

BTKi Optimization: CTCAE Grading and COSTaRS-Based Practice Guide

A guide for allied healthcare professionals to help assess and manage patient symptoms while on BTKi therapy

This guide is for nurses and pharmacists managing side effects that can occur with the use of BTK inhibitors acalabrutinib (PrCalquence®), ibrutinib (PrImbruvica®), or zanubrutinib (PrBrukinsa®) in patients with blood cancers. It is organized by patient-reported symptoms to allow you to respond rapidly, devise a personalized management plan, and follow up as needed.

This guide is an interactive PDF with buttons you can click to move through the content.

Ready to begin symptom assessment?



Symptom Library

Symptom Library

Which symptom is your patient describing?



Arrhythmias



Bleeding & Bruising



Fatigue



Fever & Infection



GI Symptoms



Headache



Hypertension



Musculoskeletal Side Effects



Rash & Nail Changes

The provided list is not inclusive of all possible side effects associated with BTKi treatments. Other side effects may occur.

Arrhythmias

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Dialogue

“Can I ask you for a few details, then we'll figure out how best to help?”



Facts about arrhythmias and BTKi's

- Cardiac arrhythmias such as atrial fibrillation (Afib) were seen in all clinical trials of BTKi's and are less common with acalabrutinib and zanubrutinib than with ibrutinib.¹
- **Ibrutinib product information has “Fatal and serious cardiac arrhythmias and cardiac failure” in the Serious Warnings and Precautions box, following a letter from Health Canada from the Recalls and Safety Alerts Database on August 29, 2022.**^{1,2}
- Cardiac comorbidities, left atrial volume, older age, and being male increase the risk of Afib.¹

Arrhythmias

COSTaRS-based assessment: How severe are the patient's symptoms?³

Use this section to evaluate the severity of the patient's symptoms, then click the button for symptom management.

COSTaRS recommendations: Questions to assess potential arrhythmias

Are you experiencing any of these typical/common symptoms of arrhythmia?

- A noticeably fast, strong, or irregular heartbeat
- A fluttering, pounding, or racing feeling in the chest
- New onset of shortness of breath
- Light-headedness, dizziness, or fainting
- Unusual fatigue or exercise intolerance
- Chest pain, pressure, or discomfort

If patient confirmed any of the above symptoms:

<i>When did they start?</i>
<i>How often do they occur?</i>
<i>Does anything make them better or worse?</i>
<i>Are you experiencing any other symptoms in addition to those listed above?</i>
<i>When did you start taking your BTKi?</i>
<i>Any pre-existing cardiac or cardiovascular issues?</i>
<i>How much caffeine (e.g., number of cups of coffee) do you usually consume per day?</i>

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0.³

Arrhythmias

COSTaRS recommendations: Symptom management

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

- Afib can be managed with usual standards of care, with due consideration of drug interactions and adverse events seen with BTKi's (e.g., use of anticoagulants in the face of increased bleeding risk; CYP3A4 interactions; interactions with rate and rhythm control drugs).¹
- Scoring systems including CHA2DS2-VASc for stroke risk can help determine whether anticoagulation is needed, and the HAS-BLED scoring system can help determine whether the bleeding risk is high and whether alternate cancer therapy should be considered.¹
- Consultation with a cardio-oncologist may be needed to determine the optimal approach to further treatment for the patient.¹

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

Bleeding & Bruising

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Dialogue

“Can I ask you for a few details, then we'll figure out how best to help?”



Facts about bleeding, bruising, and BTKi's

- Bleeding events, including both minor and potentially major bleeding, are a known class effect associated with BTKi therapy, though major events are rare.⁵
- This is thought to be a class effect due to BTKi's targeted action on BTK, which plays a vital role in platelet activation and hemostasis, as well as their off-target effects on other kinases such as TEC that are also involved in platelet activation. This leads to an irreversible inhibition of platelet aggregation, with a corresponding increase in bleeding risk.⁵
- **The Product Monographs of the BTKi's available in Canada carry a Serious Warnings and Precautions Box with the following information regarding bleeding/hemorrhage:**
 - **Acalabrutinib: Serious hemorrhage — monitor for bleeding and manage appropriately⁷**
 - **Ibrutinib: Major bleeding events, some fatal, have been reported²**
 - **Zanubrutinib: Serious hemorrhage⁶**
- Minor bleeding such as bruising, mild petechial rash (red/purple spots), or skin ecchymoses is common in patients on all BTKi's.¹
- Minor bleeding can appear at any time over the course of therapy, although it is more common in the first year.¹
- Major hemorrhage occurs in approximately 5% of patients taking BTKi's.¹
- Major bleeding is most common in the first year of treatment and can start anywhere in the body, with a range of ambiguous symptoms (see “Assess Bleeding/Bruising Severity” below).¹

Bleeding & Bruising

COSTaRS-based assessment: How severe are the patient's symptoms?

Use this section to evaluate the severity of the patient's symptoms, then click the button for symptom management.

COSTaRS-based initial assessment³

Where are you bleeding from and when did it start?

Have you started any new medications recently? If so, what are the drug names and dosages?

COSTaRS and additional expert recommendations: Questions to ask your patient¹

	Mild	Moderate	Severe
How much blood loss?	Minor (e.g., 1 tsp)	Some (e.g., 1 tbsp)	A lot (e.g., ¼ cup)
Do you have new bruises?	No	Few	Generalized
Are you bruising or bleeding more easily than normal?	No		Yes
Have you had problems with blood clotting (e.g., > 10–15 min)?	No		Yes
Do you have a fever > 38°C?	No		Yes
Do you have any blood in your: <ul style="list-style-type: none"> • Stool – is it black/tarry? • Urine? • Vomit – does it look like coffee grounds? • Nose and mouth? • Phlegm/sputum when you cough? • Other? 	No		Yes
If you are having menstrual periods, has there been an increase in bleeding?	No	Yes, some	Yes, a lot
Do you have (signs of hematological adverse effects): Weakness? Pale skin? Yellow skin/eyes?	No		Yes
Do you know what your last platelet count was?	≥ 100	20–99	< 20
Results of your last liver function blood test?	AST/ALT: ≤ 3x ULN	> 3–5x ULN	> 5x ULN
	Total bilirubin: ≤ 1.5x ULN	1.5–3x ULN	> 3x ULN
Are you taking medicines that increase risk of bleeding (e.g., NSAIDs, acetylsalicylic acid, warfarin, heparin, dalteparin, tinzaparin, apixaban enoxaparin, herbal)? If warfarin: do you know your last INR blood count?	No	Yes, acetylsalicylic acid	Yes, other blood thinners
Do you have any of the following symptoms? ¹ (Signs of major hemorrhage) <ul style="list-style-type: none"> • Localized pain (e.g., head, chest, abdomen, back)? • Severe bruising? • Thirst? • Decreased blood pressure (if known)? • Cold/clammy skin? • Dizziness? • Altered mental state? • Shortness of breath? • Decreased urination? • Increased heart rate? 	No		Some/all of these

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, and Nixon S, et al. Current Oncology 2023.^{1,3}

Bleeding & Bruising

COSTaRS and additional expert recommendations: Symptom management

Overall management of bleeding & bruising³

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

	Mild	Moderate	Severe
	If all assessment checkmarks are in mild column only:	If all assessment checkmarks are in the mild and/or moderate column, but none in the severe:	If any assessment checkmarks are in severe column:
Overall approach ³	<ul style="list-style-type: none"> Review self-care. Verify all medications. 	<ul style="list-style-type: none"> Review self-care. Verify all medications. Instruct patient to call again if symptoms get worse or new symptoms appear in 12–24 hours. 	<ul style="list-style-type: none"> Refer for medical attention immediately.
Possible medications for symptom management ¹	<ul style="list-style-type: none"> Review the patient’s other medications and reduce non-essential drugs that increase bleeding risk.¹ If a new drug is initiated, ensure the pharmacist is aware that the patient is taking a BTKi.¹ 		
Product Monograph guidance based on CTCAE grades			
Guidance on BTKi treatment ^{2,6,7}	<ul style="list-style-type: none"> Dosing modifications may not be necessary for bleeding or bruising alone. If there is significant bleeding in the context of Grade 3 or 4 thrombocytopenia, hold dose. BTKi therapy may resume once thrombocytopenia has resolved to baseline or CTCAE Grade 1. Refer to the BTKi’s product monograph for guidance on post-toxicity dose selections. Recommendations to re-start at the same dose versus a one-level dose reduction vary by the BTKi prescribed and the number of prior toxicities (i.e., 1st, 2nd, 3rd, 4th occurrence of Grade \geq3 thrombocytopenia with bruising). 		

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, Nixon S, et al. Current Oncology 2023, and the respective product monographs for BTKi’s.^{1,3,6-8}

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

COSTaRS and additional expert recommendations: Self-care

Ask	Suggest
<i>How concerned are you about the bleeding/bruising?</i>	<ul style="list-style-type: none"> Reassure patients that minor bleeding may resolve spontaneously and is not associated with the risk of major hemorrhage.¹
<i>Have you tried applying direct pressure for 15 minutes or an ice pack? Did it help?⁵</i>	<ul style="list-style-type: none"> If the measures they took did not help, recommend the other options (pressure, dressing, etc).³
<i>Have you tried any special dressing to control your bleeding? Did it help?⁵</i>	
<i>Do you have any surgeries coming up?</i>	<ul style="list-style-type: none"> Pause BTKi 3–7 days before and after surgery, depending on individual risk.^{2,6,7}
<i>For rash-type bleeding/bruising: Have you tried a topical moisturizer?¹</i>	<ul style="list-style-type: none"> Suggest specific types of moisturizer.¹
<i>Have you spoken with your pharmacist or clinician about any medicines you’re taking that could increase bleeding, including over-the-counter or “natural” treatments?¹</i>	<ul style="list-style-type: none"> If no, ask if they would like to talk to someone and recommend that they do so.¹

CTCAE Grading for this Symptom

Fatigue

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Dialogue

“Can I ask you for a few details, then we'll figure out how best to help?”



Facts about fatigue and BTKi's

- Fatigue is one of the most common symptoms of any cancer and is challenging to manage because its etiology is not always well understood.¹
- Fatigue is usually self-limited for patients on BTKi's and is most common in the first year.¹ Early fatigue could be a symptom of underlying disease rather than drug related.¹
- Frequency of fatigue in the BTKi clinical trials varied.¹

Fatigue

COSTaRS-based assessment: How severe are the patient’s symptoms?

Use this section to evaluate the severity of the patient’s symptoms, then click the button for symptom management.

COSTaRS-based initial assessment³

When did you start feeling more tired than is normal for you? Suddenly? Or gradually over time?

Have you started any new medication recently? If so, what are the drug names and dosages?

COSTaRS and CTCAE recommendations: Questions to ask your patient³

	Mild	Moderate	Severe
What number from 0 to 10 best describes how tired you are feeling, where 0=“no tiredness” and 10=“worst possible tiredness”?	1–3	4–6	7–10
Do you have: <ul style="list-style-type: none"> • Shortness of breath at rest? • Sudden-onset severe fatigue? • Need to sit or rest too much? • Pain in your chest? • Rapid heart rate? • Rapid blood loss? 	No		Yes
How would you describe the pattern of fatigue?	On and off	Constant < 2 wks	Constant ≥ 2 wks
Does your fatigue affect your daily activities?	No	Yes, some	Yes, a lot
Is your fatigue relieved by rest? ⁸	Yes	No	No
Do you have a fever > 38°C?	No		Yes
Do you know the results of your last hemoglobin (Hb) blood test?	< LLN–10.0 g/dL	< 10.0–8.0 g/dL	< 8.0 g/dL
Have you lost or gained weight in the last 4 weeks without trying? What was the percentage change between your previous weight and your current weight?	0–2.9%	3–9.9%	≥ 10%
Do you have any other symptoms? <ul style="list-style-type: none"> • Anxiety? • Depression? • Pain? • Sleep changes? • Appetite loss? • Poor fluid intake? 	No	Yes, some	Yes, a lot
Do you have conditions that cause fatigue (cardiac, lung, liver, kidney, endocrine) or drink excess alcohol?	No	Yes	
Are you taking medicines that increase fatigue? (e.g., for pain, depression, nausea/vomiting, allergies)	No	Yes	

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0 and CTCAE 5.0.³⁸

Fatigue

COSTaRS recommendations: Symptom management

Overall management of fatigue³

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

	Mild	Moderate	Severe
	If all assessment checkmarks are in mild column only:	If all assessment checkmarks are in the mild and/or moderate column, but none in the severe:	If any assessment checkmarks are in severe column:
Overall approach ³	<ul style="list-style-type: none"> Review self-care. 	<ul style="list-style-type: none"> Review self-care. Instruct patient to call again if symptoms get worse, do not improve, or new symptoms appear in 1–2 days. 	<ul style="list-style-type: none"> If stable, review self-care. If new, refer for non-urgent medical attention. Inform BTKi prescriber if fatigue is affecting basic self-care ADLs.*
Possible medications for symptom management ³	<ul style="list-style-type: none"> There is some evidence or expert opinion supporting ginseng, methylphenidate, or corticosteroids for cancer-related fatigue but all remain experimental.³ 		
Product Monograph guidance based on CTCAE grades			
Guidance on BTKi treatment ^{2,6,7}	<ul style="list-style-type: none"> BTKi doses should be WITHHELD in the setting of CTCAE Grade 3 fatigue, which is defined as fatigue not relieved by rest and that limits self-care ADLs.* BTKi therapy may resume once fatigue has resolved to baseline or CTCAE Grade 1. Refer to the BTKi’s product monograph for guidance on post-toxicity dose selections. Recommendations to re-start at the same dose versus a one-level dose reduction vary by the BTKi prescribed and the number of prior toxicities (i.e., 1st, 2nd, 3rd, 4th occurrence of CTCAE Grade 3 fatigue). 		

*Basic self-care activities of daily living (ADLs) include showering/bathing, dressing, feeding, functional mobility, personal hygiene and grooming, toileting.

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, Nixon S, et al. Current Oncology 2023, CTCAE v5.0, and the respective product monographs for BTKi’s, with input from the Steering Committee.^{1-5&6}

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

COSTaRS and additional expert recommendations: Self-care

Ask	Suggest
<i>Do you know about cancer-related fatigue?</i>	<ul style="list-style-type: none"> Educate patient: different from normal fatigue (not related to exertion, not relieved by rest, interferes with daily activities) and expected in all cancers.³
<i>What are you doing to use your energy effectively?</i>	<ul style="list-style-type: none"> Counsel on energy conservation: rest often, activity within patient’s limits, stay hydrated.^{1,3}
<i>What helps when you feel fatigued/tired?</i>	<ul style="list-style-type: none"> Reinforce any habits that seem to be working.³
<i>Have you tried any form of relaxation therapy or activities that keep your brain active (e.g., reading, games, music)?</i>	<ul style="list-style-type: none"> Suggest some of these activities if the patient has not tried them.^{1,3}
<i>What are you doing for physical activity?</i>	<ul style="list-style-type: none"> Start with light activity, gradually increase to 20 min/day of endurance (e.g., walking, swimming) and resistance (weights). Proceed with caution in presence of bone fragility.³
<i>Are you eating/drinking enough?</i>	<ul style="list-style-type: none"> Stay hydrated and try to eat a balanced diet.³
<i>What strategies have you tried to improve your sleep? Did they work?</i>	<ul style="list-style-type: none"> Avoid sleeping too long at night, or during the day; go to bed when sleepy; avoid caffeine and large meals before bed; have a routine schedule for bedtime and getting up.³
<i>Are you trying to save your energy for things that are important to you?</i>	<ul style="list-style-type: none"> Discuss these priorities with the patient.³

CTCAE Grading for this Symptom

Fever & Infection

Dialogue

“Can I ask you for a few details, then we'll figure out how best to help?”



Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Facts about fever, infection, and BTKi's

- Grade ≥ 3 infections occur in 20–30% of patients on BTK inhibitors, typically within the first year of treatment, with pneumonia the most common.¹

Infection needs urgent attention.

Patient information for all BTK inhibitors instructs patients with fever or infection to contact a healthcare professional immediately.^{2,6,7}

Fever & Infection

COSTaRS-based assessment: How severe are the patient's symptoms?

Use this section to evaluate the severity of the patient's symptoms, then click the button to proceed to the assessment table.

COSTaRS-based initial assessment³

Please describe what you're experiencing.

When did your symptoms start?

Are symptoms getting better or worse?

If you have a cough, is it dry, or congested, or productive?

Have you taken any acetaminophen or an NSAID? If yes, how much? When did you take it?

Have you taken antibiotics within the past 48 hours?

Have you taken antibiotics in the past 3 months? If so, which one(s)?

Is someone else in your household sick?

What is giving you most cause for concern?

COSTaRS recommendations: Questions to ask your patient

	Mild	Moderate	Severe
Do you have an oral temperature of $\geq 38^{\circ}\text{C}$ (100.4°F)? What is your current temperature?	No	Yes, for less than an hour	Yes, for an hour or longer
What is your last known neutrophil count?	> 1000 cells/mcl		Fever plus < 500 cells/mcl or 1000 cells/mcl with expected drop
Do you have any other symptoms? <ul style="list-style-type: none"> • Bleeding? • Mouth sores? • Vomiting? • Breathlessness? • Mouth dryness? • Rash? • Diarrhea? • Nausea? 	None	Yes, some	Yes, many

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0.³

Fever & Infection

COSTaRS recommendations: Symptom management

Overall management of fever & infection³

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

	Mild	Moderate	Severe
	If all assessment checkmarks are in mild column only:	If all assessment checkmarks are in the mild and/or moderate column, but none in the severe:	If any assessment checkmarks are in severe column:
Overall approach ³	<ul style="list-style-type: none"> Review self-care. Instruct patient to call again if symptoms get worse or new symptoms appear in 12–24 hours. 	<ul style="list-style-type: none"> Review self-care. Instruct patient to call again if symptoms get worse or new symptoms appear in 12–24 hours. 	<ul style="list-style-type: none"> Refer for medical attention immediately. Febrile neutropenia treatment with antibiotics should be initiated within 1 hour of presentation. Collect laboratory data to locate site/cause of infection prior to starting antibiotics/antifungals.
Possible medications for symptom management ⁶	<ul style="list-style-type: none"> Consider prophylactic antibiotics, antifungals, antivirals, or G(M)-CSF for at-risk patients. Weigh the risks against known drug interactions between BTK inhibitors and antibiotics and antifungals.⁶ 		
Product Monograph guidance based on CTCAE grades			
Guidance on BTKi treatment ^{2,6,7}	<ul style="list-style-type: none"> BTKi doses should be WITHHELD in the setting of CTCAE Grade 3 or 4 neutropenia along with fever/infection. BTKi therapy may resume once neutropenia has resolved to baseline or CTCAE Grade 1. Refer to the BTKi’s product monograph for guidance on post-toxicity dose selections. Recommendations to re-start at the same dose versus a one-level dose reduction vary by the BTKi prescribed and the number of prior toxicities (i.e., 1st, 2nd, 3rd, 4th occurrence of CTCAE Grade ≥3 neutropenia with fever/infection). 		

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, and the respective product monographs for BTKi’s.^{2,3,6,7}

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

COSTaRS and additional expert recommendations: Self-care

Ask	Suggest
How have you been checking your temperature?	<ul style="list-style-type: none"> Check your temperature with a thermometer by mouth (not forehead, axilla, or rectally).⁵
How much fluid are you drinking per day?	<ul style="list-style-type: none"> Drink plenty of fluids, 6–8 glasses a day.^{1,3}
Are you taking your usual medications?	<ul style="list-style-type: none"> Keep taking all medicines as prescribed.¹

CTCAE Grading for this Symptom

GI Symptoms

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Dialogue

“Can I ask you for a few details, then we'll figure out how best to help?”

Facts about GI symptoms and BTKi's

- Diarrhea, nausea, vomiting and constipation with BTK inhibitors are frequent but generally mild (grades 1 or 2).^{1,2,6,7}

Diarrhea: Assess Severity

Nausea & Vomiting: Assess Severity

Constipation: Assess Severity

GI Symptoms: Diarrhea

COSTaRS-based assessment: How severe are the patient’s symptoms?

Use this section to evaluate the severity of the patient’s symptoms, then click the button to proceed to the assessment table.

COSTaRS-based initial assessment³

When did your diarrhea start?

Does anything make it better or worse, such as particular foods/meals?

How would you describe your stools (colour, hardness, odour, amount, oily, blood, mucus, straining)?

Have you been tested for C. difficile? If so, what were the results?

Have you been treated for C. difficile?

Are you taking medication for your diarrhea? If yes, what drug and dose are you taking? (If loperamide, educate on correct use)

Are you taking a laxative at the moment? If yes, what product and dose are you taking?

Have you started any new medication recently? If yes, what drug(s) and dose(s)?

GI Symptoms: Diarrhea

COSTaRS-based assessment: How severe are the patient’s symptoms? (continued)

COSTaRS recommendations: Questions to ask your patient

	Mild	Moderate	Severe
Tell me what number from 0 to 10 best describes your diarrhea. (0=“no diarrhea”; 10=“worst possible diarrhea”)	1–3	4–6	7–10
How many extra bowel movements are you having per day above normal for you? How many bowel movements do you normally have?	< 4	4–6	≥ 7
Ostomy: Has there been an increase in output above normal?	Small	Moderate	Large
Do you have blood in your stool?	No		Yes
Do you have a fever ≥ 38° C?	No		Yes
Do you have a pain in your abdomen or rectum with or without cramping or bloating?	No	Yes, some	Yes, a lot
How much fluid are you drinking per day?	6–8 glasses	1–5 glasses	Sips
Are you feeling dehydrated, which can include feeling dizzy, a dry mouth, increased thirst, feeling faint, rapid heart rate, decreased amount of urine?	No	Yes, some	Yes, a lot
Does your diarrhea affect your daily activities?	No	Yes, some	Yes, a lot
Do you have any other symptoms? • Appetite loss? • Fatigue? • Nausea/vomiting? • Mouth sores?	No	Yes, some	Yes, many
Any recent travel or contact with others with diarrhea?	No	Yes	
Do you have any rectal or ostomy skin breakdown?	No	Yes	

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0.³

GI Symptoms: Diarrhea

COSTaRS and additional expert recommendations: Management of diarrhea

Overall management by diarrhea severity^{1,3}

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

	Mild	Moderate	Severe
	If all assessment checkmarks are in mild column only:	If all assessment checkmarks are in the mild and/or moderate column, but none in the severe:	If any assessment checkmarks are in severe column:
Overall approach ²	<ul style="list-style-type: none"> Review self-care. Verify all medications. 	<ul style="list-style-type: none"> Review self-care. Verify all medications. Instruct patient to call again if symptoms get worse, new symptoms appear, or no improvement in 12–24 hours. 	<ul style="list-style-type: none"> Refer for medical attention immediately. Inform BTKi prescriber if diarrhea is affecting basic self-care ADLs.*
Possible medications for symptom management ¹	<ul style="list-style-type: none"> Systemic treatment not generally needed unless quality of life is affected. Suggest a topical barrier or corticosteroid cream if there is excoriated perianal discomfort. 	<ul style="list-style-type: none"> If quality of life is affected, consider loperamide. Suggest a topical barrier or corticosteroid cream if there is excoriated perianal discomfort. 	<ul style="list-style-type: none"> Consider loperamide, or enoxylate/atropine, opioids, and octreotide for refractory cases. Suggest a topical barrier or corticosteroid cream if there is excoriated perianal discomfort.
Product Monograph guidance based on CTCAE grades			
Guidance on BTKi treatment ^{2,6,7}	<ul style="list-style-type: none"> BTKi doses should be WITHHELD in the setting of CTCAE Grade ≥ 3 diarrhea, which involves an increase of ≥ 7 stools per day or a severe increase in ostomy output over baseline, limitations to self-care ADLs*, and a need for hospitalization. BTKi therapy may resume once diarrhea has resolved to baseline or CTCAE Grade 1. Refer to the BTKi's product monograph for guidance on post-toxicity dose selections. Recommendations to re-start at the same dose versus a one-level dose reduction vary by the BTKi prescribed and the number of prior toxicities (i.e., 1st, 2nd, 3rd, 4th occurrence of CTCAE Grade ≥ 3 diarrhea). 		

*Basic self-care activities of daily living (ADLs) include showering/bathing, dressing, feeding, functional mobility, personal hygiene and grooming, toileting.

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, Nixon S, et al. *Current Oncology* 2023, and the respective product monographs for BTKi's.^{1,3,6,7}

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

COSTaRS recommendations: Self-care³

Ask	Suggest
<i>What strategies have you tried to help cope with your diarrhea?</i>	<ul style="list-style-type: none"> Plan outings in advance; take a change of clothes; know location of restroom; use absorbent undergarments.
<i>Are you able to drink 6–8 glasses of fluid a day?</i>	<ul style="list-style-type: none"> Increase hydration and electrolytes (bananas, potatoes, sports drinks, fruit juices, and/or oral rehydration solution). If using sports drinks or fruit juices, dilute because they contain large amounts of sugar. Avoid energy drinks and "sugar-free" sports drinks (sugar substitutes should be avoided during diarrhea).
<i>Are you trying to eat 5–6 small meals every day?</i>	<ul style="list-style-type: none"> Avoid: foods high in insoluble fibre, dairy, fatty or spicy foods, alcohol, more than 3 servings of caffeine, excess fruit drinks, very hot or cold foods/fluids.
<i>Do you wash the skin around your rectum with warm water and a little soap after each stool?</i>	<ul style="list-style-type: none"> Barrier cream may be helpful if rectum is irritated. If the area is sore, use a sitz bath or peri-wash bottle with lukewarm water for cleaning.
<i>Have you spoken to your doctor or pharmacist about medicines you're taking that might contribute to your diarrhea? Would you like to?</i>	<ul style="list-style-type: none"> Advise patient on appropriate use of over-the-counter (OTC) loperamide (e.g., Imodium®).

CTCAE Grading for this Symptom

Return to GI Symptoms

GI Symptoms: Nausea & Vomiting

COSTaRS-based assessment: How severe are the patient's symptoms?

Use this section to evaluate the severity of the patient's symptoms, then click the button for symptom management.

COSTaRS-based initial assessment³

When did your nausea/vomiting start? Does anything make it better or worse?

Are you taking medication for your nausea/vomiting? If so, what drug and dose?

COSTaRS recommendations: Questions to ask your patient

	Mild	Moderate	Severe
What number from 0 to 10 best describes how you are feeling? (0="no nausea" and 10="worst possible nausea")	0-3	4-6	7-10
If vomiting: How many times per day?	≤ 1	2-5	≥ 6
What is the amount of vomit?	Small	Modest	Large
Is there any blood or does it look like coffee grounds?	No		Yes
Have you been able to eat within the last 24 hours?	Yes	No	
Have you been able to drink anything in the last 24 hours?	Yes		No
Have you lost weight in the last 1-2 weeks without trying? What was your previous weight and what is your new weight?	0-2.9%	3-9.9%	≥ 10%
How much fluid are you drinking per day?	6-8 glasses	1-5 glasses	Sips
Are you feeling dehydrated, which can include feeling dizzy, a dry mouth, increased thirst, feeling faint, rapid heart rate, decreased amount of urine?	No	Yes, some	Yes, a lot
Do you have abdominal pain? (0="No abdominal pain" and 10="Worst possible abdominal pain")	No/Mild 0-3	Moderate 4-6	Severe 7-10
Does your nausea/vomiting affect your daily activities?	No	Yes, some	Yes, a lot
Are you taking medicines that can cause nausea/vomiting? (e.g., opioids, antidepressants, antibiotics, warfarin)	No	Yes	
Do you have any other symptoms? • Anxiety? • Diarrhea? • Pain? • Constipation? • Fever? • Headache?	No	Yes, some	Yes, many

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, and CTCAE v5.0.³⁸

GI Symptoms: Nausea & Vomiting

COSTaRS recommendations: Symptom management

Overall management by nausea/vomiting severity³

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

	Mild	Moderate	Severe
	If all assessment checkmarks are in mild column only:	If all assessment checkmarks are in the mild and/or moderate column, but none in the severe:	If any assessment checkmarks are in severe column:
Overall approach ³	<ul style="list-style-type: none"> Review self-care. Verify all medications. 	<ul style="list-style-type: none"> Review self-care. Verify all medications. Instruct patient to call again if symptoms get worse, new symptoms appear, or no improvement in 12–24 hours. 	<ul style="list-style-type: none"> Refer for medical attention immediately.
Possible medications for symptom management ³	The following medications have shown effectiveness for nausea/vomiting: <ul style="list-style-type: none"> Olanzapine (Zyprexa[®]) 5-HT₃: ondansetron (Zofran[®]), granisetron (Kytril[®]), dolasetron (Anzemet[®]) Netupitant/palonosetron (NEPA) (Akynzeo[®]) 		
Product Monograph guidance based on CTCAE grades			
Guidance on BTKi treatment ^{2,6,7}	<ul style="list-style-type: none"> BTKi doses should be WITHHELD in the setting of CTCAE Grade 3 nausea, which involves inadequate oral caloric or fluid intake, necessitating tube feeding, total parenteral nutrition, and/or hospitalization. BTKi therapy may resume once nausea has resolved to baseline or CTCAE Grade 1. Refer to the BTKi's product monograph for guidance on post-toxicity dose selections. Recommendations to re-start at the same dose versus a one-level dose reduction vary by the BTKi prescribed and the number of prior toxicities (i.e., 1st, 2nd, 3rd, 4th occurrence of CTCAE Grade 3 nausea). 		

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, CTCAE v5.0, and the respective product monographs for BTKi's.^{2,3,6-8}

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

COSTaRS recommendations: Self-care³

Ask	Suggest
What has helped in the past with nausea and vomiting?	<ul style="list-style-type: none"> Reinforce as appropriate.
How much fluid are you drinking daily?	<ul style="list-style-type: none"> Try to drink 6–8 glasses of clear fluids (e.g., sports drinks, diluted fruit juices). Avoid energy drinks.
Have you tried any relaxation techniques?	<ul style="list-style-type: none"> Consider guided imagery, progressive muscle relaxation, hypnosis, if appropriate.
Have you tried sitting upright or reclining with head raised for 30–60 minutes after meals?	<ul style="list-style-type: none"> Reinforce as appropriate.
Have you spoken with a dietitian? Would you like to?	<ul style="list-style-type: none"> Connect patient with appropriate services.
For nausea: Have you tried eating 5–6 small meals per day and avoiding certain foods?	<ul style="list-style-type: none"> Avoid greasy/fried, highly salty, spicy, or strong-smelling foods; try eating cold/room temperature "comfort foods" that they know reduce their nausea.
For vomiting: Have you tried adjusting your food and drink intake?	<ul style="list-style-type: none"> Limit food and drink until vomiting stops, then after 30–60 minutes, sip clear fluids. If that stays down, eat dry, starchy foods like crackers; if that stays down, add protein-rich foods (e.g., chicken, eggs).

CTCAE Grading for this Symptom

Return to GI Symptoms

GI Symptoms: Constipation

COSTaRS-based assessment: How severe are the patient's symptoms?

Use this section to evaluate the severity of the patient's symptoms, then click the button for symptom management.

COSTaRS-based initial assessment³

Are you taking a laxative at the moment? If so, which product and dose?

COSTaRS and CTCAE recommendations: Questions to ask your patient

	Mild	Moderate	Severe
How many days has it been since you had a bowel movement (compared to normal)?	≤ 2 days	≥ 3 days	≥ 3 days on meds
How would you describe your stools (colour, hardness, odour, amount, blood, straining)?			Blood in stool
Do you have any pain in your abdomen?	No/Mild	Moderate	Severe
Do you have loss of bladder or bowel control, numbness in your fingers, toes or buttocks, feel unsteady on your feet, or difficulty walking?	No		Yes
Does your abdomen feel bloated?	No	Yes, some	Yes, a lot
How often do you use stool softeners, laxatives, or enemas to relieve your constipation? ⁸	Occasionally (not every day)	Regularly (every day)	No matter what I try, it doesn't work and I can't have a bowel movement
Does it feel like your rectum is not emptying after a bowel movement, or diarrhea (possible overflow around blocked stool)?	No	Yes	
Have you recently had abdominal surgery?	No		Yes
Are you feeling dehydrated, which can include feeling dizzy, a dry mouth, increased thirst, feeling faint, rapid heart rate, decreased amount of urine?	No	Yes, some	Yes, a lot
Do you have any other symptoms? Appetite loss? Nausea/vomiting?	No	Yes, one	Yes, both
Are you taking medications that cause constipation?	No	Yes	
Does your constipation affect your daily activities?	No	Yes, some	Yes, a lot

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, and CTCAE v5.0.^{3,8}

GI Symptoms: Constipation

COSTaRS recommendations: Symptom management

Overall management by constipation severity³

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

	Mild	Moderate	Severe
	If all assessment checkmarks are in mild column only:	If all assessment checkmarks are in the mild and/or moderate column, but none in the severe:	If any assessment checkmarks are in severe column:
Overall approach³	<ul style="list-style-type: none"> Review self-care. Verify all medications. 	<ul style="list-style-type: none"> Review self-care. Verify all medications. Instruct patient to call again if symptoms get worse, new symptoms appear, or no improvement in 12–24 hours. 	<ul style="list-style-type: none"> Refer for medical attention immediately. Inform BTKi prescriber if constipation is affecting basic self-care ADLs.*
Possible medications for symptom management³	<ul style="list-style-type: none"> OTC medications (e.g., Senokot®, RestoraLAX®, Dulcolax®) Amidotrizoate (Gastrografin®) if laxative-resistant/advanced cancer 		<ul style="list-style-type: none"> Refer for medical attention immediately.
Product Monograph guidance based on CTCAE grades			
Guidance on BTKi treatment^{2,6,7}	<ul style="list-style-type: none"> BTKi doses should be WITHHELD in the setting of CTCAE Grade ≥ 3 constipation, which involves obstipation with a need for manual evacuation and limitations to self-care ADLs.* BTKi therapy may resume once constipation has resolved to baseline or CTCAE Grade 1. Refer to the BTKi's product monograph for guidance on post-toxicity dose selections. Recommendations to re-start at the same dose versus a one-level dose reduction vary by the BTKi prescribed and the number of prior toxicities (i.e., 1st, 2nd, 3rd, 4th occurrence of CTCAE Grade ≥ 3 constipation). 		

*Basic self-care activities of daily living (ADLs) include showering/bathing, dressing, feeding, functional mobility, personal hygiene and grooming, toileting.

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, CTCAE v5.0, and the respective product monographs for BTKi's.^{2,3,6-8}

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

COSTaRS recommendations: Self-care³

Ask	Suggest
<i>What has helped in the past with constipation?</i>	<ul style="list-style-type: none"> Reinforce as appropriate, but advise patient to avoid suppositories or enemas (see below).
<i>How much fluid are you drinking daily?</i>	<ul style="list-style-type: none"> Try to drink 6–8 glasses of clear fluids, especially warm or hot drinks.
<i>Have you tried slowly increasing the fibre in your diet?</i>	<ul style="list-style-type: none"> Try to slowly increase to 25 g/day, including laxative fruits such as pitted dates, prunes, prune nectar, and/or figs.
<i>What is your normal bowel routine?</i>	<ul style="list-style-type: none"> Try using the toilet 30–60 minutes after meals.
<i>Do you strain when trying for a bowel movement?</i>	<ul style="list-style-type: none"> Counsel patient on hemorrhoid prevention and management.
<i>Are you staying as active as possible?</i>	<ul style="list-style-type: none"> Recommend sample exercise routines (e.g., walking 15–20 minutes 1–2 times per day; 30–60 minutes 3–5 times a week).
<i>Have you spoken with a clinician or dietitian about your constipation? Would you like to?</i>	<ul style="list-style-type: none"> Connect patient with appropriate services.

CTCAE Grading for this Symptom

Return to GI Symptoms

Headache

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Dialogue

“Can I ask you for a few details, then we'll figure out how best to help?”



Facts about headache and BTKi's

- Low-grade headaches occur infrequently in patients on ibrutinib and zanubrutinib, so are often not reported in publications about these trials.¹
- Headache frequency in the acalabrutinib clinical trials was 22–51%, with the highest prevalence in the first 3 months and a drastic decrease thereafter.¹
- Low-grade headache, if any, occurs within 3 months of treatment initiation, generally resolves over a few months, and can be effectively managed with acetaminophen and/or caffeine.¹
- Patients whose headaches develop in the setting of thrombocytopenia or anti-coagulation, falls, and/or trauma should be investigated to rule out alternative etiology.¹

Headache

COSTaRS-based assessment: How severe are the patient’s symptoms?

Use the questions below and the table on the next page to evaluate the severity of the patient’s symptoms, then click the button for symptom management.

Dialogue

Tell me a bit more about your headache (location, onset, radiating, what does it feel like, what makes it better or worse, timing, e.g., constant/intermittent/only certain times of day?)

COSTaRS-based initial assessment³

- Do you have a history of headaches before starting on your BTKi?*
- Do you have a history of migraines?*
- Are you currently taking any medication for headaches or migraines? If so, what drug and dose?*
- Have you had any recent falls or head injuries?*
- Did you recently stop medications such as pain medication, sinus medication, antidepressants?*
- Can you think of anything else that may be causing your headache (surgery, injury, illness, pre-existing pain)?*
- What is giving you most cause for concern?*

Headache

COSTaRS-based assessment: How severe are the patient’s symptoms? (continued)

COSTaRS and Product Monograph recommendations: Questions to ask your patient

	Mild	Moderate	Severe
What number from 0 to 10 best describes your level of pain? (where 0=“no pain” and 10=“worst possible pain”)	0–3	4–6	7–10
Rating of worst pain?	0–3	4–6	7–10
Rating of pain 2 hrs after medicine?	0–3	4–6	7–10
Are you able to easily distract yourself from the pain?	Yes, often	Yes, sometimes	No
Was the pain onset sudden?	No	Yes	
Is the headache from a new location? Describe.	No	Yes	
Do you have loss of bladder or bowel control, numbness in your fingers, toes or buttocks, feel unsteady on your feet, or difficulty walking?	No		Yes
Do you feel confused, very sleepy, hallucinate, or have muscle spasms or muscle tenseness?	No		Yes
Do you have nausea/vomiting or photosensitivity?	No		Yes
Does your headache interfere with your daily activities?	No	Yes, but it’s manageable	Yes, I have no relief
Does your headache interfere with your mood?	No		Yes
Are you able to get pain relief from your medicines?	Yes, a lot	Yes, some	No
Do the pain medicines restrict your daily activities?	No	Yes, some	Yes, a lot
Do you have other symptoms? <ul style="list-style-type: none"> • Constipation • Fatigue • Nausea/vomiting • Sleep changes • Depression • Itchiness • Peripheral neuropathy 	No	Yes, some	Yes, many
Do you have any of the following symptoms? ^{2,6,7,9} <ul style="list-style-type: none"> • Abdominal pain/distention • Arrhythmias • Edema • Urinary symptoms: dysuria, oliguria, flank pain, hematuria • Lethargy • Syncope • Symptoms of hyperkalemia: weakness, paralysis • Symptoms of hypocalcemia: anorexia, vomiting, cramps, tetany, altered level of consciousness 	No		Some/all of these

Table adapted from Stacey 2020: "Pain Practice Guide" in COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0 and the respective product monographs for BTKi's.^{2,3,6,7,9}

Headache

COSTaRS recommendations: Symptom management

Overall management by headache severity

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

	Mild	Moderate	Severe
	If all assessment checkmarks are in mild column only:	If all assessment checkmarks are in the mild and/or moderate column, but none in the severe:	If any assessment checkmarks are in severe column:
Overall approach ³	<ul style="list-style-type: none"> Review self-care. Verify all medications. 	<ul style="list-style-type: none"> Review self-care. Verify all medications. Instruct patient to call again if symptoms get worse, new symptoms appear, or no improvement in 12–24 hours. 	<ul style="list-style-type: none"> Refer for medical attention immediately. Inform BTKi prescriber if headache is affecting basic self-care ADLs.*
Possible medications for symptom management ^{1,3}	<ul style="list-style-type: none"> Recommend acetaminophen for pain relief instead of NSAIDs (e.g., ibuprofen), which may exacerbate the bleeding risk of BTK inhibitors.³ If caffeine is not a trigger for headache, in some people it can be helpful to manage headache in addition to or in place of acetaminophen.¹ 		
Product Monograph guidance based on CTCAE grades			
Guidance on BTKi treatment ^{2,6,7}	<ul style="list-style-type: none"> BTKi doses should be WITHHELD in the setting of CTCAE Grade 3 headache, which involves severe pain and limitations to self-care ADLs.* BTKi therapy may resume once headache has resolved to baseline or CTCAE Grade 1. Refer to the BTKi's product monograph for guidance on post-toxicity dose selections. Recommendations to re-start at the same dose versus a one-level dose reduction vary by the BTKi prescribed and the number of prior toxicities (i.e., 1st, 2nd, 3rd, 4th occurrence of CTCAE Grade 3 headache). 		

*Basic self-care activities of daily living (ADLs) include showering/bathing, dressing, feeding, functional mobility, personal hygiene and grooming, toileting.

Table adapted from Stacey 2020: "Pain Practice Guide" in COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, Nixon S, et al. Current Oncology 2023, CTCAE v5.0, and the respective product monographs for BTKi's.^{1-3,6-8}

COSTaRS recommendations: Self-care³

Ask	Suggest
What has helped you deal with headaches in the past (e.g., listening to music, breathing exercises, distraction activities, relaxation, mindfulness-based stress reduction, guided imagery, hypnosis)?	<ul style="list-style-type: none"> Reinforce as appropriate.
What pain medications have you tried?	<ul style="list-style-type: none"> If patient has been using NSAIDs (e.g., ibuprofen), recommend acetaminophen instead.
Do you have any concerns with taking pain medication?	<ul style="list-style-type: none"> If so, explore and educate.
Have you kept a diary of your pain?	<ul style="list-style-type: none"> Suggest they keep a diary that tracks their headache pain level when taking medicines and 1–2 hours afterwards.

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

CTCAE Grading for this Symptom

Hypertension

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Dialogue

“Can I ask you for a few details, then we'll figure out how best to help?”



Facts about hypertension and BTKi's

- Approximately 1 in 5 patients on BTKi's will experience new or worsening hypertension.¹
- In head-to-head trials, reported rates of hypertension were:¹
 - Lower for acalabrutinib compared to ibrutinib
 - Similar between zanubrutinib and ibrutinib in one study (ALPINE), and lower for zanubrutinib than for ibrutinib in another study (ASPEN)
- Hypertension does not necessarily lead to higher rates of atrial fibrillation or other cardiac adverse events; for example, in spite of similar rates of hypertension, zanubrutinib demonstrated lower rates of atrial fibrillation (7.1% vs. 17.0%) and overall cardiac events (25.9% vs. 35.5%) compared to ibrutinib in the ALPINE trial.¹⁰

Hypertension

COSTaRS-based assessment: How severe are the patient's symptoms?

Use this section to assess whether the patient's hypertension needs medical intervention, then click the button for hypertension management.

COSTaRS-based initial assessment^{3,8}

- You said your blood pressure seemed high last time you took it. When was this?*
- What was your blood pressure?*
- How did you measure it?*
- What was your blood pressure before you started taking your new BTKi medicine?*
- Are you already taking medicine for high blood pressure? Do you remember the name of it?*
- Do you have any other symptoms?*

Hypertensive emergency:
 If your patient has a diastolic BP of ≥ 130 mm Hg, especially if he or she has any other cardiovascular symptoms, immediately refer your patient to the emergency department.^{11a}
 Otherwise, see below.

Hypertension Canada Guidelines: When to initiate therapy¹¹

Patient population	BP threshold (mm Hg) for initiation of antihypertensive therapy
Low risk (no target organ damage or cardiovascular risk factors)	SBP ≥ 160 or DBP ≥ 100
High risk of cardiovascular disease (e.g., existing CV disease, kidney disease, age ≥ 75 years, estimated 10-year global CV risk $\geq 15\%$)	SBP ≥ 130
Diabetes mellitus	SBP ≥ 130 or DBP ≥ 80
All others	SBP ≥ 140 or DBP ≥ 90

Hypertension

Hypertension Canada recommendations: Symptom management

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Hypertensive emergency:

If your patient has a diastolic BP of ≥ 130 mm Hg, especially if he or she has any other cardiovascular symptoms, immediately refer your patient to the emergency department.^{11a}

Otherwise, see below.

Hypertension Canada recommendations: Self-care

Suggest

- Advise patient to purchase home BP monitor and keep a BP diary.
- The Hypertension Canada Guidelines recommended technique for home monitoring:^{11a}
 - Rest comfortably for 5 minutes beforehand in seated position.
 - Arm should be bare.
 - Take readings before breakfast and 2 hours after dinner, before taking medication.
 - No caffeine or tobacco within an hour, and no exercise for 30 minutes before the measurement.
 - Duplicate measurements should be taken in the morning and evening for 7 days.
 - The first day's readings should be excluded; the remaining 6 days' readings should be averaged.

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

Musculoskeletal Side Effects

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Dialogue

“Can I ask you for a few details, then we'll figure out how best to help?”

Immediate referral to emergency is required if a patient early in therapy is experiencing a combination of these signs/symptoms:^{2,6,7,9}

- Abdominal pain/distention
- Urinary symptoms: dysuria, oliguria, flank pain, hematuria
- Symptoms of hypocalcemia: anorexia, vomiting, cramps, tetany, altered level of consciousness
- Symptoms of hyperkalemia: weakness, paralysis
- Lethargy
- Syncope
- Arrhythmias
- Edema

Facts about musculoskeletal side effects and BTKi's

Warning: All BTK inhibitors can cause tumour lysis syndrome (TLS)^{2,6,7,9}, especially in patients with high/bulky tumour burden^{2,6,7} and those with pre-existing renal insufficiency.⁹ It generally appears within 2–3 days of therapy.⁹

- Musculoskeletal (MSK) side effects are common in patients taking BTKi's and generally mild (Grade 1/2).¹ They present as back pain, muscle spasms, myalgias, arthralgias, and/or pain in the extremities.
- Approximate incidence of Grade 1/2 MSK events with BTKi's: arthralgia (20%), myalgia (< 10%), and muscle spasms (10–15%).¹

Musculoskeletal Side Effects

COSTaRS-based assessment: How severe are the patient’s symptoms?

Use this section to evaluate the severity of the patient’s symptoms, then click button to proceed to the assessment table.

COSTaRS-based initial assessment³

Tell me a bit more about your pain (location, onset, radiating, what does it feel like, what makes it better or worse, timing, e.g., constant/intermittent/only certain times of day).

When did it begin?

Is there anything that you think is contributing to your pain, such as previous injuries or surgeries?

Have you ever had this type of pain before?

If yes, what caused it last time and how did you resolve it?

What is giving you most cause for concern?

Musculoskeletal Side Effects

COSTaRS-based assessment: How severe are the patient’s symptoms? (continued)

COSTaRS recommendations: Questions to ask your patient

	Mild	Moderate	Severe
What number from 0 to 10 best describes your level of pain? (where 0=“no pain” and 10=“worst possible pain”)	0–3	4–6	7–10
Rating of worst pain?	0–3	4–6	7–10
Rating of pain 2 hrs after medicine?	0–3	4–6	7–10
Are you able to easily distract yourself from the pain?	Yes, often	Yes, sometimes	No
Was the pain onset sudden?	No	Yes	
Is the pain different or from a new location? Describe.	No	Yes	
Do you have loss of bladder or bowel control, numbness in your fingers, toes or buttocks, feel unsteady on your feet, or difficulty walking?	No		Yes
Do you feel confused, very sleepy, hallucinate, or have muscle spasms?	No		Yes
Does your pain interfere with your daily activities?	No	Yes, but it’s manageable	Yes, I have no relief
Does your pain interfere with your mood?	No		Yes
Are you able to get pain relief from your medicines?	Yes, a lot	Yes, some	No
Do the pain medicines restrict your daily activities?	No	Yes, some	Yes, a lot

Table adapted from Stacey 2020: “Pain Practice Guide” in COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0.³

Musculoskeletal Side Effects

COSTaRS recommendations: Symptom management

Overall management by pain severity³

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

	Mild	Moderate	Severe
	If all assessment checkmarks are in mild column only:	If all assessment checkmarks are in the mild and/or moderate column, but none in the severe:	If any assessment checkmarks are in severe column:
Overall approach ³	<ul style="list-style-type: none"> Review self-care. Verify all medications. 	<ul style="list-style-type: none"> Review self-care. Verify all medications. Instruct patient to call again if symptoms get worse, new symptoms appear, or no improvement in 12–24 hours. Consider informing BTKi prescriber if pain is affecting instrumental ADLs.[†] 	<ul style="list-style-type: none"> Refer for medical attention immediately. Inform BTKi prescriber if pain is affecting basic self-care ADLs* and/or instrumental ADLs.[†]
Possible medications for symptom management	<ul style="list-style-type: none"> Recommend acetaminophen for pain relief instead of NSAIDs (e.g., ibuprofen), which may exacerbate the bleeding risk of BTK inhibitors.³ 		
Product Monograph guidance based on CTCAE grades			
Guidance on BTKi treatment ^{2,6,7}	BTKi doses should be WITHHELD in the setting of CTCAE Grade ≥ 3 MSK toxicity, which includes: <ul style="list-style-type: none"> Severe muscle or joint pain limiting basic self-care ADLs* Severe muscle cramps/spasms limiting basic self-care ADLs* BTKi therapy may resume once musculoskeletal toxicity has resolved to baseline or CTCAE Grade 1 (mild pain/cramps not impacting instrumental or basic ADLs). Refer to the BTKi's product monograph for guidance on post-toxicity dose selections. Recommendations to re-start at the same dose versus a one-level dose reduction vary by the BTKi prescribed and the number of prior toxicities (i.e., 1 st , 2 nd , 3 rd , 4 th occurrence of CTCAE Grade ≥ 3 MSK toxicity).		

*Basic self-care activities of daily living (ADLs) include showering/bathing, dressing, feeding, functional mobility, personal hygiene and grooming, toileting.

[†]Instrumental ADLs include housekeeping/homemaking, food preparation, medical/medication management, managing finances, shopping, basic communication skills (e.g., telephone), using technology (e.g., TV remote, smartphone), transportation within the community, leisure (and the ability to access desired leisure activities, places, and roles), paid work, volunteering, other vocations.

Table adapted from Stacey 2020: "Pain Practice Guide" in COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, CTCAE v5.0, and the respective product monographs for BTKi's.^{2,3,6-8}

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

COSTaRS and additional expert recommendations: Self-care

Ask	Suggest
What has helped you deal with pain in the past (e.g., listening to music, breathing exercises, distraction activities, relaxation, mindfulness-based stress reduction, guided imagery, hypnosis)?	<ul style="list-style-type: none"> Reinforce as appropriate.³
What pain medications have you tried?	<ul style="list-style-type: none"> If patient has been using NSAIDs (e.g., ibuprofen), recommend acetaminophen instead.³
Do you have any concerns with taking pain medication?	<ul style="list-style-type: none"> If so, explore and educate.³
Have you kept a diary of your pain?	<ul style="list-style-type: none"> Suggest they keep a diary that tracks their pain level when taking medicines and 1–2 hours afterwards.³
What other (non-medication) strategies have you used to manage your pain?	<ul style="list-style-type: none"> Suggest/encourage light physical activity, especially mild stretching and strengthening, such as walking, swimming or cycling.^{1,3} Hot and cold compresses may be helpful.¹

CTCAE Grading for this Symptom

Rash & Nail Changes

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Dialogue

“Can I ask you for a few details, then we'll figure out how best to help?”



Facts about rash, nail changes, and BTKi's

- Rash was reported in up to 17% of patients in the BTKi clinical trials.¹
- Most rashes are mild and resolve within a month without adjusting dose, but severe rashes (see “Assess Rash Severity” below) may need a temporary pause in treatment.¹
- Common rashes seen with BTKi's are:¹²
 - 1) a raised/papular, red, non-blanching, palpable pruritic rash
 - 2) a petechial, non-palpable/flat rash
- Patients may also experience acne-like rashes and eczema-like rashes.¹
- Nail changes (e.g., splintering, ridging, depressions, pitting, separation from the nail bed) are seen in approximately 60% of patients on BTKi's.¹ They are one of the side effects most easily assessed by community pharmacists. BTK inhibition is thought to disrupt keratin formation by interfering with disulfide bonds between cysteine residues.¹

[Assess Severity of Nail Changes](#)

Rash

COSTaRS-based assessment: How severe are the patient’s symptoms?

Use this section to evaluate the severity of the patient’s symptoms, then click the button for symptom management.

COSTaRS-based initial assessment³

Tell me about the rash (e.g., location, when did it start, what does it look like?).

Have you started any new medication recently?

COSTaRS recommendations: Questions to ask your patient

	Mild	Moderate	Severe
What number from 0 to 10 best describes your skin rash, where 0=“no skin rash” and 10=“worst possible skin rash”?	1–3	4–6	7–10
Is the skin rash on one small part of your body (localized) or does it cover other areas (generalized)?	< 10% BSA	10–30% BSA	> 30% BSA
Do you have any open wounds or blisters?	No		Yes
Is the rash moist, weeping, or bleeding?	No/dry		Yes
Do you have pain or feel burning at the skin rash area?	No/Mild 0–3	Moderate 4–6	Severe 7–10
Is the rash itchy?	No	Yes	
Does the affected area feel tight or swollen?	No	Yes	
Have you experienced a rash like this before?	No/controlled with treatment		Yes, did not respond to treatment
Does your skin rash affect your daily activities?	No	Yes, some	Yes, a lot

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0.³

Rash

COSTaRS recommendations: Symptom management

Overall management by rash severity³

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

	Mild	Moderate	Severe
	If all assessment checkmarks are in mild column only:	If all assessment checkmarks are in the mild and/or moderate column, but none in the severe:	If any assessment checkmarks are in severe column:
Overall approach ³	<ul style="list-style-type: none"> Review self-care. Verify all medications. 	<ul style="list-style-type: none"> Review self-care. Verify all medications. Instruct patient to call again if symptoms get worse or new symptoms appear in 12–24 hours. 	<ul style="list-style-type: none"> Refer for medical attention immediately. Inform BTKi prescriber if rash is affecting basic self-care ADLs.*
Possible medications for symptom management ³	<ul style="list-style-type: none"> Topical corticosteroids, antihistamines/antipruritics, oral corticosteroids, antibiotics for infection or prophylaxis, vitamin K for prophylaxis. For itch, oatmeal baths and cool compresses may be helpful. 		<ul style="list-style-type: none"> Refer for medical attention and urgent work-up and management of symptoms.

Product Monograph guidance based on CTCAE grades

Guidance on BTKi treatment ^{2,6-8}	<p>BTKi doses should be WITHHELD in the setting of CTCAE Grade \geq 3 rash. Grading is dependent on the type of rash, so Grade 3 is defined as:</p> <ul style="list-style-type: none"> Maculo-papular: Covering > 30% body surface area, moderate or severe symptoms, limiting self-care ADLs.* Grade 4 does not exist for this rash type. Acneiform: Covering > 30% body surface area, moderate or severe symptoms, limiting self-care ADLs, associated with local superinfection and need for oral antibiotics. Grade 4 rash can be life-threatening. Eczema: Severe or medically significant but not immediately life-threatening; IV intervention indicated. Grade 4 does not exist for this rash type. <p>BTKi therapy may resume once rash has resolved to baseline or CTCAE Grade 1.</p> <p>Refer to the BTKi's product monograph for guidance on post-toxicity dose selections. Recommendations to re-start at the same dose versus a one-level dose reduction vary by the BTKi prescribed and the number of prior toxicities (i.e., 1st, 2nd, 3rd, 4th occurrence of CTCAE Grade \geq 3 rash).</p>
---	--

*Basic self-care activities of daily living (ADLs) include showering/bathing, dressing, feeding, functional mobility, personal hygiene and grooming, toileting.

Table adapted from Stacey 2020: COSTaRS Remote Symptom Practice Guides for Adults on Cancer Treatments 2020, Version 4.0, CTCAE v5.0, and the respective product monographs for BTKi's.^{2,3,6-8}

Disclaimer: This resource is intended as guidance for a multidisciplinary team in which individuals function within their own professional scope of practice. Management approaches suggested here do not replace clinical judgement.

COSTaRS recommendations:

Self-care for mild rash³

Ask	Suggest
What helps when you have a skin rash?	<ul style="list-style-type: none"> Reinforce as appropriate.
Are you using unscented, alcohol-free moisturizer daily?	<ul style="list-style-type: none"> Encourage and reinforce.
Are you doing your best to avoid skin irritants such as direct sunlight, scented laundry soap, and alcohol-based perfumed lotions?	<ul style="list-style-type: none"> Encourage and reinforce. Try short, lukewarm showers instead of hot showers, or baths with mild, non-scented soap.
Do you use sun protection?	<ul style="list-style-type: none"> Aim for at least SPF 30 and try to cover up with clothing as much as possible.
Do you have more issues with rash in areas where your clothes fit more tightly?	<ul style="list-style-type: none"> Choose loose-fitting clothing if you can.
If you have itching, what are you doing to manage it?	<ul style="list-style-type: none"> For itch, also recommend oatmeal baths and cool compresses.

[CTCAE Grading for this Symptom](#)

[Return to Rash & Nail Changes](#)

Nail Changes

COSTaRS-based assessment: How severe are the patient’s symptoms?

Use this section to evaluate the patient’s nail changes, then click the button below for symptom management.

COSTaRS-based initial assessment³

When did you first notice the changes to your nails?

(Note: Fingernail and toenail changes due to BTKi’s typically appear 6.5 and 9 months, respectively, after starting therapy.⁴)

How many nails are affected? Please describe how they are affected.

Has anything happened in the past few months that could explain these nail changes (e.g., removed gel nails or longstanding nail polish, injury)?

Apart from your BTKi medicine, have you started any new medication recently? If so, what drug and dose?

What is giving you most cause for concern?

Nail Changes

Expert recommendations: Symptom management

Please note this is intended to be a guiding resource only and should not take the place of clinical judgement.

Self-care for nail changes

Suggest

- Advise the patient to trim nails regularly.¹
- Patient should avoid putting pressure on nails, or repeated trauma, for example, by wearing wider shoes.¹
- Treatment options for damaged and brittle nails include biotin supplementation, hydrosoluble nail lacquer, and poly-ureaurethane topical therapy.⁴

Bruising: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Localized or in a dependent area	Generalized	-	-

CTCAE 5.0 Grading for Specific Bleeding Sites:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

[Return to Management of Bleeding & Bruising](#)

Fatigue: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest; limiting self-care ADL	-

[Return to Fatigue Management](#)

Fever: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
38.0–39.0 degrees C (100.4–102.2 degrees F)	> 39.0–40.0 degrees C (102.3–104.0 degrees F)	> 40.0 degrees C (> 104.0 degrees F) for ≤ 24hrs	> 40.0 degrees C (> 104.0 degrees F) for > 24hrs

CTCAE 5.0 Grading for Specific Infections:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

[Return to Fever & Infection Management](#)

Diarrhea: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

[Return to Diarrhea Management](#)

Nausea: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-

Vomiting: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences

[Return to Nausea & Vomiting Management](#)

Constipation: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

[Return to Constipation Management](#)

Headache: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-

[Return to Headache Management](#)

Arthralgia: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-

Myalgia: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-

Back pain: CTCAE 5.0 Grading Scale⁸

Grade 1	Grade 2	Grade 3	Grade 4
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-

[Return to MSK Symptom Management](#)

Maculo-papular rash: CTCAE 5.0 Grading Scale

(Skin has macules [flat] and papules [elevated]. Associated with pruritus.)⁸

Grade 1	Grade 2	Grade 3	Grade 4
Macules/papules covering < 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL	-

Acneiform rash: CTCAE 5.0 Grading Scale

(Skin has eruption of papules and pustules.)⁸

Grade 1	Grade 2	Grade 3	Grade 4
Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated

Eczema: CTCAE 5.0 Grading Scale

(Skin becomes itchy, red, inflamed, crusty, thick, scaly, and/or forms blisters.)⁸

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	-

[Return to Rash Management](#)

References

- Source 1:** Nixon S, et al. *Current Oncology* 2023;30:4222–4425.
- Source 2:** Imbruvica® Product Monograph, Janssen Inc., August 1, 2023.
- Source 3:** Stacey D, for the Pan-Canadian Oncology Symptom Triage and Remote Support (COSTaRS) Team. *Remote Symptom Practice Guides for Adults on Cancer Treatments 2020*, Version 4.0. The University of Ottawa School of Nursing and the Ottawa Hospital Research Institute, Ottawa, Canada. Available at: https://ktcanada.ohri.ca/costars/Research/docs/COSTaRS_Pocket_Guide_March2016.pdf.
- Source 4:** Bitar C, Farooqui MZH, Valdez J, et al. Hair and nail changes during long-term therapy with ibrutinib for chronic lymphocytic leukemia. *JAMA Dermatol.* 2016;152:698–701. DOI: 10.1001/jamadermatol.2016.0225.
- Source 5:** Galitzia A, Maccaferri M, Mauro FR, et al. Chronic lymphocytic leukemia: Management of adverse events in the era of targeted agents. *Cancers (Basel).* 2024 May 24;16(11):1996.
- Source 6:** BeOne Medicines GmbH. BRUKINSA® Product Monograph. Date of revision: Dec-27-2024.
- Source 7:** Calquence® Product Monograph, AstraZeneca Canada Inc., September 26, 2025.
- Source 8:** *Common Terminology Criteria for Adverse Events (CTCAE)*, Version 5.0. US Department of Health and Human Services, November 27, 2017. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.
- Source 9:** Matuszkiewicz-Rowinska J, Malyszko J. *Kidney Blood Press Res.* 2020;45:645–660.
- Source 10:** Brown JR, Eichhorst B, Lamanna N, et al. Sustained benefit of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL: final comparative analysis of ALPINE. *Blood.* 2024;144(26):2706–2717.
- Source 11:** Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. *Can J Cardiol.* 2020 May;36(5):596–624.
- Source 11a:** Supplement to Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. *Can J Cardiol.* 2020 May;36(5):596–624.
- Source 12:** Iberri DJ, et al. *Br J Haematol.* 2018;180:164–166. DOI: 10.1111/bjh.14302.

Credits

BTKi Patient Optimization Guide Steering Committee

Christine Peragine, PharmD, PhD (Chair)

Dominic Duquette, PharmD

Michelle Forman, RN

Mova Leung, PharmD

Kirsten Lewis, NP

Cheryl Page, RN, MEd

John Papastergiou, PharmD, PhD

Jonathan Stevens, PharmD

Acknowledgements

The Steering Committee wishes to acknowledge the work of the authors of the COSTaRS Remote Symptom Practice Guides³, an evidence-based synthesis of clinical practice guidelines across Canada and elsewhere, which provided key information for this guide. BeOne Medicines provided funding for the development of this BTKi Patient Optimization Guide.

