Guideline Resource Unit
guru@ahs.ca

Prevention and Treatment of Acneiform Rash in Patients Treated with EGFR Inhibitor Therapies

Effective Date: November, 2020

Cancer Care Alberta

Clinical Practice Guideline SUPP-003 – Version 2
www.ahs.ca/guru

Background

The epidermal growth factor receptor (EGFR) plays a central role in tumour growth and proliferation, and over-expression of EGFR is correlated with a poor prognosis, disease progression, and reduced sensitivity to chemotherapy.[1] EGFR-targeted agents are used in several types of cancer, including lung, colorectal, breast, pancreatic, and head and neck. Classes of EGFR inhibitors include monoclonal antibodies (e.g. cetuximab, panitumumab, pertuzumab) and small molecular weight tyrosine kinase inhibitors (e.g. erlotinib, gefitinib, lapatinib, afatinib, osimertinib). These agents have been evaluated in phase II and III trials and are increasingly being incorporated into therapeutic plans for patients, both as front-line therapy, and after progression on standard chemotherapy.

EGFR inhibitors are generally well tolerated and are not associated with the moderate or severe systemic side effects of standard cancer therapies such as chemotherapy or radiation. However, because of the role of EGFR in skin biology they are associated with a variety of dermatologic reactions.[2] The most commonly reported side effect is acneiform (papulopustular) rash; Table 1 lists the incidence rate for each EFGR inhibitor. Acneiform rash is typically localized to the face, scalp, upper chest and back. Although it is usually mild or moderate in severity, it can cause significant physical and psychosocial distress in patients, which may lead to decreased quality of life, and disruption or discontinuation of therapy.[3, 4] Thus, timely and appropriate interventions are essential.[5]

Table 1. Incidence of acneiform eruption and skin rash

EFGR Inhibitor	Incidence of Acneiform Eruption and Skin Rash
Afatinib	• Acneiform eruption: ~90%[6] • Skin rash: ≤90%[6] • In LUX-Lung 3 and 8, incidence of Grade 3 cutaneous reactions ranged from 6.6% to 16.2%[7]
Cetuximab	• Acneiform eruption: 15-88%[8] • Skin rash: 28-44%[8] • Acneiform rash occurred in 76-88% of patients; severe acneiform rash occurred in 1-18% of patients[9]

Erlotinib	• Acneiform eruption: 4-5%[10]
	• Skin rash: 49-85%[10]
	  ○ Grade 3: 5-13%
	  ○ Grade 4: <1%

Gefitinib	• Acneiform eruption: 6%[11] • Skin rash: 52%,[11] mainly mild or moderate[12]
Lapatinib	• Acneiform eruption: not reported[13] • Skin rash: 28-44% (combination therapy with capecitabine or letrozole)[13], generally low grade[14]
Osimertinib	• Acneiform eruption: not reported[15] • Skin rash: 58%,[15] mainly mild[16]

Panitumumab	• Acneiform eruption:[17]
	  ○ 57%; grades 3/4: 7% (monotherapy)
	  ○ 32%; grades 3/4: 10% (combination therapy with FOLFOX)
	• Skin rash:[17]

EFGR Inhibitor	Incidence of Acneiform Eruption and Skin Rash
	○ Pustular rash: 4% (monotherapy) ○ Papular rash: 2% (monotherapy) ○ Skin rash 56%; grades 3/4: 15-26% (combination therapy with FOLFOX)
Pertuzumab	• Acneiform eruption: not reported[18] • Skin rash: 11-34% (combination therapy with trastuzumab and docetaxel),[18] mainly mild or moderate[19]

The onset of acneiform rash is most commonly observed during the first one to two weeks of treatment with an EGFR inhibitor, although the range of onset reported in the literature is between two days and six weeks.[5] The rash typically progresses through four phases:[1]

- Phase one (weeks 0-1): sensory disturbance with erythema and edema;
- Phase two (weeks 1-3): papulopustular eruptions;
- Phase three (weeks 3-5): crusting; and,
- Phase four (weeks 5-8): erythematotelangiectasias (red areas).

The lesions are usually sterile, but a secondary bacterial or fungal infection at the site of the eruption has been described in some cases.[20-24] The severity of the rash waxes and wanes throughout these four phases, and typically resolves without permanent scarring within two months of therapy discontinuation, although scarring secondary to bacterial or fungal overgrowth can also occur.[1, 21]

The purpose of this document is to provide recommendations for the prevention and treatment of EGFR inhibitor therapy causing rash.

Guideline Questions

1. How should rash severity be graded?
2. What is the evidence for the relationship between rash and response to treatment in adult patients with advanced non-small cell lung cancer, colorectal cancer, head and neck cancers, or breast cancer treated with EGFR inhibitors?
3. What are the recommended strategies for the prevention of rash associated with EGFR inhibitor therapy in adult patients with advanced non-small cell lung cancer, colorectal cancer, head and neck, or breast cancers?
4. What are the recommended strategies for clinical management of rash associated with EGFR inhibitor therapy in adult patients with advanced non-small cell lung cancer, colorectal cancer, head and neck, or breast cancers?

Search Strategy

A literature search for articles about acneiform rash associated with the use of EFGR inhibitors in adult cancer patients was conducted at two different time points. The first literature search covered publications from 2000 to 2012 and informed recommendations in the original guideline published in

2012. The second literature search covered publications from 2012 to 2020 and informed updates to the original guideline. Existing guideline from other jurisdictions were identified during both search periods and reviewed by guideline working group members. In depth search criteria and selected articles/guidelines can be found in Appendix B.

Target Population

The recommendations outlined in this guideline apply to adult cancer patients treated with EGFR inhibitors (i.e. afatinib, cetuximab, erlotinib, gefitinib, lapatinib, osimertinib, panitumumab, pertuzumab) either alone or in combination with other treatments.

Recommendations

1. Grading

a) Accurate grading of acneiform rash associated with EGFR inhibitors is essential to ensure timely and appropriate interventions. We recommend using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), which is the most widely used classification system in clinical trials.[25] *(Level of Evidence: V, Strength of Recommendation: C).*

CTCAE defines acneiform rash as a disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, and upper chest and back.

Table 2. NCI CTCAE v5.0 acneiform rash

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Papule and/or pustules covering <10% BSA*, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering >30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfections with IV antibiotics indicated	Death

Abbreviations: *BSA=body surface area, ADL=activities of daily living, IV=intravenous*

**The simplest way to calculate BSA involvement is to use the patient's palm. One palm is roughly equivalent to 1% BSA.*

2. Rash and Response to Treatment Relationship

a) Rash occurrence has been statistically associated with efficacy of EGFR targeted therapies.[26-40] See Table 3 for a summary of key evidence. However, we cannot conclude from these studies that EGFR inhibitor therapy is ineffective if no or only mild rash occurs.[41] *(Level of Evidence: I, Strength of Recommendation: A)*

b) The goal of all cancer treatment is to minimize toxicity, maximize treatment adherence, and maintain a good health-related quality of life. Therefore, before starting treatment with an EGFR inhibitor clinicians should explore patient tolerance for cutaneous side effects through a discussion that includes occurrence, timing, severity, prevention and management of acneiform rash.[41-43] *(Level of Evidence: V, Strength of Recommendation: B)*

c) EGFR inhibitors should be administered at their maximum tolerable doses to obtain the most effective outcomes and should be accompanied with appropriate supportive care or preventive measures to counteract the rash.[44, 45] *(Level of Evidence: II, Strength of Recommendation: B)*

Table 3. Summary of key evidence examining the relationship between rash and the efficacy of EGFR inhibitors

Author, year	Study type	Types of participants, N	Treatment	Outcomes
Petrelli, 2013[26]	Meta-analysis (prospective clinical trials)	Advanced CRC, N=3833 (14 studies) All trials permitted inclusion of patients with either *KRAS* wild-type or mutated tumours	Cetuximab (C) or panitumumab (P), alone or in combination with other approved agents Almost all patients pretreated with ≥1 line of therapy	• Occurrence of skin rash significantly associated with reduced risk of death in patients treated with C or P (HR 0.51, 95% CI 0.40–0.64, P<0.00001. Results similar for C and P. • For association of risk of progression with skin rash, HR was significant (HR 0.58, 95% CI 0.49–0.68, P<0.00001. Results similar for C and P. • Patients who developed moderate or severe rash had an increased chance of response (35 vs. 13%; RR 2.23, p<0.00001).
Liu, 2013[27]	Meta-analysis (mixed study type)	NSCLC, N=6789 (33 studies)	Erlotinib or gefitinib monotherapy	• Two different standards used to group pts [standard 1: rash vs no rash, standard 2: rash (≥ stage 2) vs rash (stage 0, 1)]. • For standard 1, ORR and disease control rate of rash group significantly higher than no rash group [RR=3.28; 95% CI: 2.41-4.47(corrected RR=2.225, 95% CI: 1.658-2.986); RR=1.96, 95% CI: 1.58-2.43].

Author, year	Study type	Types of participants, N	Treatment	Outcomes
				• Same results observed for standard 2. • For standards 1 and 2, PFS (HR=0.45, 95% CI: 0.37-0.53; HR = 0.57, 95% CI: 0.50-0.65) and OS (HR=0.40, 95% CI: 0.28-0.52; HR=0.53, 95% CI: 0.35-0.71) of rash group were significantly longer than control group, and same results observed in subgroup analysis (therapy line, ethnicity, and treatment).
Petrelli, 2012[28]	Meta-analysis (prospective and retrospective case series)	NSCLC, N=3312 (24 studies) Almost patients had advanced disease	Erlotinib (E) or gefitinib (G), alone or in combination with other approved agents Almost all patients pretreated with ≥1 line of therapy	• Occurrence of skin rash significantly associated with reduced risk of death in patients treated with erlotinib or gefitinib (HR: 0.30; 95% CI: 0.21–0.43; p<0.00001. Results similar for E and G. • Association between risk of progression and skin rash statistically significant (HR: 0.50; 95% CI: 0.41–0.61; p<0.00001. Results similar for E and G. • ORR ranged between 7% and 42% for patients with no rash and those with moderate to severe rash, respectively.

3. Prevention of Rash

a) Before starting treatment with EGFR inhibitors, clinicians should perform an assessment of patients for pre-existing cutaneous conditions (e.g. psoriasis, acne vulgaris, rosacea) that could worsen with exposure to EGFR inhibitors.[46] *(Level of Evidence: V, Strength of Recommendation: B)*

b) Patients should be informed about general skin care practices to prevent or reduce the severity of acneiform rash, including:[46-48] *(Level of Evidence: II, Strength of Recommendation: B)*
   - Use alcohol-free emollients for overall skin moisturization (i.e. creams, ointments)
   - Avoid popping acne pustules and using over-the-counter acne medications
   - Adequately hydrate
   - Apply broad spectrum (UVA, UVB) sunscreens before going outdoors and avoid excessive sun exposure
   - Avoid hot water (i.e. use lukewarm water when showering, washing dishes)
   - Avoid tight-fitting clothing or irritating fabrics (e.g. wool)

c) For most patients starting EGFR-inhibitor therapy, antibiotic prophylaxis can be used concomitantly with a topical steroid (1% hydrocortisone cream) for the first six weeks to reduce the incidence and severity of acneiform rash and improve quality of life.[49-52] In this role, the antibiotics are used for their anti-inflammatory properties and not their antimicrobial effects. We recommend

second-generation tetracyclines, either minocycline or doxycycline 100-200 mg daily (single or divided doses). While minocycline is less photosensitizing, doxycycline has a more favorable safety profile.[53] See Table 4 for a summary of key evidence. *(Level of Evidence: I, Strength of Recommendation: A)* Although rare, for patients with allergies or intolerance to tetracyclines, erythromycin 500 mg twice a day or trimethoprim 160 mg/sulfamethoxazole 800 mg twice a day may be used as an alternative to minocycline or doxycycline. *(Level of Evidence: V, Strength of Recommendation: C)*

d) Studies have been unable to demonstrate a clinically significant benefit of adding tazarotene cream,[52] dapsone gel,[54] and vitamin K1 cream[55] to minocycline or doxycycline. Similarly, topical erythromycin has not been shown to be an effective replacement for oral doxycycline, and therefore these drugs are not recommended.[56] *(Level of Evidence: II, Strength of Recommendation: C [dapsone, vitamin K1] and D [tazarotene, erythromycin])*

Table 4. Summary of key evidence examining the use of prophylactic antibiotics for patients treated with EGFR inhibitors

Author, year	Study type	Types of participants, N	Treatment	Outcomes
Petrelli, 2016[49]	Meta-analysis (randomized and retrospective)	NSCLC, GI, CRC, pancreatic, other N=1073 (13 studies)	Tetracyclines (tetracyclines in 3 studies, doxycycline in 4 studies and minocycline in 6 studies)	• In 12 studies, patients in prophylactic antibiotic arms had lower risk of developing skin rash (OR 0.53, 95% CI 0.39–0.72, P<0.01) than patients without antibiotic prophylaxis • Moderate-to-severe toxicities (Grade 2–4) reduced by nearly two-thirds (OR 0.36, 95% CI 0.22–0.60, P<0.01) in 13 studies; 26% absolute difference of high-grade skin rash compared with control arms (from 50% to 24%)
Bachet, 2012[50]	Meta-analysis (randomized)	Colorectal, lung, other, N=351	Tetracyclines (doxycycline in 2 studies and minocycline in 2 studies)	• Combined odd ratio associated with incidence of folliculitis in each study was 0.19 (95% CI, 0.12-0.31; fixed effect model p<0.0001), indicating that the administration of a tetracycline in preventive therapy was associated with a significantly lower incidence of grade 2–3 folliculitis • Prophylactic tetracycline treatment also associated with an improvement in quality of life of patients in 3 of 4 studies in which this parameter analyzed

4. Management of Rash

The management of acneiform rash induced by EGFR inhibitors is largely based on small-scale prospective trials, case reports and case series. As a result, management approach varies as shown in Appendix C which summarizes relevant guidelines and consensus statements published within the last 10 years. The recommendations presented below are a consensus of members of the Alberta Provincial Tumour Teams who have experience prescribing EGFR inhibitors and/or treating skin conditions (shown as pathway in Appendix A).

a) General recommendations. Overall management strategy for acneiform rash should be individualized and will depend on the type, severity, location and need to continue treatment. Consultation with a dermatologist is recommended, particularly for rash that does not improve within one to two weeks of treatment or if the patient is severely symptomatic. *(Level of Evidence: II, Strength of Recommendation: B)*

b) Grade 1 rash. Patients should continue EGFR-inhibitor therapy at the prescribed dose. We recommend treatment with topical clindamycin 2% plus hydrocortisone 1% lotion twice daily for four weeks. If after four weeks of treatment the rash has not improved or has worsened, patients should be treated for a Grade 2 rash. *(Level of Evidence: V, Strength of Recommendation: C)*

c) Grade 2 rash. Patients should continue EGFR-inhibitor therapy at the prescribed dose. We recommend treatment with topical clindamycin 2%, hydrocortisone 1% lotion plus either oral minocycline 100 mg twice daily or doxycycline 100 mg twice daily for four weeks, if not used prophylactically. If after four weeks of treatment the rash has not improved or has worsened, patients should be treated for a Grade 3-4 rash. *(Level of Evidence: V, Strength of Recommendation: C)*

d) Grade ≥3 rash. A dose reduction of EGFR-inhibitor therapy, as per label, may be required (see Appendix D). Obtain bacterial/viral culture if infection is suspected. We recommend treatment with topical clindamycin 2%, hydrocortisone 1% lotion plus either oral minocycline 100 mg twice daily or doxycycline 100 mg twice daily for four weeks, plus oral prednisone up to 0.5 mg/kg daily for seven to 14 days. Referral to a dermatologist is recommended if rash does not improve after four to eight weeks. *(Level of Evidence: IV, Strength of Recommendation: C)*

- If after four weeks of treatment the rash does not improve or worsens, low-dose isotretinoin (20 to 30 mg/d)[57] or acitretin (25 mg/d)[58] may be considered; evidence for its efficacy is however based on case series. *(Level of Evidence: V, Strength of Recommendation: C)*

- If the rash still does not improve or worsens despite dose modification and various treatment approaches (i.e. antibiotics, corticosteroids, isotretinoin, acitretin) discontinuation of EGFR inhibitor treatment may be necessary. *(Level of Evidence: V, Strength of Recommendation: B)*

e) Secondary infection. While pustules are generally sterile, secondary infection with bacteria, dermatophytes, or viruses may occur.[20, 59, 60] Antibiotic selection for streptococcal or staphylococcal infections (culture proven with a swab), should be based on antimicrobial sensitivities. If pathogens other than streptococcal or staphylococcal are isolated, oncologists should ideally consult with a dermatologist for treatment advice (e.g. gram-negative microbes/other, saprophytic and dermatophyte fungi and yeasts). *(Level of Evidence: V, Strength of Recommendation: C)*

References

1. Lynch TJ, Jr., Kim ES, Eaby B, Garey J, West DP, Lacouture ME. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist*. May 2007;12(5):610-21.

2. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer*. Oct 2006;6(10):803-12.

3. Joshi SS, Ortiz S, Witherspoon JN, et al. Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. *Cancer*. Aug 15 2010;116(16):3916-23.

4. Boone SL, Rademaker A, Liu D, Pfeiffer C, Mauro DJ, Lacouture ME. Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. *Oncology*. 2007;72(3-4):152-9.

5. Balagula Y, Lacouture ME, Cotliar JA. Dermatologic toxicities of targeted anticancer therapies. *J Support Oncol*. Jul-Aug 2010;8(4):149-61.

6. Lexicomp. Afatinib. Updated 7/5/20.

7. Boehringr Ingelheam (Canada) Ltd. Giotrif. Product Monograph. 2019.

8. Lexicomp. Cetuximab. Updated 7/23/20.

9. ImClone LLC. Erbitux. Product Monograph. 2018.

10. Lexicomp. Erlotinib. Updated 7/18/20.

11. Lexicomp. Gefitinib. Updated 6/30/20.

12. AstraZeneca Canada Inc. Iressa. Product Monograph. 2017.

13. Lexicomp. Lapatinib. Updated 7/20/20.

14. Novartis Pharmaceuticals Canada Inc. Tykerb. Product Monograph. 2019.

15. Lexicomp. Osimertinib. Updated 7/23/20.

16. AstraZeneca Canada Inc. Tagrisso. Product Monograph. 2020.

17. Lexicomp. Panitumumab. Updated 5/18/20.

18. Lexicomp. Pertuzumab. Updated 5/7/20.

19. Hoffmann-La Roche Limited. Perjeta. Product Monograph. 2020.

20. Eilers RE, Jr., Gandhi M, Patel JD, et al. Dermatologic infections in cancer patients treated with epidermal growth factor receptor inhibitor therapy. *J Natl Cancer Inst*. Jan 6 2010;102(1):47-53.

21. Sipples R. Common side effects of anti-EGFR therapy: acneform rash. *Semin Oncol Nurs*. Feb 2006;22(1 Suppl 1):28-34.

22. Amitay-Laish I, David M, Stemmer SM. Staphylococcus coagulase-positive skin inflammation associated with epidermal growth factor receptor-targeted therapy: an early and a late phase of papulopustular eruptions. *Oncologist*. 2010;15(9):1002-8.

23. Lichtenberger BM, Gerber PA, Holcmann M, et al. Epidermal EGFR controls cutaneous host defense and prevents inflammation. *Sci Transl Med*. Aug 21 2013;5(199):199ra111.

24. Busam KJ, Capodieci P, Motzer R, Kiehn T, Phelan D, Halpern AC. Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol*. Jun 2001;144(6):1169-76.

25. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Accessed October 19, 2020. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

26. Petrelli F, Borgonovo K, Barni S. The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. *Target Oncol*. Sep 2013;8(3):173-181.

27. Liu HB, Wu Y, Lv TF, et al. Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: a systematic review and meta-analysis. *PLoS One*. 2013;8(1):e55128.

28. Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: a literature-based meta-analysis of 24 trials. *Lung Cancer*. Oct 2012;78(1):8-15.

29. Rubovszky G, Budai B, Ganofszky E, et al. Predictive Value of Early Skin Rash in Cetuximab-Based Therapy of Advanced Biliary Tract Cancer. *Pathol Oncol Res*. Apr 2018;24(2):237-244.

30. Sonnenblick A, de Azambuja E, Agbor-Tarh D, et al. Lapatinib-Related Rash and Breast Cancer Outcome in the ALTTO Phase III Randomized Trial. *J Natl Cancer Inst*. Aug 2016;108(8).

31. Holch JW, Held S, Stintzing S, et al. Relation of cetuximab-induced skin toxicity and early tumor shrinkage in metastatic colorectal cancer patients: results of the randomized phase 3 trial FIRE-3 (AIO KRK0306). *Ann Oncol*. Jan 2020;31(1):72-78.

32. Azim HA, Jr., Agbor-Tarh D, Bradbury I, et al. Pattern of rash, diarrhea, and hepatic toxicities secondary to lapatinib and their association with age and response to neoadjuvant therapy: analysis from the NeoALTTO trial. *J Clin Oncol*. Dec 20 2013;31(36):4504-11.

33. Fiala O, Pesek M, Finek J, et al. Skin rash as useful marker of erlotinib efficacy in NSCLC and its impact on clinical practice. *Neoplasma*. 2013;60(1):26-32.

34. Gatzemeier U, von Pawel J, Vynnychenko I, et al. First-cycle rash and survival in patients with advanced non-small-cell lung cancer receiving cetuximab in combination with first-line chemotherapy: a subgroup analysis of data from the FLEX phase 3 study. *Lancet Oncol*. Jan 2011;12(1):30-7.

35. Van Cutsem E, Tejpar S, Vanbeckevoort D, et al. Intrapatient cetuximab dose escalation in metastatic colorectal cancer according to the grade of early skin reactions: the randomized EVEREST study. *J Clin Oncol*. Aug 10 2012;30(23):2861-8.

36. Stintzing S, Kapaun C, Laubender RP, et al. Prognostic value of cetuximab-related skin toxicity in metastatic colorectal cancer patients and its correlation with parameters of the epidermal growth factor receptor signal transduction pathway: results from a randomized trial of the GERMAN AIO CRC Study Group. *Int J Cancer*. Jan 1 2013;132(1):236-45.

37. Aranda E, Manzano JL, Rivera F, et al. Phase II open-label study of erlotinib in combination with gemcitabine in unresectable and/or metastatic adenocarcinoma of the pancreas: relationship between skin rash and survival (Pantar study). *Ann Oncol*. Jul 2012;23(7):1919-25.

38. Pérez-Soler R, Chachoua A, Hammond LA, et al. Determinants of tumor response and survival with erlotinib in patients with non--small-cell lung cancer. *J Clin Oncol*. Aug 15 2004;22(16):3238-47.

39. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. Jul 14 2005;353(2):123-32.

40. Johnson JR, Cohen M, Sridhara R, et al. Approval summary for erlotinib for treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. *Clin Cancer Res*. Sep 15 2005;11(18):6414-21.

41. Tischer B, Huber R, Kraemer M, Lacouture ME. Dermatologic events from EGFR inhibitors: the issue of the missing patient voice. *Support Care Cancer*. Feb 2017;25(2):651-660.

42. Wallner M, Köck-Hódi S, Booze S, White KJ, Mayer H. Nursing Management of Cutaneous Toxicities From Epidermal Growth Factor Receptor Inhibitors. *Clin J Oncol Nurs*. Oct 1 2016;20(5):529-36.

43. Czupryn M, Cisneros J. BRAF/MEK Inhibitor Therapy: Consensus Statement From the Faculty of the Melanoma Nursing Initiative on Managing Adverse Events and Potential Drug Interactions. *Clin J Oncol Nurs*. Aug 1 2017;21(4 Suppl):11-29. doi:10.1188/17.cjon.s4.11-29

44. Perez-Soler R. Rash as a surrogate marker for efficacy of epidermal growth factor receptor inhibitors in lung cancer. *Clin Lung Cancer*. Dec 2006;8 Suppl 1:S7-14.

45. Peréz-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol*. Aug 1 2005;23(22):5235-46.

46. Pinto C, Barone CA, Girolomoni G, et al. Management of Skin Reactions During Cetuximab Treatment in Association With Chemotherapy or Radiotherapy: Update of the Italian Expert Recommendations. *Am J Clin Oncol*. Aug 2016;39(4):407-15.

47. Balagula Y, Garbe C, Myskowski PL, et al. Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. *Int J Dermatol*. Feb 2011;50(2):129-46.

48. BC Cancer. Symptom Management Guidelines: Acneiform Rash. Accessed October 19, 2020. http://www.bccancer.bc.ca/nursing-site/Documents/1.%20Acneiform%20Rash.pdf

49. Petrelli F, Borgonovo K, Cabiddu M, et al. Antibiotic prophylaxis for skin toxicity induced by antiepidermal growth factor receptor agents: a systematic review and meta-analysis. *Br J Dermatol*. Dec 2016;175(6):1166-1174.

50. Bachet JB, Peuvrel L, Bachmeyer C, et al. Folliculitis induced by EGFR inhibitors, preventive and curative efficacy of tetracyclines in the management and incidence rates according to the type of EGFR inhibitor administered: a systematic literature review. *Oncologist*. 2012;17(4):555-68.

51. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol*. Mar 10 2010;28(8):1351-7.

52. Scope A, Agero AL, Dusza SW, et al. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol*. Dec 1 2007;25(34):5390-6.

53. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer*. Aug 2011;19(8):1079-95.

54. Belum VR, Marchetti MA, Dusza SW, Cercek A, Kemeny NE, Lacouture ME. A prospective, randomized, double-blinded, split-face/chest study of prophylactic topical dapsone 5% gel versus moisturizer for the prevention of cetuximab-induced acneiform rash. *J Am Acad Dermatol*. Sep 2017;77(3):577-579.

55. Hofheinz RD, Lorenzen S, Trojan J, et al. EVITA-a double-blind, vehicle-controlled, randomized phase II trial of vitamin K1 cream as prophylaxis for cetuximab-induced skin toxicity. *Ann Oncol*. Apr 1 2018;29(4):1010-1015.

56. Kripp M, Prasnikar N, Vehling-Kaiser U, et al. AIO LQ-0110: a randomized phase II trial comparing oral doxycycline versus local administration of erythromycin as preemptive treatment strategies of panitumumab-mediated skin toxicity in patients with metastatic colorectal cancer. *Oncotarget*. Dec 1 2017;8(62):105061-105071.

57. Gerber PA, Meller S, Eames T, et al. Management of EGFR-inhibitor associated rash: a retrospective study in 49 patients. *Eur J Med Res*. Feb 23 2012;17(1):4.

58. Andrews ED, Garg N, Patel AB. A retrospective chart review on oral retinoids as a treatment for epidermal growth factor receptor inhibitor- and mitogen-activated protein kinase kinase inhibitor-induced acneiform eruptions. *J Am Acad Dermatol*. Apr 2020;82(4):998-1000.

59. Li J, Peccerillo J, Kaley K, Saif MW. Staphylococcus aureus bacteremia related with erlotinib skin toxicity in a patient with pancreatic cancer. *Jop*. 2009:338-40. vol. 3.

60. Grenader T, Gipps M, Goldberg A. Staphylococcus aureus bacteremia secondary to severe erlotinib skin toxicity. *Clin Lung Cancer*. Jan 2008;9(1):59-60.

61. Lacouture ME BY. Acneiform eruption secondary to epidermal growth factor receptor (EGFR) and MEK inhibitors. UpToDate; 2020.

62. Califano R, Tariq N, Compton S, et al. Expert Consensus on the Management of Adverse Events from EGFR Tyrosine Kinase Inhibitors in the UK. *Drugs*. Aug 2015;75(12):1335-48.

63. Gutzmer R, Becker JC, Enk A, et al. Management of cutaneous side effects of EGFR inhibitors: recommendations from a German expert panel for the primary treating physician. *J Dtsch Dermatol Ges*. Mar 2011;9(3):195-203.

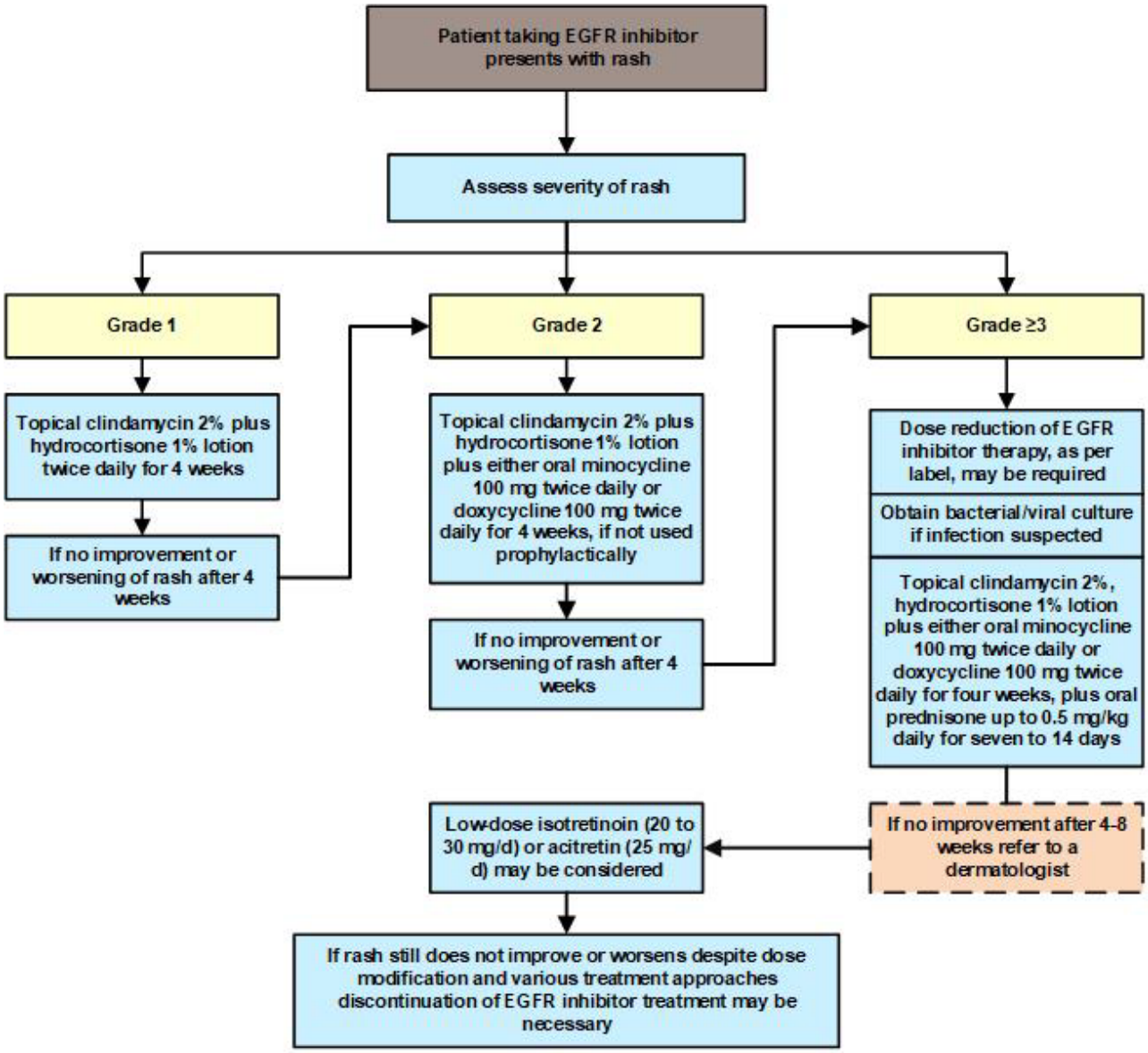
64. Potthoff K, Hofheinz R, Hassel JC, et al. Interdisciplinary management of EGFR-inhibitor-induced skin reactions: a German expert opinion. *Ann Oncol*. Mar 2011;22(3):524-535.

65. Melosky B, Burkes R, Rayson D, Alcindor T, Shear N, Lacouture M. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. *Curr Oncol*. Jan 2009;16(1):16-26.

66. Hoffmann-La Roche Limited. Erlotinib Hydrochloride Tablets. Product Monograph. 2018.

67. Amgen Canada Inc. Panitumumab. Product Monograph. 2017.

Appendix A: Treatment Pathway for Acneiform Rash in Patients Treated with EGFR Inhibitor Therapies



General skin care practices to prevent or reduce the severity of acneiform rash

- Use alcohol-free emollients for overall skin moisturization (i.e. creams, ointments)
- Avoid popping acne pustules and using over-the-counter acne medications
- Adequately hydrate
- Apply broad spectrum (UVA, UVB) sunscreens before going outdoors and avoid excessive sun exposure
- Avoid hot water (i.e. use lukewarm water when showering, washing dishes)
- Avoid tight-fitting clothing or irritating fabrics (e.g. wool)

Appendix B: Literature Search Strategy

Guideline Update: May 20, 2020

- The updated literature search was conducted in Ovid Medline using the original search strategy defined in 2010

Database: Ovid MEDLINE(R): Current = May 26, 2020

#	Searches	Results
1	exp Skin/	222503
2	exp Skin Diseases/	1011204
3	exp Exanthema/	7472
4	exp Drug Eruptions/ ci, dt, pc [Chemically Induced, Drug Therapy, Prevention & Control]	3701
5	exp Acneiform Eruptions/ ci, dt, pc [Chemically Induced, Drug Therapy, Prevention & Control]	6333
6	1 or 2 or 3 or 4 or 5	1154737
7	exp Erlotinib Hydrochloride/	3845
8	exp Gefitinib/	4401
9	exp Cetuximab/	4414
10	exp Panitumumab/	962
11	pertuzumab.mp	1052
12	exp Afatinib/	653
13	osimertinib.mp.	1008
14	exp Lapatinib/	1531
15	exp ErbB Receptors/ ai, de [Antagonists & Inhibitors, Drug Effects]	13235
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	23542
17	6 and 16	4367
18	remove duplicates from 17	4363
19	limit 18 to (English language and humans and yr=”2010-Current” and “all adult (19 plus years)”)	1068
20	limit 19 to (clinical trial, all or comparative study or controlled clinical trial or meta-analysis or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or “systematic review”)	491*
21	From 20 keep 1, 15, 17, 20, 30, 86…	17

*Articles were excluded from line 20 if study analysis included ≤10 patients, and/or full text article was unavailable through the UC library

Original Guideline: August 31, 2010

- An environmental scan of the literature was first performed to become familiar with the topic and to identify relevant search terms
- A structured literature search was conducted using the following electronic databases: MEDLINE/PubMed, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Registry of Controlled Trials, CINNAHL, and the International Pharmaceutical Abstracts Database.
- The search terms and search strategy used in MEDLINE (below) was modified and repeated for each of the electronic databases:

Database: Ovid MEDLINE(R) 1950 to August Week 3 2010

#	Searches	Results
1	exp Skin/	162167
2	exp Skin Diseases/	681308
3	exp Exanthema/	3644
4	exp Drug Eruptions/ ci, dt, pc [Chemically Induced, Drug Therapy, Prevention & Control]	1747
5	exp Acneiform Eruptions/ ci, dt, pc [Chemically Induced, Drug Therapy, Prevention & Control]	4678
6	1 or 2 or 3 or 4 or 5	789518
7	erlotinib.mp.	1674
8	gefitinib.mp.	2661
9	cetuximab.mp.	1929
10	panitumumab.mp.	356
11	exp Receptor, Epidermal Growth Factor/ ai, de [Antagonists & Inhibitors, Drug Effects]	5109
12	7 or 8 or 9 or 10 or 11	8282
13	6 and 12	1048
14	limit 13 to (english language and humans and yr=”2000-Current” and “all adult (19 plus years)”)	313
15	from 14 keep 1,8-9,13,15,19,26…	53*

*Articles were excluded from the final review if skin toxicity was not a rash or was not related to EGFR-inhibitor treatment (N=7); publication included a description of symptoms only (N=7); publication did not include enough details on treatment types or doses, timelines for observed responses, or specific outcomes (N=6); publication was not accessible through the library system (N=2).

Appendix C: Summary of Published Guidelines and Recommendations for the Treatment of Rash Associated with EGFR Inhibitor Therapy

Reference	Recommendations		
	Grade 1	Grade 2	≥ Grade 3
UpToDate 2020[61] *Acneiform Eruption Secondary to EGFR and MEK Inhibitors*	• Low-potency topical corticosteroids + clindamycin 1% or dapsone 5% BID for ≥4 weeks	• Low-potency topical corticosteroids + doxycycline 100 mg or minocycline 100 mg BID for ≥4 weeks • If patient already on oral tetracycline, use first-generation oral cephalosporin or trimethoprim-sulfamethoxazole for 4 weeks • If viral or bacterial superinfection suspected, cultures or exudates should be obtained prior to initiation of therapy	• Discontinue or interrupt therapy • Doxycycline 100 mg or minocycline 100 mg BID for ≥4 weeks + oral prednisone 0.5 mg/kg up to max. 40 mg/day for 7 days • First-generation oral cephalosporin or trimethoprim-sulfamethoxazole for 4 weeks can be used for patients who don't benefit from tetracycline antibiotics or have culture-proven infection that would be resistant to treatment • If viral or bacterial superinfection suspected, cultures or exudates should be obtained prior to initiation of therapy • Low-dose isotretinoin (20-30 mg/day) or acitretin (25 mg/day) can be used for refractory grade ≥3 rash; discontinue oral tetracycline before initiating
Pinto 2016[46] *Italian Expert Recommendations – Cetuximab in Combination with Chemotherapy or Radiotherapy*	• No dose modification or treatment interruptions • No specific treatments should be started	• No dose modification or treatment interruptions • Topical antibiotic treatment with clindamycin 1% gel, erythromycin 3% gel/cream, or metronidazole 0.75-1% cream/gel BID until improvement to grade 1 • Avoid benzoyl peroxide • When papules prevail, no systemic therapy recommended • For pustule prevalent type, oral semisynthetic	• Interrupt treatment for 21 days until improvement to grade 2 • At improvement, if response to cetuximab obtained, continue EGFR inhibitor therapy at full dose of 250 mg/m^2. If no improvement occurs, discontinue therapy • For 2nd or 3rd recurrence of skin rash modify dose. For 4th recurrence, discontinue definitively

Reference	Recommendations		
	Grade 1	Grade 2	≥ Grade 3
		tetracycline (minocycline 100 mg/day, doxycycline 100 mg/day) can be used for ≥4 weeks and until the rash is symptomatic	• Topical treatment as for grade 2 can be used together with systemic therapy with oral semisynthetic tetracycline (minocycline, doxycycline) for ≥4 weeks and until the rash asymptomatic, and oral corticosteroids (methylprednisolone 0.4 mg/kg, prednisone 0.5 mg/kg) for up to 10 days • Grade 3 highly symptomatic/ nonresponsive patients: consider oral retinoids (isotretinoin 0.3-0.5 mg/kg), IV corticosteroids (methylprednisolone, dexamethasone), IM/IV antihistamines (clorfenamine), IV antibiotics (amoxicillin/clavulanic acid, gentamicin), or hydration • Grade 4: Interrupt EGFR inhibitor treatment immediately and definitively. Provide topical treatment as indicated for grades 2 and 3. Consider systemic management with oral retinoids (isotretinoin 0.3-0.5 mg/kg), IV corticosteroids (methylprednisolone, dexamethasone), IM/IV antihistamines (clorfenamine), IV antibiotics (amoxicillin/ clavulanic acid, gentamicin), and IV hydration
Califano 2015[62] *UK Expert Consensus of*	• Continue EGFR TKI at current dose and apply emollient regularly	• Continue EGFR-TKI at current dose as rash improves	• Temporarily interrupt EGFR-TKI therapy

Reference	Recommendations		
	Grade 1	Grade 2	≥ Grade 3
Management of Adverse Events from EGFR Tyrosine Kinase Inhibtors	• If signs of superadded infection, consider application of topical antibiotics in alcohol-free formulations for ≥14 days	• Dose reduction or interruption appropriate if rash prolonged or intolerable • If chronic grade 2 rash develops, consult with dermatologist • Intensify moisturizing; topical steroids can be applied on short-term basis (i.e. for 2–3 weeks) • Topical antibiotics (as alcohol-free formulations) and/or course of oral antibiotics (e.g. tetracycline ≥2 weeks) may be indicated • Oral antihistamines can be prescribed for itchy rash	• Restart EGFR-TKI therapy only when rash has improved to ≤ grade 2 • Dose reductions recommended for erlotinib and afatinib, but not for gefitinib • Not uncommon in clinical practice to restart gefitinib on alternate days • Manage rash as recommended for grade 2 with oral antibiotics + topical corticosteroids as appropriate and refer to dermatologist • Identify and treat any potential infection associated with rash
Gutzmer 2011[63] *German Expert Panel for Primary Treating Physician – EGFR Inhibitors*	• Initiate combined therapy with topical metronidazole- or nadifloxacin-containing ointment and systemic tetracycline (doxycycline 2 x 50 or 100 mg daily, minocycline 2 x 50 mg daily or tetracycline: 2-4 x 250 mg daily • Refer to experienced dermatologist for advanced diagnostics and therapy in case of inadequate response	• Not addressed	• Not addressed
Lacouture 2011[53] *Prevention and Treatment of EGFR Inhibitor-Associated Dermatologic Toxicities*	Topical • Alclometasone 0.05% cream • Fluocinonide 0.05% cream BID • Clindamycin 1% Systemic • Doxycycline 100 mg BID • Minocycline 100 mg daily • Isotretinoin at low doses (20-30 mg/day)		
Balagula 2010[5] *Dermatologic Toxicities of*	• Prophylactic sunscreen • 2.5% hydrocortisone cream + 1% clindamycin gel daily	• 2.5% hydrocortisone cream + doxycycline 100 mg daily or minocycline 100 mg BID	• Modify EGFR inhibitor dose • Obtain bacterial/viral cultures

Reference	Recommendations		
	Grade 1	Grade 2	≥ Grade 3
Targeted Anticancer Therapies			• 2.5% hydrocortisone cream + doxycycline 100mg daily or minocycline 100 mg BID + prednisone 0.5 mg/kg x 5 days
Potthoff 2010[64] *German Expert Panel EGFR inhibitor induced skin reactions*	• Topical antibiotics (2% clindamycin, 1% erythromycin cream, 0.75% metronidazole, 1% nadifloxacin) • Cream for isolated scattered lesions; lotion for multiple scattered areas	• Topical antibiotic + short-term topical steroid (e.g. 0.02% prednicarbate cream) + oral antibiotic for at least 2 weeks • Doxycycline 100 mg BID or minocycline 100 mg BID	• Reduce EGFR inhibitor dose • Skin-type-adjusted moisturizer • Topical + systemic treatment, as per moderate rash • Refer to dermatologist • Consider oral isotretinoin or systemic steroids, but do not combine with oral tetracycline • Dose discontinuation + systemic steroids for life-threatening rash
Melosky 2009[65] *Canadian Consensus Statement Management of Skin Rash During EGFR-Targeted Monoclonal Antibody Treatment for GI Cancer*	• Topical 2% clindamycin + 1% hydrocortisone lotion BID	• Topical 2% clindamycin + 1% hydrocortisone lotion BID • Oral minocycline 100 mg BID or doxycycline 100 mg daily or BID	• Withhold treatment until toxicity improves • Topical 2% clindamycin + 1% hydrocortisone lotion BID • Oral minocycline 100mg BID or doxycycline 100 mg daily or BID • If improvement seen, re-escalate dose; if no improvement, discontinue EGFR inhibitor treatment

Appendix D: Interruptions/Dose Reductions of EFGR Inhibitors for Patients with Persistent Rash

Afatinib:[7]

- Interrupt for up to 14 days until Grade 0/1 for prolonged or intolerable Grade 2 (≥7 days of rash). Resume with dose reduction by 10 mg decrements.
- Interrupt for up to 14 days until Grade 0/1 for any Grade ≥3. Resume with dose reduction by 10 mg decrements.

Cetuximab:[9]

- If patient experiences severe acneiform rash (Grade 3/4), adjust treatment according to table below.
- If rash improves and is no longer severe, resume treatment without any change in dose level.
- If severe acneiform rash recurs further interruption of therapy with dose reductions at pretreatment after improvement (initially to 200 mg/m^2 and subsequently to 150 mg/m^2) or discontinuation of therapy may be required.

Severe Acneiform Rash	Cetuximab	Outcome	Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No improvement	Discontinue
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No improvement	Discontinue
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No improvement	Discontinue
4th occurrence	Discontinue		

Erlotinib:[66]

- Patients with severe skin reactions may require a dose reduction or temporary interruption of therapy. When dose reduction is necessary, it is recommended to reduce in 50 mg steps.

Gefitinib:[12]

- Patients with skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg daily dose once toxicity has resolved.

Lapatinib:[14]

- Consider discontinuation or interruption of dosing when patient develops toxicity Grade ≥2.
- Restart dosing at either 1250 mg/day when administered with capecitabine or 1500 mg/day when administered with letrozole, when the toxicity improves to Grade ≤1.

- If toxicity recurs, restart at a lower dose (1000 mg/day when administered with capecitabine and 1250 mg/day when administered with letrozole).

Osimertinib:[16]

- Dose adjustments are not necessary for generally manageable adverse reactions.
- If dose reduction or modification is necessary based on individual safety and tolerability, then the dose should be reduced to 40 mg taken once daily.
- Dose reduction guidelines for adverse reactions toxicities are provided in the table below.

Adverse Reaction	Dose Modification
Grade ≥3 or higher	Withhold for up to 3 weeks
If Grade ≥3 improves to Grade 0-2 after withholding for up to 3 weeks	Restart at same dose (80 mg) or lower dose (40 mg)
Grade ≥3 that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue

Panitumumab:[67]

- If patient develops dermatologic toxicities that are Grade ≥3 or are considered intolerable, dose modifications according to the table below are recommended.

Occurrence of skin symptom(s): Grade ≥3	Administration	Outcome	Dose regulation
Initial occurrence	Stop 1 or 2 doses	Improved (Grade <3)	Continue infusion at 100% of original dose
		Not recovered	Discontinue
At 2nd occurrence	Stop 1 or 2 doses	Improved (Grade <3)	Continue infusion at 80% of original dose
		Not recovered	Discontinue
At 3rd occurrence	Stop 1 or 2 doses	Improved (Grade <3)	Continue infusion at 60% of original dose
		Not recovered	Discontinue
At 4th occurrence	Discontinue permanently		

Pertuzumab:[19]

- Dose reductions not recommended for pertuzumab.

Development and Revision History

This guideline was reviewed and endorsed by members of the Alberta Provincial Thoracic Malignancies, Gastrointestinal, Head and Neck, and Breast Tumour Teams. Members of these Tumour Teams include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from these three provincial Tumour Teams and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in 2012. The guideline was revised and reposted in November 2020.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally, not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted during in 2024. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

BID, twice daily; CI, confidence interval; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; GI, gastrointestinal cancer; HR, hazard ratio; IM, intramuscular; IV, intravenous; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RR, risk ratio; TKI, tyrosine kinase inhibitor

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Supportive Care Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

Conflict of Interest Statements

Dr. Thomas Salopek has nothing to disclose.

Dr. Don Morris has nothing to disclose.

Dr. Jay Easaw has nothing to disclose.

Brae Surgeoner has nothing to disclose.