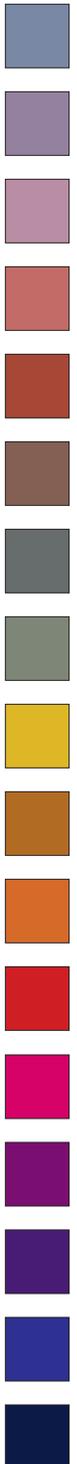


ONTarget

Resource Guide

Common Adverse events of Targeted Therapy

To Build Confidence and
Skill in the Prevention and
Management of Common
Adverse events of Targeted
Oncology Therapy



Revised 2015

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To obtain copies of this Resource Guide

This Resource Guide is available in English and French.
To order pdf copies, free of charge, contact Marie-Pascale Guay
at mguay@jgh.mcgill.ca.

Care has been taken to ensure the accuracy of the information; however, it is not intended to provide a complete description of all adverse events or to be used as a replacement for the product monographs of the targeted therapies that are discussed here. Since information on these new therapies is constantly evolving, it is advisable not to use this program as the sole source of information on this subject. You are encouraged to consult other sources of information as they become available. Use this document and any information in it at your own risk. Use of this material is subject to our Terms of Use.

The information in this document is provided solely as an educational service. Specific patient care decisions are the responsibility of the clinician who cares for the patient on a targeted therapy.



The Groupe d'étude en oncologie du Québec (GEOQ) would like to acknowledge and express our appreciation to our leading sponsor, Pfizer Canada Inc., and sponsors Novartis Pharmaceuticals Canada Inc., Boehringer Ingelheim Canada Ltd, Hoffmann-La Roche Limited, Bayer Inc., Amgen Canada Inc., and Sanofi Canada for their financial support of this project through unrestricted educational grants.

We would like to thank Bristol-Myers Squibb Canada for contributing photographs.

Overview

To view information about this program, click on the bookmarks in the panel.

Acknowledgments

Continuing Education

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Medication List



Acknowledgements

The Groupe d'étude en oncologie

The Groupe d'étude en oncologie du Québec (GEOQ) is a non-profit online organization dedicated to promoting communication and cooperation between professionals who are involved in the diagnosis, investigation, and research of treatments for different types of cancer and associated hematological conditions.

The Web site www.geoq.com provides up-to-date oncology information to healthcare professionals in Quebec.

The scientific committee and expert review committee who developed this Resource Guide would like to thank GEOQ for hosting this program and providing expertise along the way during the design and development phase.

Who created this Resource Guide?

A committee of practicing oncology pharmacists, experienced in hospital and community pharmacy practice, in conjunction with an expert review panel and in collaboration with the Groupe d'étude en oncologie du Québec, developed this Resource Guide.

The committee wishes to recognize the pivotal contribution and outstanding commitment of Lucie Surprenant, BPharm, MSc, BCOP, in the initial and ongoing development of OnTarget. Ms. Surprenant continues to serve as an advisor for the project.

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- Anne Delson, Graphic design
- Amanda Jekums, Production design

Continuing Education

Goal and objectives

The goal of this Resource Guide is to help community pharmacists confidently assess and manage the common adverse events that targeted cancer therapies may induce in patients with cancer.

Upon completion of this program, you will be able to:

- Identify the key molecular targets of medications in clinical use and under development for the treatment of cancer
- Identify the common adverse events of targeted cancer therapies, based on their specific target and the common adverse events of individual therapies
- Apply the most appropriate preventive strategies to minimize common adverse events
- Educate and inform your patients about potential common adverse events
- Assess symptoms and apply the most appropriate management strategies to minimize impact on the patient's quality of life
- Contribute to patient adherence, thereby helping to improve treatment response and outcomes
- Make appropriate referrals to oncologists or other healthcare professionals, when required

Credits (CEUs)

The Canadian Council on Continuing Education in Pharmacy (CCCEP) has awarded this program 17.50 CEUs. To obtain credits, you will need to complete a final quiz and a program evaluation. Once you have successfully completed the program, you will receive your Letter of Attendance by email. Accreditation of this program will be recognized by CCCEP under the file number #1046-2015-1363-I-P ONTARGET until April 14, 2016.

Expiry date

As of April 14, 2016, the program will expire. You will not be able to obtain any credits once the program has expired.

Quiz and Evaluation

In order to be eligible for continuing education credits, you must complete the final Quiz with a minimum grade of 70% and complete the mandatory Program Evaluation. Please note that you are permitted **only two attempts** at the final quiz. The final quiz is composed of 70 multiple-choice questions and requires approximately 70 minutes to complete.

Upon successful completion of this 2015 updated OnTarget quiz, you will receive 17.5 CEUs. Participants who successfully completed the **2012** OnTarget quiz **are not eligible** to retake the quiz and receive credits. Participants who successfully completed the **2009** OnTarget quiz **are eligible** to retake the quiz and receive credits

Instructions for Quiz and Evaluation

Once you have completed the entire program, you can access both by clicking on the bookmark **Quiz and Evaluation**. The quiz and evaluation can be found at the end of the program. Complete the quiz and evaluation questions.

Once you have successfully completed the quiz, you will receive your Letter of Attendance by email.

Note: The Letter of Attendance will be e-mailed to you. They are sometimes filtered as "junk mail". If you have not received your Letter of Attendance within 48 hours of completing quiz and program evaluation, please contact: bernard.lesperance@umontreal.ca, 514-338-2150.

Endorsements

The program has been endorsed by the Groupe d'étude en oncologie du Québec (GEOQ) 2014 and the Canadian Association of Pharmacy in Oncology (CAPHO) 2015.

Disclosure of potential conflict of interest

This educational initiative was funded by an unrestricted educational grant from the following pharmaceutical companies: Pfizer Canada Inc., Novartis Pharmaceuticals Canada Inc., Boehringer Ingelheim Canada Ltd, Hoffmann-La Roche Limited, Bayer Inc., Amgen Canada Inc., and Sanofi Canada. Industry involvement included the funding of honoraria for the independent oncology pharmacist scientific committee and all expert reviewers, who received honoraria in recognition of their time and expertise in the subject matter.

Organization of Resource Guide

Approach to content

The content in this Resource Guide is organized into fifteen lessons; each focuses on therapies that are used to block a specific molecular target in patients with cancer. Each lesson discusses the following information:

- A review of a specific target and possible therapeutic pathways
- Drug administration
- Mechanism of action
- Basic pharmacokinetics
- Presentation, prevention and management of common adverse events
- List of references

Prior to the lessons, the Resource Guide includes an Overview of ONTarget with the following information under the tabs:

- Acknowledgements
- Continuing Education
- Organization of Resource Guide
- Introduction to Resource Guide
- Targeted Therapies

Lessons

Lessons are listed below. To view information about each lesson, click on the bookmarks in the panel.

1. **ALK inhibitors:**
Ceritinib (Zykadia™), Crizotinib (Xalkori®)
2. **Anti-CD monoclonal antibodies:**
Alemtuzumab (MabCampath®), Obinutuzumab (Gazyva™), Ofatumumab (Arzerra™), Rituximab (Rituxan®)
3. **Bcr-Abl inhibitors:**
Bosutinib (Bosulif™), Dasatinib (Sprycel®), Imatinib (Gleevec®), Nilotinib (Tasigna®)
4. **BRAF inhibitors:**
Dabrafenib (Tafinlar™), Vemurafenib (Zelboraf™)
5. **Bruton kinase inhibitors:**
Ibrutinib (Imbruvica™)
6. **CTL-4 inhibitors:**
Ipilimumab (Yervoy™)
7. **EGFR inhibitors:**
Afatinib (Giotrif®), Cetuximab (Erbix®), Erlotinib (Tarceva®), Gefitinib (Iressa®), Panitumumab (Vectibix®)
8. **Hedgehog pathway inhibitors:**
Vismodegib (Erivedge®)
9. **HER2 inhibitors:**
Lapatinib (Tykerb®), Pertuzumab (Perjeta™), Trastuzumab (Herceptin®)
10. **MEK1/MEK2 inhibitors:**
Trametinib (Mekinist™)
11. **mTOR inhibitors:**
Everolimus (Afinitor®), Temsirolimus (Torisel®)
12. **Multi-targeted kinase inhibitors (MKIs):**
Imatinib (Gleevec®), Pazopanib (Votrient®), Regorafenib (Stivarga®), Sorafenib (Nexavar®), Sunitinib (Sutent®), Vandetanib (Caprelsa®)
13. **PD-1 inhibitors:**
Pembrolizumab (Keytruda®)
14. **RANKL inhibitors:**
Denosumab (Xgeva®)
15. **VEGF inhibitors:**
Aflibercept (Zaltrap™), Axitinib (Inlyta®), Bevacizumab (Avastin®)

In addition, the program contains a Photo Gallery of a few adverse events and a Quiz and Program Evaluation.

Quiz and Evaluation

To obtain credits, you will need to complete a final [Quiz and Program Evaluation](#). See detailed information in the Continuing Education section.

Introduction to Resource Guide

Target audience and purpose

ONTarget was created primarily for **community pharmacists** but may also benefit hospital pharmacists in the:

- Appropriate prevention and management of common adverse events that are associated with targeted cancer therapies
- Identification of key molecular targets that are blocked by targeted therapies in clinical use and may be targeted in future by newer agents
- Maintenance of patients on therapy and improvement of patient response and outcomes

At the outset, the scientific committee made a number of critical decisions about the type of information and degree of detail that would be most practical and suitable for the target audience.

To this end, ONTarget focuses on the **presentation, prevention and management of common adverse events**.

The Resource Guide excludes:

- Information that is not typical or relevant to the daily practice of community pharmacists, e.g. dosage adjustment
- Information that can be accessed in detail in a product monograph, e.g., detailed pharmacokinetics, clinical trial data, manufacturers' definitions of common and very common adverse events
- Information that is inconsistent in the product monographs and medical literature, e.g. frequency of occurrence (%) of common adverse events
- Information that is updated regularly and is typically accessed by pharmacists on designated websites, e.g., up-to-date reporting of drug interactions
- Information dealing with infusion reactions, which occur with intravenous (IV) agents, as they are encountered in the clinic or hospital setting
- Grading of recommendations as they are mostly expert opinions or obtained by expert consensus

Common adverse events tables in ONTarget list adverse events with a frequency of $\geq 10\%$.

Adverse events are listed alphabetically, not by frequency of occurrence. The definition of "common" adverse events is based on reports in individual product monographs. Community pharmacists should be aware that manufacturers define these terms differently and consult the product monographs for more information.

Evidence-based guidelines

There are no evidence-based guidelines on how to manage the common adverse events that targeted therapies may induce in patients with cancer. The recommendations presented here are based on a review of the medical literature, expert opinion, and best clinical practices in oncology.

Note: For complete description of all adverse events of these agents, **please consult the product monographs**.

Targeted Therapies

What are targeted therapies?

A number of new therapies in oncology target specific molecules and receptors that are involved in the development, growth, and progression of cancer in thriving human cells. Human cells receive and transmit vital information from their environment along biochemical signaling pathways. Cell surface receptors receive signals from the extracellular environment and transmit them into cells, activating a chain of signaling molecules, often called second messengers, which are aligned along specific pathways to the cell nucleus. These signals influence cellular:

- Growth
- Differentiation
- Reproduction
- Survival

A signaling pathway is triggered when a ligand binds to the extracellular portion of cell surface receptors. The ligand may be a growth factor, hormone, antibody, or other biochemical. The ligand activates the receptor, leading to signal transduction within the cell. Signaling molecules then transmit messages to a chain or pathway of other signaling molecules to the nucleus.

How targeted therapies work

Targeted therapies in oncology attack molecular targets on cell signaling pathways. The most typical targets are:

- Ligands that bind to and activate cell surface receptors
- Cell surface receptors
- Intracellular signaling molecules
- Transcription factors in the nucleus

Monoclonal antibodies (MoAb) generally work outside the cell. They target ligands that bind to cell surface receptors or the extracellular portion of cell surface receptors. Small molecule drugs generally work inside the cell. They target the intracellular portion of cell surface receptors, signaling molecules that relay messages through the cell or transcription factors within the cell nucleus.

The molecular targets of newer biologic therapies have been implicated in the development and progression of cancer. Many are overabundant, dysregulated, or abnormal in cancer cells. By targeting these molecules, newer therapies attack the mechanisms that lead to tumour formation and progression. However, they may also impact molecular targets in normal cells, leading to novel adverse events.

Common side-effect profiles

The common adverse-event profiles of these agents differ from those of traditional chemotherapeutic agents and hormonal agents. However, these common adverse events are often predictable, based on the specific mechanism of action and molecular target of each agent.

Early identification of common adverse events and timely intervention may ameliorate some common adverse events and encourage patient adherence to targeted therapy, which may improve patient survival and quality of life.

This teaching program presents the common adverse events of these agents and has compiled strategies for their prevention and management at the pharmacist level.

Practical strategies for the prevention and management of common adverse events

This Resource Guide is a practical tool for pharmacists to use in their day-to-day work. It presents practical strategies for the prevention and management of common adverse events associated with targeted therapy.

With an increase in the number of prescriptions for oral targeted therapy, **community pharmacists** need to be knowledgeable about the mechanisms of action, administration, basic pharmacokinetics, and common adverse events of these anti-cancer medications.

Targeted therapies, which include monoclonal antibodies and small molecule inhibitors, have significantly changed the treatment of cancer over the past 10 years. These drugs are now a component of therapy for many common malignancies, including breast, colorectal, lung, and pancreatic cancers as well as lymphoma, leukemia, renal cell cancer, and melanoma. The mechanisms of action and toxicities of targeted therapies differ from those of traditional cytotoxic chemotherapy.

While targeted therapies are generally better tolerated than traditional chemotherapy, they are associated with novel adverse events, such as EGFR-induced acneiform rash and MKI-induced hand-and-foot syndrome.

Medications

To view information about common adverse events of a particular medication, click on the bookmarks in the panel.

Afatinib (Giotrif[®]) [EGFR]
Aflibercept (Zaltrap[™]) [VEGF]
Alemtuzumab (MabCampath[®]) [ANTI-CD MoAB]
Axitinib (Inlyta[®]) [VEGF]
Bevacizumab (Avastin[®]) [VEGF]
Bosutinib (Bosulif[™]) [BCR-ABL]
Ceritinib (Zykadia[™]) [ALK]
Cetuximab (Erbix[®]) [EGFR]
Crizotinib (Xalkori[®]) [ALK]
Dabrafenib (Tafinlar[™]) [BRAF]
Dasatinib (Sprycel[®]) [BCR-ABL]
Denosumab (Xgeva[®]) [RANKL]
Erlotinib (Tarceva[®]) [EGFR]
Everolimus (Afinitor[®]) [mTOR]
Gefitinib (Iressa[®]) [EGFR]
Ibrutinib (Imbruvica[™]) [BKI]
Imatinib (Gleevec[®]) – CML [BCR-ABL]
Imatinib (Gleevec[®]) – GIST [MKI]
Ipilimumab (Yervoy[™]) [CTL-4]
Lapatinib (Tykerb[®]) [HER2]
Nilotinib (Tasigna[®]) [BCR-ABL]
Obinutuzumab (Gazyva[™]) [ANTI-CD MoAB]
Ofatumumab (Arzerra[™]) [ANTI-CD MoAB]
Panitumumab (Vectibix[®]) [EGFR]
Pazopanib (Votrient[®]) [MKI]
Pembrolizumab (Keytruda[®]) [PD-1]
Pertuzumab (Perjeta[™]) [HER2]
Regorafenib (Stivarga[®]) [MKI]
Rituximab (Rituxan[®]) [ANTI-CD MoAB]
Sorafenib (Nexavar[®]) [MKI]
Sunitinib (Sutent[®]) [MKI]
Temozolomide (Temodar[®]) [mTOR]
Trametinib (Mekinist[™]) [MEK1/MEK2]
Trastuzumab (Herceptin[®]) [HER2]
Vandetanib (Caprelsa[®]) [MKI]
Vemurafenib (Zelboraf[™]) [BRAF]
Vismodegib (Erivedge[®]) [HHPI]



ALK Inhibitors

Ceritinib (Zykadia™)

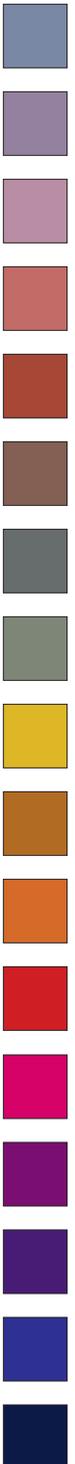
Crizotinib (Xalkori®)

.....

This chapter contains information on the prevention and management of common adverse events of ALK inhibitors (ALKI) that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage ALKI-induced adverse events. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of adverse events, please consult the product monographs.^{1,2}

ALK inhibitors block the biological activity of the tyrosine kinase (TK) domain on oncogenic fusion protein produced by mutated ALK genes.



ALK in cancer

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase (TK) receptor that spans the cell membrane. Translocations in the ALK gene lead to the expression of oncogenic fusion proteins that play a role in many diseases, including anaplastic large cell lymphoma, B cell non-Hodgkin's lymphoma, inflammatory myofibroblastic tumours, neuroblastoma and non-small-cell lung cancer (NSCLC).¹⁻⁶

In NSCLC, the EML-4 gene breaks at intron 13 and fuses to intron 19 of the ALK gene. The abnormal fusion of material from both genes creates the mutant *EML4-ALK* gene. It produces an oncogenic fusion protein that switches ALK TKs into constant activity, disrupting cell signaling and promoting:³⁻⁷

- Tumour cell proliferation
- Tumour cell survival
- Tumor cell migration

Drug administration

Ceritinib

Ceritinib is an oral medication taken once daily on an empty stomach. Patients should not take it within 2 hours of a meal, as a high-fat meal may enhance exposure to the drug.²

Crizotinib

Crizotinib is an oral medication, taken twice daily with or without food. Patients should swallow capsules whole with a glass of water. They should never be crushed, dissolved or opened.¹

For both drugs, dose modifications and drug interruptions may be required during treatment, based on the patient's level of tolerability and safety.^{1,2}

How to take ALK inhibitors

- Avoid grapefruit, star fruit, pomelo, pomegranate, Seville oranges and other foods that are CYP3A inhibitors^{1,2}
- Avoid St. John's wort and other strong CYP3A inducers¹

Mechanism of action

In diseases with evidence of EML4-ALK mutation, the ALK inhibitors crizotinib and ceritinib prevent the EML4-ALK fusion oncoprotein, which triggers transformation to a cancerous state, from becoming constitutively active (always switched on).^{1,3,7} Ceritinib prevents the constituent activation of this oncoprotein even in the presence of resistance to crizotinib.²

ALK inhibitors:^{3,18}

- Restore normal cell signalling
- Disrupt tumour growth and proliferation

Ceritinib

Ceritinib is a small molecule that inhibits the activation of ALK receptor tyrosine kinases. It binds to the adenosine triphosphate (ATP) site on ALK enzymes and on the ALK portion of EML4-ALK and NPM-ALK fusion oncoproteins. By binding to this site, ceritinib inhibits the autophosphorylation of ALK, ALK-mediated phosphorylation of the downstream signalling protein STAT3, and the proliferation of ALK-dependent cancer cells.²

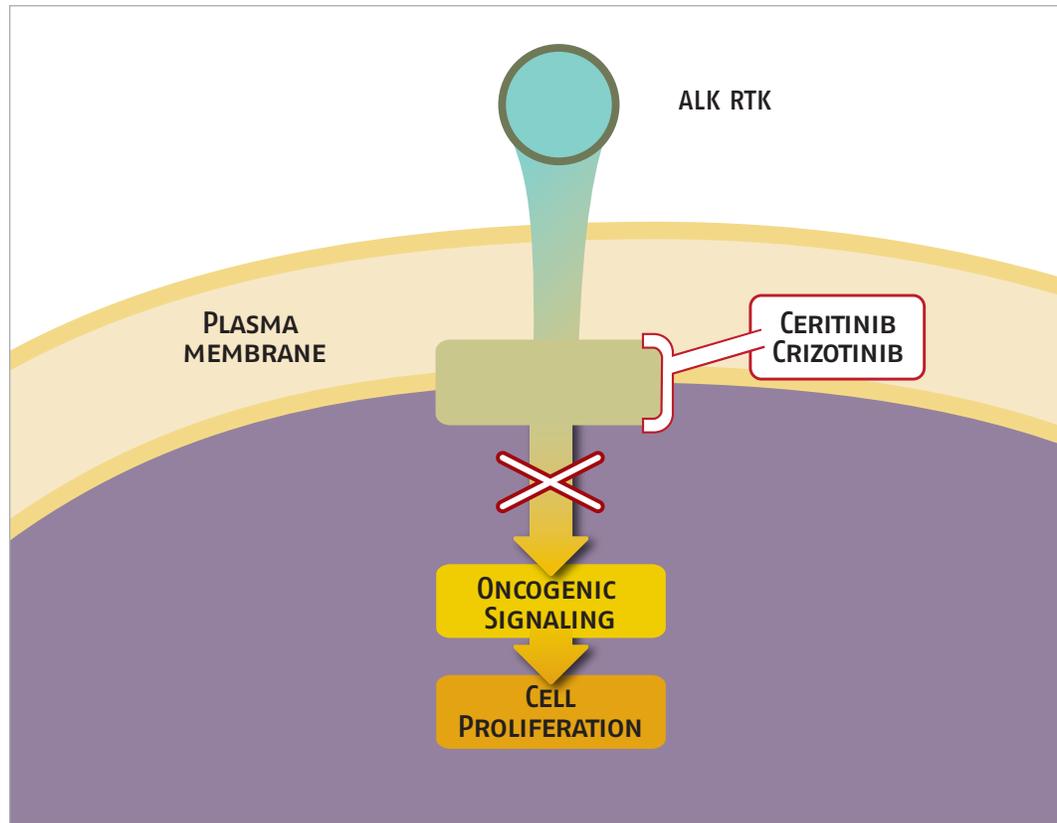
Ceritinib also inhibits the activation of insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROSI.²

In preclinical trials, ceritinib had a 20-fold higher potency than crizotinib and showed marked activity against crizotinib-sensitive and crizotinib-resistant ALK-related tumors.⁸

Crizotinib

Crizotinib is a small molecule that inhibits the activation of c-Met and ALK receptor tyrosine kinases. Crizotinib also inhibits hepatic growth factor receptor (HGFR), RTK, ROS (ROS1, c-ros) and RON RTKs.¹ It binds to the adenosine triphosphate (ATP) site on ALK enzymes and on the ALK portion of EML4-ALK, NPM-ALK and other ALK fusion oncoproteins. By binding to this site, crizotinib blocks ATP from activating these enzymes and fusion oncoproteins. In other words, it prevents ATP from switching them on.^{1,3,7}

Crizotinib also inhibits the activation of tyrosine kinases on the hepatocyte growth factor receptor (HGFR) and the "*récepteur d'origine nantais*" (RON).^{1,3,7}



Basic pharmacokinetics

The CYP3A4/5 pathways in the liver are the primary metabolizers of ALK inhibitors. Strong CYP3A inhibitors may increase plasma concentration of ALK-inhibitors, whereas strong CYP3A inducers may reduce their plasma concentrations.^{1,2} In patients who must take strong CYP3A inhibitors, the risk of adverse events increases with crizotinib and the dose of ceritinib must be reduced by one-third, rounded off to the nearest 150-mg dosage strength.²

Presentation, prevention and management of common adverse events

The following table summarizes the common adverse events with an overall frequency of $\geq 10\%$ for crizotinib and ceritinib. Mild gastrointestinal adverse events, such as diarrhea, nausea, vomiting and abdominal pain, are the most common adverse events of ALK inhibitors.^{1,2}

Common adverse events of ALK inhibitors

Click on adverse effects highlighted in blue for more information

Ceritinib²

Blood and lymphatic system disorders

- Neutropenia

Eye disorders

- **Vision disorders**

Gastrointestinal disorders

- Abdominal pain
- Constipation
- **Diarrhea**
- Nausea
- Vomiting

General disorders

- Fatigue
- **Fluid retention**

Hepatobiliary disorders

- **Elevated transaminases**

Infections

- Upper respiratory tract infections

Metabolic and nutrition disorders

- Decreased appetite

Nervous system disorders

- Dizziness
- Neuropathy
- **Taste disturbance**

Skin and subcutaneous tissue disorders

- **Rash**

Crizotinib¹

Eye disorders

- **Vision disorders**

Gastrointestinal disorders

- Abdominal pain
- Constipation
- **Diarrhea**
- Esophageal disorders
- Nausea
- Vomiting

General disorders

- Fatigue

Hepatobiliary disorders

- **Elevated transaminases**

Laboratory abnormalities

- Decreased hemoglobin

Metabolism and nutrition disorders

- Decreased appetite
- **Hyperglycemia**

Nervous system disorders

- Neuropathy

Skin and subcutaneous tissue disorders

- **Rash**

Other adverse events of interest with ALK inhibitors

Click on adverse events highlighted in blue for more information

- **Bradycardia and QT prolongation**
- **Pneumonitis**

Refer for medical attention: ceritinib

Refer patients to a doctor if any of the following adverse events develop or become severe:²

- Any symptoms of high blood sugar or worsening diabetes (frequent urination, dizziness, fatigue, confusion) (Hyperglycemia)

When to hold ceritinib

Tell patients to seek immediate emergency care if any of these uncommon adverse events develops:²

- Liver problems (yellowing of skin or eyes, upper right quadrant pain)
- Slow or irregular heartbeat (bradycardia, prolonged QT interval)
- Shortness of breath, coughing, trouble breathing, congestion (pneumonitis)

Refer for medical attention: crizotinib

Refer patients to a doctor if any of the following adverse events become persistent or severe:¹

- Vision changes (floaters, double vision, blurry vision, light sensitivity, seeing lights/sparks/colours)

When to stop crizotinib

Tell patients to seek immediate emergency care if any of these uncommon adverse events develop:¹

- An increase in vitreous floaters (potential for retinal hole or detachment)
- Liver problems (yellowing of skin or eyes, upper right quadrant pain)
- Slow or irregular heartbeat (bradycardia, prolonged QT interval)
- Shortness of breath, coughing, trouble breathing, congestion (pneumonitis)

◀ Bradycardia and QT prolongation

Some patients on ALK inhibitors develop a mild to moderate, dose-related bradycardia. Severe (sinus) bradycardia may develop in patients on ceritinib. In patients who develop moderate to severe QTc prolongation (≥ 500 msec), the dosage of crizotinib or ceritinib may be reduced or the drug may need to be stopped.^{1,2,4} Patients should be aware of symptoms of bradycardia, such as dizziness, syncope, hypotension, especially if they are receiving concomitant treatment with drugs that may lower heart rate, such as beta-blockers. ALK inhibitors should be stopped if heart rate is lower than 60 beats per minutes.

◀ Diarrhea

Diarrhea is one of the most common adverse events of ALK inhibitors, occurring in almost half (49%) of patients on crizotinib and 86% of patients on ceritinib.^{1,2} It is generally mild and, on average, not as severe as EGFR-induced diarrhea.⁴ Diarrhea is rarely severe in patients treated with crizotinib; however, 6% of patients taking ceritinib may develop severe diarrhea.^{2,9} Diarrhea-related electrolyte disturbances can elevate the risk of cardiac toxicity (torsade de pointes).¹⁰

Management OTC therapy ¹¹⁻¹³	Mild to moderate (less than 4 loose stools per day) <ul style="list-style-type: none">Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) Moderate (more than 4 to 6 loose stools per day) <ul style="list-style-type: none">2 tablets immediately, then 1 tablet every 2-4 hours until bowel movements are normal for at least 12 hours
Replace lost fluids ¹¹⁻¹³	<ul style="list-style-type: none">Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 litres per dayDrink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care ¹²	Advise patients to: <ul style="list-style-type: none">Clean the anal area with mild soap and warm water after each bowel movement to prevent irritationApply a barrier cream or ointment, such as petroleum jelly or Isle's pasteSoak in a warm bathtub or sitz bath to relieve discomfortExamine the anal area for red, scaly or broken skin
Diet ¹¹⁻¹³	Advise patients to: <ul style="list-style-type: none">Eat and drink small quantities of food oftenAvoid spicy, greasy, or fried foodsFollow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolveFollow a lactose-free dietAvoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

There are no evidence-based guidelines for the prevention or treatment of diarrhea in patients taking an ALK inhibitor. Antidiarrheal medications are usually able to control this dose-related adverse event.¹¹⁻¹³ Early assessment and management of targeted therapy-induced diarrhea is essential to prevent the worsening of this adverse event and the need for hospitalization, dose interruption or dose reduction.⁹

If mild to moderate diarrhea persists for 48 hours, despite dietary modification and loperamide, a second-line agent may be needed for control. Advise the patient to seek immediate medical attention.¹⁵

When patients seek OTC treatment for diarrhea, it is important to ask them about:^{12,13,16}

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Stomach cramps

◀ Elevated transaminases

Patients taking either crizotinib or ceritinib may need a drug holiday or dosage modification to manage elevations in liver enzyme levels.^{1,2} Patients on crizotinib may present with mild to moderate liver enzyme elevations (5 times the upper limit of normal), which may become severe in 5% to 6% of patients. This adverse event usually presents after cycle 2 and is reversible when the therapy is ceased. On the other hand, one third of patients on ceritinib may present with severe ALT elevations (5 times the upper limit of normal).² Withholding the drug then resuming therapy at a reduced dose or permanent discontinuation may be necessary to reduce liver enzyme and bilirubin levels.²

◀ Fluid retention

Fluid retention (edema) is a common adverse effect of crizotinib. It develops in at least 38% of patients.¹ Although usually peripheral, periorbital and facial fluid retention have been reported.

Prevention	<p>Advise your patients to:¹⁴</p> <ul style="list-style-type: none">• Limit salt intake• Weigh themselves twice weekly <p>For swollen eyelids or swelling around eyes:¹⁴</p> <ul style="list-style-type: none">• Elevate head during sleep
Management	<p>OTC therapy</p> <p>Mild periorbital fluid retention</p> <ul style="list-style-type: none">• For swelling around eyes, elevate the head during sleep or use skin-tightening agents, e.g., topical Preparation H® containing phenylephrine or lanolin (avoid eye contact)¹⁴
	<p>Prescribed therapy</p> <p>Mild peripheral fluid retention</p> <ul style="list-style-type: none">• Topical eye ointments with phenylephrine 0.25%¹⁹• Topical corticosteroid (e.g., hydrocortisone 1%)¹⁹ <p>Moderate fluid retention</p> <ul style="list-style-type: none">• Low-dose loop diuretic, e.g., furosemide. Potassium or magnesium supplements may be necessary¹⁴• Close electrolyte monitoring¹⁴

Key facts: Fluid retention

Patients who take crizotinib may develop generalized or localized swelling due to fluid retention (edema).¹ Peripheral fluid retention is usually mild to moderate in severity. Its occurrence is dose-related. It is usually associated with swelling of ankles, feet and lower legs.¹

◀ Hyperglycemia

Moderate to severe hyperglycemia occurs in 13% of patients on ceritinib. Patient with diabetes or glucose intolerance have a 6-fold higher risk of severe hyperglycemia. There is a 2-fold higher risk of severe hyperglycemia in patients taking corticosteroids.²

Monitoring	Advise patients, particularly those at risk for diabetes, to watch for the following symptoms and, if they appear, report them to their doctor: <ul style="list-style-type: none">• Frequent urination• Thirstiness• Feeling tired	
Management	Encourage patients to monitor blood glucose levels during treatment Refer patients to a certified diabetes educator if available in the community or at the cancer center Counsel patient about dietary modification	Prescribed therapy <ul style="list-style-type: none">• Oral antidiabetic agent and/or insulin

Key facts: Hyperglycemia

Advise patients to watch for signs and symptoms of hyperglycemia and to contact their healthcare team member, if they occur.

Monitoring glucose levels and early intervention for hyperglycemia are recommended. Patients with pre-existing diabetes may require optimization of anti-hyperglycemic therapy. If withholding ceritinib or a dose reduction does not control hyperglycemia, discontinuation is advised.²

◀ Pneumonitis

Drug-related, potentially life-threatening pneumonitis may rarely occur in patients treated with ALK inhibitors, usually within the first 2 months of treatment.^{1,2} Signs and symptoms such as dyspnea, cough, and fatigue need to be rapidly assessed by a doctor to eliminate a differential diagnosis (disease progression, pneumonia, etc.). Oral corticosteroids may be prescribed.¹⁷ If treatment-related pneumonitis is diagnosed, crizotinib should be permanently discontinued and standard treatment of interstitial lung disease should be considered.¹

◀ Rash

Rash (rash, maculopapular rash, acneiform dermatitis) is a common adverse event of ALK inhibitors. It occurs in about 16% of patients.^{1,2} An ALK inhibitor-induced rash does not resemble an EGFR-induced rash.

Management

- Moisturize two to three times a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or with thick, alcohol-free emollient creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion¹⁵
- Cleanse with mild soaps, cleaners or bath or shower oils to avoid skin dryness
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics
- Emollients and mild topical steroids (eg, 1% hydrocortisone cream) can be applied on dry skin from 2 to 3 times daily
- Topical antibiotics can be applied on papulopustular eruptions
- For skin rash with moderate pruritus or tenderness, use 0.1% triamcinolone or 2.5% hydrocortisone cream¹⁰

Key facts: Rash

There are no evidence-based guidelines for the treatment of ALK inhibitor-induced rash. Rash is usually mild.^{1,2} Early recognition of symptoms and a prompt start of symptomatic therapy are the mainstays of treatment. Mild to moderate symptoms are managed while the patient remains on therapy.^{1,2,15}

Topical preventive therapy is recommended to reduce the incidence of skin rashes.^{10,15} Patients should avoid excessive exposure to sunlight and use a broad-spectrum sunscreen that contains titanium dioxide or zinc oxide and has an SPF of 30 or higher.^{10,15}

◀ Taste disturbance

Taste changes that occur in patients on crizotinib differ from the usual lack of taste or metallic taste that is described for other drugs. These patients may become hypersensitive to sweet or sour taste sensations but experience less taste sensation when eating hot or spicy food.⁴

◀ Vision disorders

About 62% of patients who take crizotinib and considerably fewer (9%) of patients on ceritinib experience visual disturbances, which are typically described as “trails of light” that follow objects as the patient or object moves, particularly during ambient lighting changes from dark to light. This adverse event is usually transient, often starts within 2 weeks of treatment and diminishes overtime. Double vision, light sensitivity, visual floaters, accommodation disorder, presbyopia, reduced visual acuity and other visual impairments may occur. Advise patients who have visual problems to see their doctor.^{1,2} These visual disturbances may not require treatment, but doctors may want to exclude neurologic toxicity or underlying NSCLC central nervous system involvement.^{14,17}

Eye problems

Patients who experience a vision disorder should use caution when driving or operating machines.

Severe or worsening vitreous floaters with crizotinib may signal the development of a retinal hole or a pending retinal detachment.

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Anti-CD Monoclonal Antibodies

Alemtuzumab (MabCampath®)

Obinutuzumab (Gazyva™)

Ofatumumab (Arzerra™)

Rituximab (Rituxan®)

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This chapter contains information on the prevention and management of common adverse events of some anti-CD monoclonal antibodies (MoAbs) that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage anti-CD MoAb-induced adverse events. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events of these agents, please consult the product monographs.¹⁻⁴ Infusion reactions, which occur with intravenous (IV) agents, are usually encountered in the clinic or hospital setting and will not be described here.

Four medications are commonly used to inhibit the action of CD antibodies. Rituximab, alemtuzumab, ofatumumab and obinutuzumab are intravenous medications with different molecular targets.¹⁻⁴



CDs in cancer

Cancer cells survive by failing to undergo programmed cell death (apoptosis). They resist death by neutralizing the proteins within cells that control this natural process.⁵ However, there are several ways by which a cancer cell can die. MoAbs induce cell death by targeting cancer cells for destruction by the body's immune system.^{1,6}

Anti-CD MoAbs use the same method to fight cancer as the body's natural antibodies. They target specific proteins (antigens) on cancer-cell surfaces. They bind to these antigens, marking the cells. The immune system can then identify the marked cells and kill them.⁶

One such antigen is CD-20, which is located on the surface of normal and malignant B-lymphocytes.⁷ Another target is CD-52, an antigen on the surface of both T- and B-lymphocytes. CD-52 is also found on other immune-system cells – monocytes, macrophages, natural killer cells, and granulocytes.⁶⁻⁹

Because MoAbs bind to all cell surfaces with the specific antigen, they can destroy both abnormal and normal cells. The depletion of normal cells can lead to treatment-related adverse events.⁶⁻⁹

Drug administration

These four medications are administered by intravenous infusion in the hospital or clinic setting.

Because MoAbs are associated with hypersensitivity reactions and infusion-related toxicity, the rate of intravenous infusion of these drugs is usually gradually stepped up and patients are watched carefully during infusions.¹⁻⁴

To prevent low blood pressure (BP) during an infusion of rituximab, patients taking rituximab are usually instructed not to take their BP pills for 12 hours before an infusion and to resume taking their pills after the infusion is completed.⁴

Mechanism of action

Anti-CD MoAbs kill cancer cells directly by flagging them for destruction by immune cells and indirectly by recruiting complement factors to perform this function.^{1-4,5,9}

Alemtuzumab

This medication targets CD-52 antigen on B- and T-lymphocytes, monocytes, macrophages, natural killer cells, and granulocytes. It kills cancer cells by:^{1,5-9}

- Delivering a surrogate signal to cells that triggers apoptosis
- Targeting cells for destruction by immune cells
- Recruiting complement factors to kill cells

MabCampath® and Lemtrada™

Alemtuzumab is marketed under two brand names in Canada. MabCampath is used to treat patients with cancer while Lemtrada is used to treat patients with multiple sclerosis.^{1,11} Information contained in this chapter is related to MabCampath.

Obinutuzumab

This medication is a recombinant monoclonal humanized and glyco-engineered Type II anti-CD20 antibody of the IgG1 isotype. Glyco-engineering of the Fc part of obinutuzumab results in a higher affinity for specific receptors on immune effector cells, such as natural killer cells, monocytes and macrophages. It targets the CD-20 antigen on the surface of pre B- and mature B-lymphocytes.^{2,14} It kills cancer by:²

Engaging immune effector cells, causing antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis

- Directly activating intracellular death signaling pathways
- Activating the complement cascade

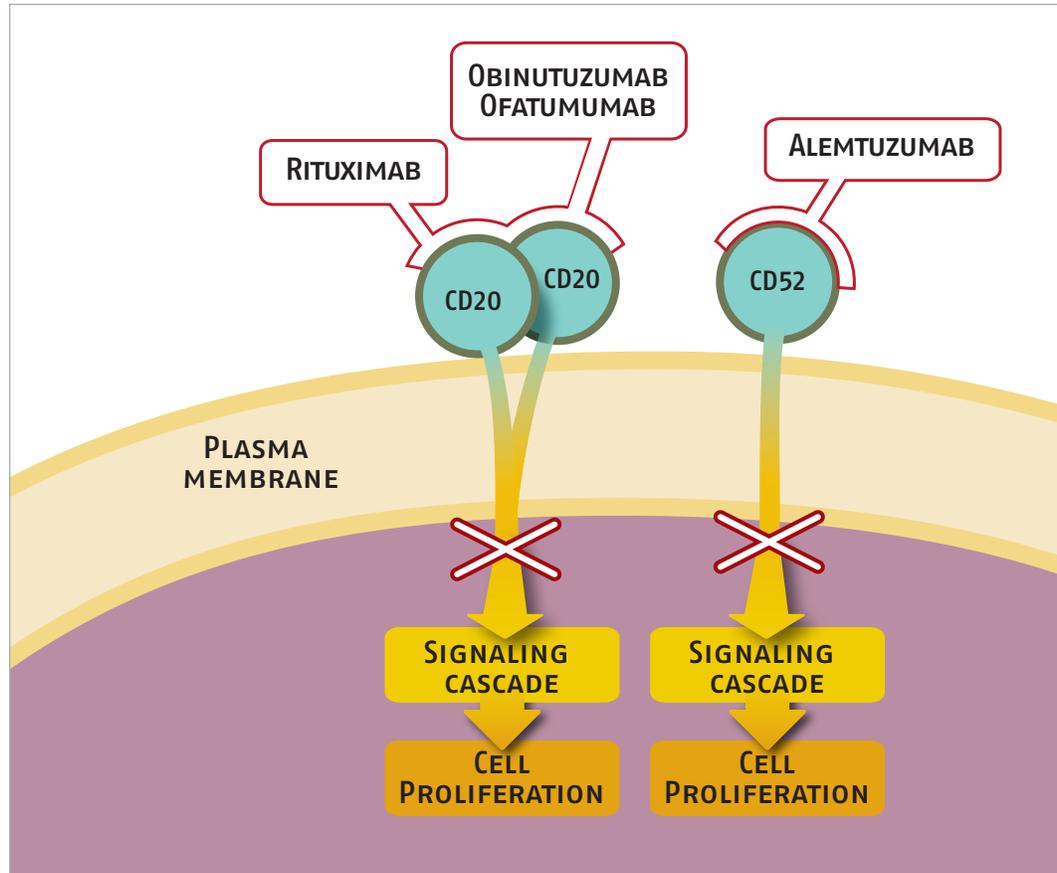
Ofatumumab

This medication targets a distinct epitope than Rituximab on extracellular loops of the CD-20 antigen, a protein on the surface of B-lymphocytes.^{3,15} It is a fully human immunoglobulin (G1 kappa) MoAb. It kills cancer by:³

- Recruiting complement factors and activating the complement pathway to kill cells by lysis (complement-dependent cytotoxicity)
- Targeting cells for destruction by immune cells (antibody-dependent, cell-mediated toxicity)

Rituximab

This medication is a chimeric murine/human MoAb, based on human IgG. It targets the CD-20 antigen, a protein on the surface of B-lymphocytes present in leukemia and lymphoma. The MoAb binds to any CD-20 antigen that it finds – whether cells are normal or abnormal – marking them for death. The immune system then kills the cells in the same way that it kills invading bacteria or viruses. The body naturally produces new, healthy B cells in a few months.^{4,9}



Basic pharmacokinetics

There are no relevant drug-interaction studies for these medications.¹⁻⁴

Presentation, prevention and management of common adverse events

The incidence of adverse events varies from one medication to another. For example, skin rash occurs in 12% of patients treated with alemtuzumab, 15% of those who receive rituximab, and 13% of patients taking ofatumumab. It is not reported as an adverse event of obinutuzumab.^{2,3}

Anti-CD MoAbs are often combined with other anticancer medications, e.g., obinutuzumab and chlorambucil. These combinations may give rise to adverse events that are not associated with anti-CD MoAbs but are attributable to another medication in the chemotherapeutic regimen.

The following table summarizes the common adverse events of anti-CD MoAbs with an overall frequency of $\geq 10\%$ or a $>10\%$ frequency in the combination group versus the control group.¹⁻⁴

Common adverse events of anti-CD monoclonal antibodies

Click on adverse effects highlighted in blue for more information.

Alemtuzumab¹

Blood and lymphatic disorders

- Leukopenia
- Neutropenia
- Thrombocytopenia

Cardiovascular disorders

- Dysrhythmia
- Hypotension

Gastrointestinal disorders

- Nausea

General disorders

- Chills
- Fatigue
- Fever

Infection

- Cytomegalovirus infection
- Cytomegalovirus viraemia
- Upper respiratory tract infection

Psychiatric disorders

- Insomnia

Skin and subcutaneous tissue disorders

- Rash
- Urticaria

Obinutuzumab²

Blood and lymphatic disorders

- Anemia
- Neutropenia
- Thrombocytopenia

Gastrointestinal disorders

- Diarrhea
- Nausea

General disorders

- Fever
- **Infusion reactions**

Laboratory abnormalities

- Hyperkalemia
- Hyponatremia
- Increased creatinine
- Abnormal liver enzymes

Respiratory disorders

- Cough

Ofatumumab³

Blood and lymphatic disorders

- Anemia
- Febrile neutropenia/sepsis
- Neutropenia

Gastrointestinal disorders

- Diarrhea
- Nausea

General disorders

- Chills
- Fatigue
- Fever
- **Infusion reactions**
- Peripheral edema

Infection

- Bronchitis
- Pneumonia
- Upper respiratory tract infection

Musculoskeletal and connective tissue disorders

- Back pain

Respiratory disorders

- Cough
- Dyspnea

Skin and subcutaneous tissue disorders

- Rash

Rituximab⁴

Blood and lymphatic disorders

- Leukopenia
- Neutropenia

Gastrointestinal disorders

- Nausea

General disorders

- Asthenia
- Chills
- Fevers
- Infusion reactions

Immune system disorders

- Angioedema

Infection

- Bacterial infections
- Viral infections

Laboratory investigations

- Decreased IgG levels

Nervous system disorders

- Headache

Skin and subcutaneous tissue disorders

- Pruritus
- Rash

Other adverse events of interest with Anti-CD monoclonal antibodies

Click on adverse events highlighted in blue for more information

- **Infusion reactions (Alemtuzumab, Rituximab)**

Refer for medical attention:¹⁻⁴

Tell patients to seek emergency care if any of these uncommon adverse events develops:

- Patients with abdominal pain, yellowing of skin or eye, and or vomiting
- Delayed infusion reaction (within 24 hours of administration)
- Hematologic abnormalities, including anemia, myelosuppression, neutropenia, thrombocytopenia
- Signs of Infection: fever, cough, pain, (bacterial, fungal, viral, or opportunistic)
- Severe skin reaction
- Confusion, memory loss, difficulty walking, trouble of thinking

◀ Infection (Alemtuzumab)

◀ Infection (Ofatumumab, Rituximab)

Patients on anti-CD MoAb therapy have a weaker immune system due to cancer and their treatments. The incidence of infection varies, depending on the type of treatment, patient's disease status, co-existing medical conditions, number of treatments, and history of prior infection.^{1,2}

Alemtuzumab is generally more toxic to the blood and immune systems than CD-20 antibody, because the CD-52 antigen is more common on immune-cell surfaces.⁸ Alemtuzumab suppresses T cells, and it is associated with opportunistic infections. Patients are usually given preventive therapy and closely monitored for signs of infection.^{1,2} Common adverse events to alemtuzumab usually occur in the first week after therapy begins. Most are generally mild to moderate and tend to improve or resolve as treatment progresses.¹

Rituximab, alemtuzumab, ofatumumab and obinutuzumab may reactivate hepatitis B in patients with a history of infection.^{1,4} Hepatitis B infections have occurred in previously uninfected patients taking ofatumumab.³ Hepatitis screening is mandatory prior to treatment with any of these four agents.^{1,4} In severely immunocompromised patients, often on concomitant chemotherapy, these anti-CD MoAbs may cause bacterial, fungal and opportunistic infections. They may also cause new, exacerbated or reactivated viral infections, such as cytomegalovirus, herpes simplex virus, hepatitis B, hepatitis C, parvovirus B19, varicella zoster virus, and West Nile virus.^{1,4} Patients at high risk of activation may be started on lamivudine, tenofovir or entecavir therapy;¹³ however, these infections are not always eliminated by preventive therapy.^{1,5}

John Cunningham (JC) virus infection, resulting in progressive multifocal leukoencephalopathy (PML), a life-threatening brain condition, may occur in patients treated with rituximab, ofatumumab or obinutuzumab. Advise patients to report new or change in pre-existing symptoms of memory loss, trouble thinking, difficulty walking or loss of vision to their doctor immediately.^{2,4}

Prevention

Physicians, nurses and pharmacists educate patients to recognize the symptoms of common infections, including:¹⁻⁴

- Bacterial infections
- Colds
- Fungal infections
- Urinary tract infections
- Viral infections, such as shingles, herpes virus
- Yeast infections

Antibiotics and antivirals may be prescribed with alemtuzumab or rituximab when combined with fludarabine and cyclophosphamide (R-FC) in primary prophylaxis, but antifungal prophylaxis is not routinely recommended¹⁰

Key facts: Infection

Anti-CD MoAbs also target normal, healthy immune cells, compromising the body's response to infection.^{7,12} The severity of anti-CD MoAb-induced infections ranges from mild to life-threatening.¹⁻⁴ Careful monitoring and management of infections are essential to enable patients to fully benefit from these therapies and improve their chances of survival.¹²

Anti-CD MoAbs may affect the body's ability to respond to live viral vaccines.^{1,10} Patients are usually advised to update their vaccines before therapy begins. Live vaccines for measles, mumps, rubella, yellow fever, and meningitis may be detrimental in these immunocompromised patients.¹⁰ Annual flu vaccination is recommended.¹⁻⁴

Advise patients with general signs of infection to seek medical care:^{6,9}

- Aching muscles
- Cough
- Feeling cold or shivery
- Fever
- Headaches
- Pain when passing urine
- Sore throat

Anti-CD MoAbs may reactivate dormant viruses, such as herpes virus, cytomegalovirus (CMV), hepatitis B and C, Epstein Barr virus, parvovirus, West Nile virus, varicella zoster virus, and even tuberculosis.¹⁻⁴ It may open the door to opportunistic infections, such as *Pneumocystis jiroveci* pneumonia (PJP), aspergilloma, escherichia infection, fungal pneumonia, systemic mycosis, or progressive multifocal leukoencephalopathy (PML) from JC virus infection, in immunocompromised patients.^{3,12}

Common adverse events of alemtuzumab include bacterial, fungal, viral, and protozoan infections.¹ Bacterial infections may appear during the first weeks of therapy and happen less often as treatment continues.⁹ Fungal infections often occur soon after therapy ends.¹² Viral infections, particularly CMV reactivation, typically occur between the third and eighth weeks of therapy then gradually tapers off.¹²

Bacterial, fungal, viral, and opportunistic infections are common in patients on obinutuzumab or ofatumumab.^{3,4} In patients on ofatumumab, lower respiratory tract infections are more common than upper respiratory tract infections.

Primary hepatitis B infection can occur in patients on ofatumumab and fatal outcomes have been reported. In previously infected patients, hepatitis B virus can reactivate in those who receive obinutuzumab, ofatumumab, alemtuzumab, or rituximab.¹⁻⁴ Refer patients with the following symptoms to their doctor for evaluation and treatment:

Abdominal pain

- Feeling sick
- Joint pain
- Loss of appetite
- Tiredness
- Yellowing of skin or eyes (jaundice)

◀ Infusion reactions (Obinutuzumab)

◀ Infusion reactions (Ofatumumab)

Infusion reactions are the most common adverse events.^{1-4,7} They range in severity from mild to life-threatening and vary widely from one patient to another.¹⁻³ Most reactions will occur during infusion or up to 24 hours after infusion. Please refer to other references for detailed information on the management of drug-related infusion reactions.¹⁻⁴

Life-threatening skin reaction

Although rash is a commonly known side effect of rituximab, severe skin reactions can be life threatening. In patients taking rituximab, rash may appear between 1 and 13 weeks after the onset of treatment. Refer any patient who has a severe rash with blistering for emergency care.⁴

Infusion reactions¹⁻⁴

- Up to 10% of patients have hypersensitivity reactions with rituximab.
- Up to 10% of patients treated with alemtuzumab presented a severe infusion reaction.
- Two-thirds of patients react to their first infusion of obinutuzumab.
- About 69% of patients react to one or more infusions of ofatumumab.
- These reactions may occur immediately or up to 24 hours after infusion.
- The risk is greatest during the first few infusions.

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Bcr-Abl Inhibitors

Bosutinib (Bosulif[™])

Dasatinib (Sprycel[®])

Imatinib (Gleevec[®])

Nilotinib (Tasigna[®])

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This chapter contains information on the prevention and management of common adverse events of Bcr-Abl inhibitors that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage the common adverse events of Bcr-Abl inhibitors. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events of these agents, please consult the product monographs.¹⁻⁴

Four oral medications are available that inhibit the action of the Bcr-Abl tyrosine kinase.¹⁻⁴ Their mechanisms of action and adverse events are similar.¹⁻⁴

While these agents may inhibit other tyrosine kinases, the focus of this chapter is Bcr-Abl inhibition and the adverse events that occur in patients who are treated for chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL).



Bcr-Abl in cancer

The primary target of Bcr-Abl inhibitors is the Bcr-Abl, an oncoprotein that is produced by the Philadelphia (Ph) chromosome, a mutated strand of DNA. This chromosome is created when small sections of DNA from chromosomes 9 and 22 switch places, a process known as translocation.⁵⁻⁷

The oncoprotein Bcr-Abl is believed to cause chronic myeloid leukemia (CML). More than 90% of adults with CML and up to 30% of adults with ALL have the abnormal Philadelphia chromosome (Ph+).⁷

Bcr-Abl inhibitors target a tyrosine kinase (TK) on the Abl portion of the oncogene. TKs are essential for normal cell signaling. Inside cells, these enzymes regulate:⁵

- Differentiation
- Function
- Motility
- Proliferation
- Survival

The Bcr-Abl TK activates other signaling proteins within the cell. These proteins in turn trigger other signaling proteins, leading to an expanding cascade of protein activation. The continuous transmission of signals triggers uncontrolled cell growth.⁶

The Bcr-Abl TK uses a phosphate from ATP to activate other signaling proteins. If the ATP binding site is occupied, ATP cannot donate the phosphate and Bcr-Abl cannot activate the signaling proteins that promote cell growth. Bcr-Abl inhibitors target this binding site to inactivate Bcr-Abl tyrosine kinase and prevent the progression of leukemia.⁶

Drug administration

The dosing schedule for these medications depends on disease and stage. Dosing modification is common, based on patient response, adverse events, and concurrent therapy.⁸ Treatment interruptions and non-adherence to these drugs may lead to undesirable clinical outcomes, including a suboptimal therapeutic response.⁸

Bosutinib

This medication is taken once daily – with a meal. Taking it without a meal reduces its effectiveness. The tablets must be swallowed whole and cannot be cut, crushed, or dissolved in a liquid.¹

Dasatinib

This medication is taken once daily – with or without food. The tablets must be swallowed whole. They cannot be cut or crushed.²

Imatinib

Advise patients to take imatinib during a meal with a glass of water, once or twice daily, depending on dosage. Patients unable to swallow the tablets can drop them into a glass of water or apple juice (50 mL for a 100-mg tablet; 200 mL for a 400-mg tablet), stir until they are disintegrated, and drink immediately. Leftover traces must be consumed. Doses greater than 800 mg or doses for children can be divided into 2 equal doses.³

Nilotinib

There are very strict requirements for taking nilotinib. Doses are taken twice daily at 12-hour intervals. Capsules are swallowed whole with a glass of water. Patients take nilotinib on an empty stomach; it must not be taken with food. Patients must not eat for at least 2 hours before taking nilotinib and for at least one hour after taking nilotinib. Patients unable to swallow the capsules can mix the contents into not more than one teaspoon of applesauce and take immediately.⁴

Patients who miss a dose of Bcr-Abl inhibitor should take their next dose as scheduled. They should not take a double dose to make up for the forgotten dose.¹⁻⁴

How to take Bcr-Abl inhibitors

- Take imatinib with food to avoid nausea and vomiting.^{3,6}
- If antacids containing aluminum hydroxide or magnesium hydroxide are needed, they must be taken up to 2 hours before or 2 hours after dasatinib.²
- Nilotinib must be taken on an empty stomach, as food increases its absorption.⁴
- Take bosutinib with a meal, as taking it without a meal reduces its effectiveness.¹
- Use caution when taking acetaminophen (e.g., Tylenol®) with imatinib, because of an increased risk of hepatotoxicity.³
- Avoid grapefruit, star fruit, pomelo, pomegranate, and Seville oranges with any of these drugs.¹⁻⁴
- Nilotinib capsules contain lactose.⁴
- Long-term suppression of gastric acid with stomach ulcer medications reduces systemic exposure to dasatinib and bosutinib.^{1,2,7}

Mechanism of action

These four drugs inhibit cell growth and proliferation and induce cell death.^{3,5}

Bosutinib

This medication is a second-generation TK inhibitor of the oncogenic Bcr-Abl kinase. It also inhibits other kinases, such as the Src-family kinases, including Src, Lyn, and Hck, which participate in Bcr-Abl signaling. It inhibits the proliferation and survival of imatinib-sensitive and imatinib-resistant CML cells. It has minimal activity against PDGFR and c-Kit.^{1,9}

Dasatinib

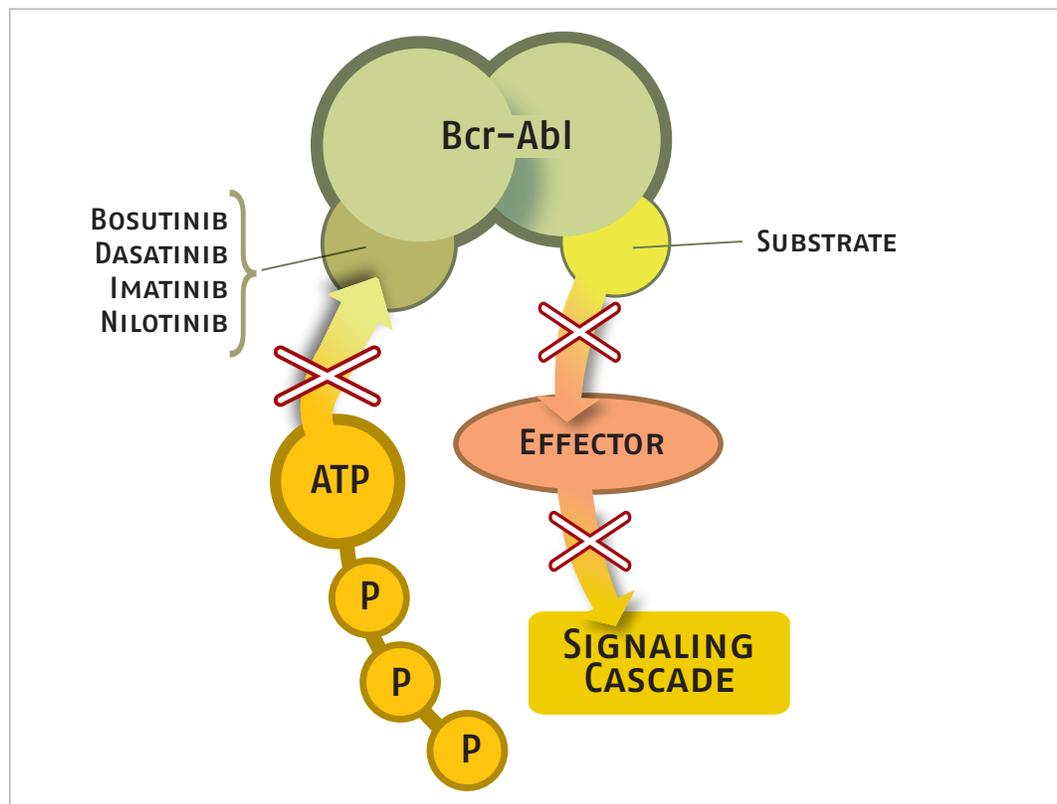
This medication inhibits the TK on Bcr-Abl, along with the src family of kinases and TKs on receptors for c-Kit, ephrin, and PDGF-beta.^{2,7} It may use these alternate signaling pathways to overcome imatinib resistance.⁷ This second-generation TK inhibitor differs structurally from imatinib.

Imatinib

This medication, the first TKI of its class, inhibits the TK on Bcr-Abl. It fills the ATP-binding pocket of Bcr-Abl, neutralizing TK activity. Imatinib also inhibits the receptor TKs for platelet-derived growth factor (PDGF) and cKit, a stem cell factor.³

Nilotinib

This medication is a second-generation TK inhibitor of Bcr-Abl, Kit, PDGFR and ephrin receptor kinase.^{4,7} It disrupts enzymatic activity by adhering to the ATP-binding pocket of the Bcr-Abl TK. Nilotinib is structurally related to imatinib.⁷



Basic pharmacokinetics

Bcr-Abl inhibitors are metabolized via the cytochrome P450 isoenzyme CYP3A4 system in the liver.^{1-4,7} Drugs that are known to induce CYP3A4/5 may decrease plasma concentrations of Bcr-Abl inhibitors, reducing the efficacy of the treatment. If these medications cannot be avoided, strict monitoring for efficacy or toxicity is recommended in patients taking Bcr-Abl inhibitors.⁷

Nilotinib also inhibits CYP3A4, 2C8, 2C9, 2D6, and UGT1A1, increasing the serum levels of medications that are metabolized by these enzymes.⁷ In addition, it induces CYP2B6, 2C8, and 2C9, reducing the serum levels of medications that are eliminated by these pathways.⁷

Imatinib may increase systemic exposure to acetaminophen, at therapeutic doses, through inhibition of acetaminophen O-glucuronidation.²⁴

Presentation, prevention and management of common adverse events

Bcr-Abl inhibitors are generally well tolerated¹⁻⁴ and most adverse events resolve after dosage reduction or drug holiday.⁸ The following tables report adverse events with an overall frequency of $\geq 10\%$ or a $>10\%$ frequency in the combination group versus the control group.

Common adverse events of Bcr-Abl inhibitors

Click on adverse effects highlighted in blue for more information.

Bosutinib¹

Blood and lymphatic disorders

- Anemia
- Leukopenia
- Neutropenia
- Thrombocytopenia

Gastrointestinal disorders

- Abdominal pain
- Anorexia
- **Diarrhea**
- Nausea
- Vomiting

General disorders

- Fatigue

Hepatobiliary disorders

- Elevated transaminases

Nervous system disorders

- Headache

Respiratory disorders

- Respiratory tract infection
- Dyspnea

Skin and subcutaneous disorders

- **Pruritus**
- **Rash**

Dasatinib²

Blood and lymphatic disorders

- Anemia
- Neutropenia
- Thrombocytopenia

Gastrointestinal disorders

- Abdominal pain
- **Diarrhea**
- Dyspepsia
- Nausea
- Vomiting

General disorders

- Asthenia
- Fatigue
- Fever
- **Fluid retention**
- Pain
- Pleural effusion

Infection

- Upper respiratory tract infection

Musculoskeletal and connective tissue disorders

- **Arthralgia**
- **Musculoskeletal pain**
- **Myalgia**
- Thoracic pain

Nervous system disorders

- Dizziness
- Headache

Respiratory disorders

- Cough
- Dyspnea

Skin and subcutaneous tissue disorders

- **Pruritus**
- **Rash**

Vascular disorders

- Hemorrhage

Imatinib³

Blood and lymphatic disorders

- Anemia
- Neutropenia
- Thrombocytopenia

Gastrointestinal disorders

- Abdominal pain
- Anorexia
- Constipation
- **Diarrhea**
- Dyspepsia
- Nausea
- Vomiting

General disorders

- Fatigue
- Fever
- **Fluid retention**
- Weight increased

Hepatobiliary disorders

- Liver toxicity

Infection

- Influenza
 - Nasopharyngitis
 - Sinusitis
 - Upper respiratory tract infection
-

Musculoskeletal and connective tissue disorders

- **Bone pain**
- **Joint pain**
- **Muscle cramps**
- **Musculoskeletal pain**
- **Myalgia**

Nervous system disorders

- Dizziness
- Headache

Psychiatric disorders

- Depression
- Insomnia

Respiratory disorders

- Cough
- Pharyngolaryngeal pain

Skin and subcutaneous tissue disorders

- **Rash**

Vascular disorders

- Hemorrhage

Nilotinib⁴

Blood and lymphatic disorders

- Anemia
- Neutropenia
- Thrombocytopenia

Cardiac disorders

- QT prolongation

Gastrointestinal disorders

- Abdominal pain
- Constipation
- **Diarrhea**
- Nausea
- Vomiting

General disorders

- Asthenia
- Fatigue

Laboratory abnormalities

- Abnormal electrolytes
- Abnormal liver enzymes
- Elevated lipase
- Hyperglycemia

Musculoskeletal and connective tissue disorders

- **Arthralgia**
- **Myalgia**

Nervous system disorders

- Headache

Skin and subcutaneous tissue disorders

- Alopecia
- **Pruritus**
- **Rash**
- Xerosis

Other adverse events of interest with BCR-ABL inhibitors

Click on adverse events highlighted in blue for more information

- **Infection**
- **Myelosuppression**

Refer for medical attention: Bosutinib

Tell patients to seek immediate emergency care if any of these adverse events develops:¹

- Liver problems, such as jaundice (yellowing of skin or eyes) or dark or brown urine
- Gastrointestinal problems, such as abdominal pain, severe diarrhea, nausea, or vomiting and signs of blood in vomit or stool (black, bloody or tarry stool)
- Heart problems, such as dizziness, heart palpitations, or fainting
- Low blood cell counts (fever, severe chills, unexpected bleeding or bruising)
- Fluid retention, which may indicate pleural or pericardial effusion (weight gain, shortness of breath, difficulty breathing, chest pain or other signs of fluid around lungs or heart)
- Bleeding disorders (hemorrhage; unexpected bleeding, no matter how mild)
- Signs of acute pancreatitis (abdominal pain)

Refer for medical attention: Dasatinib

Tell patients to seek immediate emergency care if any of these uncommon adverse events develops:²

- Bleeding disorders (hemorrhage; bleeding or bruising with an injury, no matter how mild)
- Cardiovascular disorders, such as congestive heart failure or pulmonary edema (dizziness, irregular or forceful heartbeat, or fainting)
- Low blood counts (fever, sore throat, weakness, bruising, frequent infections)
- Pleural or pericardial effusion (swelling, weight gain, increased shortness of breath, other signs of fluid around lungs or heart)
- Serious infection (fever, severe chills)

Refer for medical attention: Imatinib

Refer patients to a doctor if any of the following common adverse events develop or become severe:³

- Localised edema (swelling or pain in one part of the body)
- Low blood cell count (weakness; spontaneous bleeding or bruising; frequent infection with sore throat, chills, sore mouth or mouth ulcers)
- Peripheral edema (rapid weight gain, facial swelling or other signs of fluid retention)
- Hematologic disorders (bruising)
- Raynaud's syndrome (cold or numb fingers or toes)
- Urinary tract infection (low urine output, thirstiness)

Tell patients to seek immediate emergency care if any of these uncommon adverse events develop:³

- Acute respiratory failure or pulmonary fibrosis (difficult or painful breathing, cough)
- Cellulitis (acute skin swelling)
- Cerebral edema, increased cranial pressure, stroke (severe headache, weakness or paralysis, seizures, difficulty speaking)
- Difficulty hearing
- Eye disorders (sudden change in eyesight or visual impairment)
- Gastrointestinal disorders (stomach pain, nausea, tarry dark stools or bloody urine)
- Heart disorders (crushing chest pain or irregular heartbeat)
- Lightheadedness, dizziness or fainting
- Liver disorders (yellowing skin or eyes, light-coloured urine, loss of appetite, nausea)
- Potassium imbalance (muscle weakness, muscle spasms, abnormal heart rhythm)

Tell patients to seek immediate emergency care if any of these rare adverse events develop:³

- Avascular necrosis or hip osteonecrosis (painful hips, difficulty walking)
- Inflammatory bowel disease (nausea, diarrhea, vomiting, abdominal pain, fever)
- Low red blood cells (pale skin, fatigue, breathlessness, dark urine)
- Serious skin disorders (severe rash, blistering or peeling skin, raised red or purple skin patches, itchy burning rash)

Refer for medical attention: Nilotinib

Refer patients to a doctor if any of the following adverse events develop or become severe:⁴

- Blood disorders (fever, sore throat, weakness, bruising, frequent infections)
- Eye disorders (Blurred or loss of vision, blood in eye)
- Fluid retention (swelling, weight gain, increased shortness of breath)
- Gastrointestinal disorders (abdominal pain, nausea, vomiting, black stools, constipation, swollen abdomen)
- Hyperglycemia (excessive thirst, high urine output, increased appetite with weight loss, fatigue)
- Kidney problems (Thirst, dry skin, dark urine, low urine output)
- Liver problems (yellow skin or eyes, loss of appetite, light-colored urine, nausea)
- Skin disorders (rash, painful red lumps, joint or muscle pain)

Tell patients to seek immediate emergency care if any of these adverse events develops:⁴

- Blood clots (swelling and pain in one part of body)
- Lung disorders including pleural effusion or pulmonary edema (difficulty breathing, coughing, wheezing, swelling of hands and feet)
- QT interval prolongation or other heart problems, including chest pain, hypertension, irregular heartbeat, palpitations, fainting
- Serious infection, including pancreatitis (fever, severe chills)
- Stroke (weakness or paralysis, headache, difficulty speaking, delusions)

- ◀ **Bone, joint, and muscle pain (Dasatinib)**
- ◀ **Bone, joint, and muscle pain (Imatinib)**
- ◀ **Bone, joint, and muscle pain (Nilotinib)**

About 25% to 50% of patients on imatinib,³ 12% to 35% of patients on dasatinib,² 6% to 8% of patients on nilotinib,⁴ and less than 4.5% of patients on bosutinib¹ develop aching bones or muscles or muscle cramps. Muscle and bone pain is usually mild to moderate and manageable without a reduction of therapy.¹⁰⁻¹²

Prevention	No preventive measures are recommended.
Management	<p>The following measures may provide relief from muscle aches or cramps:^{11,12}</p> <ul style="list-style-type: none"> • Calcium supplements • Magnesium supplements • Mild pain medications (except acetaminophen with imatinib) • Avoid using quinine or drinking tonic water, which contains quinine <p>For mild bone aches and pain:¹²</p> <ul style="list-style-type: none"> • NSAIDs in patients with platelet counts of greater than 100,000/mm³ and no history of GI bleeding

Key facts: Bone, joint, and muscle pain

Muscle cramps usually occur in the hands, feet, calves, or thighs of patients on Bcr-Abl inhibitors. The cramps have been described as sustained muscular contractions. The pattern, frequency, and severity of muscle cramps do not tend to change over time. Muscle cramps may be related to exertion or tend to happen at night. Patients should avoid using quinine or drinking tonic water, which contains quinine.^{11,12}

Patients on Bcr-Abl TKIs can take NSAIDs for muscle and bone pain – as long as their platelet count is normal.¹² In patients on imatinib, use acetaminophen with caution.^{3,24}

Bone and joint pain tends to begin in the first month of therapy and often abates after a few months. Pain usually afflicts the leg bones, hips, and knees and may appear in an asymmetrical pattern.^{11,12}

There are no evidence-based guidelines for prevention or treatment, but anecdotal reports and expert experience have suggested that in some patients the use of mineral supplements may ease pain.^{11,12}

- ◀ Diarrhea (Bosutinib, Dasatinib)
- ◀ Diarrhea (Imatinib)
- ◀ Diarrhea (Nilotinib)

Diarrhea is a very common adverse event of Bcr-Abl inhibitors. It occurs in 81% of patients on bosutinib, up to 45% of patients on dasatinib or imatinib, and up to 22% of patients on nilotinib.¹⁻⁴ Most patients who take bosutinib experience mild to moderate diarrhea.¹³ Dietary modifications are not recommended in anticipation of diarrhea.^{14,15}

Management	<p>OTC therapy¹⁴⁻¹⁶</p> <p>Mild to moderate (less than 4 loose stools per day)</p> <ul style="list-style-type: none"> Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) <p>Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)</p> <ul style="list-style-type: none"> Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea
Replace lost fluids¹⁴⁻¹⁶	<ul style="list-style-type: none"> Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 litres per day Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care¹⁴	<p>Advise patients to:</p> <ul style="list-style-type: none"> Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste Soak in a warm bathtub or sitz bath to relieve discomfort Examine the anal area for red, scaly or broken skin
Diet¹⁴⁻¹⁶	<p>Advise patients to:</p> <ul style="list-style-type: none"> Eat and drink small quantities of food often Avoid spicy, greasy, or fried foods Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve Follow a lactose-free diet Avoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

Most cases of Bcr-Abl inhibitor-induced diarrhea are mild to moderate.^{1-4,8-10} There are no clinical practice guidelines for the management of this adverse event, but experts generally recommend the use of anti-diarrheal medications.^{9,14-16}

When patients seek OTC treatment for diarrhea, it is important to ask them about:¹⁴⁻¹⁶

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Stomach cramps

◀ Fluid retention (Dasatinib)

◀ Fluid retention (Imatinib)

Fluid retention, which usually manifests as periorbital edema, is a common adverse event of imatinib (62% to 72% of patients) and dasatinib (50% of patients) but not nilotinib.^{4,7,10} Bosutinib may cause severe fluid retention in a small percentage of patients.^{1,13}

Prevention	<p>Advise your patients to:¹⁰</p> <ul style="list-style-type: none">• Limit salt intake• Weigh themselves twice weekly <p>For swollen eyelids or swelling around eyes:¹⁰</p> <ul style="list-style-type: none">• Elevate head during sleep
Management	<p>OTC therapy</p> <p>Mild periorbital fluid retention</p> <ul style="list-style-type: none">• For swelling around eyes, elevate the head during sleep or use skin-tightening agents, e.g., topical Preparation H® containing phenylephrine or lanolin (avoid eye contact)¹⁰ <p>Prescribed therapy</p> <p>Mild peripheral fluid retention</p> <ul style="list-style-type: none">• Topical eye ointments with phenylephrine 0.25%¹¹• Topical corticosteroid (e.g., hydrocortisone 1%)¹¹ <p>Moderate fluid retention</p> <ul style="list-style-type: none">• Low-dose loop diuretic, e.g., furosemide. Potassium or magnesium supplements may be necessary¹⁰• Close electrolyte monitoring¹⁰

Key facts: Fluid retention

Peripheral fluid retention

Peripheral fluid retention (edema) is usually superficial and mild to moderate in severity. Its occurrence is dose-related. With imatinib, the most frequent form of fluid retention is swollen eyelids or swelling around the eyes (periorbital edema), which is more pronounced in the morning and often associated with swelling of ankles, feet and lower legs. Periorbital edema is also seen with dasatinib. Peripheral edema (leg) occurs in 50% of patients on dasatinib but happens less often with nilotinib (5% to 11%).¹¹

Peripheral edema tends to improve over time.¹⁰ It occurs more frequently in:^{10,12}

- Women
- Adults over 65 years of age
- Patients with a history of heart or kidney problems

Pleural effusion

Pleural effusion (excess fluid around the lungs) is rare in patients taking imatinib and nilotinib, but it is a common adverse event of dasatinib, occurring in 20% of patients.^{2,7,10,17} It is more common in patients on higher dosages of dasatinib, among patients in the accelerated phase of CML or blast crisis, patients with hypertension, hypercholesterolemia, skin rash, autoimmune disease or a history of cardiac problems.^{7,8,10,17}

This adverse event may occur anywhere from 5 weeks to 1 year after the start of therapy.¹⁷ Patients taking dasatinib must be monitored for the early signs of fluid retention, such as:^{10,17}

- Dry cough
- Shortness of breath
- Tight chest

Early intervention is critical; refer any patient with symptoms of fluid retention to a doctor for immediate care.^{8,10} Advise patients to weigh themselves regularly and report any weight gain ≥ 5 lbs (2.27 kg).¹¹ Central fluid retention in or around the lungs, stomach, central body tissues, heart, lungs, or brain – often associated with rapid weight gain – is potentially life-threatening.¹¹

◀ **Infection (Dasatinib)**

◀ **Infection (Imatinib)**

◀ **Infection (other adverse events)**

Infections are common in patients with CML, who are often immunocompromised and older. Relative to imatinib, infections occur more often in patients who take dasatinib and bosutinib (31% vs 34% and 41%, respectively); however, they occur in less than 5% of patients taking nilotinib. Infections include fungal respiratory tract infections, nasopharyngitis, gastrointestinal infections, urinary tract infections, bacteremia, fungal pneumonia and other opportunistic infections.¹⁻⁴

◀ **Myelosuppression (other adverse events)**

The most common adverse event of Bcr-Abl inhibitors is myelosuppression – the suppression of bone marrow activity, which results in low blood cell counts.^{1-4,10} Signs and symptoms include:^{1-4,18}

- Anemia (fatigue, weakness)
- Thrombocytopenia (spontaneous bleeding or bruising)
- Neutropenia (frequent infections with fever, chills, sore throat or stomatitis).
- Refer any patient who exhibits this constellation of symptoms to an oncologist for immediate evaluation. It is important to refer any patient with a fever due to the risk of neutropenia.

◀ Pruritus (Bosutinib, Dasatinib)

◀ Pruritus (Nilotinib)

Pruritus (itchiness) occurs in 15% to 18% of patients on nilotinib and about 10% of patients who take imatinib. It occurs in about 6.3% of patients taking bosutinib and 5% on dasatinib.¹⁻⁴

Prevention	To prevent dry skin, a common cause of itchiness, advise your patients to: ¹⁹⁻²⁰ <ul style="list-style-type: none">• Use mild soaps that contain no deodorants or fragrance, such as Dove® or Neutrogena®• Frequently apply lotions or bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion• Choose “anti-itch” products• Use liquid shower gels instead of soap	
Management	Mild to moderate pruritus <p>Advise patients to:⁸</p> <ul style="list-style-type: none">• Apply more lotion than usual to help reduce or eliminate itchiness on the trunk or extremities• Use moisturizers or emollients that contain topical corticosteroids, anesthetics (e.g., lidocaine, prilocaine) and menthol²¹• Use lotions with aloe vera or dimethicone, e.g., Moisturel®• Use antidandruff shampoos and conditioners• Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms	Moderate to severe pruritus <p>Refer to doctor for intense, widespread itching</p> <p>Oral antihistamines may provide some relief^{19,21}</p>

Key facts: Pruritus

To break the itch-scratch cycle, patients should cut fingernails short, restrict bath or shower time and use lukewarm water, use a humidifier, wear light clothing, and avoid cleansers with a high pH or that contain alcohol.²¹

- ◀ **Rash (Bosutinib, Dasatinib)**
- ◀ **Rash (Imatinib)**
- ◀ **Rash (Nilotinib)**

Rash often but not always appears soon after the start of therapy. It occurs in about one-third of all patients taking imatinib, about 28% of patients on bosutinib, and has a lower incidence of about 20% in patients on nilotinib and dasatinib.¹⁻⁴

Prevention	<p>A proactive approach is critical in managing rash. When patients begin therapy, advise them to:^{9,19,22}</p> <ul style="list-style-type: none"> • Cleanse with mild soap or hypoallergenic cleaners or shower oils to avoid skin dryness • Take short showers with warm water • Moisturize twice a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or thick, emollient-based creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion • Use only fragrance-, alcohol-, and dye-free lotions and cosmetics. • Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX® • Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove® • Use a broad-spectrum sunscreen (SPF 30 or greater) that contains zinc oxide or titanium dioxide
Management	<p>OTC therapy</p> <p>Mild to moderate rash^{10,11}</p> <ul style="list-style-type: none"> • Oral antihistamine (diphenhydramine) • Topical steroid (hydrocortisone 0.5%) • Coal tar preparations
	<p>Prescribed therapy</p> <p>Moderate to severe¹⁰⁻¹²</p> <ul style="list-style-type: none"> • A short course of oral corticosteroids, with or without topical triamcinolone acetonide 0.1% ointment • Temporary interruption of therapy until resolution of rash with a rechallenge at low dose

Key facts: Rash

Rash is more likely to occur in women and patients on higher doses.¹⁰ In the most common rash, skin spots and bumps appear on the forearms, trunk, and, sometimes, the face. They are often itchy, and with scratching, may become infected and crusty. This generalized rash is usually mild, and most cases are self-limited – have a natural lifespan.^{11,12} Rash may worsen after sun exposure.¹¹

Early recognition of rash symptoms, a prompt start of symptomatic therapy, and if necessary, withdrawal of the Bcr-Abl inhibitor are the mainstays of treatment.^{8,10} Mild to moderate symptoms are managed while the patient remains on therapy.^{10,11} Refer any patient with a severe rash to a doctor for evaluation and treatment.¹⁰

Unlike allergic rashes, Bcr-Abl inhibitor-induced rash may not recur when a medication is restarted at a lower dose after a temporary suspension of therapy.¹⁰ Patients who develop a rash on imatinib do not appear to have a recurrence on dasatinib.¹⁷

Lansoprazole may increase the dermatological toxicity of imatinib.⁹

Skin or hair colour changes with Imatinib
A small percentage of patients on imatinib may experience a repigmentation of grey hair.^{19,23}

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BRAF Inhibitors

Dabrafenib (Tafinlar™)

Vemurafenib (Zelboraf®)

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This chapter contains information on the prevention and management of common adverse events of BRAF inhibitors (BRAFI) that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage BRAFI-induced adverse events. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of adverse events, please consult the product monograph.^{1,2}

BRAF inhibitors block the biological activity of serine-threonine residues in the BRAF protein, a kinase in the MAPK signalling pathway. They may also inhibit other kinases on the MAPK or other signalling pathways inside cells.¹⁻⁷ A validated test is required to identify BRAF V600 mutation status.^{1,2}



BRAF in cancer

In about 50% to 60% of lethal skin cancers, mutations spontaneously occur in the BRAF protein, a member of the RAF family of cell-signaling enzymes, possibly due to sun damage. The BRAF protein lies along the MAPK signaling pathway within cells. Enzymes along the pathway act like a series of switches that are tripped on in response to growth factor signals from outside cells. The BRAF switch is regulated by serine-threonine kinase activity.¹⁻⁶

Extracellular signals from growth factors stimulate RAS family proteins inside cells to recruit RAF family proteins to the cell membrane. They recruit MEK family proteins downstream, which in turn recruit ERK proteins to activate cell growth, differentiation, and survival.⁴⁻⁶

Up to 90% of BRAF mutations result from a single change in an amino acid at DNA codon 600 – the substitution of valine for glutamic acid.³⁻⁵ This mutation is known as oncogenic activating V600E mutation or BRAFV600E. It causes the constitutive activation of the MAPK signalling pathway to:¹⁻⁶

- Promote cell growth and proliferation
- Prevent apoptosis
- Promote cancer cell survival
- Promote carcinogenesis

Drug administration

Dabrafenib

Dabrafenib is an oral medication that is taken twice daily consistently on an empty stomach – at least one hour before or at least two hours after a meal. Food reduces the absorption and effectiveness of this medication. Patients must leave an interval of 12 hours between doses and take them at similar times every day. Patients should swallow the capsules whole with water, one after the other.¹ If a dose is missed, it should not be taken if it is less than 6 hours until the next dose.¹

Vemurafenib

Vemurafenib is an oral medication that is taken twice daily consistently with or without food. Patients should swallow tablets whole with a glass of water. They should never be chewed or crushed.² If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. Both doses should not be taken at the same time.¹

How to take BRAF inhibitors

Advise patients who miss a dose of dabrafenib that it can be taken up to 6 hours before their next scheduled dose.¹

Avoid grapefruit, star fruit, pomelo, pomegranate, and Seville oranges with these drugs

Advise patients to avoid the concomitant use of vemurafenib with the following products, as it can potentiate their effect:²

- Coffee
- Dextromethorphan

Mechanism of action

BRAF inhibitors are small molecules that directly inhibit the activity of serine-threonine kinases on the BRAF oncoprotein.¹⁻⁶ They may also inhibit other kinases (enzymes or proteins) along the MAPK and other signaling pathways within cells. They block ATP binding sites on kinases to prevent phosphorylation, shutting down cell-signal transmission.^{1,2,4}

Dabrafenib

Dabrafenib is a highly selective, new-generation, BRAF inhibitor that is less active against wild-type and other RAF kinases. This medication inhibits mutant BRAF V600E as well as V600D/K and V600G kinases. Like vemurafenib, it is a type/class 1, ATP-competitive RAF inhibitor that binds to the active conformation of the kinase.^{1,8,9}

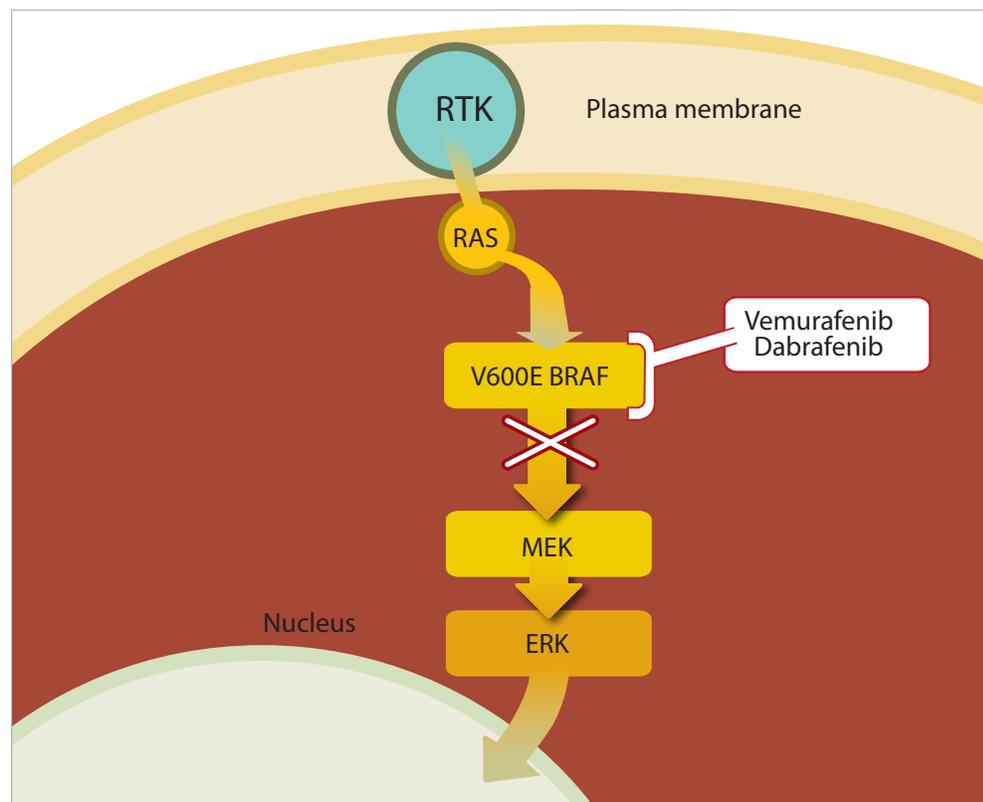
Vemurafenib

A selective BRAF inhibitor, vemurafenib inhibits the abnormal activity of serine-threonine kinases on some mutated forms of BRAF, notably BRAFV600E.² It also inhibits the CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, and FGR kinases.² This small molecule binds to ATP sites on kinases to interrupt abnormal cell signaling.⁴ By blocking this site, it prevents the biological activation of downstream enzymes on the MAPK signaling pathway.²⁻⁶

Vemurafenib and dabrafenib:¹⁻⁵

Inhibit abnormal signaling

- Disrupt abnormal cell growth and proliferation
- Induce cell death
- Inhibit carcinogenesis



Basic pharmacokinetics

Dabrafenib

The metabolism of dabrafenib is primarily mediated by the CYP2C8 and CYP3A4 pathways in the liver. It is a CYP3A4 inducer and possibly an inducer of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and glucuronide conjugating enzymes (UGTs). This medication is likely to decrease the effectiveness of and, in some cases, increase toxicities related to drugs sensitive to induction by these substrates¹.

Dabrafenib should be used with caution with medicinal products that prolong the QTc interval or are able to induce torsades de pointe.¹ Combining this drug with warfarin, hormonal contraceptives or dexamethasone may result in a loss of their efficacy. Caution is recommended when co-administering dabrafenib with statins.¹

Vemurafenib

Vemurafenib is metabolized primarily by the CYP3A4 pathway in the liver.^{2,4} It is a CYP3A4 inducer, moderate CYP1A2 inhibitor, and weak CYP2D6 inhibitor.² It inhibits the CYP2C9 pathway, which may potentially impact the use of warfarin. Vemurafenib increases the AUC of caffeine, a CYP1A2 substrate, by 2.6 fold and the AUC of dextromethorphan, a CYP2D6 substrate, by 47%.² Co-administration reduces the clearance of warfarin, resulting in a mean increase of 23% in AUCinf.¹

Vemurafenib causes QTc prolongation, and concomitant use of anti-arrhythmic drugs and medications that prolong the QTc interval should be avoided.¹

Presentation, prevention and management of common adverse events

BRAF inhibitors are generally well tolerated with low rates of moderately severe to severe adverse events.^{1,4,8} Patients who take these medications may need a drug holiday, dosage modification or discontinuation to manage troublesome adverse events.^{1,4}

The following table summarizes the common adverse events (overall frequency of $\geq 10\%$) of selective BRAF inhibitors.

Common adverse events of selective BRAF inhibitors

Click on adverse effects highlighted in blue for more information

BRAF inhibitors^{1,2}

Gastrointestinal disorders

- Abdominal pain (vemurafenib)
- Constipation
- **Diarrhea**
- Nausea
- Vomiting

General disorders

- Asthenia
- Chills (dabrafenib)
- Fatigue
- **Fever**
- Fluid retention (vemurafenib)

Laboratory abnormalities

- **Hyperglycemia** (dabrafenib)
- Hypophosphatemia (dabrafenib)
- Increased alkaline phosphatase (dabrafenib)

Metabolism and nutrition disorders

- Decreased appetite

Musculoskeletal and connective tissue disorders

- **Joint Pain** (arthralgia)
- Myalgia
- Pain in extremities

Neoplasms (incl. cysts and polyps)

- **Cutaneous squamous cell carcinoma**
- Skin papilloma

Nervous system disorders

- Headache
- Taste disturbance (vemurafenib)

Respiratory disorders

- Cough

Skin and subcutaneous tissue disorders

- Actinic Keratosis (vemurafenib)
- Alopecia
- **Hyperkeratosis**
- Erythema (vemurafenib)
- Hand-foot skin reaction (dabrafenib)
- **Photosensitivity reaction** (vemurafenib)
- **Pruritus** (vemurafenib)
- **Rash**
- Seborrhoeic keratosis (vemurafenib)
- Sunburn (vemurafenib)
- Xerosis

Other adverse events of interest with BRAF inhibitors

Click on adverse events highlighted in blue for more information

- **Eye problems**
- **Hypersensitivity reactions**
- **QT prolongation**

Refer for medical attention: dabrafenib

Refer patients to a doctor if any of the following common adverse events develop or become severe:¹

- Suspicious skin lesions (new warts, skin sore or reddish bump that bleeds and does not heal, mole that changes in size or colour)
- Uveitis and other eye problems (particularly painful red eye that does not clear quickly, vision changes, light sensitivity, eye pain, floating spots, blurred vision)

Tell patients to seek immediate emergency care if any of these uncommon adverse events develop:¹

- Any symptoms of high blood sugar or worsening diabetes (frequent urination, dizziness, fatigue, confusion)
- Any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations, fainting or seizures
- Unexplained abdominal pain or other signs of pancreatitis
- High fever or any fever with complications (rigors, dehydration, hypotension or renal failure)

Refer for medical attention: vemurafenib

Refer patients to a doctor if any of the following common adverse events develop or become severe:¹

- Suspicious skin lesions (new warts, skin sore or reddish bump that bleeds and does not heal, mole that changes in size or colour)
- Uveitis and other eye problems (redness, light sensitivity, pain, swelling, blurry vision, floaters, vision changes)

Tell patients to seek immediate emergency care if any of these uncommon adverse events develop:²

- Liver problems (yellowing of skin or eyes, upper right quadrant pain)
- Hypersensitivity reactions (generalized rash or redness, feeling faint, trouble breathing or swallowing, fast heartbeat, swelling of face, lips or tongue, throat tightness or hoarseness)
- Severe skin reactions associated with fever (skin blistering, blisters or sores in mouth, redness and swelling of face, hands or soles of feet, sunburn)
- Any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations, fainting or seizures

◀ Diarrhea

Diarrhea occurs in about 28% of vemurafenib-treated patients and about 14% of dabrafenib-treated patients.^{1,2}

Management OTC therapy ¹⁰⁻¹³	Mild to moderate (less than 4 loose stools per day) <ul style="list-style-type: none">Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) Moderate (more than 4 to 6 loose stools per day) <ul style="list-style-type: none">2 tablets immediately, then 1 tablet every 2-4 hours until bowel movements are normal for at least 12 hours
Replace lost fluids ¹⁰⁻¹³	<ul style="list-style-type: none">Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 litres per day.Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care ¹⁰	Advise patients to: <ul style="list-style-type: none">Clean the anal area with mild soap and warm water after each bowel movement to prevent irritationApply a barrier cream or ointment, such as petroleum jelly or Isle's pasteSoak in a warm bathtub or sitz bath to relieve discomfortExamine the anal area for red, scaly or broken skin
Diet ¹⁰⁻¹³	Advise patients to: <ul style="list-style-type: none">Eat and drink small quantities of food oftenAvoid spicy, greasy, or fried foodsFollow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolveFollow a lactose-free dietAvoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

There are no evidence-based guidelines for the prevention or treatment of diarrhea in patients taking BRAF inhibitors. Antidiarrheal medications are usually able to control this dose-related adverse event.^{4,13}

- If mild to moderate diarrhea persists for 48 hours, despite dietary modification and loperamide, a second-line agent may be needed for control. Advise the patient to seek immediate medical attention.^{4,13}

When patients seek OTC treatment for diarrhea, it is important to ask them about:¹⁰⁻¹³

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Stomach cramps

◀ Eye problems

Although uncommon, uveitis may occur in patients taking vemurafenib or dabrafenib.^{1,2} If untreated, uveitis can lead to vision loss. Treatment is steroid and mydriatic ophthalmic drops.

Other uncommon eye problems are blurry vision, iritis and light sensitivity. A rare adverse event is retinal vein occlusion.^{1,2} Patients should watch for the following signs and symptoms and see a doctor right away if they develop:

- Blurry vision
- Eye pain, redness or swelling
- Vision changes

◀ Fever

Dabrafenib may cause febrile drug reactions in about 30% of patients; 5% may experience serious adverse events, including severe rigors or chills, dehydration, hypotension, or renal failure. Treatment should be interrupted if the patient's temperature reaches $\geq 38.5^{\circ}\text{C}$, and the patient should be evaluated for signs or symptoms of infection. The median time to onset of febrile events is 3 weeks but it may occur at any time. After the febrile event, treatment can be resumed in conjunction with prophylactic antipyretic medication. Dose reduction or interruption may be required.¹

When dabrafenib is combined with trametinib, some evidence suggests that, while antipyretics effectively manage an initial bout of fever, they are ineffective for recurrent fevers, which may occur in nearly 80% of previously affected patients. The median time to fever recurrence was 25 days after restarting therapy. Corticosteroids were more effective in treating and preventing fever recurrence.¹⁴

◀ Hyperkeratosis

Hyperkeratosis is a thickening of the outermost layer of skin (stratum corneum). It is one of the most common adverse events of BRAF inhibitors, occurring in 24% to 30% of patients taking vemurafenib and 39% of patients on dabrafenib.¹ Skin lesions often present as smooth, raised, solid pimples, warts, or dome-shaped skin lesions, topped with scales or debris. So far, these lesions have not been cancerous.⁸

Plantar hyperkeratosis (thickening of the sole of the foot) occurs in 9% to 21% of patients treated with BRAF inhibitors. Distinct from hand-foot skin reaction, this thickening typically occurs at friction and pressure points on the sole. Blisters are infrequent and the hands are rarely involved.⁸

Management

Hyperkeratosis^{1,2,8}

- Systemic retinoids may reduce the number of hyperkeratotic lesions; doctor may refer patient to dermatologist for cryotherapy to remove lesions.⁸

Plantar hyperkeratosis⁸

- Regular use of urea creams (Uremol®)
- Advise patients to avoid friction on pressure points of soles

◀ Hyperglycemia

Unlike vemurafenib, dabrafenib may cause moderately severe high blood sugar levels in about 5% of patients, particularly those with diabetes. These patients should routinely monitor themselves for changes in blood sugar levels and be followed with regular laboratory testing. Other patients should watch for signs of diabetes, such as dizziness, frequent urination, or fatigue.¹

◀ Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported. One case of hypersensitivity reaction with rash, fever, rigors and hypotension happened 8 days after starting vemurafenib. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), generalized rash, erythema or hypotension. In patients who have severe hypersensitivity reactions, vemurafenib is permanently discontinued. Hypersensitivity reactions are less common in patients who take dabrafenib.^{1,2}

◀ Joint pain

More than half of patients on vemurafenib and one-third of patients on dabrafenib develop joint pain.^{1,2} About 18% of patients on vemurafenib feel pain in their extremities and 13% have muscle pain, aches or cramps.^{1,2} Among patients on dabrafenib, 13% experience muscle pain and 13% have pain in their extremities.¹

There are no evidence-based guidelines for prevention or treatment of BRAF-induced joint pain. A dosage reduction or temporary drug holiday may help to relieve or reduce joint pain.^{1,2} The patient's doctor may prescribe pain medication. No preventive measures are recommended.

◀ Photosensitivity

Photosensitivity reactions often occur with vemurafenib, affecting up to half of all patients exposed to ultraviolet A (UVA) rays. Up to 12% develop a moderately severe sunburn.^{2,15} These reactions are uncommon with dabrafenib, occurring in only 3% of patients.⁸

Prevention

A proactive approach is critical for the prevention of sunburn reactions. When patients begin therapy, advise them to STRICTLY avoid sun exposure and:^{2,8,9,16}

- Use a broad-spectrum sunscreen (SPF of 30 or more) that protects against UVA rays and contains UVA filters all day long, inside or outside. Wear protective clothing, including a hat, to cover the head, face, arms, legs, hands and feet.
- Remind patients that UV rays go through glass (e.g., house or car windows)

Key facts: Photosensitivity reactions

There are no evidence-based guidelines for the treatment of vemurafenib-induced photosensitivity reactions.²

Preventive therapy is recommended to avoid photosensitivity reactions.² Advise patients to avoid sun exposure while taking vemurafenib. If impossible, when in the sun, they must wear protective clothing, including hats, gloves and arm, leg and foot coverings. The use of sunscreen is mandatory. Patients should use lip balm and a broad-spectrum sunscreen (SPF of 30 or more) that contains a UVA filter.^{2,15,16}

Some patients on vemurafenib have a severe sunburn reaction with painful blistering. This reaction may interfere with daily outdoor activities.^{4,16} Some patients experience sunburn reactions through glass while driving.¹⁴ Exposure to UVA rays appears to be responsible for photosensitivity reactions.¹⁶

◀ Pruritus

Pruritus (itchiness) is a common adverse event of vemurafenib but not dabrafenib.^{1,2} Nearly 1 in 4 patients taking vemurafenib develop dry, itchy skin.² Pruritus may be associated with xerosis or rash or appear on its own. In patients on dabrafenib, pruritus is sometimes associated with Grover's disease, a benign acantholytic disorder, which presents as several scattered erythematous papules, some eroded, usually on the upper arms and trunk with varying degrees of itchiness.^{8,15}

Prevention	<p>To prevent dry skin, a common cause of itchiness, advise your patients to:^{4,15,17,18}</p> <p>Use mild soaps that contain no deodorants or fragrance, such as Dove® or Neutrogena®</p> <ul style="list-style-type: none">• Frequently apply lotions or bland, alcohol-free emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion• Topical antipruritics with pramoxine 1%, such as Polysporin® Itch Relief, either alone or in combination with a topical corticosteroid in an alternating schedule• Wear loose-fitted clothing• Take lukewarm showers and pat skin dry• Cut fingernails short to minimize damage from scratching• Use liquid shower gels instead of soap	
Management	<p>Mild to moderate pruritus</p> <p>Advise patients to:⁸</p> <ul style="list-style-type: none">• Apply more lotion than usual to help reduce or eliminate itchiness on the trunk or extremities• Use lotions with aloe vera or dimethicone Moisturel®• Use antidandruff shampoos and conditioners• Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms• Cold compresses, oatmeal baths <p>Medical management¹⁵</p> <ul style="list-style-type: none">• Medium (triamcinolone 0.1 %) or high strength (clobetasol 0.05 %) topical corticosteroids applied twice daily to affected skin.• Alternatively, topical antipruritics (pramoxine 1 %) may be used twice daily either alone or in combination with topical corticosteroids in an alternating schedule.• Non-sedating oral antihistamines or second-generation anti-H1 antihistamines (e.g., cetirizine, loratadine, desloratadine)	<p>Moderate to severe pruritus</p> <p>Refer to doctor for intense, widespread itching</p> <p>Oral first-generation anti-H1 antihistamines (e.g., diphenhydramine, hydroxyzine) may provide some relief^{4,18,19}</p>

Key facts: Pruritus

Pruritus or itchiness is the consequence of loss of skin moisture.²⁰ In patients treated with vemurafenib, it is usually associated with rash.² It may be disruptive during sleep or waking hours.¹⁹ Preventive therapy is recommended to reduce the incidence and severity of pruritus. Counsel patients to avoid excess exposure to sunlight and to use a broad-spectrum sunscreen that contains UVA filters, such as titanium dioxide, and has an SPF of 30 or more.^{4,15,19}

◀ QT prolongation

BRAF inhibitors can prolong the QT interval. Patients who take drugs that prolong the QT interval or drug that may cause torsade de pointes or have uncorrectable electrolyte abnormalities should not take these drugs.² Women and people over 65 years of age are at higher risk of this adverse event.^{1,2}

◀ Rash

Rash is a common adverse event of vemurafenib.² It occurs in about 37% of vemurafenib-treated patients, about 8% of whom may develop a moderately severe rash.² It occurs commonly but less often and with less severity in patients taking dabrafenib; 18% develop mild to moderate rash.¹ Up to 27% of patients taking dabrafenib develop Grover's disease.^{1,8} It occurs in patients taking vemurafenib with unknown frequency.⁸

Prevention

A proactive approach is recommended to prevent rash. When patients begin therapy, advise them to:^{4,15,17,18,21}

Use a broad-spectrum sunscreen (SPF of 30 or more) that contains zinc oxide or titanium dioxide¹

- Moisturize two to three times a day with a colloidal oatmeal lotion, such as Aveeno[®] lotion, or with thick, alcohol-free emollient creams, such as Neutrogena[®] Norwegian Formula hand cream, or Vaseline Intensive Care[®] Advanced Healing Lotion; ceramide-containing moisturizers may be particularly effective (e.g., Curel[®], Cerave[®], Cutibase[®], Ceramyd[®], EpiCeram[®])
- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness
- Take oatmeal baths (e.g., Aveeno[®])
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics

Management

Mild to moderate^{8,15}

If no relief occurs from the use of topical moisturizers after 1 week, medium-strength topical corticosteroids (e.g., triamcinolone 0.1 %), except in intertriginous regions where low potency topical corticosteroids (e.g., desonide 0.05 %) or topical calcineurin inhibitors (tacrolimus 0.1%) may be used.

- If no improvement after 2 weeks of treatment, high-potency topical corticosteroids (e.g., clobetasol 0.05 %) may be substituted, except in intertriginous regions. Alternatively, oral corticosteroid therapy (e.g., prednisone) may be initiated at 0.5–1 mg/kg dose per day and tapered over 2–3 weeks.
- Topical moisturizers should be maintained.
- In addition to topical moisturizers, Grover's disease is managed with oral antihistamines, intermittent oral prednisone, and acitretin.⁸

Key facts: Rash

Preventive therapy is recommended to reduce the incidence of severe skin rashes.⁴ Patients should avoid exposure to sunlight and use a broad-spectrum sunscreen that contains UVA filters, such as titanium dioxide, and has an SPF of 30 or more.^{4,15}

There are no evidence-based guidelines for the treatment of BRAF inhibitor-induced rash. Early recognition of symptoms and a prompt start of symptomatic therapy are the mainstays of treatment. Mild to moderate symptoms are managed while the patient remains on therapy.^{2,4,15}

If necessary, patients on vemurafenib may have to stop therapy until a severe rash resolves. Refer any patient who develops a severe rash to a doctor for evaluation and treatment.^{2,4}

◀ Skin cancer

From 1% to 2% of patients taking BRAF inhibitors develop new primary melanoma.^{1,2} This adverse effect occurs because of paradoxical activation of MAP kinase pathways.⁸ New skin cancers are usually removed surgically and do not prevent patients from continuing therapy.^{1,2}

Management

Routine monitoring for cutaneous squamous cell carcinoma^{1,2,8,22}

Patients taking BRAF inhibitors should have a thorough dermatological examination at baseline and regular follow-up to monitor for the development of new skin lesions. Advise patient to monitor for signs of suggestive of skin cancer and to report any of the following suspicious skin lesions to their doctor:

Moles that change in colour or size

- New warts or skin lesions (hyperkeratosis)
- Reddish bumps that bleed and have trouble healing

Key facts: Skin Cancer

Type/class 1 BRAF inhibitors promote the growth of cutaneous squamous cell carcinoma (SCC).^{1,7-9} Up to 24% of patients who take vemurafenib and up to 11% of patients who take dabrafenib develop SCC.^{1,2,7} This adverse effect usually occurs early in treatment with a median time to first appearance of 7 to 9 weeks.¹ About one-third of patients develop subsequent lesions.¹

Risk factors for the development of SCC include age ≥ 65 years, prior skin cancer, and chronic sun exposure. SCC is usually treated by surgical removal.^{1,2} Patients should have a dermatologic evaluation before therapy as well as routine monitoring while on therapy and for 6 months after therapy ends.^{1,2}

The risk of developing SCC decreases sharply when a BRAF inhibitor is used in combination with MEK inhibitors (e.g., dabrafenib and trametinib, vemurafenib and cobimetinib). The skin tumors develop owing to a paradoxical activation of the MAPK pathway in keratinocytes with upstream activation of signaling by pre-existing RAS mutations, which can be blocked with the addition of a MEK inhibitor.^{1,2}

Suspicious skin lesions

Up to 39% of patients on dabrafenib and 24% of patients taking vemurafenib develop hyperkeratosis. Advise patients to report any of the following suspicious skin lesions to their doctor:^{1,2}

- Moles that change in colour or size
- New warts or skin lesions (hyperkeratosis)
- Reddish bumps that bleed and have trouble healing

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Bruton's tyrosine kinase inhibitors

Ibrutinib (Imbruvica™)

This chapter contains information on the prevention and management of common adverse events of Bruton's kinase inhibitors (BKIs) that you are likely to encounter among cancer patients in your practice.

To date, one medication is available that inhibits Bruton's tyrosine kinase (BTK). There are no evidence-based guidelines on how to manage the adverse events of therapy with a Bruton's tyrosine kinase inhibitor. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events of these agents, please consult the product monograph.¹



BTK inhibitors in cancer

B cells send antibodies, which target foreign invaders, into the body's lymphatic system to fight cancer.

Bruton's tyrosine kinase (BTK) is an enzyme that chemically activates specific substances on B-cell antigen receptors and cytokine receptor pathways. BTK is a member of the src-related BTK/Tec family of tyrosine kinases that are released into the cytoplasm. This signaling molecule plays key roles in B-cell maturation, migration, and adhesion.^{1,2}

BTK is overexpressed in a number of B-cell cancers. When cancerous B-cells overproduce BTK, they switch on their ability to mature, migrate, and adhere to other cells. The expression of BTK in tumor cells increases tumour proliferation, migration and survival.^{1,2}

Drug administration

Ibrutinib

Ibrutinib is an oral medication, taken once daily, with a glass of water at the same time every day, with or without food.¹ Capsules should not be opened, crushed or chewed.

How to take bruton kinase inhibitors

Avoid the concomitant use of strong and moderate CYP3A inhibitors and CYP3A inducers with ibrutinib.¹

If short-term treatment with a CYP3A inhibitor is necessary, ibrutinib therapy must be interrupted.¹

If a moderate CYP3A inhibitor must be used, the dosage of ibrutinib should be reduced to 140 mg for the duration of CYP3A inhibitor use.¹

Alternative agents with less CYP3A induction should be recommended to replace strong CYP3A inducers, which can reduce the plasma exposure of ibrutinib by approximately 10-fold.¹

While taking ibrutinib, advise patients to avoid:¹

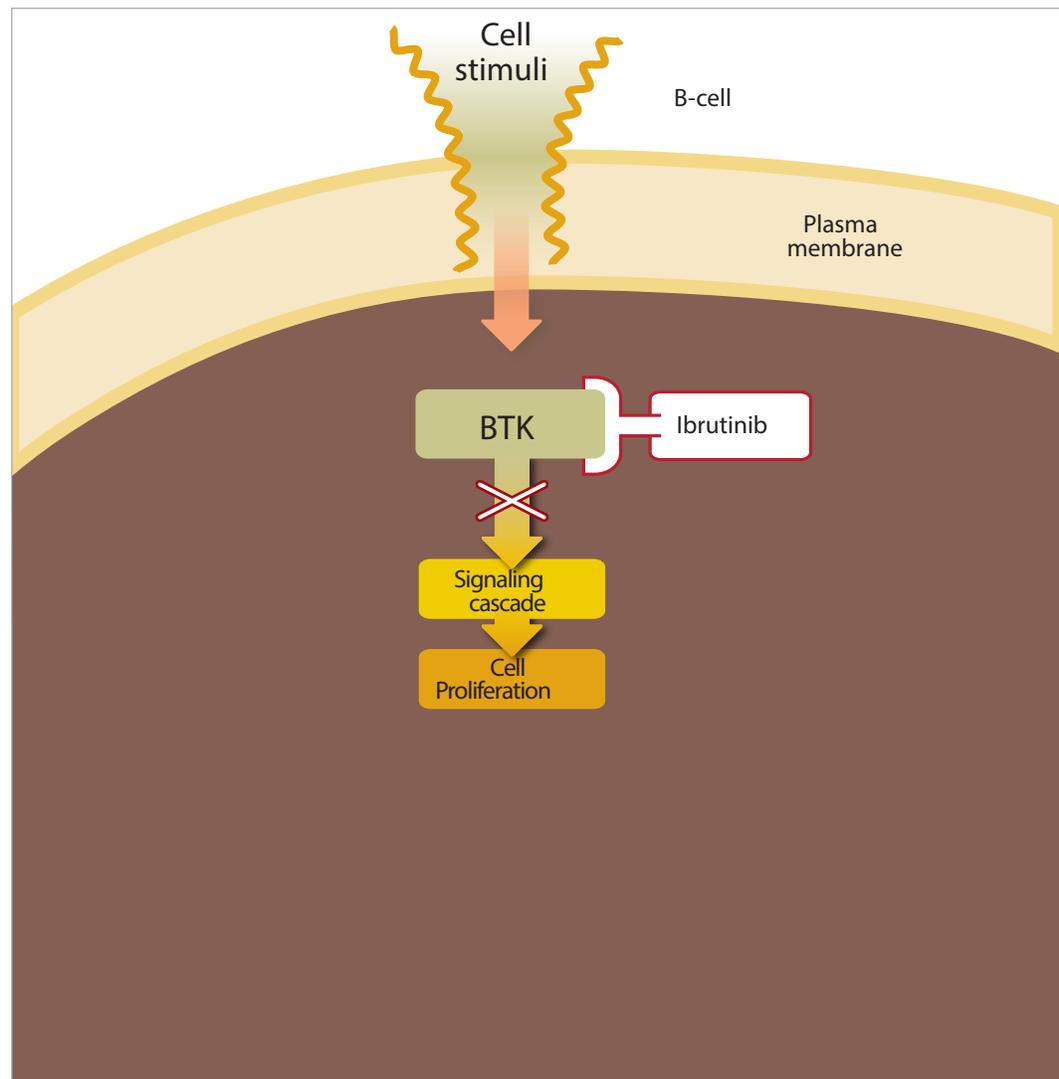
- Grapefruit, star fruit, pomelo, pomegranate and Seville oranges (moderate CYP3A inhibitors)
- St. John's wort (strong CYP3A inducer)

Driving or operating machinery

Fatigue, dizziness and asthenia are very common adverse events in ibrutinib-treated patients. Advise patients to use caution when driving or operating machinery.¹

Mechanism of action

Ibrutinib is a small-molecule drug that inhibits BTK activity. As a selective, irreversible BTK inhibitor, it prevents both B-cell activation and B-cell-mediated signaling. It inhibits the growth of cancerous B cells that overexpress BTK. Ibrutinib restricts cancerous B-cell proliferation and survival as well as cell migration and adhesion.¹



Basic pharmacokinetics

Ibrutinib is primarily metabolized by cytochrome P450 CYP3A4/5. It should not be used with strong CYP3A4/5 inhibitors or inducers. Caution must be exercised when it is prescribed with moderate CYP3A4/5 inhibitors and CYP3A4/5 inducers, which increase or reduce drug levels in blood, respectively. Ibrutinib also inhibits P-glycoprotein (PgP) and breast cancer resistant protein (BCRP). It may alter the absorption of drugs that are PgP and BCRP substrates. It is a weak inhibitor of other P450 substrates and unlikely to lead to clinically relevant interactions with these drugs.¹

Presentation, prevention and management of common adverse events

The following table summarizes the common adverse events of ibrutinib with an overall frequency of $\geq 10\%$.

Common adverse events of BTK inhibitors

Click on adverse effects highlighted in blue for more information

Ibrutinib¹

Blood and lymphatic system disorders

- Anemia
- Neutropenia
- Thrombocytopenia

Eye disorders

- Blurred vision

Gastrointestinal disorders

- Constipation
- **Diarrhea**
- Nausea
- Stomatitis
- Vomiting

General disorders

- Fever

Infection

- Pneumonia
- Sinusitis
- Upper respiratory tract infection
- Urinary tract infection

Musculoskeletal and connective tissue disorders

- Arthralgia
- Musculoskeletal pain

Nervous system disorders

- Dizziness
- Headache

Skin and subcutaneous tissue disorders

- Bruising
- Petechiae
- **Rash**

Other adverse events of interest with BTK inhibitors

Click on adverse events highlighted in blue for more information

- **Hemorrhage**
- **Lymphocytosis**
- **Myelosuppression**

Refer for immediate medical attention

Refer patients to their doctor if any of the following adverse events develop or become severe: ¹

- Gastrointestinal symptoms (diarrhea, nausea, sore mouth, vomiting, constipation)
- Fever, chills or other signs and symptoms of infection
- Rash, bruising and purple or red spots indicating bleeding under skin
- Headaches or dizziness
- Aching muscles or joints

Tell patients to seek immediate emergency care if any of these adverse events develop: ¹

- Hemorrhage (major bleeding events, blood in stool or urine, prolonged or uncontrolled bleeding)
- Signs of allergic reaction (hives, difficulty breathing, swelling of face, lips, tongue or throat)
- Signs of tumour lysis syndrome (abnormal heartbeat, changes in kidney function, seizures)
- Signs of severe infection (e.g., fever or chills, sore throat, chest congestion, cough, shortness of breath, burning while urinating)

◀ Diarrhea

Diarrhea is a common adverse event of ibrutinib, occurring in almost half (48%) of patients, and is usually mild. There are no specific guidelines for the management of ibrutinib-induced diarrhea. Dietary modifications are not recommended in anticipation of diarrhea.¹

Management OTC therapy ^{3,5}	Mild to moderate (less than 4 loose stools per day) <ul style="list-style-type: none">Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) Moderate (more than 4 to 6 loose stools per day or night-time diarrhea) <ul style="list-style-type: none">Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea: 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hoursThis dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea
Replace lost fluids ^{3,5}	<ul style="list-style-type: none">Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 litres per day.Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care ³	Advise patients to: <ul style="list-style-type: none">Clean the anal area with mild soap and warm water after each bowel movement to prevent irritationApply a barrier cream or ointment, such as petroleum jelly or Isle's pasteSoak in a warm bathtub or sitz bath to relieve discomfortExamine the anal area for red, scaly or broken skin
Diet ^{3,5}	Advise patients to: <ul style="list-style-type: none">Eat and drink small quantities of food oftenAvoid spicy, greasy, or fried foodsFollow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolveFollow a lactose-free dietAvoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

Diarrhea often has early warning signs. Early recognition and intervention may lead to a more favorable outcome.³⁻⁵ Loperamide is recommended to treat moderate to severe diarrhea in patients with diarrhea who receive targeted therapies.³⁻⁵ Close monitoring and proactive therapy are essential.

When patients seek OTC treatment for diarrhea, it is important to ask them about:³⁻⁵

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Abdominal pain

◀ Hemorrhage

Ibrutinib lowers the platelet count in 52% of patients, leading to a high risk of bleeding. Almost half (48%) of patients have minor bleeding events, including nosebleeds and bruising of any kind. About 3% of these bleeding events, such as gastrointestinal bleeding, bleeding in the brain, or blood in urine, are life-threatening.¹

Prevention

Advise patients to:⁶

- Avoid contact sports and activities that can cause injury or bleeding
- Do not shave with a razor with blades (electric razors are preferable)
- Do not take NSAIDs, which increase bleeding risk.
- Do not floss or use toothpicks
- Use a soft-bristle toothbrush

Key facts: Hemorrhage

Platelets help the blood to clot; therefore, a low platelet count puts patients at higher risk of bleeding events. Advise patients to inform their doctors of any excess or signs of bleeding, including nosebleeds, bleeding gums, bruising, and blood in the urine or stool.^{1,6} Due to the potential risk of inhibited platelet aggregation, patients taking antiplatelet or anticoagulation therapy at the same time as ibrutinib may experience more minor bleeds, and these drugs should be used with caution.¹

Advise patients to avoid supplements that inhibit platelet aggregation, such as fish oil, flaxseed and vitamin E preparations. Ibrutinib should be withheld 3 to 7 days before and after surgery.¹

Warfarin and antiplatelet agents, e.g., aspirin, clopidogrel, when prescribed concomitantly, should be used with caution, and patients should be closely monitored for signs and symptoms of bleeding.¹²

◀ Infection

Bacterial, viral or fungal infections and sepsis occur in 64% of patients who take ibrutinib. About 21% of patients develop a severe infection; 2% of infections are fatal. Most patients who report infections suffer from neutropenia. Advise patients to watch carefully for signs of fever or infection.¹

Prevention

Physicians, nurses and pharmacists educate patients to recognize the symptoms of common infections, particularly:¹

- Upper respiratory tract infections
- Pneumonia
- Sinusitis
- Urinary tract infections

Advise patients to adopt the following preventive measures:⁶

- Frequent handwashing
- Avoid large crowds and people with colds, flu or other infections
- Avoid handling pet waste
- Wear protective clothing, such as gloves and long pants, during yard work
- Shower or bathe daily; use good oral hygiene
- Keep cuts and scrapes clean
- Do not cut cuticles or ingrown nails.
- Ask your doctor before scheduling dental appointments or procedures
- Ask your doctor before getting any vaccinations

Refer any patient with signs of infections to a doctor for immediate care.

Key facts: Infection

A low white blood count (WBC) puts patients taking ibrutinib at higher risk of infection. Preventive measures may help to lower the incidence of infection.¹

◀ Lymphocytosis

At the start of therapy, a temporary increase in lymphocyte counts ($\geq 50\%$ increase from baseline and above absolute lymphocyte count of 5000/mcL) occurs in 70% of patients; however, 80% of these patients achieve resolution. The median time to treatment-emergent lymphocytosis is about 1 week, with a median time to resolution of about 14 weeks. Lymphocytosis may be a pharmacodynamic effect of the inhibition of BTK-mediated cellular homing and adhesion. It should not be considered progressive disease in the absence of other clinical findings.¹

◀ Myelosuppression

A common adverse event of BTK inhibitors is myelosuppression – the suppression of bone marrow activity, which results in low blood cell counts (cytopenias).¹ Ibrutinib causes cytopenias in 17% to 23% of treated patients. From 5% to 16% of treated patients suffer from severe cytopenias, which lead to complications, such as infection. Signs and symptoms include anemia (fatigue, weakness), thrombocytopenia (spontaneous bleeding or bruising), and neutropenia (frequent infections with fever, chills, sore throat or stomatitis). Refer any patient who exhibits this constellation of symptoms to an oncologist for immediate evaluation.^{1,6}

◀ Rash

Rash occurs in 24% of patients treated with ibrutinib.¹ Some evidence suggests that the early introduction of preventive strategies for rashes induced by targeted therapies may reduce the severity of drug-induced skin reactions;⁷ however, there is no evidence to support the use of preventive strategies in patients taking ibrutinib.

Key facts: Rash

There are no specific guidelines for the management of ibrutinib-induced rash. Similarities between it and other rashes induced by targeted therapies have not been established.

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CTL-4 Inhibitors

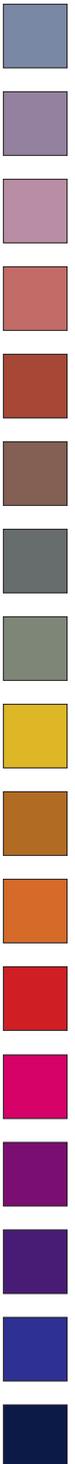
Ipilimumab (Yervoy™)

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This chapter contains information on the prevention and management of common adverse events of CTL-4 inhibitors (CTL-4I) that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage CTL-4I-induced adverse events. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of adverse events, please consult the product monograph.¹

CTL-4 inhibitors are monoclonal antibodies that bind to and block the biological activity of human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4).¹⁻⁶



CTL-4 in cancer

Human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is an inhibitory regulator of T-cell immune response. This protein acts as a checkpoint, switching off T-cells and their activators. It is a vital part of a regulatory feedback loop that shuts down the body's immune response.^{1,2,6}

Tumour cells produce antigens, which trigger an immune response. Antigen-presenting cells (APC) "consume" tumour antigens, then display antigen fragments on their surface. T-cells can only recognize and react to antigens offered up by APCs. When that happens, T-cells export two proteins, CTLA-4 and CD28, to their surface. CD28 controls the T-cell on-switch; CTLA-4 controls the off-switch.^{2,6}

When CD28 binds to CD80/86 sites on APCs, T-cells activate, grow and multiply. The body's immune response expands, and T-cells lead an all-out attack against tumour cells.^{1,2,6}

CD28-APC binding also switches on CTLA-4. It competes with CD28 for APC binding sites and wins. When CTLA-4 binds to CD80/86 sites on APCs, T-cells deactivate and their proliferation ends. The body's immune response stops. Tumour cells, no longer threatened with eradication, thrive freely.^{1,2,6}

CTLA-4:^{1,2,6}

- Inhibits T-cell growth and proliferation
- Neutralizes immune defenses against tumour cells
- Promotes cancer cell survival
- Indirectly promotes cancer cell growth, proliferation and spread

Drug administration

Ipilimumab is administered by intravenous infusion in the hospital or clinical setting.¹

Mechanism of action

CTLA-4 inhibitors are large molecules that block the activity of CTLA-4.¹⁻⁶

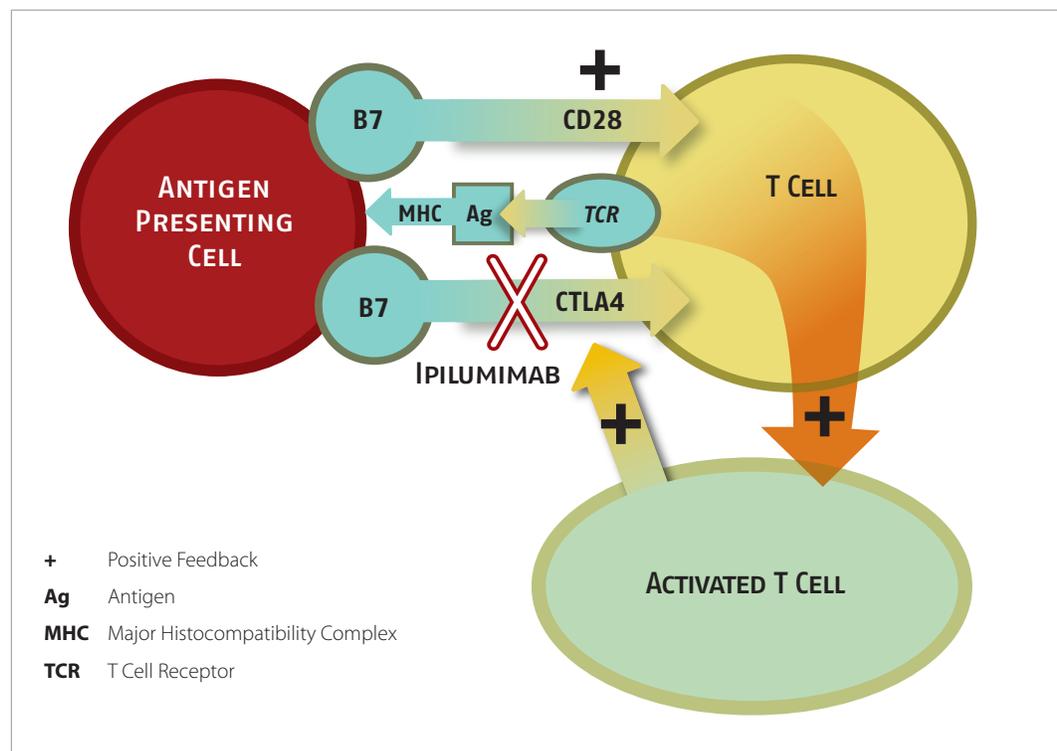
Ipilimumab

Ipilimumab is a new type of immunotherapy. It modifies the body's immune system to fight tumour cells. Ipilimumab is a recombinant, fully human monoclonal antibody and IgG1 kappa immunoglobulin. It binds to and blocks the biological activity of CTLA-4. It suppresses the inhibitory action of CTLA-4, indirectly triggering T-cell activity, growth and proliferation. In other words, ipilimumab removes the brakes from the T-cell-mediated immune response.¹

When ipilimumab switches off CTLA-4, lymphocytes infiltrate organ tissues and tumours. This enhanced immune response kills tumour cells. Because the T-cell mediated immune response infiltrates normal tissues, ipilimumab may cause immune related adverse events (irAE).¹

Ipilimumab:¹⁻⁶

- Blocks CTLA-4 inhibitory activity on T-cells
- Indirectly stimulates T-cell-mediated immune response
- Indirectly leads to cancer cell death



Basic pharmacokinetics

Clearance of ipilimumab increases with body weight but remains unaffected by liver or kidney function.^{1,2} Systemic immunosuppressants or corticosteroids (prednisone ≥ 15 mg daily) may interfere with the pharmacodynamic activity of ipilimumab; therefore, except for the treatment of irAEs, systemic immunosuppressants or corticosteroids should be avoided during ipilimumab treatment.¹

Presentation, prevention and management of common adverse events

The following table summarizes the common adverse events of ipilimumab with an overall frequency of $\geq 10\%$.¹

Common adverse events of CTL-4 inhibitors

Click on adverse events highlighted in blue for more information

Ipilimumab¹

Gastrointestinal disorders

- Abdominal pain
- **Diarrhea**
- Nausea
- Vomiting

General disorders

- Fatigue

Metabolic and nutrition disorders

- Loss of appetite

Skin and subcutaneous tissue disorders

- **Pruritus**
- **Rash**

Other adverse events of interest with CTL-4 inhibitors

Click on adverse events highlighted in blue for more information

- **Immune-mediated response**

Refer for immediate medical care

Tell patients with any of the following signs or symptoms to see their doctor or cancer care team immediately:¹

- At onset of any diarrhea
- Liver problems or signs of hepatitis (yellowing of skin or eyes, upper right quadrant pain, dark urine, nausea and vomiting, loss of appetite, tiredness, bruise easily)

Refer for medical attention

Refer patients to a doctor if any of the following adverse events develop or become severe:¹

- Onset of any diarrhea
- Liver problems or signs of hepatitis (yellowing of skin or eyes, upper right quadrant pain, dark urine, nausea and vomiting, loss of appetite, tiredness, bruise easily)
- Rash and itchy skin
- Nerve problems (loss of sensitivity, loss of function, prickling or burning sensations)
- Endocrine problems, including a decrease in pituitary, thyroid, adrenal and gonadal function (fatigue, headache, abdominal pain, feeling faint, appetite or weight loss, cessation of menstruation, loss of sex drive, vision problems)

Tell patients to seek emergency care if any of these uncommon adverse events develops:¹

- Diarrhea with 7 or more stools, fever, signs of intestinal blockage, signs of peritonitis
- Rapid onset or severe liver problems or pronounced signs of acute hepatitis (yellowing of skin or eyes, upper right quadrant pain, nausea and vomiting, dark urine, loss of appetite, tiredness, bruise easily)
- Severe skin reactions (rash with skin ulcers; skin blistering, bleeding, swelling or blackening)
- Sudden, severe nerve problems (e.g., Guillain-Barré syndrome, myasthenia gravis, peripheral motor neuropathy)
- Severe endocrine problems, such as an adrenal crisis
- Hypersensitivity reactions (generalized rash or redness, feeling faint, trouble breathing or swallowing, fast heartbeat, swelling of face, lips or tongue, throat tightness or hoarseness)

◀ Diarrhea

Diarrhea may be a sign of life-threatening colitis. Unless an alternative cause can be identified, assume that diarrhea is immune-related. Do not treat with OTC medications. Refer patients with diarrhea, no matter the severity, to their doctors for immediate medical evaluation.^{1,9} During their course of treatment, about 30% of patients on ipilimumab develop diarrhea and from 5% to 7% experience severe diarrhea (≥ 7 stools per day).¹

Refer all patients with diarrhea to their doctor for immediate medical care.

Management	Supportive care ⁶	Corticosteroid therapy ^{6,11}	Other interventions ⁶
	<ul style="list-style-type: none">• Diet modification• Hydration <p>The doctor may prescribe:</p> <ul style="list-style-type: none">• Loperamide or atropine plus diphenoxylate (Lomotil®) for mild or moderate diarrhea (≤ 6 stools per day)	<p>For prolonged (5 to 7 days) or moderate diarrhea:</p> <p>Budesonide (3 mg POTID) or prednisone (1 mg/kg daily) tapered over 4 to 6 weeks</p> <ul style="list-style-type: none">• For severe diarrhea (≥ 7 stools per day):• Methylprednisolone IV (1 to 2 mg/kg daily) OR prednisone (1 to 2 mg/kg daily), slowly tapered over 4 to 6 weeks	<ul style="list-style-type: none">• Infliximab• Total parenteral nutrition (TPN) or surgical intervention

Key facts: Diarrhea

When patients on ipilimumab complain of diarrhea, it is important to discourage the use of OTC medications and refer them for medical treatment.^{1,2} Diarrhea usually occurs after 6 weeks of treatment.¹¹

Patients on ipilimumab who develop severe diarrhea (≥ 7 stools per day) have a significant risk of bowel perforation, if untreated. Their death rate is 5%. Their symptoms include:²

- Watery stool
- Abdominal pain
- Fever
- Nausea
- Vomiting
- Anal pain

Immune-related diarrhea usually responds to restricted oral intake and steroids, but immunosuppressive therapy may be required even for patients with mild to moderate diarrhea.^{1,7}

◀ Immune-mediated response

Ipilimumab is most often associated with adverse events due to heightened or excessive immune activity. Most irAEs are inflammatory in nature. They can be treated by appropriate medical therapy or the withdrawal of ipilimumab.¹ Severe irAEs may require high-dose systemic steroids with or without immunosuppressive therapy.¹

About 64% of patients on ipilimumab experience irAEs. Most occur after 9 weeks of treatment during the induction period, but they may onset months after the last dose. Early diagnosis and appropriate management are essential to minimize life-threatening complications. irAEs can involve any organ system but most often affect the gastrointestinal tract, liver, skin, endocrine and nervous systems.

Because signs and symptoms may be non-specific, advise your patients to always suspect an irAEs and seek immediate help. The following adverse events should be considered as immune-mediated, unless an alternate cause has been identified:¹

- Diarrhea
- Increased stool frequency
- Rash
- Bloody stool
- Liver function test elevations
- Endocrine gland problems, such as hypophysitis, adrenal insufficiency (including adrenal crisis), hypopituitarism, hypo- or hyperthyroidism, decreases in serum corticotrophin levels, and Cushing's syndrome
- Other (e.g., episcleritis, uveitis, neuropathies, pancreatitis)

The development of irAEs is associated with tumour regression.

Treating irAEs with corticosteroids does not appear to affect anti-tumour activity.²

irAEs can be fatal

Advise patients to report immediately any signs or symptoms of an immune-related adverse event, particularly if it worsens.

Urge patients not to treat any of these symptoms with OTC medications without consulting their doctor

◀ Pruritus

Up to 26% of patients on ipilimumab develop pruritus. Unless an alternate cause is identified, assume that pruritus is an immune-related adverse event. Refer all patients to a doctor for immediate medical evaluation.^{1,2}

Management

Refer to doctor for mild to moderate itching

Advise patients to:⁸

- Frequently apply lotions or bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion, to help reduce or eliminate itchiness on the trunk or extremities
- Choose “anti-itch” products
- Use mild soaps that contain no deodorants or fragrance, such as Dove® or Neutrogena®
- Use lotions with aloe vera or dimethicone Moisturel®
- Use liquid shower gels instead of soap
- Use antidandruff shampoos and conditioners
- Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms

Refer to emergency for immediate care of intense, widespread itching

- Cool compresses, oral first-generation anti-H₁ antihistamines (e.g., diphenhydramine, hydroxyzine), moderate-dose topical steroids (e.g., betamethasone 0.1% cream) or urea-based topical therapies with antipruritic agents may provide symptomatic relief^{2,6}
- For pruritus with severe rash, doctors may prescribe high-dose topical steroids and oral prednisone (1 mg/kg)⁶

◀ Rash

Rash is the most common adverse event of ipilimumab.^{2,6} It occurs in about 43.5% of patients, about 3% of whom may develop a severe, potentially life-threatening rash.¹ Unless an alternative cause is identified, assume that all rash is an immune-related adverse event. Refer all patients, regardless of rash severity, to a doctor for immediate medical evaluation.¹

Key facts: Rash

In patients on ipilimumab, immune-related rash generally appears after 2 to 4 weeks of treatment. The rash is usually absent from the palms and soles but may occur on the face and the head. It can also exacerbate a pre-existing condition, such as eczema or rosacea. It can worsen after each dose.¹⁰ Refer all patients to their doctor for immediate medical evaluation.

The rash may be asymptomatic or accompanied by pruritus. Its appearance is typically reticular, erythematous, edematous and maculopapular, often on the trunk and extremities.¹²

Skin eruptions and pruritus are generally managed symptomatically and usually do not require dose interruption or the discontinuation of therapy.^{11,12}

Symptomatic treatment is recommended for mild to moderate rash, but prescribed therapy may be necessary to resolve rashes of any severity. Severe rashes may develop into life-threatening, immune-related skin diseases, such as Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and rash with full-thickness skin ulcers blisters or necrotic tissue.^{1,6}

Patients on ipilimumab may have to stop therapy until a mild to moderate rash resolves. Therapy with this drug ends if a patient develops severe immune-related skin problems.^{1,6}

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Epidermal Growth Factor Receptor Inhibitors

Afatinib (Giotrif®)

Cetuximab (Erbix®)

Erlotinib (Tarceva®)

Gefitinib (Iressa®)

Panitumumab (Vectibix®)

This chapter contains information on the prevention and management of common adverse events of epidermal growth factor receptor (EGFR) inhibitors that you are likely to encounter among cancer patients in your practice.

There are evidence-based guidelines on how to manage EGFR inhibitor-induced diarrhea and mucositis; however, evidence-based guidelines for other EGFR inhibitor-induced adverse events are lacking. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events of these agents, please consult the product monographs.¹⁻⁵ Infusion reactions, which occur with intravenous (IV) agents, are usually encountered in the clinic or hospital setting and will not be described here.

Five medications that inhibit the action of the EGFR signalling pathway are available.

- Erlotinib, gefitinib, and afatinib are oral medications with similar mechanisms of action and adverse-event profiles.^{1,3,4,6}
- Cetuximab and panitumumab are monoclonal antibodies that are administered by intravenous infusion in the hospital or clinic setting.^{2,5}



EGFR in cancer

EGFR is a protein that crosses the cell membrane. This receptor is a member of the human epidermal growth factor receptor (HER) family. It is also referred to as HER1 and EGFR/HER1.^{5,6}

EGFR and its ligands play a key role in the signal transduction pathways that regulate:⁷

- Cell proliferation
- Survival
- Differentiation

In cancer cells, the overexpression of EGFR, overproduction of EGFR ligands, or presence of EGFR mutation triggers continuous EGFR signaling. The dysregulation of EGFR signal transduction pathways:^{7,8}

- Stimulates cancer cell proliferation
- Prolongs cancer cell survival by blocking apoptosis (cell death)
- Enhances cell mobility to promote cancer invasion and metastasis
- Stimulates tumour-induced angiogenesis

Drug administration

Afatinib

Afatinib is an oral medication, taken once daily, on an empty stomach at least 1 hour before or 3 hours after eating.¹

Cetuximab

Cetuximab is administered as weekly intravenous infusions in the hospital or clinic setting.²

Erlotinib

Erlotinib is an oral medication, taken once daily at least 1 hour before or 2 hours after eating.³

Lifestyle & medication

Cigarette smoking can reduce erlotinib exposure by 50% to 60%.³

Gefitinib

Gefitinib is an oral medication, taken once daily, with or without food.⁴

Panitumumab

Panitumumab is administered as intravenous infusions once every 2 weeks in the hospital or clinic setting.⁵

How to take EGFR inhibitors

- Erlotinib is taken with a glass of water at least one hour before or two hours after a meal at the same time every day. Advise patients not to crush, cut, or chew the tablets. If they cannot swallow the tablet whole, instruct them to dissolve it in 50 ml of water. Leftover traces must be consumed.³
- Gefitinib can be taken orally with or without food.⁴ Patients unable to swallow tablets may drop a whole tablet (do not crush) into a half glass of plain drinking water and stir until dissolved (about 10 minutes). Drink immediately, add a half glass of water to the emptied glass and drink immediately. The dissolved solution may be administered to patients with a nasogastric feeding tube.⁴
- Afatinib is taken on an empty stomach at least one hour before or three hours after a meal at the same time every day. If taken with a high fat meal, exposure to afatinib may decrease by 50%. Tablets should be swallowed whole with water. Advise patients not to break or crush the tablets.¹
- Grapefruit juice, star fruit, pomelo, pomegranate, Seville oranges and other CYP3A4 inhibitors may decrease gefitinib and erlotinib metabolism and increase serum concentration.⁴

Mechanism of action

Afatinib, erlotinib, and gefitinib

Erlotinib, gefitinib, and afatinib are small-molecule, tyrosine kinase (TK) inhibitors. They interrupt the continuous EGFR signaling in cancer cells by binding to the intracellular portion of EGFR to disrupt downstream signal transmission.^{7,9} Afatinib differs from gefitinib and erlotinib in that it also binds to other members of the Erb family: HER2 and HER4. It binds irreversibly to EGFR TKs, permanently stopping TK signalling, whereas the binding actions of erlotinib and gefitinib are reversible.^{1,6,10}

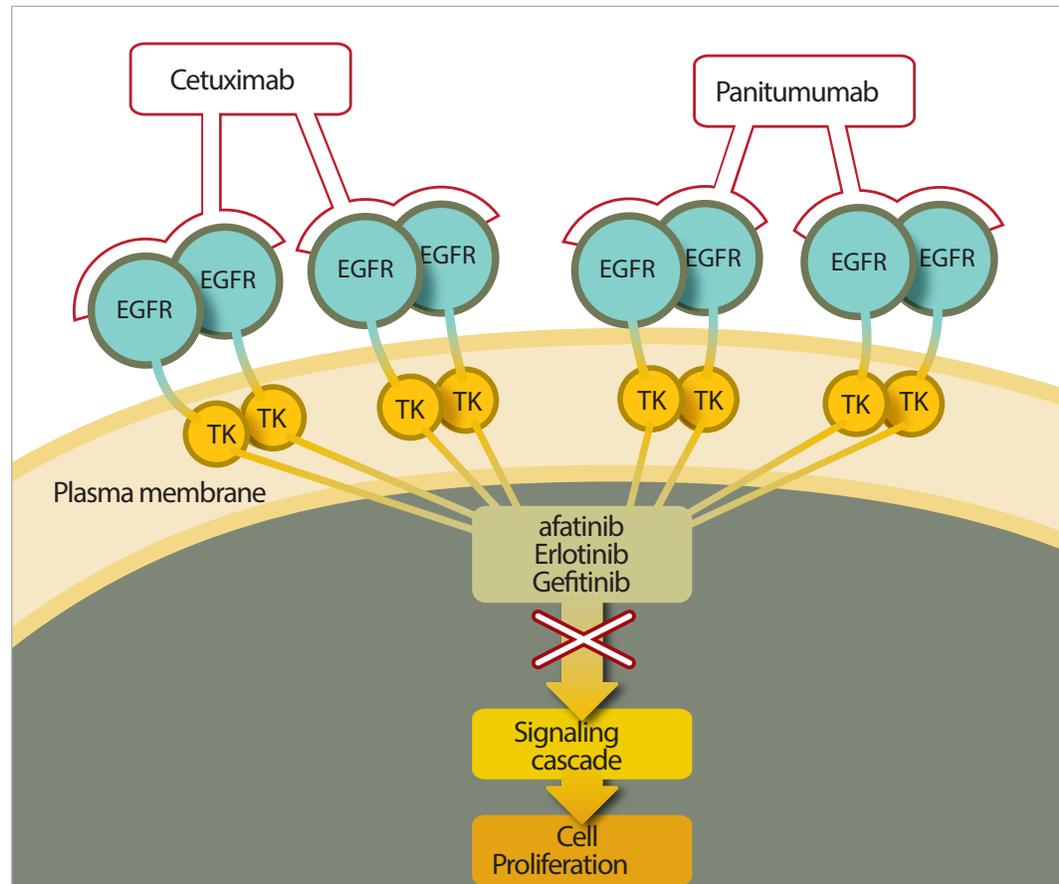
The inactivation of EGFR signaling pathways inhibits:⁷

- Cancer-cell proliferation
- Angiogenic growth factor production
- Tumour-induced angiogenesis
- Cancer-cell invasion

Cetuximab, panitumumab

Cetuximab and panitumumab are monoclonal antibodies that bind to the extracellular portion of EGFR to block other ligands from activating the EGFR signaling pathway. Blocking this pathway from outside the cell produces almost the same effects in cancer cells as small-molecule TK inhibitors that work inside the cell, inhibiting:⁷

- Cancer cell proliferation
- Angiogenic growth factor production
- Cancer cell invasion and metastasis



Basic pharmacokinetics

Afatinib is cleared mainly by biliary and fecal excretion.¹ PGP inhibitors may increase exposure to afatinib.³

Erlotinib and gefitinib are primarily metabolized in the liver via the CYP3A4 pathway. They may interact with other inducers or inhibitors of this pathway, resulting in the alteration in plasma drug concentrations within the body.^{3,4} H₂ receptor antagonists (e.g., ranitidine, famotidine) and proton pump inhibitors may decrease plasma levels of gefitinib; therefore, use them with caution.

Erlotinib is metabolized, to a lesser extent via the CYP1A2 and CYP1A1 pathways. Smoking may induce metabolism via these pathways, thereby increasing the clearance of erlotinib and decreasing the patient's response to treatment.^{3,36} The solubility of erlotinib is pH-dependent. Drugs that alter the pH of the upper GI tract, such as omeprazole, reduce erlotinib exposure by 46%.³

Because antacids, H₂ blockers, and proton pump inhibitors may reduce the pharmacological effect of erlotinib, avoid concurrent use, whenever possible. When antacids must be used, suggest separating administration by several hours.¹⁹ For twice daily ranitidine, take erlotinib at least 2 hours before or 10 hours after ranitidine.

It remains unknown whether this drug-drug interaction will lead to failure of erlotinib therapy. In the light of limited evidence to date, it is reasonable and prudent to avoid concomitant administration of erlotinib with proton pump inhibitors and H₂ receptor antagonists, if possible. Careful use of ranitidine or cimetidine may be a reasonable compromise. Any clinical decision should be made by weighing the uncertain benefit of changing or discontinuing acid-reducing therapy against the potential negative impact of such an action on the patient.³⁵

Presentation, prevention and management of common adverse events

EGFRs are found on normal epithelial tissue, such as the skin, hair follicles, and lining of the gastrointestinal (GI) tract – which may explain why skin disorders and GI disturbances are the most common adverse events of EGFR inhibitors.^{8,11,12}

The following table summarizes the most common adverse events of EGFR inhibitors with an overall frequency of $\geq 10\%$.¹⁻⁵

Common adverse events of EGFR inhibitors

Click on adverse events highlighted in blue for more information.

.....

Blood and lymphatic disorders

- Anemia (erlotinib)

Eye disorders

- Conjunctivitis
- Keratoconjunctivitis sicca (erlotinib)
- Trichomegaly **[photo]** (panitumumab)

Gastrointestinal disorders

- Abdominal pain
- Cheilitis (afatinib)
- Constipation
- **Diarrhea**
- Nausea
- **Stomatitis [photo]**
- Vomiting
- **Xerostomia**

General disorders

- Chest pain (erlotinib)
- Fatigue
- Fever
- Infusion reaction (cetuximab)
- Pain (cetuximab)
- Peripheral edema (panitumumab)

Hepatobiliary disorders

- Abnormal liver function tests

Infection

- Cystitis (afatinib)
- Upper respiratory tract infection (afatinib)

Laboratory abnormalities

- Hypomagnesemia (cetuximab)

Musculoskeletal and connective tissue disorders

- Back pain
-

Metabolism and nutrition disorders

- Anorexia
- Hypokalemia (afatinib)
- Weight loss

Nervous system disorders

- Dizziness (afatinib)
- Headache

Psychiatric disorders

- Insomnia

Respiratory disorders

- Cough
- Dyspnea
- Epistaxis (afatinib)
- Nasopharyngitis (afatinib)
- Pharyngitis (cetuximab)
- Rhinorrhea (afatinib)

Skin and subcutaneous tissue disorders

- Acne
- Alopecia (afatinib)
- Dermatitis acneiform
- Erythema (panitumumab)
- Exfoliative **rash** (panitumumab)
- **Paronychia [photo]**
- **Pruritus**
- **Rash [photo]**
- Skin exfoliation (panitumumab)
- Skin fissures
- **Xerosis**

Other adverse events of interest with EGFR inhibitors

Click on adverse events highlighted in blue for more information

- **EGFR-related hair changes**

Refer for medical attention

Refer patients to a doctor if any of the following adverse events develop or become severe:¹⁻⁵

- Patients with eye problems (eye pain, swelling, redness, blurred vision, light sensitivity, or other vision changes)
- Patients with painful, red, swollen areas around the nails or discolored or detached nails
- Patients with inflammation anywhere in the mouth (cheeks, gums, lips, palate)
- Patients with diarrhea, nausea, abdominal pain, loss of appetite or signs of dehydration
- Patients with signs and symptoms of infection

Tell patients to seek immediate emergency care if any of these uncommon adverse events develop:¹⁻⁵

- Patients with a persistent cough or fever who have sudden difficulty breathing should see a doctor immediately, as these symptoms may signal interstitial lung disease, a rare but serious adverse event. It can happen as early as 5 days and as late as >9 months after starting therapy.¹³
- Patients with signs of liver failure (feeling unwell, yellow skin or eyes), renal failure (little or no urine output), gastrointestinal hemorrhage or perforation (tarry dark stools, bloody urine, or who cough up blood), or hemorrhagic cystitis (burning or bloody urine) must contact their doctor immediately.
- Patients who develop allergic reactions to their medication (swollen lips, hives, nettle-like rash)
- Rash, discoloration, blistering or peeling of the skin, which may indicate a severe skin reaction called Stevens-Johnson syndrome
- Patients with severe weakness or fatigue, which may be a sign of very low magnesium levels in the blood
- Patients who develop signs of pulmonary embolism (shortness of breath, heavy chest, fluid in lungs)

◀ Diarrhea

Diarrhea is a very common adverse event of all EGFR inhibitors occurs in up to 54% of patients treated with EGFR inhibitors, especially the ones who take erlotinib and afatinib.¹⁻⁵ In fact, up to 96% of afatinib-treated patients experience diarrhea.¹ In 15% of afatinib-treated patients, diarrhea causes moderately severe symptoms, such as dehydration, low potassium levels, and renal impairment.¹ Dietary modifications are not recommended in anticipation of diarrhea.¹⁴

<p>Management</p> <p>OTC therapy^{14-16,37}</p>	<p>Mild to moderate (less than 4 loose stools per day)</p> <ul style="list-style-type: none"> Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours or 10tablets/24hours for afatinib)¹ <p>Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)</p> <ul style="list-style-type: none"> Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea
<p>Replace lost fluids^{14-16,37}</p>	<ul style="list-style-type: none"> Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 litres per day. Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
<p>Anal care¹⁴</p>	<p>Advise patients to:</p> <ul style="list-style-type: none"> Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation Apply a barrier cream or ointment, such as petroleum jelly or Isle’s paste Soak in a warm bathtub or sitz bath to relieve discomfort Examine the anal area for red, scaly or broken skin
<p>Diet^{14-16,37}</p>	<p>Advise patients to:</p> <ul style="list-style-type: none"> Eat and drink small quantities of food often Avoid spicy, greasy, or fried foods Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve Follow a lactose-free diet Avoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

EGFR-induced diarrhea often has early warning signs. Early recognition and intervention may lead to a more favorable outcome.¹⁵ Loperamide is recommended to treat moderate to severe diarrhea in patients treated with EGFR inhibitors.^{14,15}

EGFR-induced diarrhea usually begins during the first 4 weeks of treatment, although it may occur within the first 7 days of the start of afatinib therapy.³⁷ It is usually mild to moderate.^{6,10} Early and appropriate intervention with loperamide may prevent the development of severe diarrhea,^{6,16} which may occur within 6 weeks in patients taking afatinib.¹

When patients seek OTC treatment for diarrhea, it is important to ask them about:¹⁵

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea (e.g., radiation therapy or chemotherapy)
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Abdominal pain

◀ EGFR-related hair changes

The following changes to hair may appear 2 to 3 months after the start of EGFR treatment:³⁸

- Curly, fine or brittle hair
- Hair loss
- Eyelashes grow quickly and excessively long, bothering patients' eyes (trichomegaly) **[Photo]**

Non-scarring alopecia occurs after 2 to 3 months of therapy. It may present as frontal or patchy patterns and has a tendency to progress to diffuse alopecia with prolonged therapy. It may resolve spontaneously in some patients. Alopecia generally resolves after discontinuation of therapy, although the quality of hair regrowth may vary. No interventions to reduce or prevent nonscarring alopecia in these patients have been published, and recommended interventions are supportive (e.g., education, cosmetics) and based on studies of androgenetic (male-pattern) and female alopecia.³⁸

◀ Eye disorders

Eye disorders occur in about one-third of patients treated with most EGFR inhibitors; eye problems occur less often in patients on afatinib.^{1,17} All of these agents may cause eye and eyelid irritation, oily secretions and crustiness around the eyes; a grittiness, burning or foreign body sensation in the eye; eyelid growth; and some vision fluctuation.¹⁷

Management

OTC treatment

- Eye products with no preservatives such as lubricating eye drops, gels, gel inserts or ointments and artificial tears, 4 to 6 times daily
- Warm eye soaks
- Wear close-fitting glasses or sunglasses
- Use a humidifier to moisten indoor air and change furnace air filters often

Prescription medication

- Corticosteroid eye drops to decrease inflammation, e.g., fluorometholone (0.1%) ophthalmic ointment to the eyelid (both skin and lid margin) twice daily for 1 week

Key facts: Eye disorders

Among the most common adverse events are conjunctivitis and keratoconjunctivitis sicca (dry eye).¹⁻⁵ Mild to moderate cases of both conditions usually respond to traditional OTC therapies.¹⁷

EGFRI-induced conjunctivitis differs from pink eye in that redness, itchiness, and swelling of the clear, thin, mucous membrane under the eyelid and covering the sclera (whites of the eye) is likely caused by an inflammatory reaction to targeted therapy rather than a bacterial or viral infection. However, a typical pink eye infection may occur as a result of EGFRI-induced dry eye. Conjunctivitis of infectious origin may resolve on its own within a week (viral) or respond to topical antibiotic therapy (bacterial).^{17,18}

For mild symptoms of EGFRI-induced dry eye, prescribe artificial tears 4 to 6 times daily. For more severe symptoms or cases unresponsive to artificial tears, consider referral to an ophthalmologist for evaluation of tear film and further management with anti-inflammatory medications or any co-occurring ocular conditions that may cause symptoms.³⁹

When to refer

Advise patients who report the following symptoms to contact a doctor or an ophthalmologist:^{1,16}

- Unrelenting eye pain
- Blurred vision or loss of vision
- Extreme eye redness
- Excessive tears (lacrimation)
- Light sensitivity
- No improvement in eye symptoms after 1 week of OTC therapy

◀ Paronychia

Paronychia **[Photo]** is a painful inflammation that occurs around finger and toe nails in up to 19% of patients treated with most EGFR inhibitors;¹⁻⁵ however, up to 58% of afatinib-treated patients develop this adverse event, including 11% who experience severe nail problems.¹ It typically appears within 4 to 8 weeks or up to 6 months after therapy begins.¹⁹

Prevention	Advise your patients to: ^{21,22} Wear comfortable, loose-fitting shoes to avoid friction or pressure on nail folds ^{20,19} <ul style="list-style-type: none">• Cut toenails straight but not short²¹• Avoid biting nails or cutting them too short¹⁹	
Management	OTC treatment <ul style="list-style-type: none">• Topical antiseptics or antibiotics (soaks or creams) to prevent or treat mild infection¹²• Epsom salts or Buro sol® (aluminum acetate) soaks daily⁸• Weekly application of topical silver nitrate to treat hamburger-like bumps²⁰• Foot cushioning products for extra comfort²⁰	Refer to doctor for pain in nail bed, nail loss, signs of infection ^{8,20} Prescription medication <ul style="list-style-type: none">• Topical antimicrobials, such as mupirocin and nystatin ointment¹⁷• Topical corticosteroid, such as 1% triamcinolone ointment¹⁷• Doxycycline, 6-week course of 100 mg twice daily¹⁷

Key facts: Paronychia

Although not infective in origin, EGFR-induced paronychia makes nails more sensitive to infection.¹² Nails tend to grow slower, become brittle, and crack.²³ They rapidly develop a painful longitudinal inflammatory ridging, often associated with a watery discharge where the nail joins the lateral subungual fold. Paronychia often affects several fingers or toes, particularly those subjected to trauma. It resolves once treatment ends.²¹

Refer to a doctor

A podiatrist cannot provide adequate foot care in this context.

Paronychia can be painful and mimic an ingrown nail.²⁰ A throbbing or intense pain, along with crusting and discharge, may indicate a superinfection; refer patients to a doctor for evaluation.²¹

This condition may interfere with simple manual work or prevent the patient from wearing any shoes but sandals.²³ It may take weeks to heal and may not resolve unless therapy stops for a short period or ends.^{8,23} In severe cases, abscesses and small, red, oozing, and bleeding bumps that look like raw hamburger meat develop in nail folds.²³

◀ Pruritus

In patients treated with EGFR inhibitors, pruritus is usually associated with EGFR-induced rash or xerosis and can appear in half of patients.^{12,20,23} Although it rarely requires dose modifications or discontinuation of drug therapy, it can have a dramatic impact on the patient's quality of life.³⁸

Prevention	Advise patients to use gentle skin care: ²² Mild soaps, such as Dove® or Neutrogena® ⁸ <ul style="list-style-type: none">• Bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion⁸	
Management	Mild to moderate pruritus Advise patients to: ¹¹ <ul style="list-style-type: none">• Apply more lotion than usual to help reduce or eliminate itchiness on the trunk or extremities• Use lotions with aloe vera or dimethicone (Moisturel®)• Use antidandruff shampoos and conditioners• Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms²²• The use of topical antihistamines or lidocaine is not recommended• Menthol, 1-3%, may provide some relief	Moderate to severe pruritus Refer to doctor for intense, widespread itching Non-sedating, second-generation, systemic antihistamines may provide some relief during daytime; sedating antihistamines are preferable at night ^{8,22,23}

Key facts: Pruritus

Pruritus or itchiness is the consequence of loss of skin moisture.¹⁶ Pruritus may be mild or localized, widespread or intense, or worsen to the point where it interferes with daily activities.²⁰

Since EGFR inhibitor-induced pruritus is usually associated with rash or xerosis, it is recommended to first treat these conditions. OTC products, such as menthol, may help to relieve itchiness. Encourage patients to adopt preventive strategies. Evidence suggests that topical antihistamines and lidocaine are ineffective at reducing itch.²²

◀ Rash

Rash **[Photo]** occurs in more than 50% and up to 100% of patients treated with EGFR inhibitors (EGFRI).^{1-5,20,24,25} Most patients experience a mild to moderate rash; severe rash is uncommon.^{12,20} Rashes tend to be more common and severe among patients who receive IV agents.²⁰ Rashes tend to worsen with sun exposure.¹

Patients taking panitumumab, cetuximab, and erlotinib tend to have a more intense, severe papulopustular rash than patients taking gefitinib. Panitumumab rashes often have less inflammatory and pustular lesions but more persistent raised, reddish lesions and red, spidery capillaries on the skin surface. Skin toxicity with afatinib is not as well described as for the others EGFRI but the presentation seems similar.²¹

Growing evidence suggests that the early introduction of preventive strategies, including the prescription of oral antibiotics, such as doxycycline or minocycline, may reduce the severity of skin reactions.^{21,22,26,27}

Although EGFR inhibitor-induced rash usually peaks in 4 to 6 weeks and decreases in severity after 8 weeks, skin changes (e.g., raised red patches, skin discoloration) may persist for months or years. Therefore, preventive rather than reactive strategies are recommended.²²

Prevention

OTC therapy

A proactive approach is critical in managing EGFRI-induced rash.¹¹ When patients begin therapy, advise them to:^{12,13,20,24}

- Cleanse with mild soap or hypoallergenic cleaners or shower oils to avoid skin dryness.
- Take short showers with warm water.
- Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics.
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®, to conceal the rash
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®
- Avoid sun exposure. If not possible, use a broad-spectrum sunscreen (SPF of 30 or more) that contains zinc oxide or titanium dioxide and wear sun protection.¹
-

Medical therapy

- Prophylactic treatment with doxycycline 100 mg PO BID or minocycline PO 100mg DIE, hydrocortisone cream, sunscreen, and moisturizers reduces the frequency of severe papulopustular rash. It is suspended after 6 weeks in the absence of lesions or after their disappearance.^{21,22,40}

Management	<p>Mild²⁴</p> <ul style="list-style-type: none"> Localized Few symptoms No impact on daily activities No sign of infection 	<p>No treatment or OTC therapy:</p> <ul style="list-style-type: none"> Topical hydrocortisone 0.5% cream²⁴ Mild soap and cleansing gels (e.g., Toleriane dermo-cleanser, Cetaphil, Spectro® Cleanser for Blemish-Prone Skin and Combination Skin)^{8,21} Moisturizers twice daily⁸ <p>Advise patient to monitor the rash for changes in severity.¹⁻⁵ Refer to doctor if rash persists or worsens.²⁴</p>	<p>Prescribed medications:</p> <ul style="list-style-type: none"> Topical agents with anti-inflammatory properties, such as hydrocortisone 1% to 2.5% cream, metronidazole cream or clindamycin 1% cream or topical solution²⁴ <p>PLUS</p> <ul style="list-style-type: none"> Prophylactic use of doxycycline 100 mg PO twice daily or minocycline 100mg PO DIE or BID^{21,28}
	<p>Moderate²⁴</p> <ul style="list-style-type: none"> Generalized Mild symptoms (e.g., pruritus, tenderness) Minimal impact on daily activities 	<p>Refer to doctor as soon as possible</p>	<p>Prescribed medications:^{11,24}</p> <ul style="list-style-type: none"> Hydrocortisone 2.5% cream, clindamycin 1% cream or topical solution PLUS Doxycycline (100-mg PO BID) or minocycline (100-mg PO DIE or BID) <p>OR</p> <ul style="list-style-type: none"> Fluocinonide 0.05% cream BID with hydrocortisone 2.5% cream
	<p>Severe²⁴</p> <ul style="list-style-type: none"> Generalized Severe symptoms (e.g., pruritus, tenderness) Significant impact on daily living Potential for infection 	<p>Refer to doctor as soon as possible</p>	<p>EGFRI interruption and dose reduction is recommended. Prescribed medications:^{24,38}</p> <ul style="list-style-type: none"> Hydrocortisone 2.5% cream, clindamycin 1% cream or topical solution PLUS doxycycline (100-mg PO BID) or minocycline (100-mg PO BID) PLUS oral corticosteroid OR Fluocinonide 0.05% cream BID with hydrocortisone 2.5% cream Analgesics for patients with painful rash²⁰

Key facts: Rash

The onset of rash usually occurs from 1 to 3 weeks after therapy begins.^{8,20} It has an acne-like appearance and is often referred to as an acneiform rash or folliculitis, but it has a distinct pathology from acne vulgaris.¹² The rash develops as inflammatory papules or pustules on the face, neck, and upper torso.^{6,12,20} The limbs, scalp, and lower torso are less often involved.⁸ Rash may be accompanied by dry skin, pruritus (itchiness), or erythema (redness).¹²

The rash may wax and wane throughout therapy or peak about 4 weeks after therapy begins.^{8,12,20-22,28} In most patients, it tends to improve gradually but spontaneous resolution may occur.^{7,12,20} In patients taking IV EGFR inhibitors, the rash may flare after each infusion.¹² With the discontinuation of therapy, the rash usually disappears in a few weeks, sometimes with residual hyperpigmentation (skin-colour changes) and dry skin.²⁰

Prompt treatment of rash is important, as a major study that compared pre-emptive against reactive treatment of skin problems in cancer patients has found that rash and other skin toxicities have a negative impact on patients' quality of life.²⁸ This study supported the prophylactic use of oral doxycycline 100 mg twice daily and a topical corticosteroid (1% hydrocortisone) for 6 weeks to reduce the incidence of moderate or higher rash and other skin toxicities in patients treated with EGFR inhibitors.²⁸

EGFR inhibitors impair the skin's thickness and barrier function; therefore, the acne-like lesions, which are usually sterile, may become infected by bacteria or a virus.²⁸ The appearance of crusts may signal a severe rash or indicate a bacterial or viral superinfection. Refer patients to a doctor for evaluation.²¹

Encourage patients who are treated with topical agents to continue their use up to 7 days beyond the abatement of rash or as long as directed by their doctor.²⁴

There is no association between the severity of rash and type of skin or history of acne. The EGFR-induced rash has an inflammatory rather than infectious origin.²⁰ Unlike acne vulgaris, no true comedones are seen.¹² The rash may undergo several stages:^{20,29}

- Swelling, redness, burning sensation
- Formation of small, solid, round papules of less than 5 mm in diameter may evolve into pustules containing inflammatory (as opposed to infectious) material and cellular debris
- Yellowish crusting of drying pustules

◀ Stomatitis

In patients treated with EGFR inhibitors, the integrity of mucous membranes in the mouth may be compromised, leading to inflammation and stomatitis (mouth sores) [Photo].^{8,19,30} This condition occurs from 8% to 23% of patients treated with most EGFR inhibitors alone and up to 26% in patients on combination therapy.¹⁻⁵ It occurs more frequently in patients treated with cetuximab, afatinib, and erlotinib.¹⁻³

Prevention	Advise patients to: ^{30,31} <ul style="list-style-type: none">• Avoid cheek or lip biting• Avoid mouth breathing• Maintain good oral hygiene• Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly• Avoid spicy and highly textured foods• Avoid highly flavoured and alcohol-containing mouthwashes	
Management	OTC treatment For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips Meticulous oral hygiene: ^{30,31} <ul style="list-style-type: none">• Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles• If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®• Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria• Floss gently once daily to avoid gum injury• Salt rinses (1/2 teaspoon of salt in 1 cup of warm water at least 4 times daily, especially after meals)• Bland rinses, antimicrobial mouthwash without alcohol• OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®) Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips ⁸	Prescribed medication (moderate to severe cases): <ul style="list-style-type: none">• Topical fluoride (dentist)³¹• Topical anesthetics³¹• Corticosteroid solution^{8,30}• Topical or systemic analgesics³¹• Topical or systemic antifungals³⁰• Palliative mixtures of various agents³¹

Key facts: Stomatitis

Maintaining mucosal health, integrity, and function is crucial in patients with stomatitis. From 3 to 10 days after therapy begins, EGFR-treated patients may experience a burning sensation, followed by mouth sores (ulcerations). Treatment aims to relieve symptoms until the mucous membranes can rejuvenate, usually within 7 to 14 days. Smokers have a greater risk of stomatitis.³⁰

Clinical practice guidelines stress its importance in cancer patients, but due to a lack of supportive evidence, oral hygiene methods are usually based on personal preference and anecdotal experience.³¹

Good oral hygiene:^{30,31}

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

The use of chlorhexidine mouth rinses is not recommended.

They contain alcohol and may sting. Dilution defeats their antibacterial benefits.³⁰

Hydrogen peroxide rinses may worsen mouth ulcers.³⁰

There are no evidence-based guidelines for treatment of EGFR-induced stomatitis, and practitioners usually follow the common practices for chemotherapy-induced mouth inflammation.

Topical preparations in widespread use for stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, “magic” mouthwashes that contain lidocaine, and salt-and-baking soda rinses.³¹

◀ Xerosis

Xerosis (dry skin) occurs in up to 35% of patients treated with EGFR inhibitors and more often in patients on gefitinib therapy.¹⁹

Prevention	<p>Advise patients to:^{12,20-22,29}</p> <ul style="list-style-type: none"> • Cleanse with mild soaps or cleaners or shower oils to avoid skin dryness • Take short showers with warm water • Moisturize twice a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or thick, emollient-based creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion • Use only fragrance-, alcohol-, and dye-free lotions and cosmetics • Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove® 	
Management	<p>First signs of skin dryness Dry skin on face, back, chest</p>	<p>Use greasy water-in-oil creams or ointments²⁰</p>
	<p>Moderate to severe xerosis Dry skin on limbs</p>	<p>Use greasy water-in-oil creams or ointments¹²</p>
	<p>Eczema</p>	<p>Short-term use (1-2 weeks) of weak topical corticosteroid creams²⁰</p> <p>Refer to doctor if uncontrolled by OTC treatment</p>
	<p>Infection</p>	<p>Topical antibiotics²⁰</p> <p>Refer to doctor if uncontrolled by OTC treatment</p>
	<p>Skin fissures</p>	<p>Treatment options²³</p> <ul style="list-style-type: none"> • 50% propylene glycol under a plastic bandage • Salicylic acid 10% ointment • Colloid dressing <p>Refer to doctor if uncontrolled by OTC treatment</p>
	<p>Scaly areas</p>	<p>Treatment options²²</p> <p>Ammonium lactate or lactic acid creams (e.g., Hydrolac or Lac-Hydrin®)</p>

Key facts: Xerosis

EGFR inhibitors can alter the skin barrier, causing skin dryness (xerosis). It usually appears in the 30 to 60 days of treatment and continues until treatment stops. It may occur at the same time or succeed EGFR inhibitor-induced rash. After 6 months of therapy, virtually all patients develop skin dryness, and 30% develop painful fissures and pruritus (itchiness). Fissures are usually located on the fingers, nail folds, and heels.^{21,22}

Apart from general hydrating measures, choice of the right treatment is critical to alleviate skin dryness. The frequent application of emollients that contain ammonium lactate, e.g., hydrolac or Lac-Hydrin®, or 5% to 10% urea, e.g., Eucerin® 5 or Uremol® 10, may substantially improve xerosis.¹⁸ Advise patients to avoid occlusive topical creams and lotions that can obstruct hair follicles, which may lead to infection.^{20,32}

The dry, scaly, itchy skin, which resembles atopic eczema, usually begins between one week to 3 months after the start of therapy.^{8,20} It is persistent and often lasts several months.²³

Xerosis tends to worsen with:^{19-21,23}

Older age

- Prior history of atopic eczema
- Previous treatment with cytotoxic agents

The dry, scaly skin appears on the limbs, palms, torso, soles and areas of EGFR-induced rash. Xerosis often affects the fingertips, heels, and toes. Painful fissures may develop in these areas, in nail folds and over finger joints in excessively dry skin – a condition that can make wearing shoes or performing tasks difficult for patients.^{20,19,23,32} Thick moisturizers or zinc oxide creams can be applied. Liquid glues can be used to seal cracks to keep them from worsening or becoming infected and to promote healing.^{21,22}

Dry skin may become increasingly fragile and bruise easily. Xerosis may worsen, becoming chronically red and irritable. Secondary infection with *S. aureus* may occur.^{19,20}

For mild to moderate xerosis, thick moisturizers are recommended. They may include urea, colloidal, oatmeal, or petroleum-based creams. Greasy creams can be used on the limbs but not the chest or face, due to the risk of folliculitis. Topical steroids may be necessary for more severe xerosis. Due to their drying effect, topical retinoids and benzoyl peroxide gels must be avoided.²²

◀ Xerostomia

Dry mouth occurs in about 6% of patients who take IV EGFR inhibitors, especially when combined with other cancer therapies, particularly radiation therapy.^{1-5,33}

Prevention	<p>Advise your patients:³⁴</p> <ul style="list-style-type: none">• Examine their mouth daily for red, white or dark patches, sores or signs of tooth decay• Chew sugarless gum or candies to increase saliva flow• Avoid alcohol-containing mouthwashes or dental products• Use a cool-mist humidifier, especially at night• Sip water throughout the day or suck on ice chips• Modify your diet to drink 8 cups of water daily; eat soft, moist food; avoid alcohol, caffeinated beverages, and spicy, sugary, or acidic foods• Avoid smoking	
Management	<p>OTC treatment</p> <p>Artificial saliva (e.g., Biotène®, Moi-Stir®, Mouth Kote®)</p> <p>Meticulous oral hygiene:^{33,34}</p> <ul style="list-style-type: none">• Toothbrushing, 2-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles• Floss gently once daily to avoid gum injury• Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)• Use a low-abrasive fluoride toothpaste• Avoid products that contain sodium lauryl sulfate, which may worsen canker sores• Orajel®, Vaseline® or glycerin swabs to relieve dryness and cracks on lips and under dentures	<p>Prescribed medications^{33,34}</p> <ul style="list-style-type: none">• Fluoride gel (dentist)• Drugs, such as pilocarpine, that increase saliva production

Key facts: Xerostomia

Like other chemotherapy drugs, EGFR inhibitors may damage the salivary glands, leading to xerostomia (dry mouth). This condition differs from stomatitis and is characterized by:³⁴

- A dry, tough tongue
- Cracks in lips and at corners of mouth
- Pain or burning in mouth or on tongue
- Sticky, dry mouth
- Thick, stringy saliva

Patients may have difficulty speaking or swallowing, a constant sore throat, hoarseness, and dry nasal passages that lead to nosebleeds. Xerostomia can cause mouth sores, gum disease and tooth loss. One of the most common oral infections associated with xerostomia is oral candidiasis.³³

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Hedgehog pathway inhibitors

Vismodegib (Erivedge®)

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This chapter contains information on the prevention and management of common adverse events of Hedgehog (Hh) pathway inhibitors (HhPI) that you are likely to encounter among cancer patients in your practice.

A single, oral medication inhibiting the action of the smoothed (SMO) receptor on the hedgehog signaling network pathway is currently available.¹

There are no evidence-based guidelines on how to manage HhPI-induced adverse events. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events of this agent, please consult the product monograph.¹



The Hedgehog pathway in cancer

Basal cell carcinoma (BCC) is the most common form of cancer, occurring in 25% of all human cancers and 80% of all skin cancer.² A key signal transduction cascade involved in BCC is the Hedgehog (Hh) pathway. This pathway is mutated in almost all patients with BCC.²

The Hedgehog (Hh) pathway is fundamental in the development of embryonic cells and important in stem cell proliferation and tissue regeneration in adults. Normally, the Hh ligand binds to the patched 1 (PTCH1) receptor on target cell surfaces. PTCH1 activates the smoothened (SMO) receptor, another transmembrane protein, which triggers a downstream signaling cascade that eventually turns on genes that regulate normal cell growth and survival.²

When a PTCH1 or SMO mutation occurs, SMO signaling is always turned on. This constitutive upregulation of the Hh pathway:²

- Increases cell proliferation and survival
- Regulates transformation of healthy skin cells into a disorganized (mesenchymal) state
- Promotes the dissemination of cancer cells in solid tumours
- Enhances metastatic disease progression

Drug administration

Vismodegib

- Vismodegib, is an oral drug that should be swallowed whole at the same time once daily with or without food.¹
- Advise patients not to open or crush the capsule.¹

Patients must not donate blood or blood products while on treatment, during dose interruptions and for 24 months after treatment ends.¹

How to take vismodegib

Medications that alter upper GI tract pH, e.g., proton pump inhibitors, H2 receptor antagonists, and antacids, may reduce the effectiveness of vismodegib. Avoid these products, if possible, during treatment.¹

How to obtain vismodegib

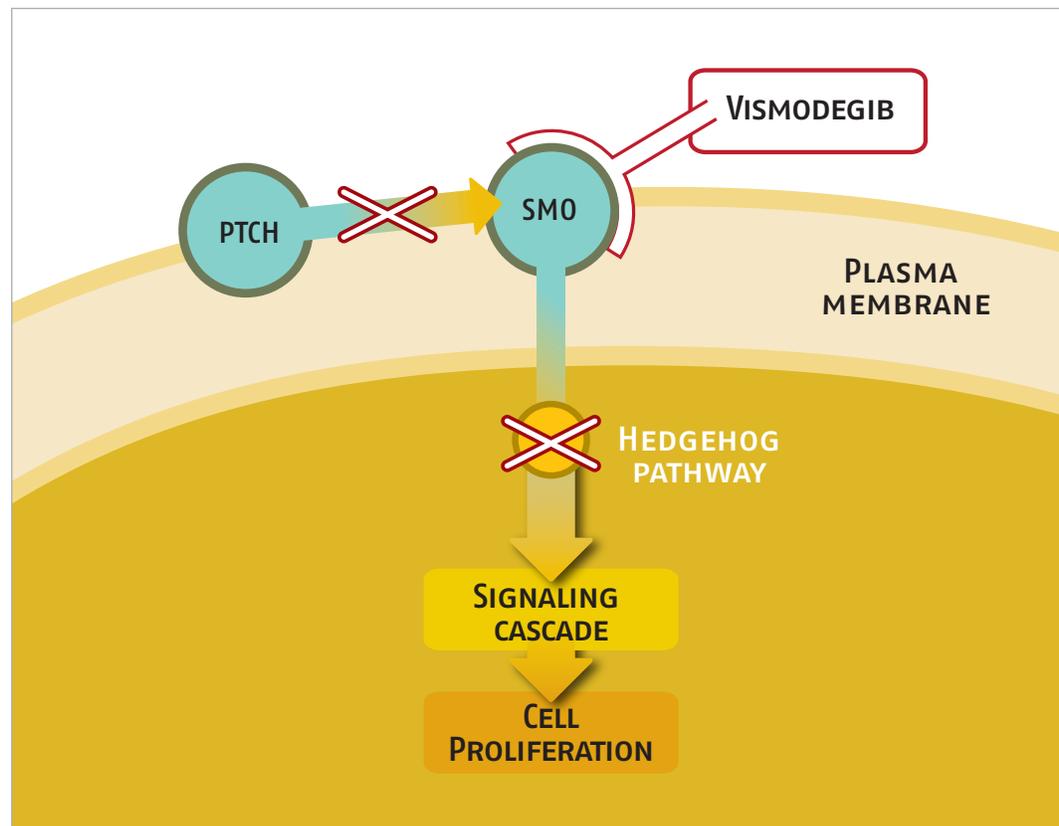
Vismodegib is only available in Canada through a controlled distribution program called the Erivedge® Pregnancy Prevention Program (EPPP). Only prescribers and pharmacies registered in this program are able to prescribe and dispense this medication. It can only be dispensed to patients who are registered in the EPPP (www.erivedge.ca).¹

Mechanism of action

Vismodegib is a first-in-class, small molecule inhibitor of the Hh signaling pathway. On the cell surface, vismodegib binds to a specific transmembrane protein, the smoothed (SMO) receptor, to neutralize its activity and block the incessant, abnormal firing of signals down the Hh pathway to stop:^{1,2}

Tumour growth

- Invasion of cancerous cells
- The spread of cancer
- Tumour survival



Basic pharmacokinetics

Vismodegib is primarily metabolized by the liver, but multiple metabolic pathways play a role, including oxidation, glucuronidation, and, uncommonly, pyridine ring cleavage.¹

This drug is a substrate of P-glycoprotein (P-gp). Co-administration with P-gp inhibitors increases systemic exposure to vismodegib, causing a higher frequency of adverse events.^{1,2}

In the liver, vismodegib inhibits CYP2C8, CYP2C9, CYP2C19, and the transporter BCRP. However, it is unlikely that CYP inhibition will alter its systemic exposure, as concomitant treatment with CYP inducers and inhibitors in clinical trials did not alter vismodegib exposure.^{1,2} Substrates of these isoenzymes may be impacted by vismodegib.

Presentation, prevention and management of common adverse events

The safety profile of vismodegib is generally regarded as mild to moderate; however, some patients discontinue treatment due to adverse effects, mostly muscle cramps and taste disturbance. It is important to understand the long-term impact of adverse events on patients' quality of life and compliance. Since mild to moderate adverse events can persist and become chronic, patients may become discouraged and unwilling to continue therapy. In clinical trials, from 25% to 54% of patients on vismodegib discontinued treatment due to adverse events.^{1,2}

The following tables report adverse events with an overall frequency of $\geq 10\%$.

Common adverse events of SMO receptor inhibitors

Click on adverse events highlighted in blue for more information.

.....

Gastrointestinal disorders

- Constipation
- **Diarrhea**
- Nausea
- Vomiting

General disorders

- Fatigue
- Weight loss

Infection

- Upper respiratory tract infection

Laboratory abnormalities

- Abnormal liver function tests
- Abnormal liver enzymes
- Abnormal electrolytes

Metabolism and nutrition disorders

- Decreased appetite
-

Musculoskeletal and connective tissue disorders

- **Bone, joint and muscle pain (arthralgia)**
- Muscle spasms
- Nervous system disorders
- Headache
- Loss of taste
- Taste disturbance

Psychiatric disorders

- Insomnia

Respiratory disorders

- Cough

Skin and cutaneous tissue disorders

- Alopecia

Other adverse events of interest with SMO receptor inhibitors

Click on adverse events highlighted in blue for more information

- **Teratogenicity**

Refer for medical attention

Refer patients to a doctor if any of the following adverse events develop or become severe:¹

- Pneumonia (cough, dyspnea, fever)

Tell patients to seek immediate emergency care if any of these uncommon adverse events develops:¹

- Heart failure (shortness of breath, fatigue, swollen legs, ankles or feet)
- Gastrointestinal bleeding (blood in stool)
- Blood clots in lungs (shortness of breath, coughing, trouble breathing, congestion)
- Blood clots in legs (leg pain when walking or exercising)
- Bleeding

◀ Bone, joint, and muscle pain

The most common adverse event of vismodegib is muscle spasms, affecting about 72% of patients. About 16% of patients on vismodegib develop joint pain. Muscle spasms and joint pain are usually mild to moderate; however, the persistence and chronic nature of muscle spasms may lead patients to discontinue therapy.^{1,2}

Prevention	No preventive measures are recommended.
Management	<p>The following measures may provide relief from muscle aches or cramps:^{3,4}</p> <ul style="list-style-type: none">• Calcium supplements• Magnesium supplements• Mild pain medications• Avoid using quinine or drinking tonic water, which contains quinine <p>For mild bone aches and pain:</p> <ul style="list-style-type: none">• NSAIDs in patients with no history of GI bleeding

Key facts: Bone, joint, and muscle pain

There are no evidence-based guidelines for prevention or treatment.

◀ Diarrhea

Diarrhea, usually mild to moderate, occurs in 29% of patients who take vismodegib. Early recognition of diarrhea and early intervention may lead to a more favorable outcome.³ Loperamide is recommended to treat mild (<4 stools per day) to moderate diarrhea (≥ 4 to 6 stools per day) in patients treated with targeted therapies.⁵⁻⁷ Dietary modifications are not recommended in anticipation of diarrhea.⁵⁻⁷

Management OTC therapy⁵⁻⁷	Mild to moderate (less than 4 loose stools per day) <ul style="list-style-type: none">Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) Moderate (more than 4 to 6 loose stools per day) <ul style="list-style-type: none">2 tablets immediately, then 1 tablet every 2-4 hours until bowel movements are normal for at least 12 hours
Replace lost fluids⁵⁻⁷	<ul style="list-style-type: none">Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 litres per day.Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care⁵	Advise patients to: <ul style="list-style-type: none">Clean the anal area with mild soap and warm water after each bowel movement to prevent irritationApply a barrier cream or ointment, such as petroleum jelly or Isle's pasteSoak in a warm bathtub or sitz bath to relieve discomfortExamine the anal area for red, scaly or broken skin
Diet⁵⁻⁷	Advise patients to: <ul style="list-style-type: none">Eat and drink small quantities of food oftenAvoid spicy, greasy, or fried foodsFollow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolveFollow a lactose-free dietAvoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

When patients seek OTC treatment for diarrhea, it is important to ask them about:5-7

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Abdominal pain

◀ Teratogenicity

Vismodegib is highly teratogenic. It can cause embryo-fetal death and birth defects. For that reason, it is only available through a special program, the Erivedge Pregnancy Prevention Program (EPPP), which controls access and its use in fertile women.¹

Teratogenicity of vismodegib

This drug causes embryo-fetal death and severe birth defects.¹

Women:

- Vismodegib must not be used during pregnancy.
- Pregnancy tests are required within 7 days before therapy begins, once monthly during treatment, and once monthly for 24 months after therapy ends.
- Women must be willing and able to comply with the mandatory use of two simultaneous, effective contraceptive methods or commit to sexual abstinence with heterosexual partners.
- Women who develop amenorrhea (loss of menstrual periods) must continue to use two simultaneous contraceptive measures. Contraceptive use should begin at least 4 weeks before therapy begins and continue throughout treatment, dosage interruptions, and for 24 months after therapy ends.
- Patients who suspect pregnancy must immediately report the possibility to their physician.

Men:

- Men must inform female sexual partners of the risk of teratogenicity.
- Men must use condoms with spermicide, even after vasectomy, during treatment, dose interruptions, and for 2 months after therapy ends.
- Sperm donation is prohibited during, after and for 2 months after therapy ends.
- Men must report the suspected pregnancy of a sexual partner.

Vismodegib may permanently impair fertility in men and women. Urge patients to discuss fertility preservation methods with their physician before therapy begins.¹

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HER2 Inhibitors

Lapatinib (Tykerb[®])

Pertuzumab (Perjeta[™])

Trastuzumab (Herceptin[®])

.....

This chapter contains information on the prevention and management of common adverse events of human epidermal growth factor-2 (HER2) inhibitors that you are likely to encounter among cancer patients in your practice.

Three medications are available that inhibit the action of HER2. There are few evidence-based guidelines on how to manage HER2 inhibitor-induced adverse events. The recommendations presented here are based on a review of clinical practice guidelines, expert opinion, and best practices in oncology. For a complete description of all adverse events, please consult the product monographs¹⁻³



HER2 in cancer

Four receptors on cell membranes transmit growth signals into cells when activated by human epidermal growth factor (HER). This family of receptors is essential for normal cell development. They include:^{1,4,5}

- HER1, also known as the epidermal growth factor receptor (EGFR)
- HER2, also known as HER2/neu
- HER3
- HER4

In about 20% of breast cancers, the HER2 receptor is overexpressed on cell surfaces or in a state of continuous activation, flooding the cell with growth signals. In HER2-positive breast cancers, too many growth signals lead to:⁵

- Uncontrolled cell proliferation
- Higher potential for the invasion and spread of cancer
- Resistance to natural cell death (apoptosis)

The HER3 protein is a potent heterodimerization partner of HER2. It is implicated in cancer development, growth and survival.⁶

HER2-positive breast cancer is likely to be aggressive and patients with this cancer have a higher risk of relapse and poorer prognosis than other breast-cancer patients.³ HER2 may be expressed in other cancers, such as gastric cancer.

Drug administration

Lapatinib

This medication is part of a dosing regimen that may contain capecitabine or letrozole.

Pertuzumab

Pertuzumab is administered as an intravenous infusion in the hospital or clinic setting.²

Trastuzumab

Trastuzumab is administered as an intravenous infusion in the hospital or clinic setting.³

How to take lapatinib

- Take lapatinib once daily on an empty stomach at least one hour before or two hours after a meal with a low fat content, as systemic exposure to lapatinib is increased when administered with food.^{1,7}
- Take pills all at once. Dividing the dose is not recommended. Do not crush, split or dissolve the tablets.⁴
- Do not consume grapefruit, star fruit, pomelo, pomegranate, or Seville oranges or take herbal medications, such as St. John's wort, while on lapatinib.^{1,4,8}

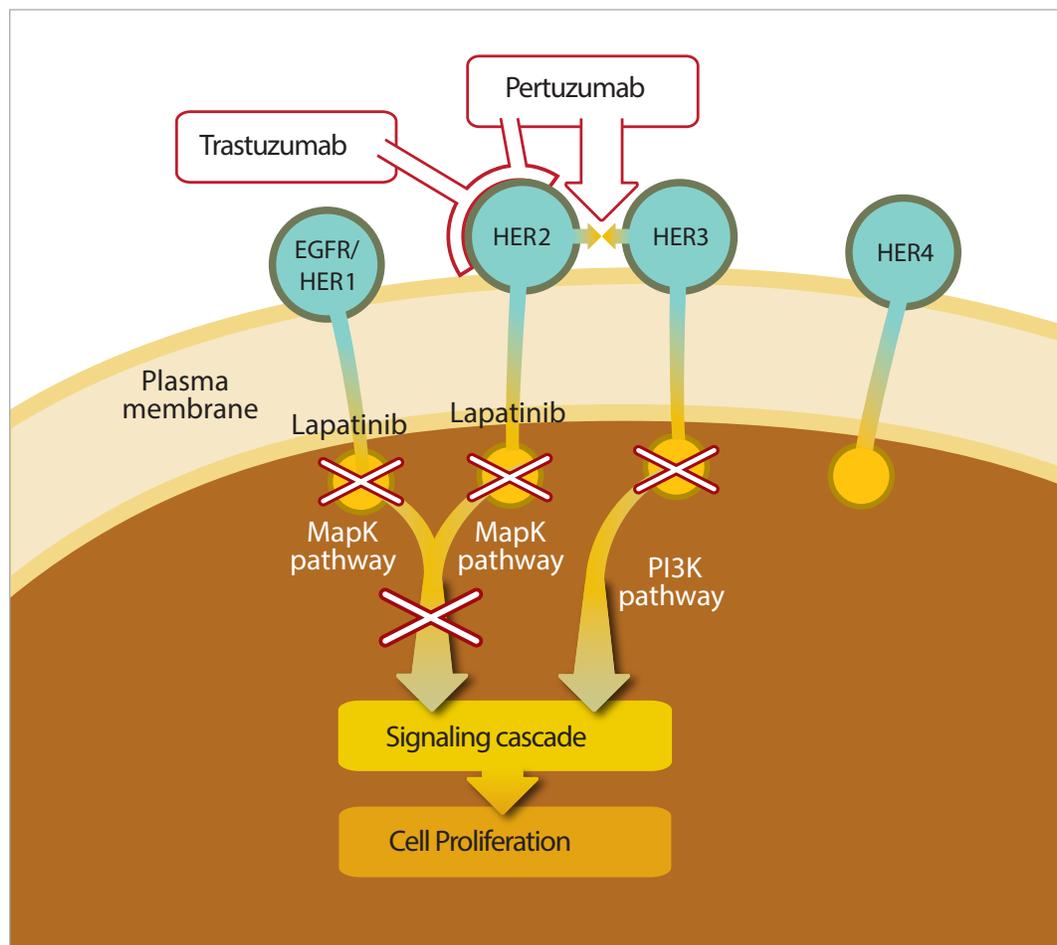
Mechanism of action

Lapatinib

This medication is a small molecule tyrosine kinase (TK) inhibitor that crosses the cell membrane to work inside cancer cells. It targets the intracellular portion of EGFR and HER2 receptors in order to prevent the transmission of biochemical signals within cells that promote cancer-cell growth and proliferation.^{1,4,5,9}

Pertuzumab, trastuzumab

- These two medications are monoclonal antibodies that work outside cancer cells. They target the extracellular portion of HER2 receptors to stop the transmission of growth signals into cells.^{2,3}
- Trastuzumab binds to the extracellular subdomain IV on the juxtamembrane region of HER2 to inhibit tumor cell growth.¹⁰
- Pertuzumab binds to the dimerization subdomain II on HER2, blocking dimerization with other HER family members. As a result, it inhibits the mitogen activated protein kinase (MAPK) and phosphoinositide 3 kinase (P13K) signalling pathways. By interrupting signal transmission along these pathways, it stops cancer cell growth and restores apoptosis.²



Basic pharmacokinetics

Lapatinib is metabolized in the liver via the CYP3A4 and CYP2C8 pathways. It will interact with strong inducers or inhibitors of these pathways, causing significant changes in plasma concentrations of lapatinib within the body.¹ For example, carbamazepine can reduce systemic exposure to lapatinib by about 72%, while ketoconazole can boost it about 3.6-fold.¹

Because lapatinib inhibits P-glycoprotein (PGP), it will alter the plasma levels of drugs that are PGP substrates. This medication can prolong the QT interval and should be used with caution in patients with hypokalemia, hypomagnesemia or congenital long QT syndrome, and patients who use anti-arrhythmic medications or other medicines that lead to QT prolongation.¹

There are no known drug-drug interactions with trastuzumab and pertuzumab; however, the use of combination therapy with anthracyclines is contraindicated due to the higher risk of cardiovascular adverse events.^{2,3}

Presentation, prevention and management of common adverse events

The following tables summarize the most common adverse events of HER2 inhibitors.¹ The adverse-event profiles differ, primarily because trastuzumab and pertuzumab block HER2, while lapatinib blocks HER1/EGFR and HER2.¹⁻³

HER2 inhibitors are often combined with other anticancer medications. These combination regimens may give rise to adverse events that are not associated with HER2 inhibitors but are attributable to another medication in the therapeutic regimen. A prime example is hand-foot skin reaction, also known as hand-foot syndrome and palmar-plantar erythrodysesthesia.^{1,10} It occurs in 53% of patients on lapatinib-capecitabine therapy but <1% of patients taking lapatinib alone.^{1,11}

When trastuzumab is used alone after surgery and/or chemotherapy, the frequency of all common adverse events is below 10%.³ When used in combination therapy after surgery, trastuzumab exacerbates common adverse events of paclitaxel or docetaxel.³

Lapatinib was evaluated in combination with capecitabine versus capecitabine alone.¹

Pertuzumab was evaluated in combination with trastuzumab and docetaxel versus trastuzumab, docetaxel and placebo. The combination of trastuzumab and pertuzumab may potentiate the severity of some adverse events.²

The following tables report adverse events with an overall frequency of $\geq 10\%$ or a $>10\%$ frequency in the combination group versus the control group.

Common adverse events of HER2 inhibitors

Click on adverse events highlighted in blue for more information.

Lapatinib¹

Gastrointestinal disorders

- **Diarrhea**
- Nausea
- **Stomatitis [Photo]**

Hepatic disorders

- Abnormal liver function tests

Skin and subcutaneous tissue disorders

- **Rash [Photo]**

Pertuzumab²

Gastrointestinal disorders

- **Diarrhea**

General disorders

Chills

Infection

- Upper respiratory tract infections

Skin and subcutaneous tissue disorders

- **Rash [Photo]**

Trastuzumab³

Endocrine disorders

- Hot flashes

General disorders

- Fatigue

Musculoskeletal and connective tissue disorders

- Arthralgia

Nervous system disorders

- Headache

Respiratory disorders

- Nasopharyngitis

Other adverse events of interest with HER2 inhibitors

Click on adverse events highlighted in blue for more information

- **Infusion reactions**

Refer for medical attention

Tell patients to seek immediate emergency care if any of these adverse events develop:¹⁻³

- 4 extra bowel movements per day or night-time diarrhea³
- Shortness of breath, which may signal heart problems in women with water retention in the lower legs, anemia with dizziness, a racing heart, or lightheadedness, or lung problems in women with a persistent wheeze or cough^{2,3}
- Signs of infection (fever, chills, sore throat, redness, pain), as these symptoms may be a sign of a reduced white blood cell count^{2,3}
- An abnormal heartbeat, which may signal a heart problem, such as left ventricular dysfunction or congestive heart failure, a less common but potentially serious adverse events of trastuzumab and pertuzumab^{3,5}
- Severe liver damage (itching, yellow eyes or skin, dark urine, tiredness, or pain in the upper right belly), a rare but potentially life-threatening adverse event of lapatinib. Symptoms can occur within days or several months after initiation of treatment^{1,4}

◀ Diarrhea

There are no evidence-based guidelines for the management of diarrhea in patients who take lapatinib.¹² Recommendations are generally based on those for chemotherapy-induced diarrhea.¹² Dietary modifications are not recommended in anticipation of diarrhea.¹³

Management OTC therapy ¹³⁻¹⁴	Mild to moderate (less than 4 loose stools per day) <ul style="list-style-type: none">Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) Moderate (more than 4 to 6 loose stools per day or night-time diarrhea) <ul style="list-style-type: none">Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hoursThis dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea
Replace lost fluids ¹³⁻¹⁵	<ul style="list-style-type: none">Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 to 4 litres per day.Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care ¹³	Advise patients to: <ul style="list-style-type: none">Clean the anal area with mild soap and warm water after each bowel movement to prevent irritationApply a barrier cream or ointment, such as petroleum jelly or Isle's pasteSoak in a warm bathtub or sitz bath to relieve discomfortExamine the anal area for red, scaly or broken skin
Diet ¹³⁻¹⁵	Advise patients to: <ul style="list-style-type: none">Eat and drink small quantities of food oftenAvoid spicy, greasy, or fried foodsFollow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolveFollow a lactose-free diet¹⁰Avoid cabbage, brussels spouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

Diarrhea occurs in 65% of patients taking lapatinib and capecitabine. Diarrhea is the most common reason for lapatinib cessation in clinical trials.¹⁵ Diarrhea develops in about 46% of patients with metastatic breast cancer who are treated with pertuzumab, trastuzumab and docetaxel, and in about 27% of patients taking trastuzumab for advanced breast cancer.¹⁻³

When patients seek OTC treatment for diarrhea, it is important to ask them about:^{5,13-15}

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Stomach cramps

When to refer

Almost 14% taking lapatinib and capecitabine develop severe diarrhea (4 extra bowel movements per day or night-time diarrhea²). Urge these patients to consult their doctor for treatment if:^{4,13,16}

- They do not respond to loperamide after >24 hours
- Fever is present

◀ Infusion reactions

Infusion reactions, associated with trastuzumab and pertuzumab, include chills, fever, or tachycardia. They are usually encountered in the clinic or hospital setting and will not be discussed here.^{2,3}

◀ Rash

Skin rash **[Photo]** occurs in up to 28% of patients on lapatinib plus capecitabine therapy versus 14% on capecitabine alone.¹ When combined with chemotherapy, trastuzumab and pertuzumab worsens rash, which occurs less often than in lapatinib-treated patients.^{2,3}

Some evidence suggests that the early introduction of preventive strategies may reduce the severity of skin reactions.¹⁷ Prevention and treatment of lapatinib-related rash are based on clinical experience with EGFR-induced rash, even though lapatinib-related rash differs from the latter in both frequency and severity.^{4,5,10,12,18}

Prevention

A proactive approach is critical in managing rash.¹⁸ When patients begin therapy, advise them to:^{5,19-21}

- Cleanse with mild soap or hypoallergenic cleaners or shower oils to avoid skin dryness.
- Take short showers with warm water
- Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion.
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics.
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®
- Use a broad-spectrum sunscreen (SPF of 30 or more) that contains zinc oxide or titanium dioxide.

Management	<p>Mild^{5,20,21}</p> <ul style="list-style-type: none"> Localized Reddish skin spots or bumps without other symptoms No impact on daily activities No sign of infection 	<p>No treatment or OTC therapy:</p> <ul style="list-style-type: none"> Topical hydrocortisone 0.5% cream²¹ <p>Advise patient to monitor the rash for changes in severity.¹⁻³ Refer to doctor if rash persists after 2 weeks of treatment or worsens.²⁰</p>	<p>Prescribed medications</p> <ul style="list-style-type: none"> Topical agents with anti-inflammatory properties, such as hydrocortisone 1% to 2.5% cream, metronidazole cream or clindamycin 1% cream or topical solution²¹
	<p>Moderate^{5,20,21}</p> <ul style="list-style-type: none"> Localized skin peeling or sloughing Reddish skin spots or bumps with other symptoms, e.g., redness, itchiness, burning, swelling, or tenderness Lesions cover <50% of body surface Minimal impact on daily activities 	<p>Advise patient to monitor the rash for changes in severity.¹⁻³</p> <p>Advise patient to consult doctor if symptoms persist or worsen after 2 weeks of treatment.²⁰</p>	<p>Prescribed medications:^{20,21}</p> <ul style="list-style-type: none"> Hydrocortisone 2.5% cream, clindamycin 1% cream or topical solution PLUS Doxycycline (100 mg PO BID or BID) or minocycline (100 mg PO BID) <p>For moderate or severe symptoms: Fluocinonide 0.05% cream BID with hydrocortisone 2.5%²⁵</p>

Key facts: Rash

Most lapatinib-related rashes are:^{19,20}

- Mild to moderate in severity
- Develop early in treatment
- Inflammatory rather than infectious in nature

Unlike EGFR-induced rash, lapatinib-related skin rashes usually appear on the trunk and infrequently on the face. Pruritus is rare. The rash usually resolves during treatment, after a temporary interruption of treatment, or when therapy ends.²⁰ There is no evidence that skin rash may signal a positive response to lapatinib in patients with breast cancer.²⁰

To determine the best strategy for managing rash, it is important to ask patients if they have other symptoms. The presence of other symptoms may indicate a need to refer patients to a doctor or dermatologist for treatment. These symptoms include:⁵

- Burning
- Edema
- Itchiness
- Redness
- Tender skin

◀ Stomatitis

Stomatitis **[Photo]** occurs in about 15% of patients taking lapatinib.¹ The incidence of stomatitis is much lower in patients taking trastuzumab and pertuzumab.²⁻³

Prevention	Advise patients to: ^{22,23} <ul style="list-style-type: none">• Avoid cheek or lip biting• Avoid mouth breathing• Maintain good oral hygiene• Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly• Avoid spicy and highly textured foods• Avoid highly flavoured and alcohol-containing mouthwashes	
Management	OTC treatment For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips Meticulous oral hygiene: ^{22,23} <ul style="list-style-type: none">• Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles• If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®• Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria• Floss gently once daily to avoid gum injury• Salt rinses (1/2 teaspoon of salt in 1 cup of warm water at least 4 times daily, especially after meals)• Bland rinses, antimicrobial mouthwash without alcohol• OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®) Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips. ¹⁶	Prescribed medication (moderate to severe cases): ^{22,23} <ul style="list-style-type: none">• Topical fluoride (dentist)• Topical anesthetics• Corticosteroid solution• Topical or systemic analgesics• Topical or systemic antifungals• Palliative mixtures of various agents

Key facts: Stomatitis

This adverse event occurs in 14% to 28% of patients taking HER2 inhibitors¹⁻³. Lapatinib-induced stomatitis may be related to its effects on EGFR, as stomatitis is a common adverse event of EGFR inhibitors.^{22,23}

There are no evidence-based strategies for its management. Maintaining mucosal health, integrity, and function is crucial in patients with stomatitis. Treatment aims to relieve symptoms until the mucous membranes can rejuvenate themselves, usually within 7 to 14 days. Smokers have a greater risk of stomatitis.²³

Clinical practice guidelines stress the importance of oral hygiene in cancer patients, but due to a lack of supportive evidence, the methods are usually based on personal preference and anecdotal experience.²²

The use of chlorhexidine mouth rinses is not recommended.

They contain alcohol and may sting. Dilution defeats their antibacterial benefits.²³

Hydrogen peroxide rinses may worsen mouth ulcers.²³

Good oral hygiene:^{22,23}

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

There are no evidence-based guidelines for treatment of EGFRi-induced stomatitis, and practitioners usually follow the common practices for chemotherapy-induced dry mouth.

Topical preparations in widespread use for stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. Antiseptic mouthwashes may provide some symptomatic relief.²⁴ There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Patients should avoid alcohol or peroxide-based mouthwashes.²⁴ Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, “magic” mouthwashes that contain lidocaine, versus salt-and-baking soda rinses.²² Refer patients to a doctor for treatment.²⁴

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MEK1/MEK2 inhibitors

Trametinib (Mekinist™)

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This chapter contains information on the prevention and management of common adverse events of mitogen-activated extracellular signal-regulated kinase 1 and 2 (MEK1/MEK2) inhibitors that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage MEK1/MEK2 inhibitor-induced adverse events. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events of this agent, please consult the product monograph.¹

One oral medication is currently available that inhibits the action of MEK1/MEK2, which are critical components of the mitogen-activated protein kinase (MAPK) signaling pathway.¹



MEK1/MEK2 in cancer

The RAS effector pathway, RAS-MEK-ERK, is an essential component of the mitogenic signaling network. When activated, protein kinase receptors pass signals along this series of pathways to provoke a wide range of normal cellular responses, including:¹

- Cell growth
- Cell differentiation
- Inflammation
- Cell death (apoptosis)

Mutant BRAF and RAS proteins permanently switch on MEK1 and MEK2 protein kinase receptors, which send a constant flood of signals along the MAPK pathway. This consecutive action stimulates cell growth. BRAF mutations occur with high frequency in specific cancers, including about 50% of melanoma.¹

Drug administration

Trametinib

- Patients should swallow this medication with a full glass of water at the same time once daily. Advise them to take trametinib on an empty stomach without food, at least one hour before or two hours after a meal.¹
- Patients who miss a dose should take it as soon as they remember. However, advise them not to take a missed dose within 12 hours of their next dose.¹

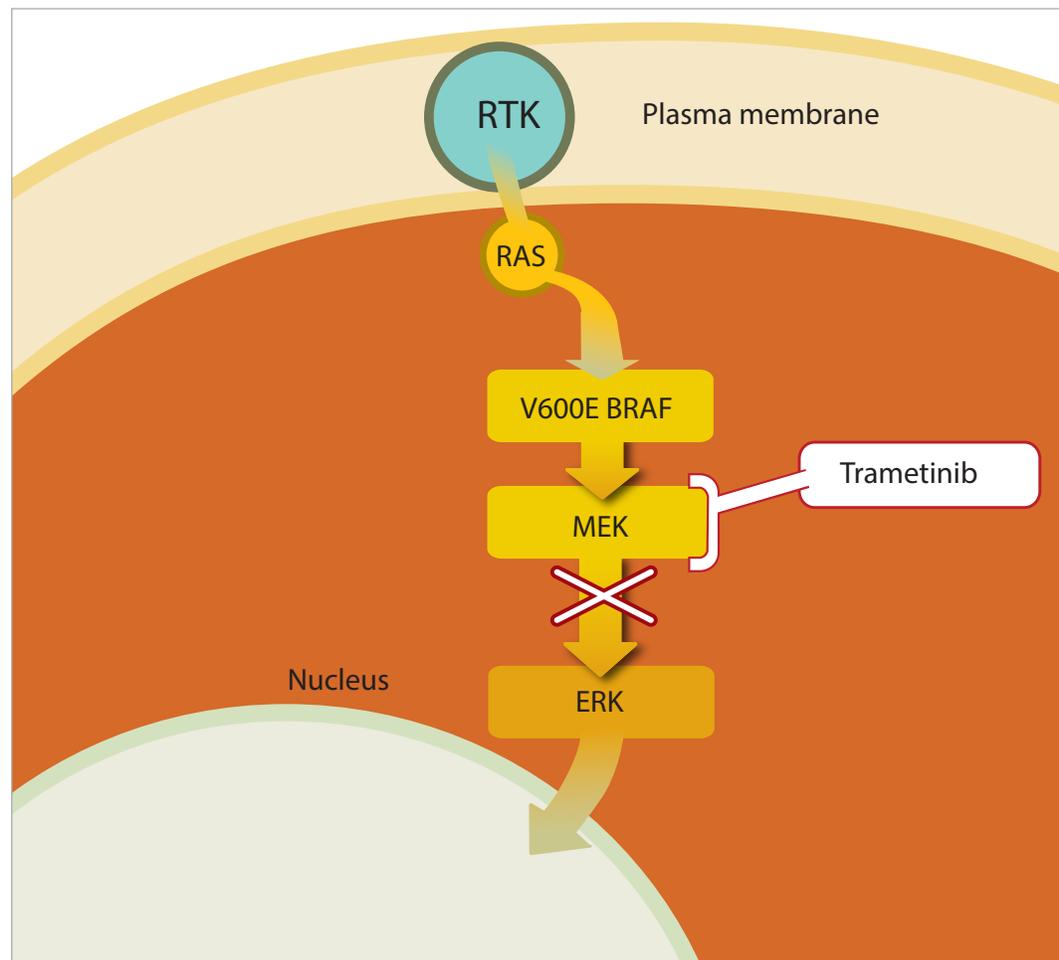
Mechanism of action

Trametinib reversibly inhibits MEK1 and MEK2 activation and kinase activity, switching off abnormal signaling along the MAPK pathway, which is activated by BRAF V600 mutation.

This action inhibits:¹

- Cancer cell growth
- Cancer cell proliferation

When combined with a BRAF inhibitor, trametinib may prevent the BRAF inhibitor-induced, concurrent, paradoxical activation of the MAPK pathway downstream of RAF kinases.^{2,3}



Basic pharmacokinetics

Trametinib is unlikely to interact with CYP metabolizing enzymes and transporters.¹

Trametinib can affect heart rhythm. Advise caution, particularly in patients with heart problems, when trametinib is combined with antiarrhythmics, beta blockers, non-dihydropyridine calcium channel blockers, digoxin, and some HIV protease inhibitors, which prolong the heart's PR interval.¹

Presentation, prevention and management of common adverse events

Because trametinib acts on the MAPK pathway, some adverse events are similar to those of BRAF inhibitors. Almost all patients taking trametinib have adverse events of one kind or another; 1 of 5 patients experience severe adverse events. Women with lower body weights tend to experience more adverse events than men. Older patients ≥ 65 years may experience common and serious adverse events more often than younger patients.¹

The following table summarizes the common adverse events of MEK1/MEK2 inhibitors with an overall frequency of $\geq 10\%$.

Common adverse events of MEK1/MEK2 inhibitors

Click on adverse events highlighted in blue for more information.

Trametinib¹

Gastrointestinal disorders

- Constipation
- **Diarrhea**
- Nausea
- Vomiting

General disorders

- Fatigue
- **Fluid retention** (peripheral edema)

Hepatic disorders

- Abnormal liver enzyme levels
- Infection

Nervous system disorders

- Headache

Respiratory disorders

- Cough

Skin and subcutaneous disorders

- Acne-like rash
- Alopecia
- Folliculitis
- **Paronychia [photo]**
- **Pruritus**
- **Rash [photo]**
- **Xerosis**

Vascular disorders

- **Hypertension**
- Hemorrhage

Other adverse events of interest with MEK1/MEK2 inhibitors

Click on adverse events highlighted in blue for more information.

- **Eye disorders**
- **Left ventricular dysfunction**
- **PR interval prolongation**

Refer for immediate medical attention

Tell patients to seek immediate emergency care if any of these uncommon adverse events develop:¹

- Patients with signs or symptoms of serious heart problems: pounding, racing or irregularly beating heart
- Patients with vision problems, such as seeing coloured dots, halos or blurred outlines around objects, blurred vision, loss of vision
- Patients with signs or symptoms of interstitial lung disease or non-infectious pneumonitis (shortness of breath, fever, cough, feeling out of breath, new or worsening respiratory symptoms)

◀ Diarrhea

Diarrhea occurs in 44% of patients who take trametinib but is rarely severe.¹ It often has early warning signs. Early recognition and intervention may lead to a more favorable outcome. Loperamide is recommended to treat mild (<4 stools per day) to moderate diarrhea (≥4 to 6 stools per day) in patients treated with targeted therapies.^{1,3,6} Dietary modifications are not recommended in anticipation of diarrhea.⁸

Management OTC therapy ⁷⁻⁹	Mild to moderate (less than 4 loose stools per day) <ul style="list-style-type: none">Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) Moderate (more than 4 to 6 loose stools per day) <ul style="list-style-type: none">2 tablets immediately, then 1 tablet every 2-4 hours until bowel movements are normal for at least 12 hours
Replace lost fluids ⁷⁻⁹	<ul style="list-style-type: none">Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 to 4 litres per day.Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care ⁷	Advise patients to: <ul style="list-style-type: none">Clean the anal area with mild soap and warm water after each bowel movement to prevent irritationApply a barrier cream or ointment, such as petroleum jelly or Isle's pasteSoak in a warm bathtub or sitz bath to relieve discomfortExamine the anal area for red, scaly or broken skin
Diet ⁷⁻⁹	Advise patients to: <ul style="list-style-type: none">Eat and drink small quantities of food oftenAvoid spicy, greasy, or fried foodsFollow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolveFollow a lactose-free diet¹¹Avoid cabbage, brussels spouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

When patients seek OTC treatment for diarrhea, it is important to ask them about:^{8,9}

Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal

- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Abdominal pain

◀ Eye disorders

Patients are advised, if clinically relevant, to have a thorough eye examination before they start trametinib and to see their ophthalmologist for eye evaluation, if vision problems develop. Uncommonly, this medication may block the retinal vein that drains the eye, causing retinal vein occlusion (RVO). This adverse event causes a progressive loss of vision, glaucoma, and other serious eye problems. People with hypertension, diabetes, high cholesterol levels, and glaucoma are at higher risk of RVO. As RVO can result in blindness, immediately refer patients with symptoms to a doctor for evaluation.^{1,6,22}

Most trametinib-induced vision or eye problems are usually mild, reversible, and improve spontaneously. Another uncommon ocular adverse event of trametinib is retinal detachment (RPED). Usually bilateral and multifocal, it occurs in the macular region of the retina. Symptoms include blurred vision and loss of visual acuity. They usually resolve after dose interruption or discontinuation of treatment; however, RPED may recur after treatment resumes.^{1,6,22}

◀ Fluid retention

Fluid retention (edema) is a common adverse event of trametinib, occurring in about 30% of patients.^{1,3,10}

Prevention	<p>Advise your patients to:^{11,12}</p> <ul style="list-style-type: none">• Limit salt intake <p>For swollen eyelids or swelling around eyes:¹¹</p> <ul style="list-style-type: none">• Use cold compresses³• Elevate head during sleep <p>For swollen legs:³</p> <ul style="list-style-type: none">• Elevate legs• Use compression therapy
Management	<p>OTC therapy</p> <p>Mild periorbital fluid retention</p> <ul style="list-style-type: none">• For swelling around eyes, elevate the head during sleep or use skin-tightening agents, e.g., topical Preparation H® containing phenylephrine or lanolin (avoid eye contact)¹¹ <p>Prescribed therapy</p> <p>Mild peripheral fluid retention</p> <ul style="list-style-type: none">• Topical eye ointments with phenylephrine 0.25%^{11,12}• Topical corticosteroid (e.g., hydrocortisone 1%)¹¹ <p>Moderate fluid retention</p> <ul style="list-style-type: none">• Low-dose loop diuretic, e.g., furosemide. Potassium or magnesium supplements may be necessary¹¹• Close electrolyte monitoring¹¹ <p>Refer severe cases to a doctor for evaluation and treatment.³</p>

Key facts: Fluid retention

Peripheral fluid retention

Peripheral fluid retention (edema) is usually superficial and mild to moderate in severity. The most frequent forms of fluid retention are in the extremities (hands and legs) Some patients may have swelling around the eyes (periorbital edema).^{3,10}

◀ Hypertension

About 17% of patients on trametinib develop hypertension, and the presentation is often severe (systolic BP \geq 160 mm Hg or diastolic BP \geq 100 mm Hg). The onset of high blood pressure (hypertension) may occur between 3 and 9 weeks after therapy begins.¹

Monitoring	Encourage patients to: ¹ <ul style="list-style-type: none">• Monitor their blood pressure (BP) at weekly intervals or at more frequent intervals if they already have hypertension	
Management	Refer for antihypertensive therapy: ¹³ <ul style="list-style-type: none">• Patients with recurrent, symptomatic, or persistent systolic BP \geq140 mm Hg	Prescribed therapy: <ul style="list-style-type: none">• Most hypertension can be managed with standard oral antihypertensive therapy.¹

Key facts: Hypertension

Trametinib may cause an average rise of 5 mm Hg in systolic BP and 4 mm Hg in diastolic BP in some patients. For that reason, patients are encouraged to routinely monitor their blood pressure (BP) levels during treatment and should be referred to their doctor for antihypertensive therapy, if appropriate.¹

◀ Left ventricular dysfunction

Notably, trametinib may cause left ventricular dysfunction (LVD).¹ This adverse event, which can lead to heart failure, occurs in 8% of patients. The median time of onset is 8 weeks. For that reason, patients are evaluated for LVD before therapy begins, 8 weeks later, and periodically throughout treatment. Patients with LVD or other heart problems are at higher risk of developing this complication.¹

◀ PR interval prolongation

On electrocardiography (ECG), trametinib causes a concentration-dependent prolongation of the PR interval. For that reason, caution is used when treating patients with pre-existing conduction system defects in the heart, such as AV block, and syncope.¹

◀ Paronychia

Paronychia **[Photo]** is a painful inflammation that occurs around finger and toe nails in up to 11% of patients treated with trametinib.¹ It typically appears after 3 months of treatment and is similar to and managed in the same way as EGFR-induced paronychia.¹⁰

Prevention	Advise your patients to: <ul style="list-style-type: none">• Wear comfortable, loose-fitting shoes to avoid friction or pressure on nail folds^{14,15}• Avoid biting nails or cutting them too short¹⁵• Maintain clean, short fingernails• Keep hands dry; minimize water exposure by wearing waterproof gloves• Soak fingertips in a 1:1 mixture of water and vinegar³	
Management	OTC treatment <ul style="list-style-type: none">• Topical antiseptics, antifungals, or antibiotics (soaks or creams) to prevent or treat mild infection^{3,14}• Epsom salts or Buro sol® (aluminum acetate) soaks daily¹⁶• Weekly application of topical silver nitrate to treat hamburger-like bumps¹⁴• Foot cushioning products for extra comfort¹⁴	Refer to doctor for pain in nail bed, nail loss, signs of infection ^{14,16} Prescription medication <ul style="list-style-type: none">• Topical antimicrobials, such as mupirocin and nystatin ointment¹⁵• Topical corticosteroid, such as 1% triamcinolone ointment¹⁵• For severe cases, oral antifungals or antibiotics⁶

Key facts: Paronychia

Although not infective in origin, paronychia makes nails more sensitive to infection.¹⁴ Nails tend to grow slower, become brittle, and crack.¹⁷

Paronychia can be painful and mimic an ingrown nail.¹² It may interfere with simple manual work or prevent the patient from wearing any shoes but sandals.¹⁷ It may take weeks to heal and may not resolve unless therapy stops for a short period or ends.^{16,17} In severe cases, abscesses and small, red, oozing, and bleeding bumps that look like raw hamburger meat develop in nail folds.¹⁷

Refer to a doctor
A podiatrist may not provide adequate foot care in this context.

◀ Pruritus

About 11% (1 in 10) patients treated with trametinib develop pruritus (itchy skin).¹

Prevention	<p>Advise patients to use:¹⁷</p> <ul style="list-style-type: none">• Mild soaps, such as Dove® or Neutrogena®• Bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion <p>Advise patients to:³</p> <ul style="list-style-type: none">• Maintain a cool ambient environment• Wear loose-fitting clothing• Take lukewarm showers, pat dry, and moisturize skin• Avoid fragranced soaps and alcohol-based topical products	
Management	<p>Mild to moderate pruritus</p> <p>Advise patients to:^{3,18}</p> <ul style="list-style-type: none">• Apply more lotion than usual to help reduce or eliminate itchiness on the trunk or extremities• Use lotions with aloe vera or dimethicone Moisturel®• Use antidandruff shampoos and conditioners• Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms¹⁷• Use cold compresses• Take oatmeal baths• Cut fingernails short to curtail scratching <p>Medical management:</p> <ul style="list-style-type: none">• Medium- or high-strength topical corticosteroids• Oral antihistamines	<p>Moderate to severe pruritus</p> <p>Refer to doctor for intense, widespread itching</p> <p>Oral anti-H1 (first or second generation) antihistamines may provide some relief¹⁷</p> <p>Dose reduction or temporary discontinuation should be considered.³</p>

Key facts: Pruritus

Pruritus or itchiness is the consequence of loss of skin moisture. Pruritus may be mild or localized, widespread or intense, or worsen to the point where it interferes with daily activities. Pruritus may be an isolated finding or appear in association with rash or xerosis (dry skin).³

◀ Rash

Various forms of rash **[Photo]** are a very common adverse event of trametinib. Rash occurs in 59% of patients, while acne-like rash (dermatitis acneiform) occurs in 19% of patients.¹

<h3>Prevention</h3>	<p>A proactive approach is critical in managing rash.¹⁷ When patients begin therapy, advise them to:^{14,19,20}</p> <ul style="list-style-type: none"> • Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness • Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion. • Take oatmeal baths to soothe skin³ • Use only fragrance-, alcohol-, and dye-free lotions and cosmetics • Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX® • Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove® • Use a broad-spectrum sunscreen (SPF of 30 or more) that contains zinc oxide or titanium dioxide 		
<h3>Management</h3>	<p>Mild²⁰</p> <ul style="list-style-type: none"> • Localized • Few symptoms • No impact on daily activities • No sign of infection 	<p>No treatment or OTC therapy:</p> <ul style="list-style-type: none"> • Topical corticosteroids (e.g., hydrocortisone 0.5% cream)²⁰ • Mild soap and cleansing gels (eg: Toleriane dermo-cleanser, Cetaphil, Spectro® Cleanser for Blemish-Prone Skin and Combination Skin)^{10,16} • Moisturizers twice daily, particularly ceramide-containing products (e.g., Curel®, Cerave®, Cutibase®, Ceramyl®, EpiCeram®)³ <p>Advise patient to monitor the rash for changes in severity.¹ Refer to doctor if rash persists after 1-2 weeks of treatment or worsens in severity.^{3,15}</p>	<p>Prescribed medications:</p> <ul style="list-style-type: none"> • Topical agents with anti-inflammatory properties, such as hydrocortisone 1% to 2.5% cream, metronidazole cream or clindamycin 1% cream or topical solution²⁰

	<p>Moderate²⁰</p> <ul style="list-style-type: none"> • Generalized • Mild symptoms (e.g., itching, tenderness) • Minimal impact on daily activities <p>Refer to doctor.</p>	<p>Advise patient to monitor the rash for changes in severity.¹</p> <p>Advise patient to consult doctor if symptoms persist or worsen after 1-2 weeks of treatment.^{3,15}</p>	<p>Prescribed medications:^{3,18,20}</p> <ul style="list-style-type: none"> • Hydrocortisone 2.5% cream, clindamycin 1% cream or topical solution, or other topical corticosteroid <p>PLUS</p> <ul style="list-style-type: none"> • Doxycycline (100 mg PO BID) or minocycline (100 mg PO BID)¹⁰
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Key facts: Rash

Trametinib-induced skin reactions are similar to EGFR inhibitor-induced, papulopustular rashes. Spots or small raised bumps with or without fluid appear on the face and trunk. This rash occurs early in treatment, usually within the first 2 to 4 weeks of therapy. The incidence decreases when trametinib is combined with a BRAF inhibitor. The rash is dose-dependent and mostly mild to moderate in severity. Dose adjustment is rarely necessary, unless the rash becomes severe. Less than 7% of rashes are moderately severe or severe.^{3,10}

Dose modification occurs when patients develop a moderate to moderately severe rash. If an intolerable rash does not improve within 3 weeks of dose reduction or the patient has a severe rash, treatment is withheld for up to 3 weeks, then resumed at a lower dose. If a rash persists at this point, treatment is permanently discontinued.¹

Due to its resemblance to EGFR-induced rashes, trametinib-induced papulopustular rashes are managed similarly.¹⁰

◀ Xerosis

Xerosis (dry skin) occurs in about 13% of patients treated with trametinib and usually appears after the rash.^{1,10}

Prevention	<p>Advise patients to:^{3,6,10,14,19,20}</p> <ul style="list-style-type: none"> • Cleanse with mild soaps or cleaners or shower oils to avoid skin dryness • Take short showers with warm water, pat dry after bathing • Moisturize twice a day with a colloidal oatmeal lotion, such as Aveeno® lotion, ceramide-containing moisturizer, or thick, emollient-based creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion • Use only fragrance-, alcohol-, and dye-free lotions and cosmetics • Use a broad-spectrum sunscreen • Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®
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Management

First signs of skin dryness
Dry skin on face, back, chest

Advise patient to:

- Switch to oil-in-water creams¹⁴
- Apply ceramide-containing moisturizer to affected areas 2 to 3 times daily³
- Concurrent application of prescription-strength emollients that contain ammonium lactate, urea, and salicylic acid or topical corticosteroids to all regions except the face, skin folds, and genitalia³

For mild xerosis, apply ammonium lactate 12% cream (Hydrolac or Lac-Hydrin[®]) on the body twice daily; if no relief occurs after 2 weeks, utilize salicylic acid 6% cream twice daily as tolerated; if still no relief proceed to recommendations for moderate xerosis³

Moderate to severe xerosis
Dry skin on limbs

- Use greasy water-in-oil creams or ointments¹⁴
- Apply ceramide-containing moisturizer to affected areas 2 to 3 times daily (e.g., Curel[®], Cerave[®], Cutibase[®], Ceramyl[®], EpiCeram[®])³
- Concurrent application of prescription-strength emollients that contain lactate, urea, and salicylic acid or topical corticosteroids to all regions except the face, skin folds, and genitalia³

For moderate xerosis, apply either ammonium lactate 12% cream or salicylic acid 6% cream twice daily; if no relief occurs after 2 weeks, refer to doctor³

Eczema

Short-term use (1-2 weeks) of weak topical corticosteroid creams¹⁴

Refer to doctor if uncontrolled by OTC treatment

Infection

Topical antibiotics¹⁴

Refer to doctor if uncontrolled by OTC treatment

Skin fissures

Treatment options¹⁷

- 50% propylene glycol under a plastic bandage
- Salicylic acid 10% ointment
- Colloid dressing

Refer to doctor if uncontrolled by OTC treatment

Key facts: Xerosis

Trametinib-induced xerosis is similar to EGFR-induced xerosis. Dry, scaly skin appears on the limbs, torso and areas of trametinib-induced rash, usually after several weeks of therapy. It is sometimes associated with fissures and pruritus. Management is similar to the treatment of EGFR-induced dry skin.¹⁰

Xerosis often affects the fingertips, heels, and toes. Painful fissures may develop in these areas, in nail folds and over finger joints in excessively dry skin – a condition that can make wearing shoes or performing tasks difficult for patients.^{14,15,17,21}

Apart from general hydrating measures, choice of the right treatment is critical to alleviate skin dryness. The frequent application of emollients that contain ammonium lactate, e.g., hydrolac or Lac-Hydrin®, or 5% to 10% urea, e.g., Eucerin® 5 or Uremol® 10, may substantially improve xerosis.¹⁸ Advise patients to avoid occlusive topical creams and lotions that can obstruct hair follicles, which may lead to infection.^{10,17}

Xerosis tends to worsen with:^{10,14,15,17}

- Older age
- Prior history of atopic eczema
- Previous treatment with cytotoxic agents

Dry skin may become increasingly fragile and bruise easily. Xerosis may worsen, becoming chronically red and irritable. Secondary infection with *S. aureus* may occur.^{14,15}

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mTOR inhibitors

Everolimus (Afinitor®)

Temsirolimus (Torisel®)

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This chapter contains information on the prevention and management of common adverse events of mTOR inhibitors that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage mTOR-induced adverse events. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events of these agents, please consult the product monographs.^{1,2} Infusion reactions, which may occur with intravenous medications, are usually encountered in the clinic or hospital setting and will not be described here.

Two medications are available that inhibit the action of the mammalian target of rapamycin (mTOR) signaling network. The route of delivery, dosing schedule, and adverse events of these medications differ.^{1,2}



mTOR in cancer

In the 1970s, rapamycin, a natural product with antiproliferative effects, was discovered in the soil of Easter Island. Two decades later, the mammalian target of rapamycin (mTOR) was identified as a serine-threonine protein kinase that regulates a cell-signaling pathway that controls cell-cycle progression, cell proliferation, and angiogenesis.^{3,4}

The mTOR signaling pathway is incredibly complex, but one of its essential functions is to balance growth factor and nutrient signals. Growth factors activate mTOR, whereas low nutrient availability, e.g., low glucose or oxygen supplies, inhibits mTOR. When well regulated, this signaling network ensures that cell growth occurs under favourable conditions. When conditions are unfavourable, mTOR slows growth.⁴

The mTOR pathway acts like an on-off switch to regulate cell-cycle progression (cell division) in response to growth signals. It regulates the:⁴

- Cellular machinery that controls protein synthesis
- Proteins that control cell division
- Tumour suppressor functions that control new blood-vessel growth and cell survival

Drug administration

Everolimus

This oral medication should be swallowed at the same time (preferably in the morning) once daily, either consistently on an empty stomach or consistently with food. Advise your patients not to chew or crush the tablets.¹

Temsirolimus

This medication is administered as a weekly intravenous infusion in the hospital or clinic setting.²

How to administer mTor inhibitors

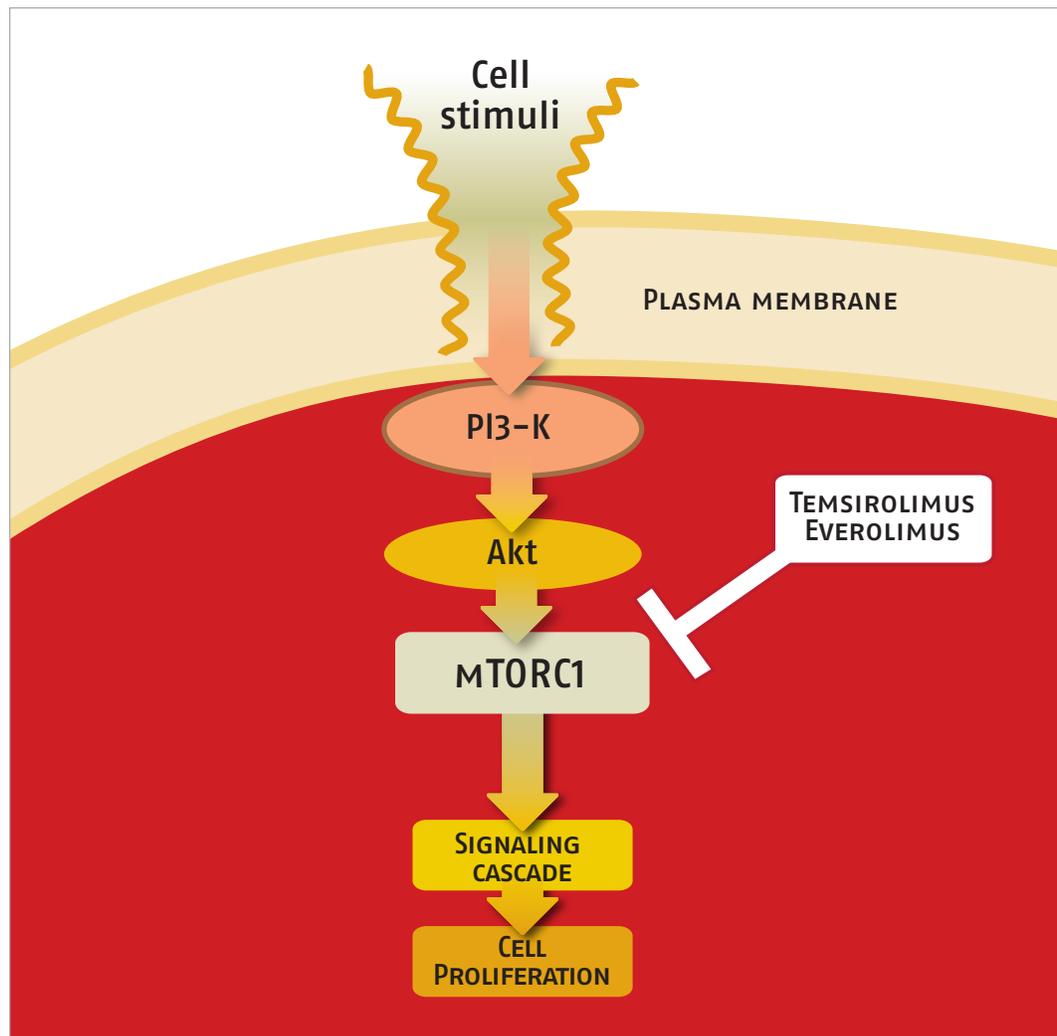
- Avoid grapefruit, star fruit, pomelo, pomegranate and Seville oranges or other foods known to affect cytochrome P450 and PgP activity while taking everolimus.^{1,2}
- Avoid live vaccines and close contact with people who receive them. Examples of live vaccines include BCG, varicella, yellow fever, typhoid, mumps, measles, and rubella.^{1,2}
- mTor inhibitors may inhibit the metabolism of CYP3A4/5 substrates, including statins. Patients taking statins and mTor inhibitors may have a higher risk of developing rhabdomyolysis and should report any muscle pain or weakness.¹

Mechanism of action

Within the cell, everolimus and temsirolimus bind to a specific protein, FKBP-12, to produce a protein-drug complex. This complex binds to the mTOR kinase to neutralize its activity.^{1,2,4,5}

Because the mTOR pathway is dysfunctional in many cancers, mTOR has become an important target for therapy.⁵ In cancer cells, deactivation of the mTOR signaling network by mTOR inhibitors induces cell death and suppresses:^{3,4}

- Protein synthesis (cell growth)
- Cell proliferation
- Angiogenesis
- Spread of cancer cells



Basic pharmacokinetics

Both mTOR inhibitors are metabolized by the CYP3A4 pathway, and co-administration with CYP3A4/5 inducers and inhibitors should be avoided.^{1,2} Temsirolimus inhibits the metabolism of CYP3A4/5 substrates. Both medications are moderate inhibitors of the multidrug efflux pump P-gP and mixed inhibitors of CYP2D6.^{1,2}

Patients who miss a dose of everolimus may still take it up to 6 hours after their usual time. After more than 6 hours, they must skip the dose for the day. They should not take 2 doses on the next day to make up for the missed dose.¹

Presentation, prevention and management of common adverse events

The onset and duration of common adverse events of mTOR inhibitors are often predictable and almost always reversible after treatment ends. There are many ways to minimize or prevent these adverse events.^{1,2} The common adverse events of everolimus generally appear to be similar in type and severity to those of temsirolimus.^{1,2,5}

The following table describes the common adverse events of mTOR inhibitors with an overall frequency of $\geq 10\%$.^{1,2}

Common adverse events of mTOR inhibitors

Click on adverse events highlighted in blue for more information.

Blood and lymphatic system disorders

- Anemia
- Leukopenia (everolimus)
- Neutropenia
- Thrombocytopenia

Cardiovascular disorders

- Hypertension (everolimus)

Gastrointestinal disorders

- Constipation (temsirolimus)
- **Diarrhea**
- Dry mouth (everolimus)
- Nausea
- **Stomatitis [Photo]**
- Vomiting

General disorders

- Asthenia
- Chest pain (temsirolimus)
- Edema
- Fatigue
- Fever
- Nose bleeds
- Pain
- Weight loss

Infection

- Infections
- Upper respiratory tract infections
- Urinary tract infection

Laboratory abnormalities

- Increased creatinine levels
- Increased hepatic enzymes

Metabolism and nutrition disorders

- Anorexia
- Diabetes mellitus
- Hypercholesterolemia
- **Hyperglycemia**
- **Hyperlipidemia**
- Hypertriglyceridemia
- Hypophosphatemia
- Loss of appetite (everolimus)

Musculoskeletal and connective tissue disorders

- Arthralgia
- Back pain
- Pain in extremities (everolimus)
- Muscle spasms (everolimus)

Nervous system disorders

- Dizziness (everolimus)
- Headache
- Taste disturbance

Psychiatric disorders

- Insomnia

Respiratory disorders

- Cough
- Dyspnea
- Oropharyngeal pain (everolimus)
- Pharyngitis (temsirolimus)
- Pneumonitis (everolimus)
- Rhinitis (temsirolimus)

Skin and subcutaneous tissue disorders

- Acne
- Alopecia (everolimus)
- Paronychia
- **Pruritus**
- **Rash [Photo]**
- Xerosis

Refer for medical attention^{1,2,6}

Tell patients to seek emergency care if any of these uncommon adverse events develops:

- Gastrointestinal hemorrhage, bowel perforation. Patients with abdominal pain and constipation or vomiting need to seek immediate medical attention. Early detection of this life-threatening condition is essential.
- Hemorrhage (vaginal, retinal, lung, bloody stool, bloody urine)
- Hemorrhagic stroke (severe headache, weakness or paralysis of limbs or face, difficulty speaking, sudden loss of consciousness)
- Hematologic abnormalities, such as neutropenia, fever, thrombocytopenia
- Infection (bacterial, fungal, viral, protozoal or opportunistic)
- Interstitial lung disease (shortness of breath, fever, cough)
- Metabolic abnormalities, severe hyperglycemia
- Renal failure (low urine output, body swelling, fatigue, abdominal pain)
- Stroke

◀ Diarrhea

Diarrhea occurs in 27% to 50% of patients who take mTOR inhibitors.^{1,2} mTOR inhibitor-induced diarrhea often has early warning signs. Early recognition and intervention may lead to a more favorable outcome.⁷ Loperamide is recommended to treat mild (<4 stools per day) to moderate diarrhea (≥4 to 6 stools per day) in patients treated with targeted therapies.^{1,7,8} Dietary modifications are not recommended in anticipation of diarrhea.⁸

Management	
OTC therapy⁷⁻⁹	<p>Mild to moderate (less than 4 loose stools per day)</p> <ul style="list-style-type: none">• Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) <p>Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)</p> <p>Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea</p> <ul style="list-style-type: none">• 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours• This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea
Replace lost fluids⁷⁻⁹	<ul style="list-style-type: none">• Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 litres per day.• Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care⁸	<p>Advise patients to:</p> <ul style="list-style-type: none">• Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation• Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste• Soak in a warm bathtub or sitz bath to relieve discomfort• Examine the anal area for red, scaly or broken skin
Diet⁷⁻⁹	<p>Advise patients to:</p> <ul style="list-style-type: none">• Eat and drink small quantities of food often• Avoid spicy, greasy, or fried foods• Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve• Follow a lactose-free diet• Avoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

When patients seek OTC treatment for diarrhea, it is important to ask them about:^{7,8}

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Abdominal pain

◀ Hyperglycemia

Hyperglycemia and glucose intolerance are common adverse events of mTOR inhibitors. Ten percent of patients taking everolimus developed diabetes mellitus, and 12% of patients have experienced hyperglycemia (severe 6%). Over 82% of patients taking temsirolimus had at least one episode of hyperglycemia and 26% of patients (severe 11%) developed this adverse event.^{1,2}

Monitoring	Advise patients, particularly those at risk for diabetes, to watch for the following symptoms and, if they appear, report them to their doctor: ^{1,2} <ul style="list-style-type: none">• Frequent urination• Thirstiness• Feeling tired	
Management	Encourage patients to monitor blood glucose levels during treatment ⁶ Refer patients to a certified diabetes educator if available in the community or at the cancer center ⁶ Counsel patient about dietary modification	Prescribed therapy <ul style="list-style-type: none">• Oral antidiabetic agent and/or insulin¹⁰

Key facts: Hyperglycemia

Both oral and intravenous mTOR inhibitors may raise blood glucose levels.^{1,2}

Close monitoring of fasting blood glucose levels and hemoglobin A1c and early intervention for hyperglycemia are recommended.⁵ Patients with pre-existing diabetes may require dosage adjustments to oral antidiabetic medications and/or insulin.⁶

◀ Hyperlipidemia

mTOR inhibitors may increase cholesterol and triglyceride levels. In studies of everolimus, 77% of patients had higher levels of cholesterol and 73%, higher triglycerides.¹ In patients taking temsirolimus, up to 87% had higher levels of cholesterol and 83% had higher triglycerides.²

Because mTor plays a key role in glucose and lipid metabolism, patients may develop glucose intolerance/hyperglycemia and hyperlipidemia while taking mTor inhibitors. At least one study has correlated these adverse events with successful mTor inhibition – an indication that this therapy is working. Since patients who take mTor inhibitors have advanced cancer, it is preferable to control the adverse events than to reduce the therapeutic dosage or stop treatment.^{4,5} The following table lists the common adverse events of both mTor inhibitors.^{1,2}

Prevention	Counsel patients about dietary modification and exercise. ⁵
Management	Prescribed therapy <ul style="list-style-type: none">• Dietary modification• Appropriate lipid-lowering therapy

Key facts: Hyperlipidemia

Due to the possibility of drug interaction, patients who take mTOR inhibitors and statins have a greater risk of rhabdomyolysis – the breakdown of muscle cells that leads to kidney failure.²

◀ Infection

From 25% to 50% of patients taking mTOR inhibitors may develop an infection.^{1,2}

Prevention	Advise patients to: ^{1,2,6} <ul style="list-style-type: none">• To wash their hands frequently and avoid crowded areas• Avoid live vaccines or close contact with people who receive live vaccines, e.g., influenza, measles, mumps, rubella, oral polio, bacillus Calmette-Guérin, yellow fever, TY21a typhoid	
Management	Advise patients to: ⁶ <ul style="list-style-type: none">• Know whom to contact if their temperature rises above 38° C for more than 1 hour or they have a one-time reading of 38.3° C Refer all patients with signs of infection for immediate care	Prescribed therapy depends on type and severity of infection

Key facts: Infection

Because mTOR inhibitors suppress the immune system, patients may be especially vulnerable to opportunistic infections, such as herpes simplex, urinary tract infections, and upper respiratory infections.⁶

Non-infectious pneumonitis

Patients on mTOR inhibitors may develop a non-infectious pneumonitis. Symptoms may be similar to respiratory tract infection and include:^{1,2}

- Shortness of breath
- New or worsening respiratory symptoms
- Cough
- Fever

Refer patients to a doctor immediately.

◀ Pruritus

From 13% to 21% patients treated with mTOR inhibitors have developed pruritus in clinical trials.^{1,2}

Prevention	<p>Advise patients to use:¹⁹</p> <ul style="list-style-type: none">• Mild soaps, such as Dove® or Neutrogena®• Bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion <p>Advise patients to:³</p> <ul style="list-style-type: none">• Maintain a cool ambient environment• Wear loose-fitting clothing• Take lukewarm showers, pat dry, and moisturize skin• Avoid fragranced soaps and alcohol-based topical products	
Management	<p>Mild to moderate pruritus</p> <p>Advise patients to:^{17,20}</p> <ul style="list-style-type: none">• Apply more lotion than usual to help reduce or eliminate itchiness on the trunk or extremities• Use lotions with aloe vera or dimethicone Moisturel®• Use antidandruff shampoos and conditioners• Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms¹⁹• Use cold compresses• Take oatmeal baths• Cut fingernails short to curtail scratching <p>Medical management:</p> <ul style="list-style-type: none">• Medium- or high-strength topical corticosteroids• Oral antihistamines	<p>Moderate to severe pruritus</p> <p>Refer to doctor for intense, widespread itching</p> <p>Oral anti-H1 (first or second generation) medications may provide some relief¹⁹</p> <p>Dose reduction or temporary discontinuation should be considered²⁰</p>

Key facts: Pruritus

Pruritus or itchiness is the consequence of loss of skin moisture. Pruritus may be mild or localized, widespread or intense, or worsen to the point where it interferes with daily activities.¹¹

◀ Rash

Rash [Photo] is a very common adverse event of mTOR inhibitors, occurring in 29% to 59% of patients on everolimus and 47% of those on temsirolimus. Most cases are mild to moderate in severity.^{1,2,4,5}

<h3>Prevention</h3>	<p>A proactive approach is critical in managing rash.¹⁴ When patients begin therapy, advise them to:¹⁴⁻¹⁷</p> <ul style="list-style-type: none"> • Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness • Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion • Use only fragrance-, alcohol-, and dye-free lotions and cosmetics • Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX® • Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove® • Use a broad-spectrum sunscreen (SPF of 30 or more) that contains zinc oxide or titanium dioxide 		
<h3>Management</h3>	<p>Mild¹⁴</p> <ul style="list-style-type: none"> • Localized • Few symptoms • No impact on daily activities • No sign of infection 	<p>No treatment or OTC therapy:</p> <ul style="list-style-type: none"> • Topical corticosteroids (e.g., hydrocortisone 0.5% cream)¹⁴ • Mild soap and cleansers¹⁷ • Moisturizers twice daily¹⁷ <p>Advise patient to monitor the rash for changes in severity.¹⁻⁴ Refer to doctor if rash persists after 2 weeks of treatment or worsens in severity.¹⁴</p>	<p>Prescribed medications:</p> <ul style="list-style-type: none"> • Topical agents with anti-inflammatory properties, such as hydrocortisone 1% to 2.5% cream, metronidazole cream or clindamycin 1% cream or topical solution¹⁴
<p>Moderate¹⁴</p> <ul style="list-style-type: none"> • Generalized • Mild symptoms (e.g., itching, tenderness) • Minimal impact on daily activities <p>Refer to doctor.</p>	<p>Advise patient to monitor the rash for changes in severity.^{1,2}</p> <p>Advise patient to consult doctor if symptoms persist or worsen after 2 weeks of treatment.¹⁷</p>	<p>Prescribed medications:^{14,17}</p> <ul style="list-style-type: none"> • Hydrocortisone 2.5% cream, clindamycin 1% cream or topical solution <p>PLUS</p> <ul style="list-style-type: none"> • Doxycycline (100 mg BID PO) or minocycline (100 mg BID PO) 	

Key facts: Rash

Skin rashes are usually spots or small raised bumps with or without fluid that appear on the chest, upper back and, sometimes, the face. The rash is not as severe as EGFR-related rash but tends to be treated by similar means.^{5,11}

Everolimus-induced rash generally occurs within the first month of therapy (as early as one week), and most cases are either mild or moderate in severity, with severe rash described only rarely. Inhibition of the mTOR pathway has been shown to interrupt the epidermal growth factor receptor (EGFR)-driven signalling cascade.²¹

◀ Stomatitis

In patients treated with mTOR inhibitors, the integrity of mucous membranes in the mouth and gastrointestinal tract may be compromised, leading to inflammation and stomatitis (mouth sores) [Photo].^{1,2,4,22} This adverse event occurs in up to 67% of patients and can be a dose-limiting condition.^{1,2,4}

Prevention	Advise patients to: ^{12,13} <ul style="list-style-type: none">• Avoid cheek or lip biting• Avoid mouth breathing• Maintain good oral hygiene• Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly• Avoid spicy and highly textured foods• Avoid alcohol-containing mouthwashes	
Management	OTC treatment For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips Meticulous oral hygiene: ^{12,13} <ul style="list-style-type: none">• Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles• If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®• Biotène® toothpaste is non-irritating contains natural salivary enzymes to control bacteria• Floss gently once daily to avoid gum injury• Salt-and-water rinses (1/2 teaspoon of salt in 1 cup of warm water at least 4 times daily, especially after meals)• Bland rinses, antimicrobial mouthwash without alcohol• OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®) Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips ¹²	Prescribed medication (moderate to severe cases): ^{12,13} <ul style="list-style-type: none">• Topical fluoride (dentist)• Topical anesthetics with or without topical• corticosteroids• Topical or systemic analgesics• Topical antifungals are preferable if a fungal infection is diagnosed• Palliative mixtures of various agents

Key facts: Stomatitis

Changes in the oral cavity differ from those in patients treated with traditional chemotherapy. Mouth ulcers (cankers) often appear on the tongue, inside the lips, or inside cheeks. The ulcers do not appear to be contagious. These oral lesions have an “aphthous-like” appearance.^{18,22}

Mouth lesions usually appear during the first cycle of therapy, often during the first week and usually within two month of starting an mTor inhibitor. In about 90% of patients, oral lesions are mild to moderate. However, they are generally painful, long lasting, and more severe and functionally limiting than their small size, typically less than 0.5 cm, would suggest.^{11,18,22}

Patients with signs of a herpes-like superinfection (with clusters of very painful oral lesions), fungal superinfection with whitish deposits, a varnished-looking tongue, or mirror effect on the palate should be referred to a doctor for evaluation.¹¹

This adverse event decreases in prevalence and severity with subsequent cycles of treatment. About 27% of patients who develop this complication require a dose reduction to resolve it. Mucositis generally resolves and does not recur after dose reduction.¹⁸

Maintaining the health, integrity, and function of oral mucosa is crucial in patients with stomatitis. Treatment aims to relieve symptoms, until the mucous membranes can rejuvenate themselves, usually within 7 to 14 days. Smokers have a greater risk of stomatitis.¹³

Antiseptic mouthwashes are inconsistently effective in preventing mTor inhibitor-induced stomatitis. Sodium bicarbonate rinses are ineffective in preventing and managing oral lesions. Topical or systemic corticosteroid therapy resolves oral lesions in 87% of patients. However, patients who develop multiple oral lesions may require intravenous nutritional support.^{18,22}

There are no evidence-based guidelines for treatment of mTOR inhibitor-induced stomatitis, and practitioners usually follow the common practices for chemotherapy-induced mouth inflammation. The guidelines stress the importance of good oral hygiene but, due to a lack of supportive evidence, oral hygiene methods are usually based on personal preference and anecdotal experience.¹²

Good oral hygiene:^{12,13}

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

The use of chlorhexidine mouth rinses is not recommended. They contain alcohol and may sting. Dilution defeats their antibacterial benefits.¹³ Hydrogen peroxide rinses, thyme derivatives, or iodine may worsen mouth ulcers.¹³

Topical preparations in widespread use for stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, “magic” mouthwashes that contain lidocaine, and salt-and-baking soda rinses.¹²

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Multi-targeted Kinase Inhibitors

Imatinib (Gleevec®)

Sorafenib (Nexavar®)

Pazopanib (Votrient®)

Sunitinib (Sutent®)

Regorafenib (Stivarga®)

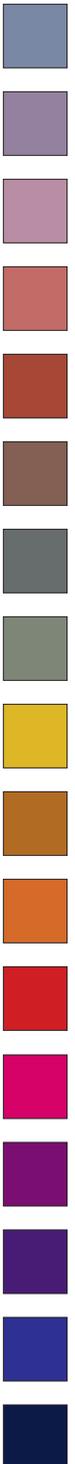
Vandetanib (Caprelsa®)

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This chapter contains information on the prevention and management of common adverse events of multi-targeted kinase inhibitors (MKIs) that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage MKI-induced adverse events. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events of these agents, please consult the product monographs.¹⁻⁶

Several medications are available that inhibit the action of multiple tyrosine kinases (TKs).¹⁻⁶ They target different TKs; hence, their adverse-event profiles vary.¹⁻⁶



Multiple TKs in cancer

Tyrosine kinases (TKs) are essential for normal cell signaling. These enzymes regulate cell proliferation, survival, differentiation, function, and motility.¹⁻⁷ They fall into two main classes:⁷

- Receptor TKs are an integral part of receptors that traverse the cell membrane. The targeted TKs may be located on receptor sites outside or inside the cell.
- TKs (non-receptor TKs) are found in the cytosol, nucleus, or inner surface of cells.

In cancer cells, the normal regulatory activity of TKs can be disrupted in three ways:⁷

- The cell produces too many normal TK receptors, their ligands, or both
- A local mutation permanently “switches on” the TK receptor
- DNA mutations create oncoproteins that bind to TKs or TK receptors

Whatever the cause of TK dysregulation, the result is the same. The TK or TK receptor is continuously activated. It transmits a constant stream of signals into cancer cells, promoting cell growth and proliferation, inhibiting apoptosis, and enhancing cell motility, which leads to the spread of cancer.⁷

c-Kit in cancer

Some oral medications, including imatinib, pazopanib, regorafenib and sunitinib, inhibit the action of TKs on stem cell factor (c-Kit) receptors.^{1-3,5} Sorafenib, dasatinib and nilotinib also inhibit c-Kit to some degree. The c-Kit or KIT protein is a transmembrane cell receptor. Because it binds to stem cell factor, it is also called the stem cell factor receptor. When stem cell factor binds to c-Kit, it activates a cell-signaling cascade that induces:⁸

- Cell growth
- Cell differentiation
- Cell survival

c-Kit mutations are present in about 95% of GIST cells. These mutations enable the c-Kit receptor to activate independently and send growth signals into the cell without binding to stem cell factor.⁸ Hence, GIST cells are able to grow, proliferate, and survive without stem cell factor regulation.⁸

A number of genetic mutations can alter the c-Kit receptor, activating the continuous transmission of growth signals within GIST cells. Some research suggests that the site of c-Kit mutation may have prognostic significance, and mutational analysis may provide clues to tumour aggressiveness and potential response to therapy.⁸

Drug administration

Imatinib

This oral medication should be taken during a meal once or twice daily, as required, with a glass of water. Patients unable to swallow the tablets can drop them into a glass of water or apple juice, stir until they are disintegrated, and drink immediately. Leftover traces must be consumed.¹

Pazopanib

This oral medication should be taken once daily without food. Advise patients to take pazopanib at least 1 hour before meals or 2 hours after a meal. Tablets must be taken whole with a glass of water and must not be broken or crushed.²

Regorafenib

This oral medication is taken once daily for 3 weeks on therapy, with 1 week off therapy for a cycle of 4 weeks, after a light, low-fat, low-calorie meal (<30% fat, ~300-550 calories).³

Sorafenib

Sorafenib is taken twice daily with a glass of water and without food or with low-fat to moderate-fat meals. With a high-fat meal, the bioavailability of sorafenib is 29% lower than when it is taken without food.⁴

Patients who take MKIs should avoid grapefruit, star fruit, pomelo, pomegranate, Seville oranges and other CYP3A4 inhibitors, as they can increase drug plasma concentrations.¹⁻⁶

Sunitinib

This oral medication is taken once daily with or without food in a cyclic (4 weeks on treatment, 2 weeks off treatment) or continuous regimen, depending on the diagnosis.⁵

Vandetanib

This oral medication is taken once daily, with or without food.⁶

Patients who miss a dose of these oral medications should not take a double dose on the next day to make up for it.¹⁻⁶ Patients who cannot swallow tablets whole may drop them into a glass of non-carbonated water and wait about 10 minutes, until the tablets are mostly dissolved, before drinking the dispersion.

How to take imatinib

- Use caution when taking acetaminophen (e.g., Tylenol®) with imatinib, due to an increased risk of hepatotoxicity.¹

How to take regorafenib

- Take regorafenib at the same time each day after a low-fat, low calorie meal (<30% fat, about 300-550 calories). Example: Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 oz. of skim milk (about 319 calories, 8.2 g of fat).
- Tablets are swallowed whole with a glass of water.³

How to obtain vandetanib

In Canada, vandetanib is only available through the Caprelsa Restricted Distribution Program (CRDP). Physicians and pharmacists must complete the certification and register with the program before they are able to prescribe or dispense this medication. Only patients who are enrolled in the CRPD can receive vandetanib.⁶

Mechanism of action

Multi-targeted kinase inhibitors (MKIs) are small molecules that directly inhibit the activity of tyrosine kinases (TKs). They bind to TKs to prevent ATP or other substances from interacting with these enzymes, shutting down the biochemical transmission of cell signals. Different MKIs target different TKs and receptor TKs.⁷

Imatinib

Imatinib inhibits the activity of TKs on c-Kit receptors. In GIST cells, it binds to the ATP site on c-Kit receptors to interrupt cell signaling. By blocking this site, imatinib prevents the TK from biochemically activating signaling proteins within the cell. Imatinib also inhibits the Bcr-Abl TK in chronic myeloid leukemia and TK receptors for platelet-derived growth factor (PDGF).¹ Imatinib:^{1,7}

- Inhibits abnormal signaling
- Inhibits cell growth and proliferation
- Induces cell death

Pazopanib

Pazopanib is a potent inhibitor of vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3; PDGF receptors a and b; and stem cell factor receptor (c-KIT).² Pazopanib binds to intracellular TK receptors, competing with adenosine triphosphate (ATP). ATP normally binds to TK receptors to activate signaling inside cells. By blocking the intracellular activation of the three vascular endothelial growth factor receptors (VEGFRs) and two PDGFR receptor subtypes, pazopanib inhibits angiogenesis – the development of new blood vessels to feed tumours – by preventing the activation of signaling pathways that trigger:⁹

- Tumour cell growth and proliferation
- Tumour cell survival
- Vascular permeability
- Tumour cell migration

Pazopanib also inhibits fibroblast growth factor receptor (FGFR)-1 and -3, interleukin-2 receptor inducible T-cell kinase (Lck), and transmembrane glycoprotein receptor TK (c-Fms). The clinical benefits of these actions are unknown.⁹

Regorafenib

Regorafenib inhibits multiple TKs, including those involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (PDGFR, FGFR). It inhibits mutated KIT, a major oncogenic driver in GIST. By targeting multiple TKs, regorafenib inhibits the:³

- Growth and proliferation of tumours
- Tumour angiogenesis

Sorafenib

Sorafenib also targets a number of TKs and receptor TKs that are implicated in tumour cell signaling, angiogenesis, and cell death. The most important of these pathways are VEGF and PDGF, which play crucial roles in angiogenesis. By blocking TKs on VEGF and PDGF receptors, sorafenib disrupts the abnormal signaling activity that switches on angiogenesis. This MKI also blocks abnormal signaling activity along the Raf-kinase, FLT-3, Kit, and RET pathways.^{4,10}

By targeting multiple TKs, sorafenib inhibits the:^{4,10}

- Growth and proliferation of tumours
- Tumour angiogenesis
- Survival of cancer cells

Sunitinib

This medication targets different signaling pathways to block the activity of a number of TKs that are implicated in tumour growth and spread. One pathway is activated by VEGF. This pathway plays a critical role in the proliferation, migration, and survival of cells that grow new blood vessels (angiogenesis). In cancer, dysregulation of the VEGF pathway “switches on” angiogenesis, leading to new blood-vessel formation within and near tumours. Sunitinib inhibits the TKs of VEGF, disrupting the growth of new blood vessels that feed tumours.^{5,7}

Sunitinib targets a second signaling pathway that is vital for angiogenesis. This pathway is mediated by platelet-derived growth factor (PDGF), which contributes to the stability and maturity of blood vessels. Dysregulation of this pathway leads to tumour growth and proliferation. By blocking PDGF TKs, sunitinib disrupts the stability and maturation of existing blood vessels that feed tumours.^{5,7} Sunitinib also blocks the activity of stem cell factor receptors (c-Kit), FMS-like TK-3 (FLT3), colony stimulating factor receptor (SCF-1R), and neurotrophic factor receptor (RET). By targeting multiple receptor TKs to disrupt abnormal cell signaling, sunitinib inhibits the:^{5,7}

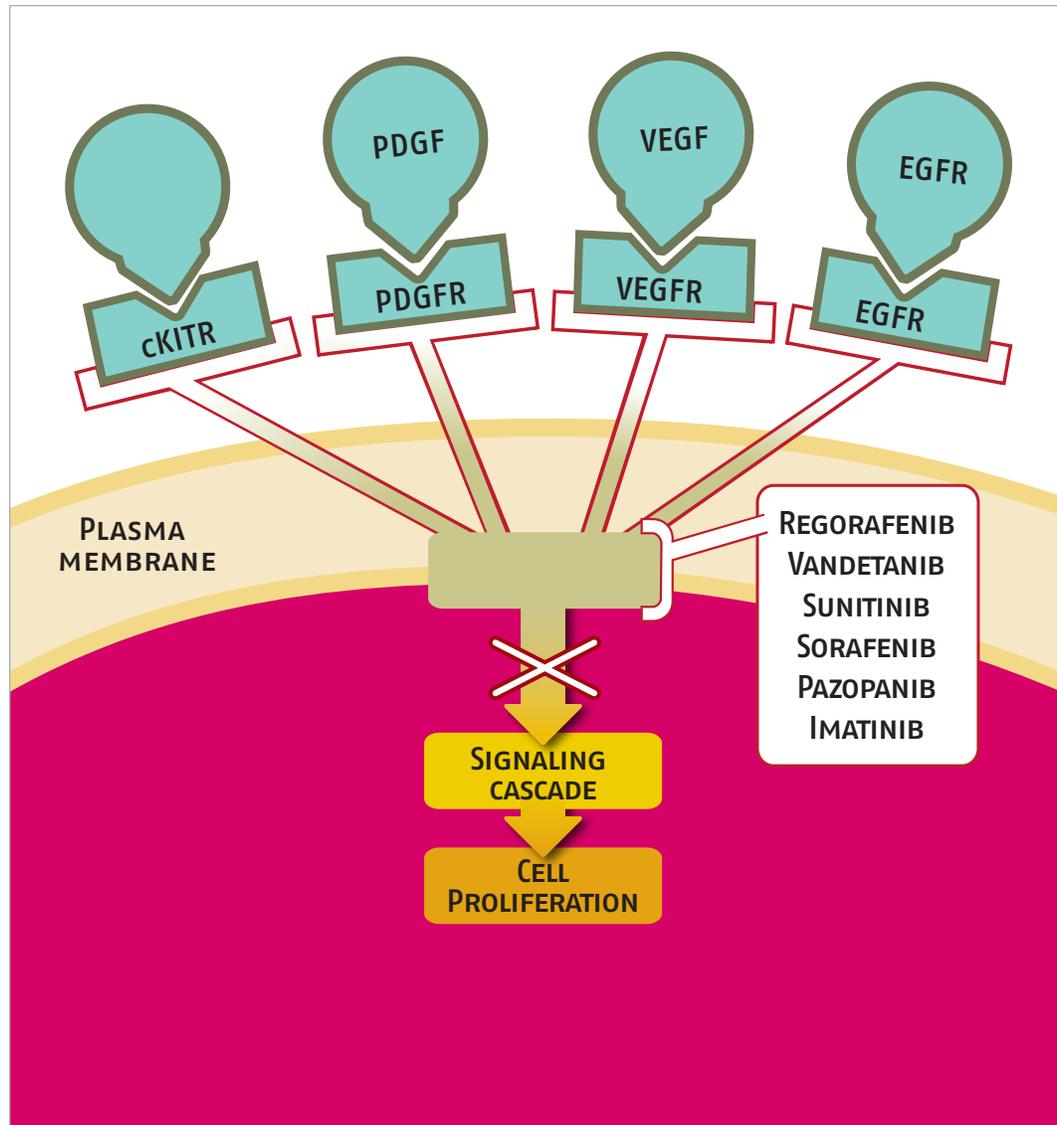
- Growth and proliferation of cancer cells
- New blood-vessel growth in and near tumours
- Migration of cancer cells

Vandetanib

Vandetanib is a potent and selective inhibitor of VEGFR-2, KDR, epidermal growth factor receptor (EGFR), and Rearranged during Transfection (RET) receptor TKs. It inhibits VEGFR-3 (Flt-4) and VEGFR-1 (Flt-1).⁶

By targeting multiple TKs, vandetanib inhibits the:⁶

- Cell growth and proliferation
- Cell migration
- Cell survival
- Tumour angiogenesis



Basic pharmacokinetics

Imatinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib are metabolized primarily via the CYP3A4 pathway in the liver.¹⁻⁶ These MKIs interact with a host of CYP3A4 inducers, inhibitors, and substrates.¹⁻⁶ Imatinib and pazopanib also interact with the CYP2D6 metabolic pathway.^{1,2} In addition, pazopanib inhibits other metabolic pathways, including CYP2C8, UGT1A1, and OATP1B1.² Regorafenib also interacts with other metabolic substrates, including UGT1A1, UGT1A9, BCRP, P-glycoprotein, CYP2C8, CYP2C9, CYP2B6, and CYP2C19.³ Sorafenib is a minor inhibitor of other metabolic pathways, including UGT1A9, CYP2C9, 2C19, and 2D6.⁴ Vandetanib interacts with OCT2 and P-glycoprotein substrates.⁶

Because regorafenib undergoes entero-hepatic circulation and metabolism, co-administration of antibiotics that affect the flora of the gastrointestinal tract has the potential to induce changes in regorafenib exposure.³

Presentation, prevention and management of common adverse events

Most patients who are treated with MKIs have adverse events.⁵ Patients with different cancers and different stages of cancer may react differently to the same MKI, mainly because their dosages may differ.¹⁻⁷

The following tables summarize the common adverse events of each medication. The following tables report adverse events with an overall frequency of $\geq 10\%$.¹⁻⁶

Common adverse events of multi-kinase inhibitors

Click on adverse events highlighted in blue for more information.

Imatinib¹

Blood and lymphatic disorders

- Anemia
- Neutropenia

Eye disorders

- Increased lacrimation

Gastrointestinal disorders

- Abdominal pain
 - Constipation
 - **Diarrhea**
 - Dyspepsia
 - Flatulence
 - Nausea
 - Vomiting
- General disorders
- Fatigue
 - Fever
 - **Fluid retention** (Peripheral edema)
 - Weight increased

Hepatobiliary disorders

- **Liver toxicity**

Infection

- Influenza
- Nasopharyngitis
- Sinusitis
- Upper respiratory tract infection

Musculoskeletal and connective tissue disorders

- **Back pain**
- **Joint pain**
- **Muscle cramps** and spasm
- **Musculoskeletal pain**
- **Myalgia**

Nervous system disorders

- Dizziness
- Headache

Psychiatric disorders

- Depression
- Insomnia

Respiratory disorders

- Cough

Skin and subcutaneous tissue disorders

- **Rash [photo]**
- **Pruritus**

Vascular disorders

- Hemorrhage

Pazopanib²

Blood and lymphatic disorders

- Leukopenia
- Neutropenia
- Thrombocytopenia

Cardiovascular disorders

- **Hypertension**

Gastrointestinal disorders

- Abdominal pain
- **Diarrhea**
- Gastrointestinal pain
- Nausea
- Pain
- **Stomatitis [photo]**
- Vomiting

General disorders

- Asthenia
- Fatigue
- Weight loss

Laboratory abnormalities

- Abnormal electrolytes
- **Abnormal liver enzymes**
- Changes in glucose levels
- Increased TSH

Metabolism and nutrition disorders

- Anorexia
- Loss of appetite

Musculoskeletal and connective tissue disorders

- **Muscle Pain (Myalgia)**

Nervous system disorders

- Dizziness
- Headache
- Taste disturbance

Respiratory disorders

- Cough
- Dyspnea

Skin and subcutaneous disorders

- Alopecia
- **Exfoliative rash**
- **Hand-foot skin reaction**
- **Hair and skin colour changes**

Regorafenib³

Blood and lymphatic disorders

- Anemia
- Lymphopenia
- Thrombocytopenia

Cardiovascular disorders

- **Hypertension**

Gastrointestinal disorders

- **Diarrhea**
- Nausea
- **Stomatitis [Photo]**
- Vomiting

General disorders

- Asthenia/fatigue
- Fever
- Mucosal inflammation
- Pain
- Weight loss

Hemorrhagic disorders

- Bleeding events

Hepatobiliary disorders

- Abnormal liver enzymes
- Hyperbilirubinemia

Infection

Metabolism and nutrition disorders

- Hypothyroidism
- Loss of appetite/low food intake

Nervous system disorders

- Headache

Musculoskeletal and connective tissue disorders

- **Musculoskeletal stiffness**

Respiratory disorders

- Voice changes

Renal disorders

- Proteinuria

Skin and subcutaneous disorders

- Alopecia
- **Hand-foot skin reaction**
- **Rash [Photo]**

Sorafenib⁴

Blood and lymphatic disorders

- Anemia
- Leukopenia
- Lymphopenia
- Neutropenia
- Cardiovascular disorders

- **Hypertension**

Gastrointestinal disorders

- Constipation
- **Diarrhea**
- Nausea
- **Stomatitis [photo]/mucositis**
- Vomiting

General disorders

- Asthenia
- Fatigue
- Fever
- Pain
- Weight loss

Hemorrhagic disorders

- Bleeding events

Hepatobiliary disorders

- Liver dysfunction

Infection

Laboratory investigations

- Increased amylase
- Increased lipase

Metabolism and nutrition disorders

- Anorexia
- Hypocalcemia
- Hypophosphatemia

Nervous system disorders

- Respiratory disorders
- Sensory neuropathy
- Voice changes

Skin and subcutaneous disorders

- Alopecia
- Erythema
- **Hand-foot skin reaction**
- **Pruritus**
- **Rash [Photo]**
- Xerosis

Sunitinib⁵

Blood and lymphatic disorders

- Anemia
- Lymphopenia
- Neutropenia
- Thrombocytopenia

Cardiovascular disorders

- Decreased LVEF
- **Hypertension**

Gastrointestinal disorders

- Abdominal pain
- Constipation
- **Diarrhea**
- Dyspepsia
- Nausea
- **Stomatitis [photo]**
- Vomiting

General disorders

- Asthenia
- Fatigue
- Fever
- Nose bleeds

Laboratory abnormalities

- Abnormal electrolytes
- Abnormal lipase, amylase
- Abnormal liver function tests
- Abnormal renal function tests

Metabolism and nutrition disorders

- Anorexia

Musculoskeletal and connective tissue disorders

- **Join Pain** (Arthralgia)
- **Pain in back or extremities**

Nervous system disorders

- Headache
- Taste disturbance

Psychiatric disorders

- Insomnia

Skin and subcutaneous disorders

- Erythema
- **Hair and skin colour changes**
- **Hand-foot skin reaction**
- **Rash [Photo]**
- Xerosis

Vandetanib⁶

Blood and lymphatic disorders

- Anemia

Cardiac disorders

- **Prolonged QT interval on ECG**

Cardiovascular disorders

- **Hypertension**

Gastrointestinal disorders

- Abdominal pain
- **Diarrhea**
- Dyspepsia
- Nausea
- Vomiting

General disorders

- Asthenia
- Fatigue
- Weight loss

Hepatobiliary disorders

- Abnormal liver enzymes

Laboratory abnormalities

- Hypocalcemia
- Increased creatinine

Metabolism and nutrition disorders

- Loss of appetite

Nervous system disorders

- Headache

Psychiatric disorders

- Insomnia

Respiratory disorders

- Cough
- Nasopharyngitis

Skin and subcutaneous disorders

- Acne
- Dermatitis acneiform
- **Photosensitivity reaction**
- **Pruritus**
- **Rash [Photo]**
- Xerosis

Other adverse events of interest with multi-kinase inhibitors

Click on adverse events highlighted in blue for more information.

- [Liver toxicity \(pazopanib, regorafenib\)](#)
- [Thyroid function \(pazopanib, sunitinib, vandetanib\)](#)
- [Severe heart problems \(vandetanib\)](#)

Refer for medical attention: Imatinib

Refer patients to a doctor if any of the following common adverse events develop or become severe:³

- Localised edema (swelling or pain in one part of the body)
- Low blood cell count (weakness; spontaneous bleeding or bruising; frequent infection with sore throat, chills, sore mouth or mouth ulcers)
- Peripheral edema (rapid weight gain, facial swelling or other signs of fluid retention)
- Hematologic disorders (bruising)
- Raynaud's syndrome (cold or numb fingers or toes)
- Urinary tract infection (low urine output, thirstiness)

Tell patients to seek immediate emergency care if any of these uncommon adverse events develop:³

- Acute respiratory failure or pulmonary fibrosis (difficult or painful breathing, cough)
- Cellulitis (acute skin swelling)
- Cerebral edema, increased cranial pressure, stroke (severe headache, weakness or paralysis, seizures, difficulty speaking)
- Difficulty hearing
- Eye disorders (sudden change in eyesight or visual impairment)
- Gastrointestinal disorders (stomach pain, nausea, tarry dark stools or bloody urine)
- Heart disorders (crushing chest pain or irregular heartbeat)
- Lightheadedness, dizziness or fainting
- Liver disorders (yellowing skin or eyes, light-coloured urine, loss of appetite, nausea)
- Potassium imbalance (muscle weakness, muscle spasms, abnormal heart rhythm)

Tell patients to seek immediate emergency care if any of these rare adverse events develop:³

- Avascular necrosis or hip osteonecrosis (painful hips, difficulty walking)
- Inflammatory bowel disease (nausea, diarrhea, vomiting, abdominal pain, fever)
- Low red blood cells (pale skin, fatigue, breathlessness, dark urine)
- Serious skin disorders (severe rash, blistering or peeling skin, raised red or purple skin patches, itchy burning rash)

Refer for medical attention: Pazopanib

Refer patients to a doctor if any of the following adverse events develop or become severe:²

- Diarrhea, nausea or vomiting
- Worsening or high blood pressure (SBP \geq 150 mm Hg, DBP; \geq 100 mm Hg)
- Low thyroid function (fatigue, constipation, dry skin, weight gain)
- Low white blood cell count (Infection, fever, bleeding)

Tell patients to seek emergency care if any of these uncommon adverse events develops:²

- Liver problems (jaundice, unusual darkening of urine, weight loss, nausea, vomiting, fatigue, upper right abdominal discomfort)
- Gastrointestinal fistula or perforation (blood in stool, severe stomach pain)
- Blood clots (severe pain, swelling, or redness in legs or severe chest pain with shortness of breath)
- Heart problems (shortness of breath, fatigue, swollen feet and ankles)
- Hemorrhage (stroke, coughing up blood, blood in stool)
- Posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (headache, seizure, confusion, blindness, lethargy, other visual or neurological disturbance in combination with hypertension)

Refer for medical attention: Regorafenib

Tell patients to seek emergency care if any uncommon adverse event develops.³

- Liver problems (yellowish discoloration of skin or eyes [jaundice], dark urine, confusion, and/or disorientation)
- Bleeding problems (blood in urine or stool; severe nose bleeds)
- Heart problems (shortness of breath, fatigue, swollen feet and ankles)
- High blood pressure (severe or persistent headache, visual disturbances, SBP \geq 150 mm Hg, DBP \geq 100 mm Hg)
- Skin problems (redness, pain, swelling, blisters on palms or soles)
- Posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (headache, seizure, confusion, blindness, lethargy, other visual or neurological disturbance in combination with hypertension)
- Signs of gastrointestinal perforation and fistula (tar-like, bloody or dark stool, severe stomach cramps or pain, GI bleeding)

Refer for medical attention: Sorafenib

Refer patients to a doctor if any of the following adverse events develops or become severe:

- Worsening or high blood pressure (SBP \geq 150 mm Hg, DBP \geq 100 mm Hg)

Tell patients to seek emergency care if any of these uncommon adverse events develops:³

- Dehydration
- Heart attack
- Multiple skin eruptions
- Severe eczema
- Yellowing of skin or eyes (signs of jaundice)
- Signs of gastrointestinal perforation and fistula (tar-like, bloody or dark stool, severe stomach cramps or pain, GI bleeding)

Refer for medical attention: Sunitinib

Refer patients to a doctor if any of the following common adverse events become severe:⁵

- A change in thyroid function (fatigue, constipation, dry skin, weight gain or weight loss, sweating and irritability)
- Painful skin ulcers
- Worsening or high blood pressure (SBP \geq 150 mm Hg, DBP \geq 100 mm Hg)

Tell patients to seek emergency care if any uncommon adverse event develops:⁵

- Blood clots (severe pain, swelling, or redness in legs or severe chest pain with shortness of breath)
- Cholecystitis (gall bladder inflammation, abdominal pain, vomiting)
- Decreased heart function (shortness of breath, fatigue, swollen ankles and feet)
- Posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (headache, seizure, confusion, blindness, lethargy, other visual or neurological disturbance in combination with hypertension)

Life-threatening soft-tissue infections (infection around a skin injury, fever, pain, redness, swelling, or drainage of pus or blood)

- Heart rhythm problems (rapid, pounding, or irregular heartbeat; dizziness, fainting, or seizures)
- Severe skin rashes (reddish target-like spots or circular patches often with central blisters on trunk, spreading to widespread blistering or skin peeling), particularly after fever, fatigue, headache, and cough
- Hypoglycemia (sweating, trembling, weakness, seizures, loss of consciousness)
- Pancreatitis (abdominal pain, fever, nausea, vomiting)
- Bleeding problems (blood in urine or stool; nose bleeds) and infections
- Myopathy or rhabdomyolysis (muscle aches or weakness, dark urine)
- Signs of osteonecrosis in the jaw (tooth or jaw pain, mouth swelling or sores, numbness or heaviness, exposed bone, loss of teeth)

Refer for medical attention: Vandetanib

Refer patients to a doctor if any of the following common adverse events become severe:⁶

- Headache
- Blurred vision or corneal opacity
- Worsening or high blood pressure (SBP \geq 150 mm Hg, DBP \geq 100 mm Hg)

Tell patients to seek emergency care if any uncommon adverse event develops:

- Severe skin reactions (redness, pain, skin ulcers, blisters, shedding of skin)
- Signs of heart problems, such as hypertensive crisis (dizziness, fainting), heart failure (fatigue) or prolonged QT interval (abnormal heartbeat)
- Signs of reversible posterior leukoencephalopathy syndrome (visual disturbances, seizures, confusion, altered mental state)
- Signs of stroke (confusion, weakness, difficulty speaking)
- Signs of interstitial lung disease or pneumonitis (hypoxia, pleural effusion, cough, shortness of breath)

◀ Bone, joint, and muscle pain (Imatinib, Pazopanib)

◀ Bone, joint, and muscle pain (Regorafenib)

◀ Bone, joint, and muscle pain (Sunitinib)

Arthralgia, myalgia, muscle cramps, pain in the extremities and back pain are common in most patients on all MKI inhibitors, except vandetanib.¹⁻⁶ They commonly occur in sorafenib-treated patients and in 10% to 17% of patients taking sunitinib.^{4,5} About 23% of patients on pazopanib develop myalgia and musculoskeletal pain.² From 25% to 50% of patients on imatinib develop aching bones or muscles or muscle cramps.¹ Muscle and bone pain is usually mild to moderate and manageable without a reduction of imatinib therapy.¹ Musculoskeletal problems happen in about 6% of patients taking regorafenib.³

Prevention	No preventive measures are recommended.
Management	<p>The following measures may provide relief from muscle aches or cramps:^{13,14}</p> <ul style="list-style-type: none">• Calcium supplements• Magnesium supplements• Mild pain medications (except acetaminophen with imatinib)• Avoid using quinine or drinking tonic water, which contains quinine <p>For mild bone aches and pain:¹⁴</p> <ul style="list-style-type: none">• NSAIDs in patients with platelet counts of greater than 100,000/mm³ and no history of GI bleeding

Key facts: Bone, joint, and muscle pain

Muscle cramps usually occur in the hands, feet, calves, or thighs of patients on imatinib. The cramps have been described as sustained muscular contractions. The pattern, frequency, and severity of muscle cramps do not tend to change over time. Muscle cramps may be related to exertion or tend to happen at night. Patients should avoid using quinine or drinking tonic water, which contains quinine.^{13,14}

Bone and joint pain tends to begin in the first month of therapy and often abates after a few months. Pain usually afflicts the leg bones, hips, and knees and may appear in an asymmetrical pattern.¹²

There are no evidence-based guidelines for prevention or treatment, but anecdotal reports and expert experience have suggested that in some patients the use of mineral supplements may ease pain.^{10,11}

- ◀ **Diarrhea (Imatinib, Pazopanib)**
- ◀ **Diarrhea (Regorafenib, Sorafenib)**
- ◀ **Diarrhea (Sunitinib, Vandetanib)**

Diarrhea is very common in patients treated with MKI inhibitors.¹⁻⁶ Up to 65% of imatinib-treated patients with GIST, 56% of patients on vandetanib, and from 41% to 61% of sunitinib-treated patients have diarrhea.^{1,5,6} Sorafenib causes diarrhea in up to 55% of patients.⁴ More than half (52%) of pazopanib-treated patients develop diarrhea.² Regorafenib causes diarrhea in 43% of patients.³ Dietary modifications are not recommended in anticipation of diarrhea.¹⁵⁻¹⁷

<p>Management</p> <p>OTC therapy¹⁵⁻¹⁷</p>	<p>Mild to moderate (less than 4 loose stools per day)</p> <ul style="list-style-type: none"> • Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) <p>Moderate (more than 4 to 6 loose stools per day or night-time diarrhea)</p> <p>Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea</p> <ul style="list-style-type: none"> • 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours • This dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea
<p>Replace lost fluids¹⁵⁻¹⁷</p>	<ul style="list-style-type: none"> • Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 litres per day. • Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
<p>Anal care¹⁵</p>	<p>Advise patients to:</p> <ul style="list-style-type: none"> • Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation • Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste • Soak in a warm bathtub or sitz bath to relieve discomfort • Examine the anal area for red, scaly or broken skin
<p>Diet¹⁵⁻¹⁷</p>	<p>Advise patients to:</p> <ul style="list-style-type: none"> • Eat and drink small quantities of food often • Avoid spicy, greasy, or fried foods • Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve • Follow a lactose-free diet • Avoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

There are no evidence-based guidelines for the prevention or treatment of diarrhea in patients taking MKIs. Antidiarrheal medications are usually able to control this dose-related adverse event.¹² Loperamide is standard in mild to moderate cases at dosage intervals and levels recommended for uncomplicated, targeted therapy-induced diarrhea.¹⁸

When patients seek OTC treatment for diarrhea, it is important to ask them about:¹⁵⁻¹⁷

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Stomach cramps

◀ Fluid retention (Imatinib)

Fluid retention (edema) affects up to 81% of patients taking imatinib for GIST and about 14% of patients who take pazopanib.^{1,2}

Prevention	Advise your patients to: ¹² <ul style="list-style-type: none">• Limit salt intake For swollen eyelids or swelling around eyes: ¹² <ul style="list-style-type: none">• Elevate head during sleep	
Management	OTC therapy Mild peripheral fluid retention <ul style="list-style-type: none">• For swelling around eyes, use skin-tightening agents, e.g., topical Preparation H® containing phenylephrine or lanolin (avoid eye contact)¹²	Prescribed therapy Mild peripheral fluid retention <ul style="list-style-type: none">• Topical eye ointments with phenylephrine 0.25%¹²• Topical corticosteroid (e.g., hydrocortisone 1%)¹² Moderate fluid retention <ul style="list-style-type: none">• Low-dose loop diuretic, e.g., furosemide with calcium and magnesium supplements¹²• Close electrolyte monitoring¹²

Key facts: Fluid retention

Peripheral fluid retention (edema) is usually superficial and mild to moderate in nature. Its occurrence is dose-related. The most frequent form of fluid retention is swollen eyelids or swelling around the eyes (periorbital or periocular edema), which is more pronounced in the morning and often associated with swelling of ankles, feet and lower legs.¹²⁻¹⁴ This adverse event may also occur among patients taking sunitinib.¹⁹ It does not usually require treatment.¹⁹

Peripheral fluid retention tends to improve over time.²⁰ It occurs more frequently in:¹⁴

- Women
- Adults over 65 years of age
- Patients with a history of heart or kidney problems

Early intervention is critical; refer any patient with symptoms of fluid retention to a doctor for care.¹² Advise patients to weigh themselves regularly and report any weight gain ≥ 5 lb. (2.27 kg).¹⁹ Generalized fluid retention in or around the lungs, stomach, central body tissues, heart, lungs, or brain – often associated with rapid weight gain – is potentially life-threatening.¹²⁻¹⁴

◀ Hand-foot skin reaction (HFSR) (Pazopanib)

◀ Hand-foot skin reaction (HFSR) (Regorafenib, Sorafenib)

◀ Hand-foot skin reaction (HFSR) (Sunitinib)

From 30% to 60% of patients taking sorafenib, at least 47% of patients taking regorafenib, 15% to 20% of patients taking sunitinib, and 6% to 11% of patients taking pazopanib develop hand-foot skin reaction (HFSR), also known as hand-foot syndrome and palmar-plantar erythrodysesthesia.^{2,3,5} HFSR is the most clinically significant, dose-limiting, skin-related adverse event of these MKIs.^{3,20-25} HFSR is an uncommon adverse event of imatinib and vandetanib.^{1,6}

Most cases of HFSR are mild to moderate, but about 5% to 6% of patients on most MKIs develop a severe reaction that impairs daily-living activities.²¹⁻²⁴ Among patients taking regorafenib, from 17% to 22% develop moderately severe HFSR.³ These patients may experience extreme tenderness of the hands and feet – enough to affect hand or foot function and disrupt their quality of life.^{21,25} Patients taking sorafenib are 6.6 times more likely and patients taking sunitinib are 9.9 times more likely to develop HFSR than others.^{22,42} Urea cream may be administered as primary prophylaxis with sorafenib.⁴²

Prevention

During the first 2–4 weeks of therapy, prevention of traumatic activity and rest are crucial.²² Urge your patients to:^{22,24}

- Have a manicure or pedicure to remove thickened skin or calluses; follow with moisturizing cream
- Use a moisturizing cream
- Urea cream 10% three times daily may be used as primary prophylaxis for sorafenib
- Wear loose-fitting, soft shoes or slippers, foam-absorbing soles, gel inserts to cushion pressure points, cotton socks
- Cushion callused areas with soft or padded shoes
- Reduce exposure of hands and feet to hot water (showers, dishwashing, etc.)
- Avoid excessive friction to hands or feet when performing tasks
- Avoid vigorous exercise or activities that place undue stress on the hands and feet
- Wear thick cotton gloves or socks to protect hands and feet and keep them dry
- Report any signs or symptoms immediately to ensure early-stage treatment

Management

OTC treatment
(Mild; Discomfort, no disruption of activities)²²

Advise patients to add the following:^{22,24,25}

- Avoid hot water; cool water or cold compresses may ease symptoms
- Diligently apply moisturizers to keep palms and soles soft and pliable to prevent cracks or breaks in skin integrity
 - Use moisturizing creams twice daily
 - Use aloe vera lotion
 - Use 20% urea cream or 6% salicylic acid on callused areas
- Soak feet in magnesium sulfate (Epsom salts) to soften calluses and reduce pain on pressure
- Use low to moderate dose pain killers

Advise patients to consult their doctor about reducing their dosage of MKI, if symptoms of HFSR worsen after being treated for 2 weeks²²

Prescribed therapy
(Moderate; Disrupts daily activity)²²

Add the following:²²

- Topical corticosteroid (e.g., clobetasol 0.05% ointment)
- Topical keratolytic creams, e.g., urea, salicylic acid, or alpha hydroxyl acid-based creams applied sparingly only on affected areas³
- 2% lidocaine topical ointment
- Oral NSAIDs, codeine, pregabalin, for pain
- Dose modification is required
- If symptoms worsen after 2 weeks, treatment interruption may be required

Prescribed therapy
(Severe)²²

- Treat as moderate
- Further dose modification is required
- If symptoms worsen after 2 weeks, treatment interruption may be required

For thick, tender sores after acute rash with/without blisters resolves:²²

- 40% urea cream
- Tazarotene 0.1% cream
- Fluorouracil 5% cream

Skin products in use for HFSR²⁴

- Cetaphil® skin cleansers
- Aveeno® shower gel
- Udderly Smooth®, Gold Bond®, Aveeno® lotions
- Norwegian Formula moisturizer and foot cream (Neutrogena®)
- Bag Balm®
- Eucerin® cream and Dry Skin Therapy
- Aquaphor® Healing Ointment
- Kerasal®
- Lipikar, Lipikar balm, and Xerand
- Sunblock

Key facts: HFSR

HFSR has a serious impact on the physical, psychological, and social well-being of patients who receive MKIs.²¹⁻²⁴ Early detection and prompt treatment can reduce its severity and duration.^{25,26} Treatment may require dosage adjustment or the interruption of life-prolonging therapy in cancer patients.^{22,24} **The look and onset of this reaction is different than capecitabine-induced HFSR.** The typical pattern of localized sensitive lesions with skin thickening, surrounded by redness, differs from classic HFSR, in which symmetrical changes in skin sensation, redness and swelling occurs.²⁴ In patients taking regorafenib, HFSR occurs more often in Asians vs non-Asians.³

HFSR usually occurs within the first 2 to 4 weeks of MKI therapy.²² Patients should be monitored weekly during their first two cycles of treatment for early detection.²⁶ Tender, scaly sores – with or without blistering – appear on the palms and soles. The edges of thickened skin patches on fingertips, toes, and other pressure or flexure points, such as elbows or knuckles, may be surrounded by a swollen, reddish halo.^{21,22,25,28} The hands or feet may tingle or feel sensitive to touch or heat.²⁸ After several weeks, thickened, callus-like skin develops over the sores. These areas are usually painful and impair range of motion, function, and weight bearing.²²

There are no evidence-based guidelines for the treatment of MKI-induced HFSR. In patients taking sorafenib, using a 10% urea cream reduced the incidence and delayed the onset of HFSR.^{27,42}

- ◀ **Hypertension (Pazopanib)**
- ◀ **Hypertension (Regorafenib, Sorafenib)**
- ◀ **Hypertension (Sunitinib, Vandetanib)**

The incidence of high blood pressure (hypertension) varies among MKIs and in patients with different cancers.¹⁻⁶ Patients taking sorafenib are at least 6 times more likely to develop hypertension than others.^{20,29} In patients on sunitinib, hypertension developed in 15-28%.²⁹ Hypertension developed in 40% of patients with pazopanib.² Patients taking regorafenib are 2 to 3 times more likely to develop arterial hypertension than others, usually within the first cycle of treatment, and patients over 65 years of age have a 10% higher incidence of severe hypertension than others.³ Hypertension develops in 32% of patients taking vandetanib; about 7% develop severe hypertension or a hypertensive crisis.⁶

Monitoring	Encourage patients to: <ul style="list-style-type: none">• Monitor their blood pressure (BP) weekly for the first 6 weeks of treatment then on a regular basis²⁰• Keep a diary of BP readings¹⁰
Management	<p>Advise patients with uncontrolled hypertension (recurrent, symptomatic or persistent systolic BP \geq 140 mm Hg) to see their doctor immediately for treatment.^{2-6,13,20}</p> <p>Prescribed therapy: Most hypertension can be managed with standard antihypertensive therapy, taking into account possible drug interactions.^{2-6,10,20}</p> <p>Discontinuation of MKI therapy for severe hypertension or persistent hypertension despite treatment²⁻⁶</p>

Key facts: Hypertension

Like other anti-angiogenic agents that inhibit VEGF, pazopanib, sunitinib, sorafenib, regorafenib, and vandetanib may cause a significant and sustained increase in blood pressure (BP).^{2-6,29} Patients who receive these medications should be monitored for the onset or worsening of hypertension.²⁻⁶ For vandetanib, blood pressure (BP) should be measured at baseline, 2 to 4 weeks, 8 to 12 weeks and for three months after therapy ends.⁶ BP should be monitored routinely in patients taking either sunitinib or pazopanib.^{2,5} For sorafenib, BP should be monitored on a weekly basis at the beginning of therapy and regularly thereafter.⁴ Weekly BP monitoring is recommended for the first 6 weeks of regorafenib, prior to every treatment cycle, and more often, if required.³

Patients should be encouraged to monitor their blood pressure at home, recording their blood-pressure readings in a diary and reporting any elevations to their healthcare team.^{26,30}

Hypertension may develop in the first few weeks of therapy or slowly over time. It may disappear after the first few treatment cycles.³¹ Patients with MKI-induced hypertension may also develop proteinuria and should be screened for this adverse event.^{2-6,10,29}

Hypertension is usually mild to moderate and manageable with standard antihypertensive therapy. From 4% to 10% of patients develop moderately severe or severe hypertension or a hypertensive crisis.^{3,6,29} Lifestyle modification is recommended for all patients with hypertension.^{10,20,29}

◀ Liver toxicity (Imatinib, Pazopanib)

◀ Liver toxicity (other adverse events)

Pazopanib may cause severe or potentially fatal liver toxicity. It increases the risk of liver toxicity in patients who take statins to control high cholesterol. Elevation of the liver enzyme ALT typically occurs within the first 18 weeks of treatment.^{2,9}

Regorafenib may cause liver dysfunction and severe, potentially fatal liver injury.

◀ Photosensitivity (Vandetanib)

Photosensitivity occurs in all vandetanib-treated patients, even through glass behind closed windows. Up to 13% of patients develop photosensitivity skin reactions.^{6,32}

Prevention

A proactive approach is critical for the prevention of photosensitivity reactions. When patients begin therapy, advise them to STRICTLY avoid sun exposure and:³²

- Use a broad-spectrum sunscreen (SPF of 30 or more) that protects against UVA rays and contains UVA filters all day long, inside or outside.
- Wear protective clothing, including a hat, to cover the head, face, arms, legs, hands and feet.
- Avoid products that dry the skin, e.g., soaps, alcohol or perfumed products.
- Remind patients that UV rays go through glass (e.g., house or car windows)

Key facts: Photosensitivity reactions

There are no evidence-based guidelines for the treatment of vandetanib-induced photosensitivity reactions.^{6,32}

Preventive therapy is recommended to avoid photosensitivity reactions. Advise patients to avoid sun exposure while taking vandetanib. When in the sun, they must wear protective clothing, including hats, gloves and arm, leg, and foot coverings. The use of sunscreen is mandatory. Patients should use lip balm and a broad-spectrum sunscreen (SPF of 30 or higher) that contains UVA/UVB filters.³²

Photosensitivity skin reactions usually appear as blue-grey spots, varying in size and usually located on the face, scalp, or trunk. They occur after several months of treatment and disappear after treatment interruption.³² Due to long half-life of vandetanib, protective clothing and sunblock should be continued for 4 months after the end of treatment.⁶

- ◀ Pruritus (Imatinib)
- ◀ Pruritus (Sorafenib)
- ◀ Pruritus (Vandetanib)

Pruritus is a common adverse event of imatinib, sorafenib and vandetanib.^{1,4,6}

<p>Prevention</p>	<p>To prevent dry skin, a common cause of itchiness, advise your patients to:^{33,34}</p> <ul style="list-style-type: none"> • Use mild soaps that contain no deodorants or fragrance, such as Dove® or Neutrogena® • Frequently apply lotions or bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion • Use liquid shower gels instead of soap 	
<p>Management</p>	<p>Mild to moderate pruritus</p> <p>Advise patients to:</p> <ul style="list-style-type: none"> • Apply more lotion than usual to help reduce or eliminate itchiness on the trunk or extremities • Use moisturizers or emollients that contain topical corticosteroids, anesthetics (e.g., lidocaine, prilocaine), capsaicin, salicylic acid, and menthol³⁵ • Use lotions with aloe vera or dimethicone Moisture![®] • Use antidandruff shampoos and conditioners • Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms 	<p>Moderate to severe pruritus</p> <p>Refer to doctor for intense, widespread itching</p> <p>Oral anti-H1 (first or second generation) antihistamines may provide some relief^{33,34}</p>

Key facts: Pruritus

Pruritus or itchiness is the consequence of loss of skin moisture.³⁶ In patients treated with imatinib or sorafenib, it is usually associated with rash or xerosis.^{1,4} It may be disruptive during sleep or waking hours.¹⁰

- ◀ **Rash (Imatinib, Pazopanib)**
- ◀ **Rash (Regorafenib, Sorafenib)**
- ◀ **Rash (Sunitinib, Vandetanib)**

Rash [Photo] is a common adverse events of imatinib, occurring in up to 46% of patients with advanced GIST.¹ About 45% of patients taking vandetanib develop rash, while another 15% to 20% develop acneiform dermatitis.⁶ Rash occurs in 26% to 30% of patients taking regorafenib for colorectal cancer and GIST, respectively.³ It is also a common adverse event of sorafenib and sunitinib, occurring in up to 19% of patients.^{4,5,11} Rash is less common in patients on pazopanib (8% of patients).²

<p>Prevention</p>	<p>A proactive approach is critical in managing rash. When patients begin therapy, advise them to:^{34,37,38}</p> <ul style="list-style-type: none"> • Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness • Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion • Use only fragrance-, alcohol-, and dye-free lotions and cosmetics • Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX® • Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove® • Use a broad-spectrum sunscreen (SPF of 30 or more) that contains zinc oxide or titanium dioxide 	
<p>Management</p>	<p>OTC therapy</p> <p>Mild to moderate rash^{12-14,32}</p> <p>Lidocaine is not recommended, as it can be systemically absorbed</p> <ul style="list-style-type: none"> • Topical steroid (hydrocortisone 0.5%) • Coal tar preparations <p>Reassess after 2 weeks; if reactions do not improve or worsen, refer to doctor.</p>	<p>Prescribed therapy</p> <p>Moderate to severe rash^{11,12}</p> <ul style="list-style-type: none"> • Topical corticosteroids (e.g., hydrocortisone 2.5%) • Oral corticosteroids (e.g., prednisone 1 mg/kg daily with or without topical triamcinolone acetonide 0.1% ointment)³⁷ • Systemic antihistamines³² • Topical clindamycin 1%¹¹

Key facts: Rash

Among imatinib-treated patients, rash is more likely to occur in women and patients on higher doses.¹² In the most common type of imatinib-induced rash, skin spots and bumps appear on the forearms, trunk, and, sometimes, the face. They are often itchy, and may become infected and crusty, if scratched. This generalized rash is usually mild and, in most cases, self-limited – it has a natural lifespan.¹³

Rash symptoms may occur after 6 weeks of sorafenib and 3 to 4 weeks of sunitinib.²⁰ This rash is similar to EGFR-induced rashes – albeit less frequent and milder – with spots and bumps on the upper chest, back or face that may or may not contain sterile fluid.¹¹ Generalized skin rashes are usually mild to moderate, tend to decrease over time, and rarely require dose reduction.^{11,20}

Patients taking sorafenib may develop a reddish rash with scaly patches on the face and scalp from 1 to 2 weeks after treatment begins. This rash resembles acne but is inflammatory rather than bacterial in nature. It may be associated with a loss or distortion of sensation on the scalp. This rash generally fades or disappears after several weeks and prescribed therapy is not usually necessary.²⁹

Regorafenib-treated patients develop a maculopapular rash of flat, discolored spots and solid, raised bumps. Rash may be accompanied by photosensitivity, redness, dry or peeling skin, blistering, and itchiness. Most rashes are mild to moderate and occur predominantly during the first cycle of therapy. The incident of rash lessens considerably in subsequent treatment cycles. Weekly monitoring is recommended during the first few weeks of therapy, followed by monthly monitoring in subsequent cycles.²⁶

Rashes associated with vandetanib usually occur within the first few months of treatment. About 8% of patients develop moderately severe to severe rashes, usually within 2 to 3 months after therapy begins. Rashes are likely due to the anti-EGFR action of this medication. Its ability to block EGFR is thought to trigger follicular hyperkeratosis, leading to follicle obstruction and an inflammatory response. Superinfection of these lesions may occur.^{32,39}

There are no evidence-based guidelines for the treatment of MKI-induced rash. Early recognition of symptoms and a prompt start of symptomatic therapy are the mainstays of treatment. Mild to moderate symptoms are managed while the patient remains on therapy. Refer any patient who develops a severe rash while taking MKIs to a doctor for evaluation and treatment.¹¹

◀ Severe heart problems (Vandetanib)

◀ Severe heart problems (other adverse events)

Vandetanib can prolong the QTcF interval by 35 ms or more. Due to the uncommon risks of torsades de pointes and sudden death, all patients require routine ECG monitoring. Due to this drug's long half-life, the QTcF interval is measured at baseline, 2 to 4 weeks, and 8 to 12 weeks during treatment and every 3 months thereafter as well as after dose adjustment. Patients are routinely monitored for electrolyte imbalances, such as low potassium, magnesium, and calcium levels, and tests for thyroid dysfunction. This drug is contraindicated in patients with electrolyte imbalances and pre-existing QT prolongation.⁶ Patients are advised to stop medication when the QTc \geq 500ms on ECG.⁶

Other serious cardiovascular problems, including heart failure (>1 in 100 patients) and severe hypertension or a hypertensive crisis may occur in a small percentage of patients taking vandetanib. Heart failure may not be reversible after vandetanib therapy.⁶

◀ Skin and hair colour changes (Pazopanib)

◀ Skin and hair colour changes (Sunitinib)

Pazopanib and sunitinib may cause skin or hair colour changes, particularly a yellowing or complete loss of colour. With sunitinib, these changes may occur after the first week of treatment in up to 26% of patients. Pazopanib-induced loss of skin colour may develop after one or two months of treatment. Hair colour changes occur in about 38% of pazopanib-treated patients. Assure your patients that these adverse events are reversible with dosage adjustment or when therapy ends.^{9,11}

- ◀ Stomatitis (Pazopanib)
- ◀ Stomatitis (Regorafenib, Sorafenib)
- ◀ Stomatitis (Sunitinib)

Stomatitis (mouth sores) [Photo] is a symptom of mucositis, a common adverse event of sunitinib, sorafenib, and regorafenib.³⁻⁵ The incidence varies, depending on the MKI, but this adverse event may lead to dosage reductions that limit therapeutic benefit in a group of patients with advanced cancer.¹⁰

Prevention	<p>Advise patients to:^{40,41}</p> <ul style="list-style-type: none"> Avoid cheek or lip biting Avoid mouth breathing Maintain good oral hygiene Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly Avoid spicy and highly textured foods Avoid highly flavoured and alcohol-containing mouthwashes 	
Management	<p>OTC therapy For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips</p> <p>Meticulous oral hygiene:^{40,41}</p> <ul style="list-style-type: none"> Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik® Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria Floss gently once daily to avoid gum injury Salt rinses (1/2 teaspoon of salt in 1 cup of warm water at least 4 times daily, especially after meals) Bland rinses, antimicrobial mouthwash without alcohol OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®) <p>Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips³³</p>	<p>Prescribed therapy (moderate to severe cases):</p> <ul style="list-style-type: none"> Topical fluoride (dentist)⁴⁰ Topical anesthetics⁴⁰ Corticosteroid solution⁴¹ Topical or systemic analgesics⁴⁰ Topical or systemic antifungals⁴¹ Palliative mixtures of various agents⁴⁰

Key facts: Stomatitis

In patients treated with MKIs, the integrity of mucous membranes may be compromised, leading to the swelling and reddening of membranes lining the mouth. Mouth sores or cankers may develop. Patients may complain of changes on the inner cheeks or mouth surfaces, even when mouth sores are not present or only a mild redness is evident. Patients may experience:¹⁰

- Mouth pain
- Difficulty chewing
- Painful swallowing (dysphagia)

Maintaining mucosal health, integrity, and function is crucial in patients with stomatitis. Aggressive intervention can make a significant impact on this adverse event.¹⁰ Treatment aims to relieve symptoms until the mucous membranes can rejuvenate, usually within 7 to 14 days. Smokers have a greater risk of stomatitis.⁴¹

With regorafenib, stomatitis tends to occur between 5 and 14 days after a treatment cycle begins. It may occur only in cycle 1 or recurrently during therapy. Dose reduction may be required. Patient-related factors, such as older age, poor dental hygiene, poor nutritional status, related infections, and dental pathology increase the risk of stomatitis.²⁶

There are no evidence-based guidelines for the prevention or treatment of MKI-induced stomatitis, and experts tend to follow the clinical practice guidelines for chemotherapy- or EGFR-induced oral mucositis.^{33,40,41}

Clinical practice guidelines stress the importance of oral hygiene in cancer patients, but due to a lack of supportive evidence, methods are usually based on personal preference and anecdotal experience.⁴⁰

Good oral hygiene:^{40,41}

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

The use of chlorhexidine mouth rinses is not recommended. They contain alcohol and may sting. Dilution defeats their antibacterial benefits.⁴⁰ Hydrogen peroxide rinses may worsen mouth ulcers.⁴⁰

Topical preparations in widespread use for chemotherapy-induced stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, “magic” mouthwashes that contain lidocaine, and salt-and-baking soda rinses.⁴⁰

◀ Thyroid function (other adverse events)

Pazopanib and sunitinib can affect thyroid function as early as 2 weeks after therapy begins. Advise your patient to see their oncologist for thyroid function testing if they experience any of these symptoms:^{2,5,9,20}

- Anorexia
- Cold intolerance
- Fatigue
- Swelling or fluid retention

Dosage adjustments in thyroid replacement therapy (TRT) are often required after thyroidectomy in patients taking vandetanib. In clinical trials, TRT increases were necessary in 49% of patients on vandetanib vs 17% on placebo.⁶

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PD-1 inhibitors

Pembrolizumab (Keytruda®)

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This chapter contains information on the prevention and management of common adverse events of PD-1 inhibitors that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage the adverse events of therapy with a human programmed death receptor-1 (PD-1) inhibitor. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events of these agents, please consult the product monograph.¹ Infusion reactions, which occur with intravenous (IV) agents are usually encountered in the clinic or hospital setting and will not be described here.



PD-1 in cancer

T-cells, also called T-lymphocytes, are white blood cells that protect the body against harmful invaders, including cancer. However, cancer has found a way to fight back.

On the surface of cancer-fighting T-cells are PD-1 receptors. Normally, the body produces PD-1 ligands (PD-L1 and PD-L2) to bind to this receptor to inhibit (switch off) the T cell-mediated immune response, when it is no longer needed.^{1,2}

Some cancers cells overproduce PD-1 ligands, flooding PD-1 receptors to inactivate T-cells. By doing so, they effectively switch off the body's immune response, even when it's needed. Hence, T-cells and other immune cells that they control are "blind" to tumour invasion, growth and proliferation.¹

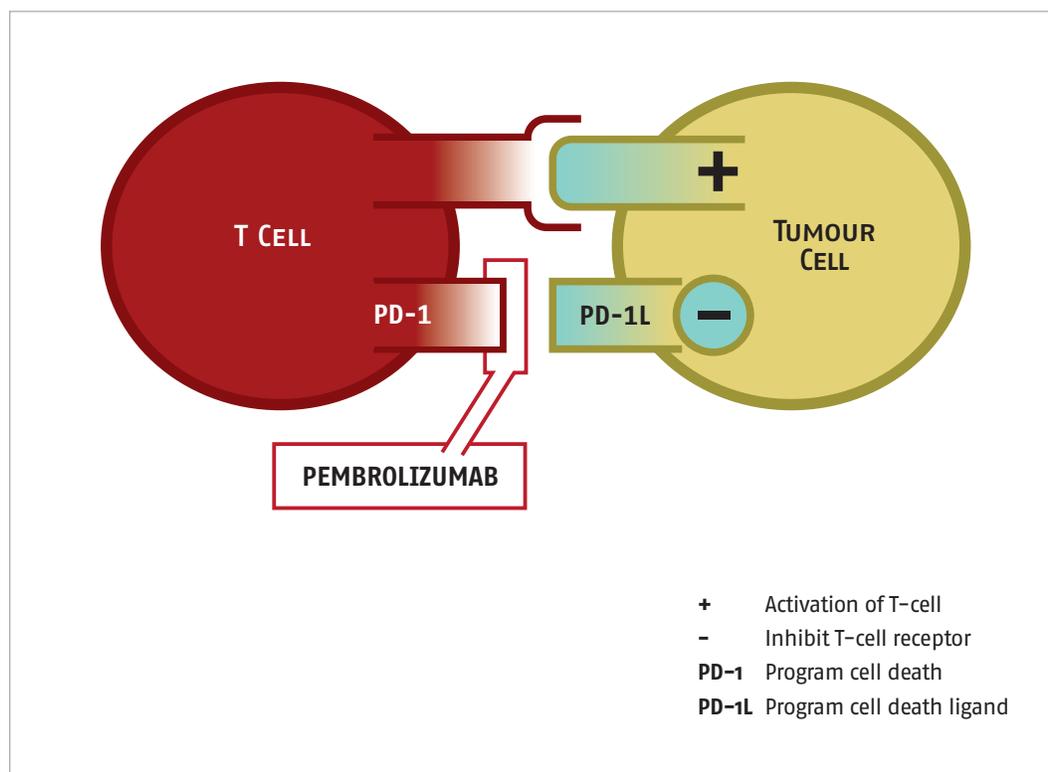
Drug administration

Pembrolizumab

This medication is administered by intravenous infusion in the hospital or clinic setting every 3 weeks.¹

Mechanism of action

Pembrolizumab is a monoclonal antibody that binds to PD-1 receptor and blocks PD-1 ligands (PD-L1 and PD-L2) from binding to PD-1 receptors on T-cells. This blockade removes the off-switch that PD-1 ligands impose on T-cells and reactivates the T-cell-mediated anti-tumour immune response. Once reactivated, the T-cells and other immune cells are no longer “blind”. They are free to attack and kill cancer cells, shrinking tumours.¹



Basic pharmacokinetics

No drug interactions have been reported with pembrolizumab.¹

Presentation, prevention and management of common adverse events

The following table summarizes the common adverse events of pembrolizumab with an overall frequency of $\geq 10\%$.¹

Common adverse events of anti-PD1 monoclonal antibodies

Click on adverse events highlighted in blue for more information.¹

Pembrolizumab¹

Blood and lymphatic system disorders

- Anemia

Gastrointestinal disorders

- Abdominal pain
- Constipation
- **Diarrhea**
- Nausea
- Vomiting

General disorders

- Chills
- Fatigue
- Fever
- Peripheral edema

Infection

- Upper respiratory tract infection

Laboratory abnormalities

- Hyperglycemia
- Hypertriglyceridemia
- Hypoalbuminemia
- Hypocalcemia
- Hyponatremia
- Increased aspartate aminotransferase

Metabolism and nutrition disorders

- Loss of appetite

Musculoskeletal and connective tissue disorders

- Arthralgia
- Back pain
- Myalgia
- Pain in extremities

Nervous system disorders

- Dizziness
- Headache

Psychiatric disorders

- Insomnia

Respiratory disorders

- Cough
- Dyspnea

Skin and subcutaneous tissue disorders

- **Pruritus**
- **Rash**
- Skin colour changes

Other adverse events of interest with anti-PD1 monoclonal antibodies

Click on adverse events highlighted in blue for more information.

- **Immune-mediated responses**
- **Teratogenicity**

Refer for medical attention

Tell patients to seek emergency care if any of these uncommon immune-mediated adverse events develops:¹

- Pneumonitis: new or worsening cough, chest pain, or shortness of breath
- Colitis: diarrhea, severe abdominal pain
- Hepatitis: yellowing of skin or eyes (jaundice), severe nausea or vomiting, easy bleeding or bruising
- Hypophysitis: persistent or unusual headache, extreme weakness, dizziness or fainting, vision changes
- Kidney inflammation (nephritis): pain or burning sensation on urination, frequent need to urinate, cloudy or bloody urine, back pain in kidney area; puffy face, legs, or feet
- Hypothyroidism (underactive thyroid): fatigue, weight gain, muscle weakness, dry skin, hair loss, impaired memory, hoarseness, constipation, cold sensitivity, slow heartbeat, depression
- Hyperthyroidism (overactive thyroid): weight loss, heat sensitivity, sweating, tremor, nervousness, anxiety, fatigue and muscle weakness, more frequent bowel movements, thin skin, fine, brittle hair, changes in menstrual patterns, rapid heartbeat

◀ Diarrhea

Diarrhea is a common adverse event of pembrolizumab, occurring in about 20% of patients.¹ This adverse event may be an immune-mediated response that may lead to immune-mediated colitis (reported in 1% of patients). Do not treat with OTC medications. Refer patients with diarrhea to their doctors, no matter the severity, for immediate medical evaluation.¹

Refer all patients with diarrhea to their doctor for immediate medical care.¹

Management

Supportive care³

- Diet modification
- Hydration

The doctor may prescribe:^{3,8}

- For mild or moderate diarrhea (≤ 6 stools/day):
Loperamide or atropine plus diphenoxylate (Lomotil®)
- For prolonged (5 to 7 days) or moderate diarrhea:
Budesonide (3 mg PO TID) or prednisone (1 mg/kg daily), tapered over 4 to 6 weeks
- For severe diarrhea (≥ 7 stools per day):
Methylprednisolone IV (1-2 mg/kg daily) or prednisone (1-2 mg/kg daily), tapered over 4-6 weeks

Other interventions³

- Infliximab
- Total parenteral nutrition (TPN) or surgical intervention

Key facts: Diarrhea

When patients on pembrolizumab complain of diarrhea that is complicated by the following symptoms, it is important to discourage the use of OTC medications and refer them for medical treatment.^{1,4} Symptoms of colitis include:⁴

- Watery stool
- Abdominal pain
- Fever
- Nausea
- Vomiting

Anal pain

Immune-related colitis usually responds to restricted oral intake and glucocorticoids, but immunosuppressive therapy may be required even for patients with mild to moderate diarrhea.^{1,5}

◀ Immune-mediated responses

This medication may cause immune-mediated responses (immune system attacks on normal tissue), some of which may be severe or fatal.^{1,6} Among the serious immune-mediated adverse events are:¹

- Pneumonitis
- Colitis
- Hepatitis
- Hypophysitis (pituitary gland inflammation)
- Nephritis (which may lead to renal failure)
- Hyperthyroidism or hypothyroidism

Less common severe immune-mediated responses include exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures and adrenal insufficiency.¹

Advise patients to seek immediate medical attention if they develop any signs and symptoms of immune-mediated response. These adverse events are treated with corticosteroid therapy or, in more severe cases, drug interruption or discontinuation.¹

◀ Pruritus

In patients treated with pembrolizumab, pruritus occurs in 30% of patients, slightly more frequently than rash.¹ Although uncommon, pruritus may be an immune-mediated response. If suspected, refer patients to a doctor for immediate medical evaluation.^{1,2}

Management

Refer to doctor for mild to moderate itching

Advise patients to:⁷

- Frequently apply lotions or bland emollients, such as Eucerin® cream, Neutrogena® Norwegian Formula Hand Cream, or Vaseline Intensive Care® Advanced Healing Lotion, to help reduce or eliminate itchiness on the trunk or extremities
- Choose “anti-itch” products
- Use mild soaps that contain no deodorants or fragrance, such as Dove® or Neutrogena®
- Use lotions with aloe vera or dimethicone Moisturel®
- Use liquid shower gels instead of soap
- Use antidandruff shampoos and conditioners
- Use hair products that contain tea tree oil, which contain extra moisturizers and may relieve symptoms

Refer to emergency for immediate care of intense, widespread itching

Cool compresses, oral antihistamines, low-dose topical steroids (hydrocortisone 1%) or urea-based topical therapies with antipruritic agents may provide symptomatic relief.^{3,4}

For pruritus with severe rash, doctors may prescribe high-dose topical steroids and oral prednisone (1 mg/kg/day)³

Key facts: Pruritus

Pruritus or itchiness is the consequence of loss of skin moisture. Pruritus caused by targeted therapies may be mild or localized, widespread or intense, or worsen to the point where it interferes with daily activities.³ At present, there are no specific treatment guidelines for pembrolizumab-induced pruritus.

◀ Rash

Rash occurs in 29% of patients treated with pembrolizumab and is usually mild to moderate in severity.¹ Although uncommon, rash may be an immune-mediated response. Refer patients with rash, regardless of severity, to a doctor for immediate medical evaluation.^{1,2}

Key facts: Rash

Symptomatic treatment with moisturizers is recommended for mild to moderate rash, but prescribed therapy may be necessary to resolve rashes of any severity.^{1,6} There are no specific guidelines for the management of pembrolizumab-induced rash. Similarities between it and other rashes induced by targeted therapies have not been established.

◀ Teratogenicity

Pembrolizumab may cause fetal harm, because it interferes with the PD-1/PDL-1 pathway, which maintains pregnancy by making the mother's immune system tolerate the presence of the fetus. Fertile women are advised to use effective contraceptive measures while taking this drug.¹

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RANKL Inhibitors

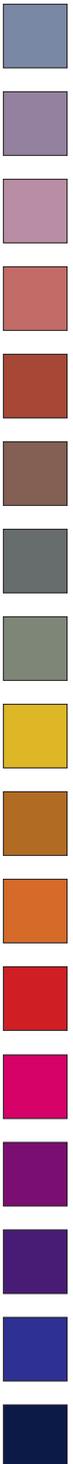
Denosumab (Xgeva™)

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This chapter contains information on the prevention and management of common adverse events of RANK ligand (RANKL) inhibitors that you are likely to encounter among cancer patients in your practice.

There are no evidence-based guidelines on how to manage the adverse events of RANKL inhibitors. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of adverse events, please consult the product monograph.¹

RANKL inhibitors block the biological activity of the RANK ligand (RANKL), which activates a transmembrane cell receptor on the surface of osteoclasts and cells that develop into osteoclasts. These cells are responsible for bone resorption.¹⁻³ To date, denosumab is the only available agent in this class.



Xgeva™ and Prolia®

Denosumab is marketed under two brand names in Canada. Xgeva 120 mg is used to treat patients whose cancer spreads into bone. Prolia 60 mg is used to treat bone loss in postmenopausal women with osteoporosis. Patients should not take both medications at the same time. Information contained in this chapter is related to Xgeva.

Bone physiology

Bone is a living, dynamic tissue in a constant state of renewal. During the 17-day cycle of bone remodeling in humans, osteoblasts build and reshape bone tissue. After bone forms, osteoclasts break it down, a process known as bone resorption, before the bone remodeling cycle renews.²

RANKL in cancer

Tumour cells that spread into bone may increase the expression of the receptor activator of nuclear factor kappa-B ligand (RANKL). This ligand activates osteoclasts, which are responsible for bone resorption. RANKL is a key mediator of osteoclast formation, function and survival. The overexpression of RANKL triggers an overabundance of osteoclasts in bone. Osteoclasts destroy bone and release growth factors, which feed tumours.¹⁻³

Tumour cells in bone initiate a vicious cycle of bone resorption and tumour expansion by increasing RANKL levels.³ The overexpression of RANKL leads to:²

- Abnormal bone resorption
- Tumour cell proliferation
- Spread of tumour cells
- Tumour cell survival

Drug administration

Denosumab is given by subcutaneous injection, once every 4 weeks, in the upper arm, upper thigh or abdominal area.¹

Dosing considerations

All patients who take denosumab, except those with hypercalcemia, should take:

- At least 500 mg of calcium daily
- At least 400 IU of vitamin D daily

Mechanism of action

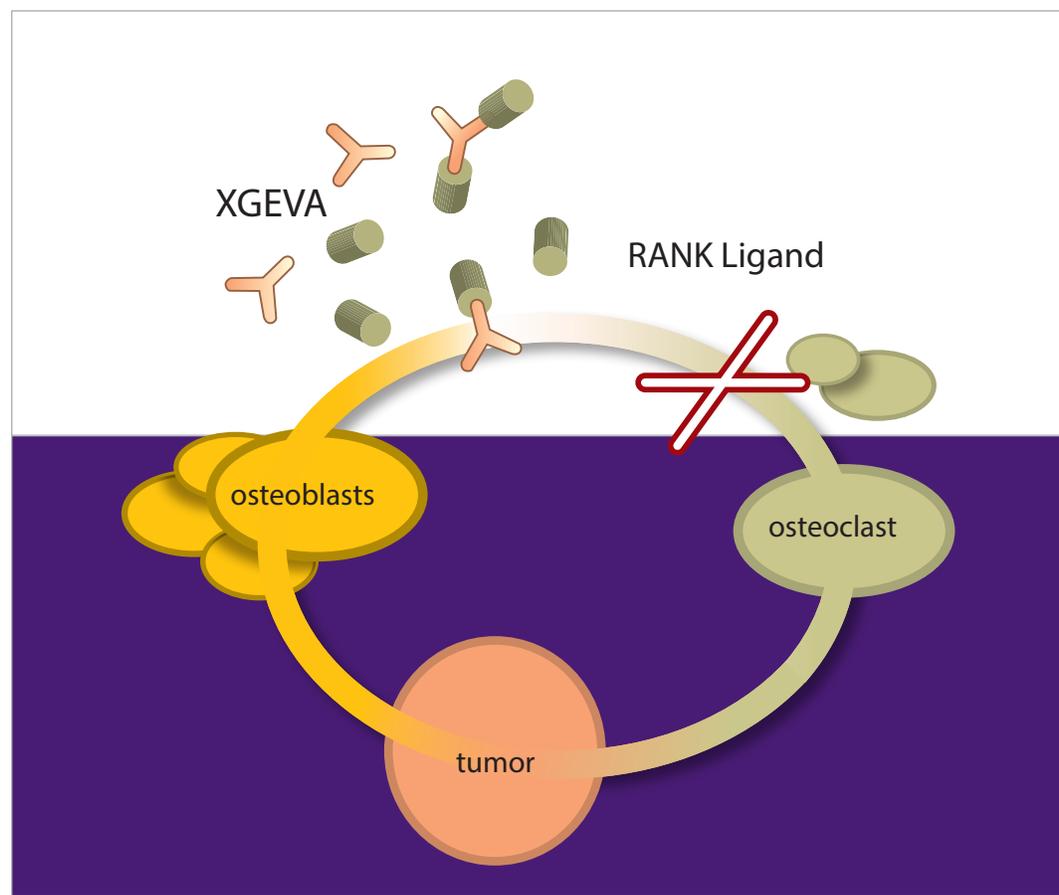
A RANKL inhibitor binds to RANKL, a ligand that controls the formation, function and survival of osteoclasts. By binding to this ligand, these agents block RANKL from binding to its receptor, RANK, on the surface of osteoclasts. They prevent RANKL from stimulating osteoclast overactivity. The overactivity of osteoclasts in patients with bone metastasis accelerates bone resorption, weakening bone. Osteoblasts release growth factors that promote tumour proliferation and spread.^{1,3}

Denosumab

Denosumab is a fully human monoclonal antibody that binds to and neutralizes RANKL. It prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. This action inhibits osteoclast formation, function and survival to decrease bone resorption and interrupt cancer-induced bone destruction. Denosumab causes a rapid, sustained suppression of bone turnover markers.

Denosumab prevents:¹⁻³

- Generalized bone resorption
- Local bone destruction
- Skeletal-related events
- Release of tumour-promoting growth factors



Basic pharmacokinetics

The mean half-life of denosumab is 28 days after the discontinuation of therapy. Pharmacokinetic parameters do not change with age, body weight, race, gender or type of solid tumour.¹ There are no known drug interactions with denosumab.¹

Presentation, prevention and management of common adverse events

Over 95% of patients who take this medication will experience some type of adverse event. Nausea, fatigue and lack of energy, and low phosphorous level are most common in patients with bone metastasis from solid tumours (per-patient incidence $\geq 25\%$). The most common adverse events in patients with giant cell tumour of bone (GCTB) are arthralgia, headache, nausea, fatigue, back pain, and pain in extremity (per-patient incidence $\geq 10\%$). Shortness of breath is the most common serious adverse event. The most common adverse reactions resulting in discontinuation of denosumab were osteonecrosis and hypocalcemia.¹

The following table summarizes the common adverse events of denosumab with an overall frequency of $\geq 10\%$.¹

Common adverse events of RANKL inhibitors

Click on adverse events highlighted in blue for more information

Denosumab¹

Blood and lymphatic disorders

- Anemia

Gastrointestinal disorders

- Abdominal pain
- Constipation
- **Diarrhea**
- Nausea
- Vomiting

General disorders

- Asthenia
- Fatigue
- Fever
- Fluid retention

Respiratory disorders

- Cough
- Shortness of breath

Laboratory abnormalities

- **Hypocalcemia**
- Low phosphorous level

Metabolic and nutrition disorders

- Decreased appetite
- Weight loss

Musculoskeletal and connective tissue disorders

- Arthralgia
- Back pain
- Bone pain
- Musculoskeletal pain
- Pain in extremities

Nervous system disorders

- Headache

Psychiatric disorders

- Insomnia

Other adverse events of interest with RANKL inhibitors

Click on adverse events highlighted in blue for more information

- **Osteonecrosis of the jaw**

Refer for immediate medical attention

Tell patients to seek immediate emergency care if they experience:¹

- Red, painful, swollen skin infection that won't heal, fever (cellulitis)
- Seizures, feeling faint, irregular heartbeat, involuntary muscle contractions (severe hypocalcemia)
- Jaw pain, toothache, tooth or gum infection, mouth or gum ulcers, jaw bone or gum erosion, swelling or redness of jaw, fever, feeling ill (osteonecrosis of jaw)

◀ Diarrhea

About 20% of patients on denosumab experience diarrhea.

Management OTC therapy ⁶⁻⁹	<p>Mild to moderate (less than 4 loose stools per day)</p> <ul style="list-style-type: none">• Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) <p>Moderate (more than 4 to 6 loose stools per day)</p> <ul style="list-style-type: none">• 2 tablets immediately, then 1 tablet every 2-4 hours until bowel movements are normal for at least 12 hours
Replace lost fluids ⁶⁻⁹	<ul style="list-style-type: none">• Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 litres per day.• Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care ⁶	<p>Advise patients to:</p> <ul style="list-style-type: none">• Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation• Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste• Soak in a warm bathtub or sitz bath to relieve discomfort• Examine the anal area for red, scaly or broken skin
Diet ⁶⁻⁹	<p>Advise patients to:</p> <ul style="list-style-type: none">• Eat and drink small quantities of food often• Avoid spicy, greasy, or fried foods• Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve• Follow a lactose-free diet• Avoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

There are no evidence-based guidelines for the prevention or treatment of diarrhea in patients taking a RANKL inhibitor. Antidiarrheal medications are usually able to control this dose-related adverse event.¹⁰

- If mild to moderate diarrhea persists for 48 hours, despite dietary modification and loperamide, a second-line agent may be needed for control. Advise the patient to seek immediate medical attention.¹¹

When patients seek OTC treatment for diarrhea, it is important to ask them about:^{6,7,12}

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Stomach cramps

◀ Hypocalcemia

Decreases in calcium levels are generally mild, transient and not associated with clinical problems. This adverse event typically occurs within the first 6 months of treatment. Although infrequent, severe hypocalcemia can occur with denosumab therapy. Calcium and vitamin D supplements are recommended with denosumab. Advise your patients to watch for signs and symptoms, including Seizures, feeling faint, irregular heartbeat, involuntary muscle contractions^{1,3,13}

◀ Osteonecrosis of the jaw

An infrequent yet serious adverse event, osteonecrosis of the jaw (ONJ) can manifest in many ways, including jaw pain, toothache, mouth or gum ulcers, bone or gum erosion, tooth or gum infection, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. The patient may experience local swelling, redness and a feeling of warmth in the jaw. Fever, general discomfort, and feeling ill are common symptoms.^{1,14}

Patients at risk of ONJ

Some patients who take denosumab have a higher risk of ONJ. Risk factors include:¹⁻³

- Use of dental appliance
- Tooth extraction
- Poor oral hygiene

Advise your patients that good oral hygiene is important. Warn patients taking denosumab to avoid invasive dental surgeries and talk to their dentist and oncologist about these procedures beforehand, as dental surgery precedes 60% of ONJ.⁵ This condition may resolve with the use of oral rinses or antibiotics; more severe cases may require limited surgery.^{1-5,14}

Denosumab combined with risk factors, such as dental extraction, poor oral hygiene, use of removable apparatus, and chemotherapy may favour the development of ONJ.¹⁴

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Vascular Endothelial Growth Factor Inhibitor

Aflibercept (Zaltrap™)

Axitinib (Inlyta®)

Bevacizumab (Avastin®)

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This chapter contains information on the prevention and management of common adverse events of vascular endothelial growth factor (VEGF) inhibitors that you are likely to encounter among cancer patients in your practice.

Three medications are available that inhibit the action of vascular endothelial growth factor (VEGF). Some medications that inhibit multiple kinases, particularly sunitinib, pazopanib, sorafenib, regorafenib and vandetanib can also inhibit VEGF activity. These medications, which appear in the chapter on multiple kinase inhibitors (MKIs), may have similar adverse events to the VEGF target inhibitors. However, these MKIs are not exclusively used to inhibit VEGF.

There are no evidence-based guidelines on how to manage VEGF inhibitor-induced adverse events. The recommendations presented here are based on a review of expert opinion and best practices in oncology. For a complete description of all adverse events, please consult the product monographs.¹⁻³



VEGF in cancer

The formation of new blood vessels in an established circulatory system, a process known as angiogenesis, is a critical step in cancer development.^{2,4} As tumours grow, the need for oxygen and nutrients outpaces the supply from nearby blood vessels. In response, they release VEGF, which increases the permeability of blood vessels near tumours, enabling plasma proteins and other large molecules to leak out of small blood vessels. These molecules form a fibrin gel, which acts as a supportive matrix for the endothelial cells and fibroblasts that form new blood vessels. The circulatory network that feeds tumours expands, enabling cancer to grow and progress.^{5,6} VEGF is one of the body's most potent promoters of angiogenesis.⁷ VEGF regulates tumour:^{5,6}

- Angiogenesis
- Growth
- Progression

Drug administration

Aflibercept

Aflibercept is an intravenous infusion that is administered in the hospital or clinic setting.¹

Axitinib

Axitinib is an oral medication that is taken twice daily, approximately 12 hours apart, with or without food. Patients swallow the tablet whole with a glass of water.²

Bevacizumab

Bevacizumab is an intravenous infusion that is administered in the hospital or clinic setting.³

How to take Axitinib

Patients taking axitinib should avoid grapefruit, star fruit, pomelo, pomegranate and Seville oranges and other foods that inhibit CYP3A4/5, as they may increase drug plasma concentrations.²

Mechanism of action

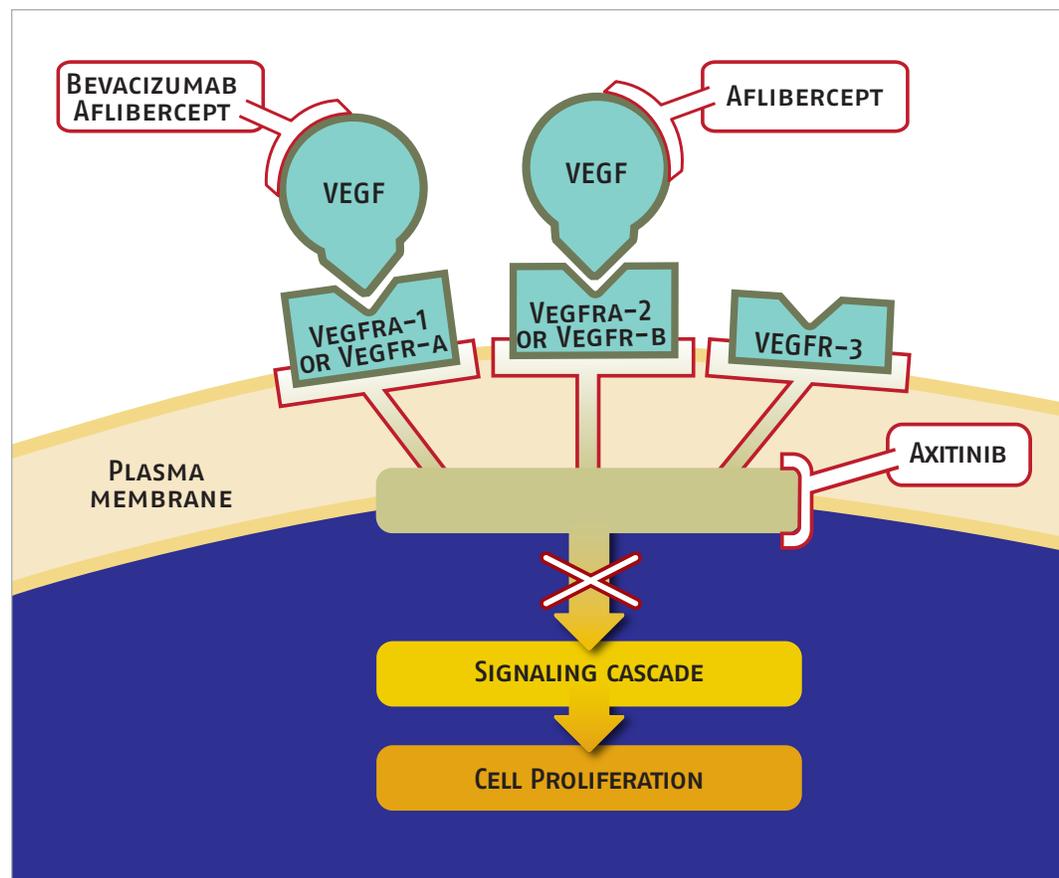
Bevacizumab is a monoclonal antibody that binds specifically to VEGF to neutralize its biological activity.³ By binding to VEGF, bevacizumab prevents this protein from attaching to VEGF receptors on blood-vessel walls, thus preventing the changes in vascular permeability that are necessary for angiogenesis. In short, bevacizumab chokes off the blood supply to tumours.⁸

Like bevacizumab, aflibercept is a monoclonal antibody that traps VEGF ligands. It acts as a decoy receptor that binds VEGF-A, VEGF-B and placental growth factor (PlGF). It prevents these proteins from binding to their true receptors, neutralizing their biological activity. As a result, aflibercept inhibits the growth of new blood vessels.¹

Axitinib is a highly selective, tyrosine kinase (TK) inhibitor that binds to three VEGF receptors (VEGFR-1, VEGFR-2, and VEGFR-3). This small-molecule drug binds tightly to a deep pocket in the TK domain of these receptors. Consequently, VEGF cannot bind to them. By blocking VEGF, axitinib prevents its biological activity. Like bevacizumab and aflibercept, axitinib prevents a tumour from developing new blood vessels to feed its growth.^{2,4}

By neutralizing VEGF, bevacizumab, aflibercept, and axitinib:¹⁻⁶

- Inhibit tumour vascularization and blood flow
- Slow tumour growth
- Slow the spread of cancer



Basic pharmacokinetics

There are no formal drug metabolism studies for bevacizumab and aflibercept.^{1,3} Bevacizumab is not metabolized by the kidney or liver but is managed in the body like the natural antibody IgG.³ Aflibercept is expected to degrade into small peptides and individual amino acids.¹

Exercise caution when combining aflibercept, axitinib or bevacizumab with anticoagulant medication due to increased risk of bleeding.¹⁻³

Axitinib is metabolized primarily via the CYP3A4/5 pathway in the liver and, to a lesser extent, by CYP1A2, CYP2C19, and UGT1A1. The use of axitinib with potent CYP3A4 and CYP1A2 inducers and inhibitors should be avoided.^{2,4} Axitinib is a CYP1A2 and CYP2C8 inhibitor.²

Presentation, prevention and management of common adverse events

The common adverse events of VEGF inhibitors are predictable, generally mild to moderate but occasionally severe, and manageable.¹⁻⁵ Since these agents are often studied in combination with other drugs, it can be difficult to distinguish adverse effects due to VEGF inhibitors versus chemotherapeutic drugs.^{1-3,8}

The following tables report adverse events with an overall frequency of $\geq 10\%$ or a $>10\%$ frequency in the combination group versus the control group.

Common adverse events of VEGF inhibitors

Click on adverse events highlighted in blue for more information.

Blood and lymphatic disorders	General disorders	Musculoskeletal and connective tissue disorders
<ul style="list-style-type: none">• Anemia• Leukopenia• Neutropenia• Thrombocytopenia	<ul style="list-style-type: none">• Asthenia• Fatigue• Fever• Mucosal inflammation• Pain• Weight loss	<ul style="list-style-type: none">• Arthralgia• Back pain
Cardiovascular disorders	Hemorrhagic disorders	Pain in extremities Nervous system disorders
<ul style="list-style-type: none">• Hypertension	(Bleeding) <ul style="list-style-type: none">• Major hemorrhagic events (axitinib)• Minor bleeding	<ul style="list-style-type: none">• Headache• Taste disturbance
Endocrine disorders	Metabolism and nutrition disorders	Renal disorders
<ul style="list-style-type: none">• Hypothyroidism (axitinib)• Ovarian failure (bevacizumab)	<ul style="list-style-type: none">• Laboratory abnormalities• Abnormal electrolytes (axitinib)• Anorexia (bevacizumab)• Hyperglycemia (axitinib, bevacizumab)• Loss of appetite	<ul style="list-style-type: none">• Increased creatinine (axitinib)• Proteinuria
Eye disorders		Respiratory disorders
<ul style="list-style-type: none">• Eye disorders (aflibercept, bevacizumab)• Increased tear production (bevacizumab)		<ul style="list-style-type: none">• Cough (axitinib)• Dyspnea• Rhinitis (bevacizumab)• Voice changes (axitinib)
Gastrointestinal disorders		Skin disorders
<ul style="list-style-type: none">• Abdominal pain• Constipation• Diarrhea• Dyspepsia• Nausea• Stomatitis [photo]• Vomiting		<ul style="list-style-type: none">• Hand-foot skin reaction (axitinib)• Dry skin• Rash• Skin discoloration (bevacizumab)

Refer for medical attention

Refer patients to a doctor if any of the following adverse events develop or become severe:¹⁻³

- Bleeding events (rectal bleeding, blood in stool)
- Hyperglycemia (hunger, thirst, increased urination, fatigue)
- Decreased thyroid function (fatigue, constipation, dry skin, weight gain)
- Fever (38.3° C or 38° C sustained over 1 hour)
- Hypertension (headache, blurred vision, fatigue) or hypotension (dizziness, lightheadedness, fainting)
- Low blood cell counts (red: fatigue, weakness, poor concentration) (white: fever, sore throat, infection)
- Proteinuria
- Wound-healing complications

Tell patients to seek immediate emergency care if any of these uncommon adverse events develop:¹⁻³

- Bleeding events (unstoppable nosebleeds)
- Gastrointestinal perforation (abdominal pain, fever, chills or vomiting)
- Heart attack or stroke
- Blood clots (chest pain, shortness of breath, coughing up blood, leg swelling or discoloration)
- Heart problems (fatigue, shortness of breath, swollen feet or ankles, faster heart rate)

◀ Bleeding

Minor bleeding from the skin and mucous membranes have occurred in 20% to 40% of patients on bevacizumab.³ Mucosal inflammation, which may lead to bleeding, occurs in 15% of patients on axitinib.² Episodes of bleeding or hemorrhage occur in about 38% of patients on aflibercept/FOLFIRI.¹ The most common form of bleeding is minor nosebleed, occurring in up to 28% of patients.¹

Monitoring	Encourage patients to: <ul style="list-style-type: none">• Monitor and report bleeding events to their doctor⁸
Management	Nosebleeds <ul style="list-style-type: none">• Apply first-aid techniques for minor episodes• Refer to hospital for emergency care of bleeding events that require intervention

Key facts: Bleeding

Bleeding events are usually minor, occurring mostly as nosebleeds that respond to first-aid treatment and stop within 5 minutes.^{5,10} Bleeding from the gums may occur, and women may have longer and heavier uterine bleeding during their periods. Tumour-related bleeding may also occur.^{5,10} In certain cancers, life-threatening bleeding complications may occur in up to 9.4% of patients on bevacizumab and about 3% of patients on aflibercept combined with chemotherapy.^{1-3,5,10}

Life-threatening hemorrhages, which may present as stroke, blood in urine or stool, or coughing up blood, have occurred in some patients.¹⁻³ They are 5 times more likely to occur in patients treated with VEGF inhibitors than others. Any bleeding event should be reported to the patient's doctor.^{3,8}

For nosebleeds, the most common first-aid method is to instruct the patient to lean forward, pinching the bridge of the nose between thumb and forefinger until bleeding stops. If a nosebleed lasts longer than 10 to 15 minutes or the patient feels faint or dizzy, advise him or her to seek immediate care.⁸

◀ Diarrhea

Diarrhea is very common in patients treated with VEGF inhibitors, particularly axitinib and aflibercept.¹⁻³ Up to 55% of patients on axitinib and 69% of patients on aflibercept have developed diarrhea in clinical trials.^{1,2} Dietary modifications are not recommended in anticipation of diarrhea.^{13,14}

VEGF inhibitors may be combined with chemotherapy regimens that contain irinotecan, an agent known to cause diarrhea, e.g., aflibercept and FOLFIRI. If the patient's regimen contains irinotecan, modify the following recommendations to use a more aggressive approach to resolve diarrhea. The patient should take 4 mg loperamide at the first sign of diarrhea (STAT), then 2 mg of loperamide every 2 hours.

Management OTC therapy ¹²⁻¹⁴	Mild to moderate (less than 4 loose stools per day) <ul style="list-style-type: none">Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours) Moderate (more than 4 to 6 loose stools per day or night-time diarrhea) <p>Aggressive use of loperamide (e.g., Imodium®) for early-onset diarrhea</p> <ul style="list-style-type: none">2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hoursThis dosage is higher than packaging recommendations. Advise your patients that it is important to take the medication at higher doses to stop diarrhea
Replace lost fluids ¹²⁻¹⁴	<ul style="list-style-type: none">Fluid intake is more critical than food intake in patients with diarrhea. To replace lost fluid, advise patients with no contraindication to increase intake by up to 3 liters per day.Drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea
Anal care ¹³	Advise patients to: <ul style="list-style-type: none">Clean the anal area with mild soap and warm water after each bowel movement to prevent irritationApply a barrier cream or ointment, such as petroleum jelly or Isle's pasteSoak in a warm bathtub or sitz bath to relieve discomfortExamine the anal area for red, scaly or broken skin
Diet ¹²⁻¹⁴	Advise patients to: <ul style="list-style-type: none">Eat and drink small quantities of food oftenAvoid spicy, greasy, or fried foodsFollow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolveFollow a lactose-free dietAvoid cabbage, brussels sprouts, and broccoli, which may produce stomach gas, bloating and cramps

Key facts: Diarrhea

When patients seek OTC treatment for diarrhea, it is important to ask them about:^{5,12-14}

- Number of stools per day and stool composition, e.g., watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including:
 - Blood in stool
 - Dehydration, e.g., oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
 - Fever
 - Lethargy or altered mental state
 - Nausea and vomiting
 - Signs of infection
 - Stomach cramps

◀ Hand-foot skin reaction (HFSR)

More than 1 in 4 patients (27%) taking axitinib have developed hand-foot skin reaction (HFSR), also known as hand-foot syndrome and palmar-plantar erythrodysesthesia.^{2,15-18,24} With aflibercept and bevacizumab, HFSR worsens when this medication is combined with chemotherapy.^{1,19}

Prevention

During the first 2–4 weeks of therapy, prevention of traumatic activity and rest are crucial.¹²

Urge your patients to:¹⁵⁻¹⁷

- Have a manicure or pedicure to remove thickened skin or calluses; follow with moisturizing cream
- Use a moisturizing cream
- Wear loose-fitting, soft shoes or slippers, foam absorbing soles, gel inserts to cushion pressure points, cotton socks
- Cushion callused areas with soft or padded shoes
- Reduce exposure of hands and feet to hot water (showers, dishwashing, etc.)
- Avoid excessive friction to hands or feet when performing tasks
- Avoid vigorous exercise or activities that place undue stress on the hands and feet
- Wear thick cotton gloves or socks to protect hands and feet and keep them dry
- Report any signs or symptoms immediately to ensure early-stage treatment

Management

OTC treatment

Mild

Discomfort, no disruption of activities¹⁵

Advise patients to add the following:^{15,17,18}

- Avoid hot water; cool water or cold compresses may ease symptoms
- Diligently apply moisturizers to keep palms and soles soft and pliable to prevent cracks or breaks in skin integrity
 - Use moisturizing creams twice daily
 - Use aloe vera lotion
 - Use 20% urea cream (Uremol®) or 6% salicylic acid on callused areas
- Soak feet in magnesium sulfate (Epsom salts) to soften calluses and reduce pain on pressure
- Use low to moderate dose pain killers

Advise patients to consult their doctor about reducing their dosage of VEGF inhibitor, if symptoms of HFSR worsen after being treated for 2 weeks¹⁵

Prescribed therapy

Moderate

Disrupts daily activity¹⁵

Add the following:¹⁵

- Dose modification is required
- Topical corticosteroid (e.g., clobetasol 0.05% ointment)
- 2% lidocaine topical ointment
- Oral NSAIDs, codeine, pregabalin, for pain
- If symptoms worsen after 2 weeks, treatment interruption may be required

Prescribed therapy

Severe¹⁵

- Treat as moderate
- Further dose modification is required
- If symptoms worsen after 2 weeks, treatment interruption may be required

For thick, tender sores after acute rash with/without blisters resolves:¹⁵

- 40% urea cream
- Tazarotene 0.1% cream

Key facts: HFSR

HFSR has a serious impact on the physical, psychological, and social well-being of patients who receive VEGF inhibitors.^{15-18,20} Early detection and prompt treatment can reduce its severity and duration. Treatment may require dosage adjustment or the interruption of life-prolonging therapy in cancer patients.^{15,17} **The look and onset of this reaction is different than capecitabine-induced HFSR.** The typical pattern of localized sensitive lesions with skin thickening, surrounded by redness, differs from classic HFSR, in which symmetrical changes in skin sensation, redness and swelling occurs.^{17,20}

HFSR usually occurs within the first 2 to 6 weeks of therapy.²⁰ Tender, scaly sores – with or without blistering – appear on the palms and soles. The edges of thickened skin patches on fingertips, toes, and other pressure or flexure points, such as elbows or knuckles, may be surrounded by a swollen, reddish halo.^{15,16,20} The hands or feet may tingle or feel sensitive to touch or heat.^{18,20} After several weeks, thickened, callus-like skin develops over the sores. These areas are usually painful and impair range of motion, function, and weight bearing.^{15,20}

There are no evidence-based guidelines for the treatment of VEGF inhibitor-induced HFSR. Most cases are mild to moderate, but some patients develop a severe reaction that impairs daily-living activities.^{2,15-18,20} These patients may experience extreme tenderness of the hands and feet – enough to affect hand or foot function and disrupt their quality of life.^{1,15,20}

Skin products in use for HFSR¹⁸

- Cetaphil® skin cleansers
- Aveeno® shower gel
- Udderly Smooth®, Gold Bond®, Aveeno® lotions
- Norwegian Formula moisturizer and foot cream (Neutrogena®)
- Bag Balm®
- Eucerin® cream and Dry Skin Therapy
- Aquaphor® Healing Ointment
- Kerasal®
- Lipikar, Lipikar balm, and Xerand
- Sunblock

◀ Hypertension

The onset of hypertension may occur at any time during therapy with a VEGF inhibitor.² Hypertension is usually manageable but may be severe in 20% of patients with aflibercept.¹ Severe hypertension occurs in 3% to 17.9% of patients taking bevacizumab.³ Less than 1% of patients discontinue VEGF inhibitors due to this adverse event.¹⁻³ However, patients may need to delay treatment until hypertension is controlled.

Up to 40% of cancer patients have experienced new or worsened hypertension on VEGF inhibitors.^{1-3,5}

- Between 16% and 19% of patients taking VEGF inhibitors have developed moderate to severe hypertension that required oral antihypertensive therapy or a change in dosage of existing antihypertensive medication.¹⁻³
- While rare, hypertensive crisis and other serious complications of hypertension may occur with VEGF inhibitors.¹⁻³

Monitoring	Encourage patients to: ^{1-3,5-8} <ul style="list-style-type: none">• Monitor blood pressure (BP) at weekly intervals or at more frequent intervals often if they already have hypertension• Monitor blood pressure every 2 weeks after infusion of bevacizumab or aflibercept	
Management	Refer for antihypertensive therapy: ⁷ <ul style="list-style-type: none">• Patients with recurrent, symptomatic, or persistent >20 mm Hg increase in systolic BP	Prescribed therapy: <ul style="list-style-type: none">• Most hypertension can be managed with standard oral antihypertensive therapy.^{2,7}

Key facts: Hypertension

Patients taking VEGF inhibitors are 8 to 9 times more likely to develop hypertension than others. Onset is usually within the first 4 weeks of treatment. Hypertension is often transient and typically resolves after therapy ends. It is more likely to occur and have more impact in patients who already have hypertension.

Refer patients with systolic blood pressure (BP) increases of greater than 20 mm Hg or an overall BP reading of greater than 160 mm Hg systolic and 100 mm Hg diastolic to their physician for evaluation.

If an antihypertensive therapy is started during treatment, it should be re-evaluated after the cessation of a VEGF inhibitor.

In patients with severe hypertension or persistent hypertension despite treatment, or who experience a hypertensive crisis, VEGF therapy will be discontinued.^{3,9} All patients who develop hypertension should be screened for proteinuria.⁹

◀ Stomatitis

In patients treated with a VEGF inhibitor, the integrity of mucous membranes in the mouth and gastrointestinal tract may become compromised, leading to mucosal inflammation and stomatitis (mouth sores) [Photo].¹⁻³ This adverse event occurs in about 50% of patients on an aflibercept-chemotherapy regimen, 15% of axitinib-treated patients, and at least 10% of patients on bevacizumab.¹⁻³

Prevention	Advise patients to: ^{21,22} <ul style="list-style-type: none">• Avoid cheek or lip biting• Avoid mouth breathing• Maintain good oral hygiene• Maintain dentures by brushing daily and soaking in antimicrobial solution for at least 30 minutes/day and rinse thoroughly• Avoid spicy and highly textured foods• Avoid alcohol-containing mouthwashes	
Management	OTC treatment For mild cases of mouth sores, pain, or redness on the inner cheeks, tongue, or lips Meticulous oral hygiene: ^{21,22} <ul style="list-style-type: none">• Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles• If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®• Biotène® toothpaste is non-irritating contains natural salivary enzymes to control bacteria• Floss gently once daily to avoid gum injury• Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)• Bland rinses, antimicrobial mouthwashes without alcohol• OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®) Refer to doctor if patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips ²³	Prescribed medication (moderate to severe cases): ^{21,22} <ul style="list-style-type: none">• Topical fluoride (dentist)• Topical anesthetics with or without topical• Corticosteroids• Topical or systemic analgesics• Topical antifungals are preferable if a fungal infection is diagnosed• Palliative mixtures of various agents

Key facts: Stomatitis

Changes in the oral cavity differ from those in patients treated with traditional chemotherapy. Mouth ulcers (cankers) often appear on the tongue, inside the lips, or inside cheeks. The ulcers do not appear to be contagious.

Maintaining the health, integrity, and function of oral mucosa is crucial in patients with stomatitis. Treatment aims to relieve symptoms, until the mucous membranes can rejuvenate themselves, usually within 7 to 14 days.

There are no evidence-based guidelines for treatment of VEGF inhibitor-induced stomatitis, and practitioners usually follow the common practices for chemotherapy-induced mouth inflammation. The guidelines stress the importance of good oral hygiene but, due to a lack of supportive evidence, oral hygiene methods are usually based on personal preference and anecdotal experience.²¹

Good oral hygiene:^{21,22}

- Reduces the severity of stomatitis
- Reduces mouth pain
- Reduces oral bleeding
- Reduces the risk of dental complications
- Minimizes the risk of soft tissue infections
- Enables patients to maintain a nutritious diet

The use of chlorhexidine mouth rinses is not recommended. They contain alcohol and may sting. Dilution defeats their antibacterial benefits.¹¹ Hydrogen peroxide rinses may worsen mouth ulcers.¹¹

Topical preparations in widespread use for stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. There is no significant evidence of the effectiveness or tolerability of these concoctions, and some may be only minimally better than saline rinses. Clinical trials in chemotherapy patients with stomatitis have shown no difference in the effectiveness of chlorhexidine mouthwash, “magic” mouthwashes that contain lidocaine, and salt-and-baking soda rinses.²¹⁻²³

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Photo Gallery

Drug-related side effects



Stomatitis

EGFR inhibitors

- ◀ Common adverse events
- ◀ Key facts

HER2 inhibitors

- ◀ Common adverse events
- ◀ Key facts

MK inhibitors

- ◀ Common adverse events (Imatinib, Pazopanib)
- ◀ Common adverse events (Regorafenib, Sorafenib)
- ◀ Common adverse events (Sunitinib, Vandetanib)
- ◀ Key facts

mTOR inhibitors

- ◀ Common adverse events
- ◀ Key facts

VEGF inhibitors

- ◀ Common side effects
- ◀ Key facts



Courtesy of Novartis Pharmaceuticals Canada Inc.

Paronychia

EGFR inhibitors

- ◀ Common adverse events
- ◀ Key facts

MEK1/MEK2 inhibitors

- ◀ Common adverse events
- ◀ Key facts

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Trichomegaly

EGFR inhibitors

- ◀ Common adverse events

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Dueland S et al. Acta Oncolog 2003;42:345-346



Rash

EGFR inhibitors

- ◀ Common adverse events
- ◀ Key facts

HER2 inhibitors

- ◀ Common adverse events
- ◀ Key facts

MEK1/MEK2 inhibitors

- ◀ Common side effects
- ◀ Key facts

MK inhibitors

- ◀ Common adverse events (Imatinib, Pazopanib)
- ◀ Common adverse events (Regorafenib, Sorafenib)
- ◀ Common adverse events (Sunitinib, Vandetanib)
- ◀ Key facts

mTOR inhibitors

- ◀ Common adverse events
- ◀ Key facts



Mild



Moderate



Severe

Courtesy of Pamela Vale, RN

Quiz and Evaluation

In order to be eligible for continuing education credits, you must complete this final Quiz with a minimum grade of 70% and complete the Program Evaluation. Please note that you are permitted only two attempts at the final Quiz. The final Quiz is comprised of 70 multiple-choice questions and requires approximately 70 minutes to complete.

Upon successful completion of this 2015 updated OnTarget quiz, you will receive 17.5 CEUs. Participants who successfully completed the **2012** OnTarget quiz **are not eligible** to retake the quiz and receive credits. Participants who successfully completed the **2009** OnTarget quiz **are eligible** to retake the quiz and receive credits

Once you have successfully completed the program, you will receive your Letter of Attendance by email.

Note: The Letter of Attendance will be emailed to you. They are sometimes filtered as "junk mail". If you have not received your Letter of Attendance within 48 hours of completing quiz and program evaluation, please contact:

bernard.lesperance@umontreal.ca, 514-338-2150.

Click on this link to access the final quiz:

<http://www.geog.info/access-questionnaire-partial-ontarget/en/list16/no66,65>

