Published in final edited form as:

Dermatol Clin. 2018 July ; 36(3): 315–324. doi:10.1016/j.det.2018.02.010.

Pruritus Associated with Targeted Anticancer Therapies and Their Management

Jennifer Wu, MD and

Visiting Investigator, Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Attending Physician, Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, College of Medicine Chang Gung University, Keelung, Linkou, and Taipei, Taiwan

Mario E. Lacouture, MD

Director, Oncodermatology Program, Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Associate Professor, Department of Medicine, Weill Cornell Medical College

Summary

Targeted anticancer therapies have significantly increased the survival of patients with a variety of malignancies, improved the tolerability, and prolonged treatment duration.¹ The increased lifespan and the expanded use of these targeted agents have led to a variety of treatment-related adverse events. Pruritus is a common dermatologic adverse event with various incidences ranged from 2.2 to 47% across different categories of targeted anticancer therapies, yet has been overlooked in the past. In this article, we reviewed the incidence, accompanied skin conditions, possible pathomechanism and proposed management algorithms of pruritus associated with targeted therapies including immunotherapies.

Keywords

Pruritus; Itch; Targeted therapy; Immunotherapy; Cancer; Management

Introduction of targeted anticancer therapies

Aberrations in cell signaling transduction pathways from epidermal growth factor receptor (EGFR) to downstream pathways including the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol-3-OH kinase (PI3K)-Akt (a serine/threonine protein kinase)-mammalian target of rapamycin (mTOR) pathway play an important role in tumorigenesis and disease progression.² The MAPK pathway have four core protein kinases including rat

Direct Correspondence to: Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 60th Street Outpatient Center, 16 E 60th St., Suite 407, Room 4312, New York, NY 10022, USA; lacoutum@mskcc.org.

Disclosure: Jennifer Wu and Mario E. Lacouture have nothing to disclose.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

sarcoma virus gene homolog (RAS), rapidly accelerated fibrosarcoma serine/threonine kinase (RAF), mitogen-activated protein kinase (MEK) and extracellular signal-regulated kinase (ERK). In recent years, several anti-cancer targeted therapies which inhibit the EGFR, RAF, MEK, PI3K-Akt-mTOR, and other pathways have been developed with tumor response.¹⁻⁸ Monoclonal antibodies (mAbs; e.g., cetuximab, panitumumab) and tyrosine kinase inhibitors (TKIs; e.g., erlotinib, gefitinib) targeting EGFR, and multitargeted TKIs (e.g. axitinib, pazopanib, sunitinib) targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), or Bcr-Abl tyrosine kinase are therefore indispensable elements of cancer treatment.³

Recent developments in cancer immunology have generated a new era of immunotherapy for cancer treatment. The cytotoxic T lymphocyte antigen-4 (CTLA-4) and the programmed death receptor-1 (PD-1)/PD ligand-1 (PD-L1/PD-L2) signaling pathway are immune checkpoints of tumor-induced immunosuppression. Inhibition of immune checkpoints using anti-CTLA-4, anti-PD-1/PD-L1 agents has revolutionized the treatments of patients for a variety of cancers.^{9,10}

Dermatologic adverse events to targeted anticancer therapies

Targeted anticancer agents have significantly increased the survival of patients with various malignancies, improved the tolerability and prolonged treatment duration, resulting from the reduced risk of systemic toxicities of these agents such as myelosuppression, infection, nausea, and vomiting compared to traditional cytotoxic chemotherapy.¹ The increased lifespan and the expanded use of these targeted agents have led to a variety of treatment-related adverse events (AEs). The inhibition of signaling pathways essential for cutaneous homeostasis and functioning leads to specific dermatologic AEs (dAEs).¹¹ dAEs can involve cosmetically sensitive areas, cause symptoms such as itching and pain, interfere with activities of daily living, negatively impact patients' quality of life (QoL), all of which may lead to dose reduction and even discontinuation.³

Pruritus in patients treated with targeted therapies

Pruritus is a common dAE across different categories of targeted therapies but received few attention in the past. A survey conducted by Gandhi et al. reported 36% of 379 cancer survivors experienced pruritus during treatments, with 44% having a negative impact on QoL.¹² An analysis reported that rash and pruritus have the greatest negative impact on QoL among dAEs such as alopecia, nail changes, hand-foot syndrome, mucosal changes, and fissures and that patients may withdraw from anticancer treatment for intractable pruritus.⁷ Clabbers, et al examined health-related QoL (HR-QoL) using questionnaires to patients receiving EGFR inhibitors during the first 6 weeks, and reported xerosis (22.3 %) and pruritus (16.9 %) the most impactful AEs.¹³ Rash, pruritus, and vitiligo are among the earliest and most common AEs of immune checkpoint inhibitors^{9,14-16}

Incidences of pruritus in patients treated with targeted anticancer therapies

A meta-analysis of 17368 patients from 141 trials reported the incidence of all-grade pruritus of patients treated with EGFR, multitargeted TK, BRAF, mTOR, Bcr-Abl inhibitors,

anti-CD 20, and anti-CTLA-4 monoclonal antibodies ranged between 3.0–30.7% and the overall summary incidence of all-grade pruritus was 17.4%.⁷ The overall incidence of high-grade pruritus for all patients was 1.4%.⁷ The incidences of all-grade and high-grade pruritus associated with targeted anticancer therapies including novel agents (MEK inhibitors and anti-PD-1 monoclonal antibodies) are summarized in Table 1. The highest incidence of pruritus was 33.2–47% in patients treated with combination therapy of ipilimumab and nivolumab while the lowest incidences were less than 10% in patients treated with VEGFR inhibitors (axitinib, pazopanib, vandetanib).^{1,7,30} The incidences of all-grade pruritus in patients treated with EGFR inhibitors ranged from 18.2 (cetuximab) to 54.9% (panitumumab).^{1,7} The incidences of all-grade pruritus in patients receiving BRAF inhibitors and MEK inhibitors were reported to be 18% and 45%, respectively. And the incidences of pruritus in those treated with immunotherapies including anti-CTLA4 and anti-PD1 monoclonal antibodies ranged from 17% to 47%.^{9,10,26,27,30}

The incidence of high-grade pruritus ranged between 0.5% and 2.6%, with the highest incidence in patients treated with EGFR inhibitors.^{1,7} The incidence of high-grade pruritus in patients receiving immunotherapies ranged from 0.5 to 1.9%.^{1,7} A systemic review and meta-analysis including 24 phase III trials done by Santoni et al. found that the relative risk of developing all-grade and high-grade pruritus with targeted therapies compared to that of control groups or placebos were 2.2 and 2.6, respectively.²¹

Possible pathogenesis of pruritus associated with targeted anticancer therapies

The pathogenesis of pruritus remained not clear. Possible pathogenesis of pruritus may involve cutaneous nerve endings, unmyelinated C fibers and neurotransmitters or regulation of various receptors, such as serotonin, neurokinin 1 (NK-1) receptor, opioid receptors, and gamma-aminobutyric acid (GABA).^{1,35–37} Xerosis and skin inflammation i.e. papulopustular eruption resulting from alteration of skin barrier function and increased dermal mast cells were proposed to be the possible mechanisms of pruritus induced by these targeted therapies.²⁰ Pruritus was reported to be associated with papulopustular eruption in 62% of cases and xerosis in 50%, respectively.^{1,7} A study using cell culture and animal model suggested sorafenib induces pruritus via stem cell factor activation of mast cell degranulation and maturation.²⁰

Proposed management algorithm of pruritus

Prevention and treatment of papulopustular/ maculopapular rash and xerosis induced by targeted therapies have been considered important for pruritus prophylaxis and management.^{1,26,27,38–40} The CTCAE grading and proposed management algorithms for pruritus and related skin conditions were summarized in Table 2. Prophylactic strategy with gentle skin care including proper cleaning and moisturizer use is suggested. Management usually starts from topical antipruritic agents and topical steroids for grades 1–2 pruritus. Oral antihistamine can be added for grade 2 pruritus which is not controllable by topical treatments. Systemic treatments including oral antihistamine, GABA agonist (gabapentin, pregabalin), doxepin, antidepressants, NK-1 receptor antagonist (aprepitant), or corticosteroids are often necessary for grade 3 or intolerable grade 2 pruritus.^{1,26,27,38–40}

Understanding the incidences of pruritus and the associated conditions such as papulopustular eruptions and xerosis in patients receiving targeted therapies, pretreatment patient counseling, proper prophylactic skin care and management of pruritus are essential to maintain patients on the anticancer therapies and their quality of life.

References

1. Fischer A, Rosen AC, Ensslin CJ, Wu S, Lacouture ME. Pruritus to anticancer agents targeting the EGFR, BRAF, and CTLA-4. *Dermatologic therapy*. 2013; 26(2):135–148. [PubMed: 23551370]
2. 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*. 2007; 12(5):610–621. [PubMed: 17522250]
3. Tischer B, Huber R, Kraemer M, Lacouture ME. Dermatologic events from EGFR inhibitors: the issue of the missing patient voice. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2017; 25(2):651–660. [PubMed: 27718067]
4. Barton-Burke M, Ciccolini K, Mekas M, Burke S. Dermatologic Reactions to Targeted Therapy: A Focus on Epidermal Growth Factor Receptor Inhibitors and Nursing Care. *The Nursing clinics of North America*. 2017; 52(1):83–113. [PubMed: 28189168]
5. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. *J Am Acad Dermatol*. 2015; 72(2):221–236. quiz 237–228. [PubMed: 25592339]
6. Belum VR, Washington C, Pratilas CA, Sibaud V, Boralevi F, Lacouture ME. Dermatologic adverse events in pediatric patients receiving targeted anticancer therapies: a pooled analysis. *Pediatric blood & cancer*. 2015; 62(5):798–806. [PubMed: 25683226]
7. Ensslin CJ, Rosen AC, Wu S, Lacouture ME. Pruritus in patients treated with targeted cancer therapies: systematic review and meta-analysis. *J Am Acad Dermatol*. 2013; 69(5):708–720. [PubMed: 23981682]
8. Belum VR, Fontanilla Patel H, Lacouture ME, Rodeck U. Skin toxicity of targeted cancer agents: mechanisms and intervention. *Future oncology (London, England)*. 2013; 9(8):1161–1170.
9. Belum VR, Benhuri B, Postow MA, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *European journal of cancer (Oxford, England : 1990)*. 2016; 60:12–25.
10. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nature reviews Clinical oncology*. 2016; 13(8):473–486.
11. Valentine J, Belum VR, Duran J, et al. Incidence and risk of xerosis with targeted anticancer therapies. *J Am Acad Dermatol*. 2015; 72(4):656–667. [PubMed: 25637330]
12. Gandhi M, Oishi K, Zubal B, Lacouture ME. Unanticipated toxicities from anticancer therapies: survivors' perspectives. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2010; 18(11):1461–1468. [PubMed: 19956983]
13. Clabbers JMK, Boers-Doets CB, Gelderblom H, et al. Xerosis and pruritus as major EGFRi-associated adverse events. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2016; 24(2):513–521. [PubMed: 26111953]
14. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2015; 372(26):2521–2532. [PubMed: 25891173]
15. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *The Lancet Oncology*. 2010; 11(2):155–164. [PubMed: 20004617]
16. Larsabal M, Marti A, Jacquemin C, et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo. *J Am Acad Dermatol*. 2017
17. Choi JN. Dermatologic adverse events to chemotherapeutic agents, Part 2: BRAF inhibitors, MEK inhibitors, and ipilimumab. *Seminars in cutaneous medicine and surgery*. 2014; 33(1):40–48. [PubMed: 25037257]

18. Balagula Y, Barth Huston K, Busam KJ, Lacouture ME, Chapman PB, Myskowski PL. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). *Investigational new drugs*. 2011; 29(5):1114–1121. [PubMed: 20978926]
19. Belum VR, Fischer A, Choi JN, Lacouture ME. Dermatological adverse events from BRAF inhibitors: a growing problem. *Current oncology reports*. 2013; 15(3):249–259. [PubMed: 23463215]
20. Mizukami Y, Sugawara K, Kira Y, Tsuruta D. Sorafenib stimulates human skin type mast cell degranulation and maturation. *J Dermatol Sci*. 2017
21. Santoni M, Conti A, Andrikou K, et al. Risk of pruritus in cancer patients treated with biological therapies: A systematic review and meta-analysis of clinical trials. *Crit Rev Oncol Hematol*. 2015; 96(2):206–219. [PubMed: 26070625]
22. Bryce J, Boers-Doets CB. Non-rash dermatologic adverse events related to targeted therapies. *Seminars in oncology nursing*. 2014; 30(3):155–168. [PubMed: 25085027]
23. Rosen AC, Case EC, Dusza SW, et al. Impact of dermatologic adverse events on quality of life in 283 cancer patients: a questionnaire study in a dermatology referral clinic. *American journal of clinical dermatology*. 2013; 14(4):327–333. [PubMed: 23625802]
24. Ebata T. Drug-Induced Itch Management. *Current problems in dermatology*. 2016; 50:155–163. [PubMed: 27578085]
25. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapy for cancer: Part II. Targeted therapy. *Journal of the American Academy of Dermatology*. 2014; 71(2):217e211–217.e211. quiz 227–218. [PubMed: 25037801]
26. de Golan E, Kwong BY, Swetter SM, Pugliese SB. Cutaneous Complications of Targeted Melanoma Therapy. *Current treatment options in oncology*. 2016; 17(11):57. [PubMed: 27645330]
27. Collins LK, Chapman MS, Carter JB, Samie FH. Cutaneous adverse effects of the immune checkpoint inhibitors. *Current problems in cancer*. 2017; 41(2):125–128. [PubMed: 28190531]
28. Minkis K, Garden BC, Wu S, Pulitzer MP, Lacouture ME. The risk of rash associated with ipilimumab in patients with cancer: a systematic review of the literature and meta-analysis. *J Am Acad Dermatol*. 2013; 69(3):e121–128. [PubMed: 23357570]
29. Lacouture ME, Wolchok JD, Yosipovitch G, Kahler KC, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. *J Am Acad Dermatol*. 2014; 71(1):161–169. [PubMed: 24767731]
30. Sibaud V, Meyer N, Lamant L, Vigarios E, Mazieres J, Delord JP. Dermatologic complications of anti-PD-1/PD-L1 immune checkpoint antibodies. *Curr Opin Oncol*. 2016; 28(4):254–263. [PubMed: 27136138]
31. Habre M, Habre SB, Kourie HR. Dermatologic adverse events of checkpoint inhibitors: what an oncologist should know. *Immunotherapy*. 2016; 8(12):1437–1446. [PubMed: 28000535]
32. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapy for cancer: Part II. Targeted therapy. *Journal of the American Academy of Dermatology*. 2014; 71(2):217e211–217.e211. quiz 227–218. [PubMed: 25037801]
33. Mochel MC, Ming ME, Imadojemu S, et al. Cutaneous autoimmune effects in the setting of therapeutic immune checkpoint inhibition for metastatic melanoma. *J Cutan Pathol*. 2016; 43(9):787–791. [PubMed: 27161449]
34. Ito J, Fujimoto D, Nakamura A, et al. Aprepitant for refractory nivolumab-induced pruritus. *Lung cancer (Amsterdam, Netherlands)*. 2017; 109:58–61.
35. Pereira MP, Kremer AE, Mettang T, Stander S. Chronic Pruritus in the Absence of Skin Disease: Pathophysiology, Diagnosis and Treatment. *American journal of clinical dermatology*. 2016; 17(4):337–348. [PubMed: 27216284]
36. Wong LS, Wu T, Lee CH. Inflammatory and Noninflammatory Itch: Implications in Pathophysiology-Directed Treatments. *International journal of molecular sciences*. 2017; 18(7)
37. Oetjen LK, Mack MR, Feng J, et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch. *Cell*. 2017; 171(1):217–228. e213. [PubMed: 28890086]
38. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Supportive care in cancer* :

- official journal of the Multinational Association of Supportive Care in Cancer. 2011; 19(8):1079–1095. [PubMed: 21630130]
39. Melosky B, Leighl NB, Rothenstein J, Sangha R, Stewart D, Papp K. Management of egfr tki-induced dermatologic adverse events. *Current oncology* (Toronto, Ont). 2015; 22(2):123–132.
 40. Bergman H, Walton T, Del Bel R, et al. Managing skin toxicities related to panitumumab. *J Am Acad Dermatol*. 2014; 71(4):754–759. [PubMed: 25085331]
 41. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES. National Institutes of Health. National Cancer Institute; Published: May 28 vJ, 2010
 42. Lacouture ME, Maitland ML, Segal S, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2010; 18(4):509–522. [PubMed: 20145956]
 43. Perez-Soler R, Delord JP, Halpern A, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. *Oncologist*. 2005; 10(5):345–356. [PubMed: 15851793]
 44. Eaby B, Culkin A, Lacouture ME. An interdisciplinary consensus on managing skin reactions associated with human epidermal growth factor receptor inhibitors. *Clinical journal of oncology nursing*. 2008; 12(2):283–290. [PubMed: 18390464]
 45. 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. *Current oncology* (Toronto, Ont). 2009; 16(1):16–26.
 46. Jatoti A, Thrower A, Sloan JA, et al. Does sunscreen prevent epidermal growth factor receptor (EGFR) inhibitor-induced rash? Results of a placebo-controlled trial from the North Central Cancer Treatment Group (N05C4). *Oncologist*. 2010; 15(9):1016–1022. [PubMed: 20798191]
 47. 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*. 2010; 28(8):1351–1357. [PubMed: 20142600]
 48. Ouwerkerk J, Boers-Doets C. Best practices in the management of toxicities related to anti-EGFR agents for metastatic colorectal cancer. *European journal of oncology nursing : the official journal of European Oncology Nursing Society*. 2010; 14(4):337–349. [PubMed: 20580896]
 49. Melosky B, Hirsh V. Management of Common Toxicities in Metastatic NSCLC Related to Anti-Lung Cancer Therapies with EGFR-TKIs. *Frontiers in oncology*. 2014; 4:238. [PubMed: 25279350]
 50. Melosky B, Anderson H, Burkes RL, et al. Pan Canadian Rash Trial: A Randomized Phase III Trial Evaluating the Impact of a Prophylactic Skin Treatment Regimen on Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor-Induced Skin Toxicities in Patients With Metastatic Lung Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016; 34(8):810–815. [PubMed: 26573073]
 51. 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*. 2017; 77(3):577–579. [PubMed: 28807114]

Key Points

- Aberrations in cell signal transduction pathways including EGFR, MAPK (RAS-RAF-MEK-ERK), and PI3K-Akt-mTOR pathways play an essential role in tumorigenesis and disease progression; targeted therapies acting on these signaling pathways cause dermatologic adverse events.
- Immune checkpoints inhibitors targeting CTLA-4, PD-1, or PD-L1 have revolutionized cancer treatments with promising outcomes, and collaterally caused immune-related adverse events such as rash and pruritus.
- Pruritus is a common dermatologic adverse event with incidences ranged from 2.2 to 47% across different categories of targeted anticancer therapies with the highest incidence in patients treated with panitumumab (54.9%) and ipilimumab plus nivolumab combination treatment (33.2–47%).
- Possible mechanisms of pruritus include alteration of skin barrier function and homeostasis, pruritus preceding by xerosis and skin inflammation, and increasing numbers of dermal mast cells induced by targeted therapies.

Table 1

Incidences of all-grade and high-grade pruritus associated with targeted anticancer therapies

Data from Refs^{1,4–7,9,10,13,17–34}

Category of targeted anticancer therapy	Drug names	All-grade (%)	High-grade (%)
EGFR inhibitors- Monoclonal antibodies	Cetuximab	18.2	2.1
	Panitumumab	54.9	2.6
EGFR inhibitors- Tyrosine kinase inhibitors	Erlotinib	20.8	2.3
	Gefitinib	21.0	1.0
EGFR-HER2 inhibitors	Lapatinib	14.6	1.0
EGFR-VEGFR inhibitors	Vandetanib	9.1	0.5
Mutitargeted tyrosine kinase inhibitors (VEGFR/PDGFR/c-KIT inhibitors)	Axitinib	8.3	3.9
	Pazopanib	2.2	1.1
BRAF+VEGFR	Sorafenib	18.2	1.0
BRAF inhibitors	Vemurafenib	18.5	1.7
MEK inhibitors	Selumetinib	45	-
mTOR inhibitors	Everolimus	14.3	1.3
	Temsirolimus	37.7	1.0
Bcr-Abl inhibitors	Dasatinib	9.7	0.8
	Imatinib	10.2	0.8
	Nilotinib	17.1	1.0
Anti-CD20 monoclonal antibodies	Rituximab	10.2	1.2
	Tositumomab	13.7	0.8
Anti-CTLA4 monoclonal antibodies	Ipilimumab	24.4–35.4	1.0
	Tremelimumab	30.8	0.9
Anti-PD1 monoclonal antibodies	Nivolumab	17–18.8	0.5
	Pemprolizumab	14.1–20.7	1.0
	Ipilimumab+Nivolumab	33.2–47	0–1.9

Table 2

Grading and management algorithms for pruritus and associated skin conditions of targeted therapies

Adapted from U.S. Department of Health and Human Services. CTCAE Grading Scale (v4.0: May 28, 2009). Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed on July 27 2017; with permission, using data from Refs 2, 38, 41–51

CTCAE grading scale and management algorithms for dAEs to targeted therapy						
Adverse events						
Grading						
	1	2	3	4	5	
	Mild	Moderate	Severe or medically significant but not immediately life-threatening	Life-threatening consequences	Death related to AE	
Description	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**	Urgent intervention indicated	Death related to AE	
General approach	Moisturizer, sunscreen, gentle skin care instructions	Continue the drug at current dose and monitor for change in severity	Continue the drug at current dose and monitor for change in severity; continue treatment of skin reaction	Interrupt the drug until severity decreases to grade 1/2 and dose modify per label and monitor for change in severity; continue treatment of skin reaction; reassess after 2 weeks, if reactions worsen, dose reduction or discontinuation may be necessary		
		Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to next grade therapy (Refer to a dermatologist for evaluation and management is considered)				
Pruritus	A disorder characterized by an intense itching sensation.	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated		
Management		Topicals: Doxepin 5% cream, menthol 0.5%, topical calcineurin inhibitors (pimecrolimus, tacrolimus), medium- to high-potency steroids (triamcinolone acetate 0.025%; desonide 0.05%; fluticasone propionate	Topicals: Medium- to high-potency steroids (including clobetasol 0.05%) AND Oral antihistamines	Topicals: Medium- to high-potency steroids (including clobetasol 0.05%) AND Oral antihistamines AND Gabapentin/ pregabalin / Doxepin/ Aprepitant/ antidepressants AND/OR		

CTCAE grading scale and management algorithms for dAEs to targeted therapy						
Adverse events	Grading					5
	1	2	3	4	Death	
	Mild	Moderate	Severe or medically significant but not immediately life-threatening	Life-threatening consequences	Death	
	0.05%; alclometasone 0.05%)		Prednisone 0.5–1mg/Kg/day for 5 days			
Rash acneiform (papulopustular eruption) A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death	
Management	Pre-emptive treatment for week 1–6					
	Hydrocortisone 2.5% cream AND Clindamycin 1% gel AND Doxycycline 100 mg BID OR Minocycline 100 mg BID					
Reactive treatment	Hydrocortisone 2.5% cream AND Clindamycin 1% gel/ dapson 5% gel	Hydrocortisone 2.5% cream/ Alclometasone 0.05% cream/ Fluocinonide 0.05% cream BID AND Doxycycline 100 mg BID/ AND Doxycycline 100 mg BID/BID/Minocycline 100 mg BID	Hydrocortisone 2.5% cream/ Alclometasone 0.05% cream/ Fluocinonide 0.05% cream BID AND Doxycycline 100 mg minocycline 100 mg QD AND Oral prednisone (0.5mg/kg/day) for 5 days			
	Macules/ papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/ papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/ papules covering >30% BSA with or without associated symptoms; limiting self-care ADL			
Management	Hydrocortisone 2.5% cream to face AND triamcinolone 0.1% cream to body BID	Hydrocortisone 2.5% cream to face AND Fluocinonide 0.1% cream to body bid AND/OR Oral antihistamines	Hydrocortisone 2.5% cream to face AND Fluocinonide 0.1% cream to body AND Oral antihistamines AND Prednisone 0.5–1 mg/kg for 10 days			

CTCAE grading scale and management algorithms for dAEs to targeted therapy					
Adverse events					
Grading					
	1	2	3	4	5
	Mild	Moderate	Severe or medically significant but not immediately life-threatening	Life-threatening consequences	Death
Dry skin A disorder characterized by flaky and dull skin; the pores are generally fine; the texture is a papery thin texture.	Covering <10% BSA and no associated erythema or pruritus	Covering 10 – 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self-care ADL		
Management					
Pre-emptive treatment	Bathing techniques; gentle skin care; avoid extreme temperatures and direct sunlight				
Reactive treatment	OTC moisturizing cream or ointment to face BID AND Ammonium lactate 12% cream to body	OTC moisturizing cream or ointment to face BID AND Ammonium lactate 12% cream/ lactic acid cream 6%/ salicylic acid 12% cream 12% to body BID	OTC moisturizing cream or ointment to face BID AND Ammonium lactate 12% cream/ salicylic acid 6%/ lactic acid cream 12% to body BID AND Mid- to high-potency steroids (triamcinolone acetonide 0.025%; desonide 0.05%; fluticasone propionate 0.05%; alclometasone 0.05%)		

Note: A single dash (-) indicates a grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL):

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.