15-19]: • Continue IO therapy, consult guidelines for lab values and indications for further testing Symptomatic endocrinopathy[15-19]: • Withhold IO therapy if abnormal lab or pituitary scan • Consult endocrinologist • Initiate corticosteroids (1-2 mg/kg/day prednisone PO or equivalent) Suspicion of adrenal crisis[15-19]: • Rule out sepsis • Withhold IO therapy • Consult endocrinologist • Provide IV fluids and stress dose of IV steroids with mineralocorticoid activity

*Frequency of events reported are for urothelial carcinoma patients and non-small cell lung cancer patients receiving atezolizumab[3].
†Frequency reported from Reference Safety Data Set (includes melanoma and non-small cell lung cancer patients only)[6]

ACRONYMS AND ABBREVIATIONS: AST, aspartate aminotransferase; ALT, alanine aminotransferase; MMF, Mycophenolate mofetil; NR, not reported; LFTs, liver function tests; PO, orally; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Table 4 (Continued): Common immune-mediated adverse events

PULMONARY imAEs				
ADVERSE EVENT	**FREQUENCY**			
	ATEZOLIZUMAB[3]	**AVELUMAB[4]**	**DURVALUMAB[5]**	**PEMBROLIZUMAB[6]**
PNEUMONITIS	3.1%*	1.2%	0.5%	3.4%†

PATIENT EDUCATION	**MANAGEMENT**
• Patient education on pneumonitis symptoms and potential lethality if left untreated[13] • Patient education on steroid use[15,16,18,19]	Monitoring • Monitor patients for signs and symptoms of pneumonitis • Evaluate patients with suspected pneumonitis with radiographic imaging For all grades of imAEs: • Consult with pulmonologist and infectious disease specialist Grade 1: • Consider withholding IO therapy • Monitor every 2 to 3 days Grade 2: • Withhold IO therapy • Initiate corticosteroid (1 to 2 mg/kg/day prednisone PO or equivalent) • Consider prophylactic antibiotics for opportunistic infections, bronchoscopy and lung biopsy Grade 3 or 4[13,15,16,18,19]: • Permanently discontinue IO therapy • Hospitalize and initiate corticosteroid (2 to 4 mg/kg/day prednisone PO or IV equivalent), followed by a taper • Consider non-steroid immunosuppressive agents if persists or worsens after 2 days • Consider prophylactic antibiotics for opportunistic infections, bronchoscopy and lung biopsy

*Frequency of events reported are for urothelial carcinoma patients and non-small cell lung cancer patients receiving atezolizumab[3].
†Frequency reported from Reference Safety Data Set (includes melanoma and non-small cell lung cancer patients only)[6]

ACRONYMS AND ABBREVIATIONS: PO, orally.

RARE BUT SERIOUS ADVERSE EVENTS

- Other imAEs are infrequent (<1%), but can be very serious and potentially lethal, such as neurological disorders and myocarditis.[13]
- Consult the product monographs for extensive list of other rare but serious imAEs.

Table 5: Rare but serious adverse events

ADVERSE EVENT	PATIENT EDUCATION	MANAGEMENT[3-6]
Myocarditis	• Educate patient on symptoms of myocarditis (inflammation of the heart muscle), which may include: chest pain, irregular heartbeat, shortness of breath, fluid retention and swelling of the legs, ankles and feet, and/or decreased exercise tolerance[3-6] • Patient education on steroid use and/or immunosuppressive drugs	• Monitor patients with signs and symptoms • Administer corticosteroids or immunosuppressive drugs • Consult cardiologist Grade 2: Withhold IO therapy Grade 3 or 4: Permanently discontinue IO therapy
Neurological disorders and encephalitis: neuropathy, Guillain Barré syndrome, myelopathy, meningitis, encephalitis, myasthenia	Educate patients on[3-6]: • Symptoms of neuropathy (inflammation of the nerves), which may include: muscle weakness and numbness, or tingling in hands and feet • Symptoms of encephalitis (inflammation of the brain) and meningitis (inflammation of the membrane around the spinal cord and brain) which include: neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness • Education about steroid use and tapering	• Permanently discontinue IO therapy for any grade neuropathy or encephalopathy • Consider initiation of corticosteroids (1 to 2 mg/kg/day prednisone PO or equivalent) • Consider neurology consult

ACRONYMS AND ABBREVIATIONS: PO, orally.

CORTICOSTEROIDS FOR imAEs

- Key points for patient education:
  - Use the teach-back method to confirm whether the patient understands the rationale for corticosteroid treatment and associated-risks of corticosteroid use.
  - Rationale for use:
    - Prolonged immunosuppressive treatment with corticosteroids may be required for management of refractory or severe imAEs[8,20].
  - Corticosteroid treatment initiation:
    - Grade 2 toxicities are generally managed with a treatment break until symptoms recover or toxicity returns to grade ≤1[10].
    - Initiate corticosteroids if grade 2 symptoms do not resolve after a few days (0.5 mg/kg/day prednisone)[10].
    - Severe toxicities (grades 3 or 4) should be treated with high doses of corticosteroids (1 to 2 mg/kg/day prednisone) and occasionally may require permanent discontinuation of immunotherapy[10].
    - Nurses should advise and support patients in seeking a corticosteroid prescription proactively from the medical oncologist.
      - Proactive prescriptions for corticosteroids ensure the patient has quicker access to corticosteroids when needed.
      - The teach-back method should be used to confirm whether the patient understands the purpose of proactive corticosteroid prescriptions.

- Corticosteroid treatment termination/tapering:
  - Corticosteroids should be terminated by following a gradual decrease/tapering of doses over a period of at least 1 month[8,10].
  - If symptoms resolve and toxicity is reduced to grade 1, IO therapy can usually be resumed once corticosteroids have been reduced to ≤10 mg oral prednisone or equivalent per day and in the absence of other immunosuppressive drugs[8].
- Prolonged steroid use:
  - Prolonged steroid use, particularly when used at high doses, has been associated with additional adverse events, including osteoporosis, adrenal suppression, hyperglycemia/diabetes, cardiovascular disease, Cushing's syndrome, psychiatric disorders and infection[10,20,21].
  - There is also a risk of severe opportunistic infection from prolonged steroid use in the management of imAEs[20].
    - Anti-infective prophylaxis may be considered in patients receiving long-term immunosuppressive drugs[8,20].

More information

British Columbia Cancer Agency: Immunotherapy Checkpoint Inhibitors
http://www.bccancer.bc.ca/health-professionals/clinical-resources/nursing/immunotherapy-checkpoint-inhibitors

Canadian Cancer Society: Immunotherapy
http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/chemotherapy-and-other-drug-therapies/immunotherapy/?region=on

Cancer.Net: Immunotherapy and Vaccines
https://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines

Oncology Nursing Society: Immunotherapy Resources
https://www.ons.org/practice-resources/cancer-therapies/immunotherapy-resources

References

1. Kamta J, Chaar M, Ande A, Altomare DA, Ait-Oudhia S. Advancing cancer therapy with present and emerging immuno-oncology approaches. Front Oncol. 2017;7:64.
2. Bellmunt J, Powles T, and NJ Vogelzang. A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: The future is now. Cancer Treatment Reviews 54 (2017) 58–67.
3. TECENTRIQ® Product Monograph, Hoffmann-La Roche Limited, April 2018.
4. BAVENCIO™ Product Monograph, EMD Serono/Pfizer, May 2018.
5. IMFINZI® Product Monograph, AstraZeneca Canada Inc., May 2018.
6. KEYTRUDA® Product Monograph, Merck Canada Inc., June 2018.
7. Kreamer KM. Immune checkpoint blockade: a new paradigm in treating advanced cancer. Journal of the Advanced Practitioner in Oncology. 2014;5:418-431.
8. Champiat S, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol. 2016;27(4):559-574.
9. Brigden M, Humphreys M and Imbulgoda A. Delivering immuno-oncology therapies in the community oncology setting. Oncology Exchange. 2016;15(3):10-14.
10. Fay AP, Moreira RB, Filho P, Albuquerque C, Barrios C. The management of immune-related adverse events associated with immune checkpoint blockade. Expert Review of Quality of Life in Cancer Care. 2016;1(1)89-97.
11. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. J Clin Oncol. 2015;33:2092-2099.
12. Weber JS, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol. 2017;35:785-792.
13. Haanen JBAG, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl4):iv119-iv142.
14. Kumar V, et al. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. Front Pharmacol. 2017;8:49.
15. British Columbia Cancer Agency. Treatment of Advanced Non-Small Cell Lung Cancer Using Nivolumab (ULUAVNIV Protocol).
16. British Columbia Cancer Agency. Treatment of Metastatic or Advanced Renal Cell Carcinoma Using Nivolumab (UGUAVNIV Protocol).
17. British Columbia Cancer Agency. First-Line Treatment of Unresectable or Metastatic Melanoma Using Ipilimumab (USMAVFIPI Protocol).
18. British Columbia Cancer Agency. Treatment of Unresectable or Metastatic Melanoma Using Pembrolizumab (USMAVPEM Protocol).
19. British Columbia Cancer Agency. Treatment of Unresectable or Metastatic Melanoma Using Nivolumab (USMAVNIV Protocol).
20. Kyi C, Hellmann MD, Wolchok JD et al. Opportunistic infections in patients treated with immunotherapy for cancer. J Immunother Cancer. 2014;2(1):19.
21. Liu D, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30.