Incidence and risk of xerosis with targeted anticancer therapies

Johannah Valentine, MD,[a] Viswanath Reddy Belum, MD,[b] Juanita Duran, MD,[c] Kathryn Ciccolini, RN, BSN,[b] Katja Schindler, MD,[b,d] Shenhong Wu, MD, PhD,[e,f] and Mario E. Lacouture, MD[b]
San Diego, California; New York, Stony Brook, and Northport, New York; Bogota, Colombia; and Vienna, Austria

Background: Many targeted therapies used in the treatment of cancer can lead to the development of xerosis, but the incidence and relative risk of xerosis have not been ascertained.

Objective: We conducted a systematic review and metaanalysis of clinical trials, to ascertain the incidence and risk of developing xerosis after taking anticancer drugs.

Methods: The PubMed (1966-October 2013), Web of Science (January 1998-October 2013), and American Society of Clinical Oncology abstracts (2004-2013) databases were searched for clinical trials of 58 targeted agents. Results were calculated using random or fixed effects models.

Results: The incidences of all- and high-grade xerosis were 17.9% (95% confidence interval [CI]: 15.6-20.4%) and 1.0% (95% CI: 0.9-1.5%), respectively. The risk of developing all-grade xerosis was 2.99 (95% CI: 2.0-4.3), and it varied across different drugs ($P < .001$).

Limitations: The reporting of xerosis may vary among clinicians and institutions, and the incidence may be affected by age, concomitant medications, comorbidities, and underlying malignancies or skin conditions.

Conclusion: Patients receiving targeted therapies have a significant risk of developing xerosis. Patients should be counseled and treated early for this symptom to prevent suboptimal dosing and quality of life impairment. (J Am Acad Dermatol 2015;72:656-67.)

Key words: Bcr-Abl; CD20; CD52; dry skin; EGFR; HDAC; HER2; incidence; MEK; mTOR; Raf; risk; xerosis; VEGFR.

Targeted therapies have improved survival in numerous cancer patients because of their ability to inhibit specific pathways essential for tumor growth and survival.[1,2] Because of this selective pharmacologic action, targeted therapies have a more favorable systemic toxicity profile than conventional cytotoxic chemotherapies.[3,4] The signaling pathways inhibited, however, are also

From the Department of Dermatology,[a] Naval Medical Center San Diego; Dermatology Service,[b] Memorial Sloan Kettering Cancer Center, New York; Department of Dermatology,[c] Universidad del Rosario, Bogota; Department of Dermatology,[d] Medical University of Vienna; Division of Hematology and Oncology,[e] Stony Brook University Cancer Center; and the Division of Hematology and Oncology,[f] Department of Medicine, Northport Veterans Affairs Medical Center.

Supported by the Memorial Sloan Kettering Cancer Center.

Ms Ciccolini is a speaker for Amgen. Dr Wu is a speaker, consultant, or advisor for Bayer-Onyx, Dendeon, Medivation, Novartis, and Pfizer. Dr Lacouture is a speaker, consultant, or advisor for Advancell, Amgen, AstraZeneca, Augmentium, Aveo, Bayer, Berg Pharma, Biopharm Communications, Boehringer Ingelheim, Brickell Biotech, Bristol-Myers Squibb, Clinical Assistance Programs, Clinical Care Options, EMD Serono, Envision Communications, Foamix, Galderma, Genentech, GlaxoSmithKline, Helsinn, Institute for Medical Education and Research, Integro-MC, Lindi Skin, Medscape, Medtrend International, Merck, Nerre Therapeutics, Novartis, Novocure, Oncology Specialty Group, OSI Pharmaceuticals, Permanyer, Physicians Education Resource, Pierre Fabre, Pfizer, Reata Pharmaceuticals, Roche, Sandoz, Sanofi Aventis, and Threshold Pharmaceuticals. The remaining authors have conflicts of interest to declare.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the US government. Dr Valentine is a military service member, and this work was prepared as part of her official duty.

Accepted for publication December 8, 2014.

Reprint requests: Mario E. Lacouture, MD, Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 60th St Outpatient Center, Ste 407, Rm 4312, 16 East 60th St, New York, NY 10022. E-mail: lacoutum@mskcc.org.

Published online January 27, 2015.
0190-9622
Published by Elsevier on behalf of the American Academy of Dermatology, Inc.
http://dx.doi.org/10.1016/j.jaad.2014.12.010

essential for cutaneous homeostasis and functioning. Consequently, these agents lead to the development of unique dermatologic adverse events (dAEs).[5] With improved survival rates and the increasing use of targeted therapies, dAEs are now at the forefront for many patients,[6] and dermatologists have a greater role in the health care teams of patients with cancer.

The dAEs of targeted therapies, while usually not life threatening, are common and may result in interruptions or the discontinuation of life-saving anticancer therapy.[7] Whereas toxicities such as acneiform rash, paronychia, and hair changes have received considerable attention, the incidence and characteristics of xerosis have not been systematically ascertained. In oncologic clinical trials of epidermal growth factor receptor inhibitors (EGFRIs), for example, xerosis is reported in 7% to 90% of patients; evaluation by a dermatologist reveals 100% incidence in patients who are treated for >6 months.[8-10]

CAPSULE SUMMARY

- Xerosis is reported as an adverse event in cancer clinical trials, but its true incidence and risk have not been systematically analyzed, and the associated drugs are not known.
- Targeted anticancer therapies are associated with a significant risk of xerosis.
- Dermatologists should assist in the prevention and treatment of xerosis in cancer patients to ensure improved quality of life while maximizing the dose intensity of cancer treatment.

The clinical and psychosocial importance of xerosis and its association with pruritus has received little consideration in the oncology field. It must be emphasized that the use of targeted anticancer agents is the most common cause of pruritus in cancer patients and that these therapies may impair patients' quality of life (QoL).[11] A systematic review revealed a significant risk of pruritus with targeted therapies.[12] In addition, a questionnaire study of 283 cancer patients revealed that patients receiving targeted therapies experience a significantly greater amount of dAEs in comparison to those treated with nontargeted therapies.[11] In that study, dAEs were associated with a diminished QoL. A separate survey of 379 cancer survivors revealed that xerosis occurred in 34% of patients, of which 44% reported a negative effect on QoL.[13]

Awareness, early recognition, and management of xerosis may prevent suboptimal treatment, infections, and improve the overall QoL of patients receiving targeted therapies. Therefore, we conducted a systematic review and metaanalysis of the literature to determine the overall incidence and risk of developing xerosis with anticancer drugs.

METHODS

Data source and extraction

We conducted a PubMed search (1966-October 2013) by combining the following 2 concepts using the operator "and": the generic name of the drug (ie, ado-trastuzumab, afatinib, alemtuzumab, alitretinoin, anastrozole, axitinib, bevacizumab, bexarotene, bortezomib, brentuximab, bosutinib, cabozantinib, carfilzomib, ceritinib, cetuximab, crizotinib, dabrafenib, daclizumab, dasatinib, denileukin diftitox, denosumab, erlotinib, everolimus, exemestane, fulvestrant, gefitinib, ibritumomab, ibrutinib, imatinib, ipilimumab, lapatinib, letrozole, nilotinib, ofatumumab, panitumumab, pazopanib, pertuzumab, ponatinib, pralatrexate, ramcirumab, regorafenib, rituximab, romidepsin, ruxolitinib, sorafenib, sunitinib, tamoxifen, temsirolimus, toremifene, trametinib, trastuzumab, tositumomab, tretinoin, vandetanib, vemurafenib, vismodegib, vorinostat, and ziv-aflibercept) and "phase II OR phase III." The results were limited to human-only reports published in English. In addition, we reviewed abstracts (2004-2013) presented at the American Society of Clinical Oncology meetings to identify relevant clinical trials. An independent search on the Web of Science database was also conducted.

We reviewed each publication and included only the complete or most recent report of the clinical trial when duplicate publications were identified. The first author's name, year of publication, trial design, type of malignancy, enrollment number, treatment numbers, treatment arms, numbers of patients with all- and high-grade xerosis in each treatment group, and the Common Terminology Criteria for Adverse Events (CTCAE) grading used were extracted from selected trials. Data were available for analysis for only afatinib, alemtuzumab, anastrozole, axitinib, bexarotene, cabozantinib, cetuximab, dasatinib, erlotinib, everolimus, exemestane, gefitinib, imatinib, lapatinib, letrozole, panitumumab, pazopanib, regorafenib, sorafenib, sunitinib, temsirolimus, trametinib, vandetanib, and vorinostat.

Abbreviations used:

ADL:	activities of daily living
AE:	adverse event
CI:	confidence interval
CTCAE:	Common Terminology Criteria for Adverse Events
dAE:	dermatologic adverse event
EGFR:	epidermal growth factor receptor
EGFRI:	epidermal growth factor receptor inhibitor
MEK:	mitogen-activated extracellular kinase
mTOR:	mammalian target of rapamycin
QoL:	quality of life
RR:	relative risk
VEGF:	vascular endothelial growth factor
VEGFR:	vascular endothelial growth factor receptor

Study selection

Targeted therapies are approved for the treatment of various malignancies at specific doses. To ensure clinical significance, we calculated the incidence of xerosis at these dosing levels. Accordingly, phase I and clinical trials using unapproved doses were excluded from analysis. We also excluded trials that combined targeted therapies with other chemotherapies and/or treatment modalities (eg, radiotherapy). Trials that met the following criteria were selected for the final analysis: (1) prospective phase II and III clinical trials in cancer patients, (2) assigned participants to treatment with targeted agents at their approved doses, and (3) reported data regarding the occurrence of xerosis.

Clinical end points

The clinical end point of xerosis was extracted from the safety data of each trial. Xerosis was recorded according to the National Cancer Institute Common Toxicity Criteria (v 2.0) and CTCAE versions 3.0 and 4.0.[14,15] CTCAE version 2.0 has only 2 grades for xerosis: grade 1, controlled with emollients and grade 2, not controlled with emollients. In version 3.0, xerosis is rated with the following grades: grade 1, asymptomatic; grade 2, symptomatic but not interfering with activities of daily living (ADL); and grade 3, interfering with ADL.[14] With version 4.0, body surface area (BSA) is taken into account as follows: grade 1, covering <10% of the body surface area (BSA) and not associated erythema or pruritus; grade 2, covering 10% to 30% BSA and associated with erythema or pruritus, limiting instrumental ADL; and grade 3, covering >30% BSA and associated with pruritus, limiting self-care ADL.[15]

Statistical analysis

Statistical analyses were performed with the Comprehensive MetaAnalysis program (v 2; Biostat, Englewood, NJ).[16] The numbers of patients with all- and high-grade xerosis in treatment and control groups (if applicable) were identified from trials that met the aforementioned criteria. The incidence of xerosis and 95% confidence intervals (CIs) were calculated for each trial. For placebo-controlled trials, the relative risk (RR) of xerosis was determined.

The fixed effects (weighted with inverse variance) and random effects models were both applied during the metaanalysis.[17] Cochran's Q statistic was first calculated to assess the heterogeneity of the included trials. For $P < .1$, the trial was deemed heterogenous, and the random effects model was used.[18] Otherwise, data from both statistical models were evaluated. If the results of the fixed and the random effects models were comparable, only fixed effects model results were reported. $P < .05$ was considered statistically significant.

RESULTS

Search results

In our systematic search, we identified 12,734 published articles on targeted therapies (Fig 1). A total of 130 clinical trials met criteria for this analysis, including 99 phase II and 31 phase III trials. One hundred twenty-seven of these studies focused on solid organ malignancies and 3 involved hematologic malignancies.[19-145]

Incidence of all-grade xerosis

The calculated aggregate (overall) incidence of all-grade xerosis using the random effects model (heterogeneity: $Q = 39.7$, $I^2 = 62.2$, and $P \leq .001$) was 17.9% (95% CI: 15.6-20.4%); it was lowest for anastrozole (1.0% [95% CI: 0-8.0%]) and highest for panitumumab (46.5% [95% CI: 16.5-79.3%]). When individual trials of different drugs were analyzed, the incidence ranged from 1.0% to 84.0%. The lowest incidence was noted with anastrozole (1.0% [95% CI: 0-8.0%]), in a trial of anastrazole alone or with gefitinib in early breast cancer (n = 270).[22] On the other hand, the highest incidence was noted with sorafenib (84.0% [95% CI: 72.0-91.0%]) in a phase II trial of sorafenib in metastatic thyroid cancer (n = 58; Table I).[123]

Incidence of high-grade xerosis

High-grade xerosis (grade 3) is a significant dAE and may result in dose reduction or interruption. The calculated aggregate (overall) incidence of high-grade xerosis using the random effects model was 1.0%. The highest overall incidence of high-grade xerosis for an individual drug was noted with dasatinib (4.0% [95% CI: 1.0-15.0%]), in a phase II study of dasatinib in patients with metastatic

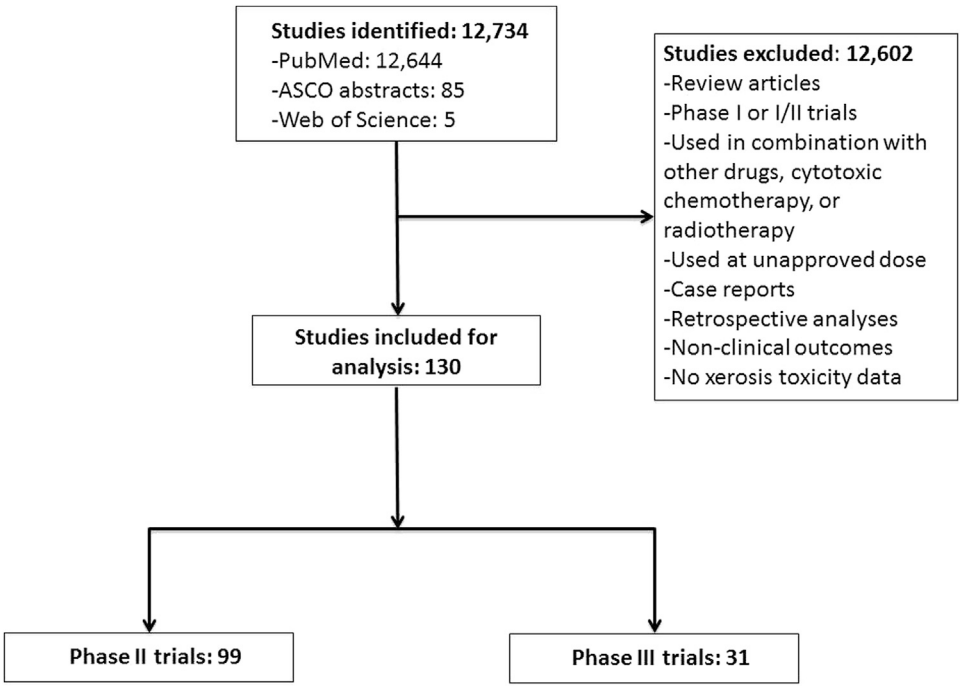

Fig 1. Selection process for studies included in this metaanalysis. *ASCO*, American Society of Clinical Oncology.

castration-resistant prostate cancer (n = 47).[37] High-grade xerosis was not noted with vandetanib, regorafenib, cabozantinib, letrozole, and exemestane; for lapatinib, axitinib, pazopanib, trametinib, alemtuzumab, bexarotene, vorinostat, and anastrozole, the calculated overall incidence appeared to be <0.1% (95% CI: 0.01-2%; Table I).

Relative risk of all-grade xerosis (compared to placebo)

We calculated the RR of developing all-grade xerosis in patients receiving targeted therapies compared to placebo and performed a metaanalysis of 16 randomized, controlled trials (RCTs) involving imatinib,[95] erlotinib,[49] gefitinib,[67,79,89] lapatinib,[102] vandetanib,[142,143] regorafenib,[113] cabozantinib,[27] sorafenib,[115,122,126,130] and everolimus.[38,39] All-grade xerosis was noted in 551 of 5055 patients receiving targeted therapies, which presented an overall RR of 2.99 (95% CI: 2.0-4.3) compared to placebo (134/4421 patients), according to the random effects model (Fig 2). Statistical heterogeneity was moderate (Q = 39.7, I^2 = 62.2, and $P \leq .001$). The RR was lowest with sorafenib (0.86 [95% CI: 0.43-1.7]; P = .68) and highest with gefitinib (19.19 [95% CI: 2.6-140.6]; $P \leq .004$; Fig 2).

DISCUSSION

Pruritus associated with targeted therapies has been shown to be a source of chemotherapy dose reduction and interruption,[12] but the effect of xerosis had not been assessed. In our metaanalysis of published trials, we found that patients receiving targeted therapies were at a significantly increased risk of developing xerosis during treatment (Fig 3). The calculated overall incidence of all-grade xerosis was 17.9% (95% CI: 15.6-20.4%), with near negligible rates of high-grade xerosis. Among the drug classes that were examined, inhibitors of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), mitogen-activated extracellular kinase (MEK), and mammalian target of rapamycin (mTOR) pathways were associated with the highest rates of xerosis.

EGFRIs had among the highest rates of xerosis, especially panitumumab, with a 47% incidence of all-grade xerosis. Panitumumab, approved for the treatment of metastatic colon cancer, has been shown to result in skin toxicities in 90% to 97% of patients. Because it improves progression-free survival, panitumumab will likely continue to be prescribed.[146-149] The pathogenesis of xerosis associated with EGFRIs appears to be a mechanism-based effect. Previous research has indicated that EGFR plays a prominent role in epidermal differentiation and homeostasis.[5] Indeed, administration of EGFRIs results in increased inflammation, keratinocyte apoptosis, ultraviolet radiation sensitivity, and altered differentiation.[150]

Dysregulation of epidermal differentiation during treatment with an EGFRI results in an abnormal

Table I. Incidence of xerosis with approved targeted agents in monotherapy (n = 130)

Drug class	Drug and reference(s)	No. of eligible studies	All-grade xerosis incidence (95% CI)	High-grade xerosis incidence (95% CI)
VEGFR inhibitors	Axitinib[23,24,114]	2	17.7% (7.9-35.0%)	1.0% (0.1-7.2%)
	Cabozantinib[27]	1	19.2% (14.4-25.0%)	0.2% (0.0-3.6%)
	Pazopanib[111,112]	2	2.8% (0.7-10.4%)	1.4% (0.2-9.0%)
	Regorafenib[113]	1	7.8% (5.8-10.5%)	0.1% (0.0-1.6%)
	Sorafenib[114-130]	17	14.3% (8.7-22.6%)	0.6% (0.3-1.1%)
	Sunitinib[131-137]	7	10.6% (6.0-18.1%)	1.2% (0.4-3.2%)
Monoclonal antibody to CD52	Alemtuzumab[21]	1	5.3% (0.7-29.4%)	2.5% (0.2-29.8%)
HDAC inhibitor	Vorinostat[145]	1	8.6% (2.8-23.4%)	1.4% (0.8-18.7%)
EGFR/VEGFR inhibitor	Vandetanib[54,77,142-144]	5	13.4% (9.8-18.1%)	0.4% (0.1-1.5%)
Retinoid	Bexarotene[25,26]	2	13.5% (5.6-29.0%)	0.9% (0.1-6.3%)
Bcr-Abl inhibitors	Dasatinib[37]	1	10.6% (4.5-23.1%)	4.3% (1.1-15.5%)
	Imatinib[95-99]	5	6.6% (5.1-8.5%)	2.6% (0.8-8.5%)
EGFR/HER2 inhibitors	Afatinib[19,20]*	2	28.6% (23.4-34.4%)	1.2% (0.2-8.4%)
	Lapatinib[100-106]	7	16.5% (13.1-20.6%)	0.9% (0.2-4.7%)
Endocrine therapies	Anastrozole[22]	1	1.2% (0.2-7.9%)	0.6% (0.0-8.6%)
	Exemestane[42]	1	1.2% (0.54-2.7%)	0.2% (0.0-1.4%)
	Letrozole[107]	1	4.3% (3.0-6.2%)	0.0% (0.0-1.3%)
MEK inhibitor	Trametinib[141]	1	22.6% (14.6-30.9%)	0.5% (0.0-7.6%)
EGFR inhibitors	Cetuximab[28-36]	9	20.1% (16.0-24.8%)	3.4% (1.8-6.3%)
	Erlotinib[43-67]*	24	27.3% (19.6-36.6%)	1.3% (0.8-2.2%)
	Gefitinib[52,67-94]*	29	24.7% (19.2-31.1%)	0.9% (0.5-1.5%)
	Panitumumab[108-110]*	3	46.5% (16.5-79.3%)	1.7% (0.3-8.4%)
mTOR inhibitors	Everolimus[38-41]	4	10.8% (8.0-14.5%)	0.4% (0.1-1.5%)
	Temsirolimus[138-140]	3	17.6% (9.0-31.6%)	3.0% (0.8-10.5%)

CI, Confidence interval; *EGFR*, epidermal growth factor receptor; *HDAC*, histone deacetylase; *HER2*, human epidermal growth factor receptor 2; *MEK*, mitogen-activated extracellular kinase; *mTOR*, mammalian target of rapamycin; *VEGFR*, vascular endothelial growth factor receptor.
*Drugs with an incidence of xerosis ≥25%.

stratum corneum and inadequate function of sebaceous glands, leading to dry skin. Inhibition of EGFR largely affects basal keratinocytes, leading to growth arrest and premature differentiation. Patients who are taking EGFRIs have decreased epidermal thickness and a thin, parakeratotic stratum corneum. As in atopic dermatitis, a defective corneum from EGFR inhibition compromises barrier function and leads to transepidermal water loss (TEWL) and xerosis.[150,151]

In addition to aberrant keratinocyte differentiation, EGFRIs disrupt barrier function in other ways. Claudin-1, an essential component of tight junctions, is downregulated with the use of EGFRIs.[152] Tight junctions are known to be critical to maintaining skin barrier and preventing TEWL.[153] Mouse models with faulty EGFRs have increased TEWL, resulting in skin dryness similar to patients who are taking EGFRIs.[152]

The use of trametinib, a small-molecule inhibitor that was recently approved for the treatment of metastatic melanoma, is also accompanied by a high incidence of xerosis (22%). The drug inhibits MEK, an integral component of the Raf pathway, which is frequently mutated in melanoma. In addition to xerosis, rashes, including papulopustular eruptions involving the face and chest, are also common dAEs of this drug, described in 75% to 85% of patients.[141,154,155] MEK is downstream of EGFR in the EGFR-Ras-Raf-MEK-ERK signaling pathway.[156,157] The effector role of MEK in this pathway likely explains the overlap of dAEs for trametinib and EGFR inhibitors.

The VEGFRIs, axitinib, cabozantinib, sorafenib, and sunitinib, exhibited a >10% incidence of all-grade xerosis; pazopanib and regorafenib had lower rates of xerosis. These drugs target VEGFR, an essential modulator of angiogenesis, tumor growth and invasion, and wound repair of healthy skin.[158,159] The discrepancy in xerosis between the individual VEGFRIs may be explained by the low number of trials that met criteria for regorafenib and pazopanib. In addition, pazopanib is mostly eliminated in the feces, while the other VEGFRIs are eliminated renally.[160] Interestingly, there were no eligible trials reporting xerosis with bevacizumab, a monoclonal antibody to the VEGF molecule. The discrepancy suggests that xerosis is more likely with inhibition of the receptor kinases than general inhibition of the VEGF pathway. While the association between VEGFR inhibition and xerosis is not well defined, the inhibition of angiogenesis

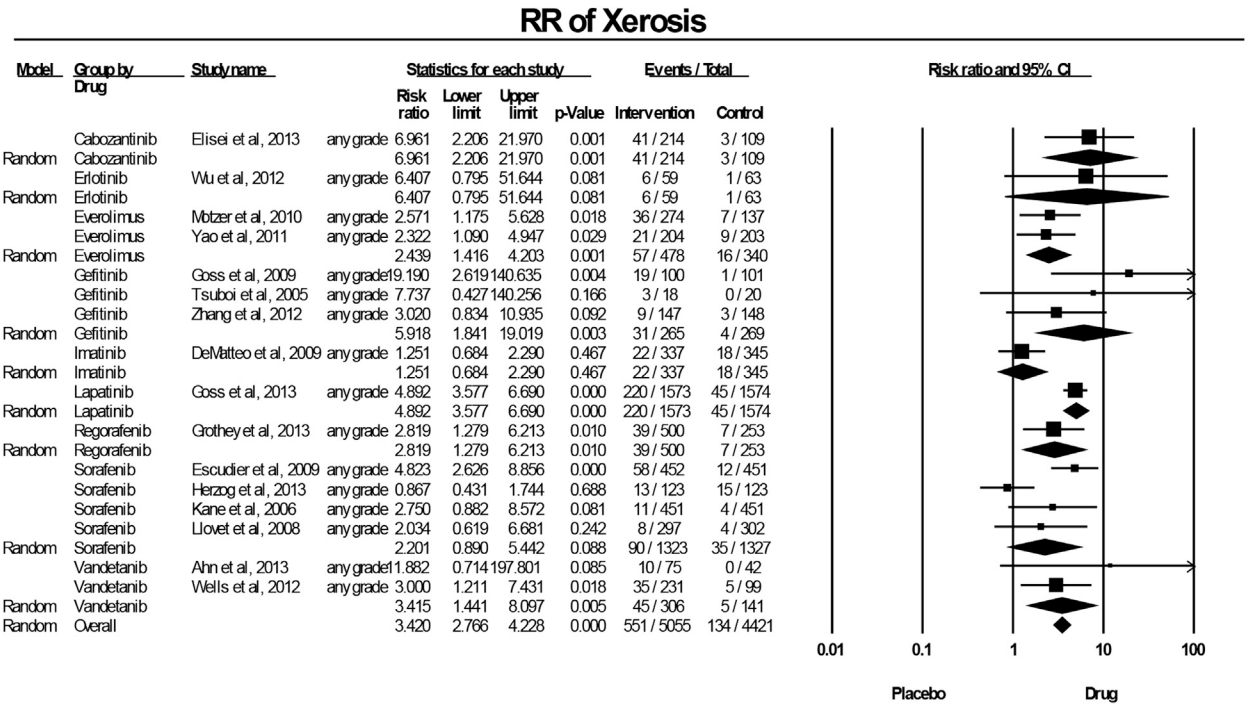

Fig 2. Relative risk (RR) of all-grade xerosis associated with targeted therapies compared to controls. The first author's name was used to represent each trial. Final combined results are shown numerically on the left and graphically as a forest plot on the right. *Squares* indicate the incidence in each trial; the *solid line* indicates the 95% confidence interval; and the *diamond* indicates the overall results of the included trials. The size of the squares represents the weight of the study.

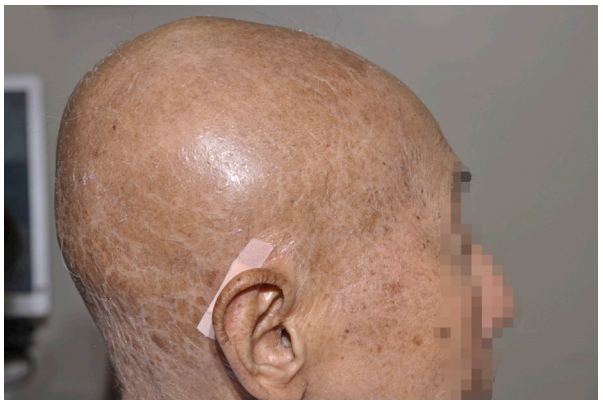

Fig 3. Grade 1 xerosis in a patient receiving erlotinib for non–small cell lung carcinoma.

may make the skin more susceptible to damage and impact overall skin health.

Aside from being a psychosocial concern, xerosis can be a precursor to more significant skin complications, such as infections, sensitization to allergens, and pruritus. Patients receiving anticancer therapies may be relatively immunosuppressed, and are therefore at greater risk of infection as a consequence of a dAE.[161] Untreated dry skin is often the precursor of pruritus and excoriated skin, perpetuating breakdown of the skin barrier.[12] Timely identification and treatment of xerosis may halt the evolution into more serious skin complications.

The successful management of xerosis begins with prevention. Skin care is essential for patients who begin a targeted therapy, and cancer patients who begin a gentle skin care regimen report improved QoL.[162] Providers should ensure that patients avoid hot showers, scrubbing, and products containing fragrances, alcohol, or elevated pH. Moisturization and barrier replacement are central to treatment. Agents containing urea have been shown to prevent TEWL, and salicylic acid preparations are helpful for their keratolytic, bacteriostatic,

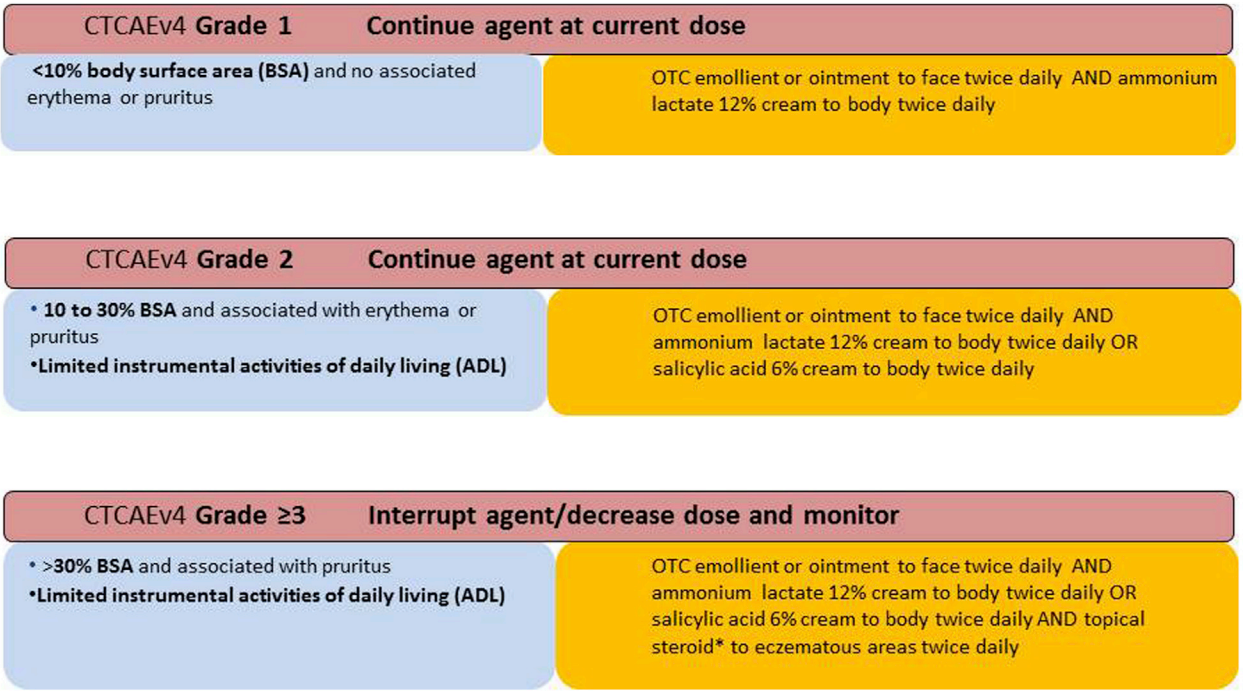

Fig 4. Treatment algorithm for xerosis associated with targeted agents. *CTCAEv4*, Common Terminology Criteria for Adverse Events, version 4.0; *OTC*, over-the-counter. *Hydrocortisone 2.5% ointment to the face and skin folds or triamcinolone 0.1% ointment to the rest of the body.

and fungicidal effects.[163] Finally, alpha-hydroxy acids thin out a thickened stratum corneum and are thought to increase ceramide production in the epidermis.[164,165] If pruritus occurs, patients should be reminded to avoid scratching to prevent the itch-scratch cycle, which further perpetuates dry skin. Previous recommendations for EGFRI-related xerosis include the use of potent topical steroids for xerosis greater than grade 1, and then lower potency steroids as symptoms improve.[166] The use of CTCAE grading can guide the provider toward appropriate treatment options (Fig 4).

Inconsistent reporting of xerosis across investigators/institutions was a limiting factor in our analysis. A number of studies clubbed all dAEs together in their safety data, while others grouped xerosis with rash, desquamation, or pruritus. Such disparity in reporting may decrease our ability to accurately assess the risk and prevalence of xerosis in patients who are undergoing targeted therapies. In addition, xerosis reported in clinical trials (performed in major institutions) may not reflect real-world scenarios. Finally, there is a possibility of sampling bias. There were 130 studies that met our criteria for analysis (see "Study selection" in "Methods" section for details); our estimates may therefore be an underrepresentation of the actual burden.

In conclusion, our results show that there is a significant risk of all-grade xerosis with targeted cancer agents. While xerosis was largely mild, this symptom may lead to patient distress. Additional research is needed to improve the understanding of the pathogenesis, prevention, and management of xerosis in the oncology setting. Improved awareness among oncologists and consistent reporting in forthcoming trials may prevent these shortcomings. With better comprehension of adverse events of anticancer therapies, dermatologic health is critical to ensure that cancer patients have an improved QoL and to avoid suboptimal dosing.

REFERENCES

1. Tiseo M, Loprevite M, Ardizzoni A. Epidermal growth factor receptor inhibitors: a new prospective in the treatment of lung cancer. *Curr Med Chem Anticancer Agents*. 2004;4:139-148.
2. Soreide K, Berg M, Skudal BS, Nedreboe BS. Advances in the understanding and treatment of colorectal cancer. *Discov Med*. 2011;12:393-404.
3. Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat Rev Cancer*. 2005;5:341-354.
4. Balagula Y, Lacouture ME, Cotliar JA. Dermatologic toxicities of targeted anticancer therapies. *J Support Oncol*. 2010;8:149-161.
5. Van Doorn R, Kirtschig G, Scheffer E, Stoof TJ, Giaccone G. Follicular and epidermal alterations in patients treated with ZD1839 (Iressa), an inhibitor of the epidermal growth factor receptor. *Br J Dermatol*. 2002;147:598-601.

6. Heidary N, Naik H, Burgin S. Chemotherapeutic agents and the skin: an update. *J Am Acad Dermatol*. 2008;58:545-570.
7. Joshi A, Ortiz S, Witherspoon J, et al. Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. *Cancer*. 2010;116:3916-3923.
8. Agero A, Dusza S, Benvenuto-Andrade C, Busam K, Myskowski P, Halpern A. Dermatologic side effects associated with the epidermal growth factor receptor inhibitors. *J Am Acad Dermatol*. 2006;55:657-670.
9. Lacouture ME, Lai S. The PRIDE (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to Epidermal growth factor receptor inhibitors) syndrome. *Br J Dermatol*. 2006;155:852-854.
10. Osio A, Mateus C, Soria JC, et al. Cutaneous side effects in patients on long-term treatment with epidermal growth factor receptor inhibitors. *Br J Dermatol*. 2009;161:515-521.
11. 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. *Am J Clin Dermatol*. 2013;14:327-333.
12. Ensslin C, Rosen A, Wu S, Lacouture ME. Pruritus in patients treated with targeted cancer therapies: systemic review and meta-analysis. *J Am Acad Dermatol*. 2013;69:708-720.
13. Gandhi M, Oishi K, Zubal B, Lacouture ME. Unanticipated toxicities from anticancer therapies: survivors' perspectives. *Support Care Cancer*. 2010;18:1461-1468.
14. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003;13:176-181.
15. Chen AP, Setser A, Anadkat MJ, et al. Grading of dermatologic adverse events of cancer treatments: the common terminology criteria for adverse events version 4.0. *J Am Acad Dermatol*. 2012;67:1025-1039.
16. Borenstein M, Hedges L, Higgins J, Rothstein H. *Comprehensive Meta-analysis, Version 2*. Englewood (NJ): Biostat; 2005
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
18. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;127:820-826.
19. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;3:3327-3334.
20. Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol*. 2012;13:539-548.
21. Querfeld C, Mehta N, Rosen ST, et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. *Leuk Lymphoma*. 2009;50:1969-1976.
22. Smith IE, Walsh G, Skene A, et al. A phase II placebo-controlled trial of neoadjuvant anastrozole alone or with gefitinib in early breast cancer. *J Clin Oncol*. 2007;25:3816-3822.
23. Rini BI, Wilding G, Hudes G, et al. Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27:4462-4468.
24. Rixe O, Bukowski RM, Michaelson MD, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. *Lancet Oncol*. 2007;8:975-984.
25. Govindan R, Crowley J, Schwartzberg L, et al. Phase II trial of bexarotene capsules in patients with advanced non-small-cell lung cancer after failure of two or more previous therapies. *J Clin Oncol*. 2006;24:4848-4854.
26. Querfeld C, Rosen ST, Guitart J, et al. Comparison of selective retinoic acid receptor- and retinoic X receptor-mediated efficacy, tolerance, and survival in cutaneous t-cell lymphoma. *J Am Acad Dermatol*. 2004;51:25-32.
27. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol*. 2013;31:3639-3646.
28. Ramalingam SS, Lee JW, Belani CP, et al. Cetuximab for the treatment of advanced bronchioloalveolar carcinoma (BAC): an Eastern Cooperative Oncology Group phase II study (ECOG 1504). *J Clin Oncol*. 2011;29:3419-3426.
29. Chan JA, Blaszkowsky LS, Enzinger PC, et al. A multicenter phase II trial of single-agent cetuximab in advanced esophageal and gastric adenocarcinoma. *Ann Oncol*. 2011;22:1367-1373.
30. Neal JW, Heist RS, Fidias P, et al. Cetuximab monotherapy in patients with advanced non-small cell lung cancer after prior epidermal growth factor receptor tyrosine kinase inhibitor therapy. *J Thorac Oncol*. 2010;5:1855-1858.
31. Locati LD, Bossi P, Perrone F, et al. Cetuximab in recurrent and/or metastatic salivary gland carcinomas: a phase II study. *Oral Oncol*. 2009;45:574-578.
32. Pessino A, Artale S, Sciallero S, et al. First-line single-agent cetuximab in patients with advanced colorectal cancer. *Ann Oncol*. 2008;19:711-716.
33. Zhu AX, Stuart K, Blaszkowsky LS, et al. Phase 2 study of cetuximab in patients with advanced hepatocellular carcinoma. *Cancer*. 2007;110:581-589.
34. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol*. 2007;25:2171-2177.
35. Motzer RJ, Amato R, Todd M, et al. Phase II trial of antiepidermal growth factor receptor antibody C225 in patients with advanced renal cell carcinoma. *Invest New Drugs*. 2003;21:99-101.
36. Wierzbicki R, Jonker DJ, Moore MJ, et al. A phase II, multicenter study of cetuximab monotherapy in patients with refractory metastatic colorectal carcinoma with absent epidermal growth factor receptor immunostaining. *Invest New Drugs*. 2011;29:167-174.
37. Yu EY, Wilding G, Posadas E, et al. Phase II study of dasatinib in patients with metastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2009;15:7421-7428.
38. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:514-523.
39. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer*. 2010;116:4256-4265.
40. Yao JC, Lombard-Bohas C, Baudin E, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol*. 2010;28:69-76.
41. Milowsky MI, Iyer G, Regazzi AM, et al. Phase II study of everolimus in metastatic urothelial cancer. *BJU Int*. 2013;112:462-470.

42. Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncol*. 2013;14:989-998.
43. Goto K, Nishio M, Yamamoto N, et al. A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC). *Lung Cancer*. 2013;82:109-114.
44. Groen HJ, Socinski MA, Grossi F, et al. A randomized, double-blind, phase II study of erlotinib with or without sunitinib for the second-line treatment of metastatic non-small-cell lung cancer (NSCLC). *Ann Oncol*. 2013;24: 2382-2389.
45. Yamada K, Takayama K, Kawakami S, et al. Phase II trial of erlotinib for Japanese patients with previously treated non-small-cell lung cancer harboring EGFR mutations: results of Lung Oncology Group in Kyushu (LOGiK0803). *Jpn J Clin Oncol*. 2013;43:629-635.
46. Ramalingam SS, Blackhall F, Krzakowski M, et al. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2012;30:3337-3344.
47. Schaake EE, Kappers I, Codrington HE, et al. Tumor response and toxicity of neoadjuvant erlotinib in patients with early-stage non-small-cell lung cancer. *J Clin Oncol*. 2012;30: 2731-2738.
48. Scagliotti GV, Krzakowski M, Szczesna A, et al. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non-small-cell lung cancer: a phase III trial. *J Clin Oncol*. 2012;30:2070-2078.
49. Wu YL, Kim JH, Park K, Zaatar A, Klingelschmitt G, Ng C. Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: a subanalysis of the phase III, randomized SATURN study. *Lung Cancer*. 2012; 77:339-345.
50. Ciuleanu T, Stelmakh L, Cicenas S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol*. 2012;13:300-308.
51. Sequist LV, von Pawel J, Garmey EG, et al. Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small-cell lung cancer. *J Clin Oncol*. 2011;29:3307-3315.
52. Kim ST, Uhm JE, Lee J, et al. Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. *Lung Cancer*. 2012;75:82-88.
53. Nagai H, Tanaka S, Niimi M, et al. Safety of erlotinib treatment in outpatients with previously treated non-small-cell lung cancer in Japan. *Int J Clin Oncol*. 2011;16:560-567.
54. Natale RB, Thongprasert S, Greco FA, et al. Phase III trial of vandetanib compared with erlotinib in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol*. 2011;29:1059-1066.
55. Pruthi RS, Nielsen M, Heathcote S, et al. A phase II trial of neoadjuvant erlotinib in patients with muscle-invasive bladder cancer undergoing radical cystectomy: clinical and pathological results. *BJU Int*. 2010;106:349-354.
56. Akerley W, Boucher KM, Bentz JS, Arbogast K, Walters T. A phase II study of erlotinib as initial treatment for patients with stage IIIB-IV non-small cell lung cancer. *J Thorac Oncol*. 2009;4:214-219.
57. Kubota K, Nishiwaki Y, Tamura T, et al. Efficacy and safety of erlotinib monotherapy for Japanese patients with advanced non-small cell lung cancer: a phase II study. *J Thorac Oncol*. 2008;3:1439-1445.
58. Oza AM, Eisenhauer EA, Elit L, et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. *J Clin Oncol*. 2008;26:4319-4325.
59. Dickler MN, Cobleigh MA, Miller KD, Klein PM, Winer EP. Efficacy and safety of erlotinib in patients with locally advanced or metastatic breast cancer. *Breast Cancer Res Treat*. 2009;115:115-121.
60. Thomas MB, Chadha R, Glover K, et al. Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. *Cancer*. 2007;110:1059-1067.
61. Garland LL, Rankin C, Gandara DR, et al. Phase II study of erlotinib in patients with malignant pleural mesothelioma: a Southwest Oncology Group Study. *J Clin Oncol*. 2007;25: 2406-2413.
62. Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. *J Clin Oncol*. 2007;25:760-766.
63. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib in patients with advanced biliary cancer. *J Clin Oncol*. 2006;24:3069-3074.
64. Gordon AN, Finkler N, Edwards RP, et al. Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. *Int J Gynecol Cancer*. 2005;15:785-792.
65. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol*. 2005;23:6657-6663.
66. Neal JW, Pennell NA, Goodgame BW, et al. A multicenter phase II trial of adjuvant erlotinib in patients with resected non-small cell lung cancer (NSCLC) and mutations in the epidermal growth factor receptor (EGFR): toxicity evaluation. *J Clin Oncol*. 2010;28:15s [abstr 7078].
67. Zhang L, Ma S, Song X, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. *Lancet Oncol*. 2012;13:466-475.
68. Grossi F, Rijavec E, Dal Bello MG, et al. The administration of gefitinib in patients with advanced non-small-cell lung cancer after the failure of erlotinib. *Cancer Chemother Pharmacol*. 2012;69:1407-1412.
69. Joensuu G, Joensuu T, Nupponen N, et al. A phase II trial of gefitinib in patients with rising PSA following radical prostatectomy or radiotherapy. *Acta Oncol*. 2012;51: 130-133.
70. Asami K, Koizumi T, Hirai K, et al. Gefitinib as first-line treatment in elderly epidermal growth factor receptor-mutated patients with advanced lung adenocarcinoma: results of a Nagano Lung Cancer Research Group study. *Clin Lung Cancer*. 2011;12:387-392.
71. Han JY, Lee SH, Yoo NJ, et al. A randomized phase II study of gefitinib plus simvastatin versus gefitinib alone in previously treated patients with advanced non-small cell lung cancer. *Clin Cancer Res*. 2011;17:1553-1560.

72. Kim DW, Lee SH, Lee JS, et al. A multicenter phase II study to evaluate the efficacy and safety of gefitinib as first-line treatment for Korean patients with advanced pulmonary adenocarcinoma harboring EGFR mutations. *Lung Cancer*. 2011;71:65-69.
73. Lee DH, Park K, Kim JH, et al. Randomized phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. *Clin Cancer Res*. 2010;16:1307-1314.
74. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11:121-128.
75. Lara-Guerra H, Waddell TK, Salvarrey MA, et al. Phase II study of preoperative gefitinib in clinical stage I non-small-cell lung cancer. *J Clin Oncol*. 2009;27:6229-6236.
76. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947-957.
77. Natale RB, Bodkin D, Govindan R, et al. Vandetanib versus gefitinib in patients with advanced non-small-cell lung cancer: results from a two-part, double-blind, randomized phase II study. *J Clin Oncol*. 2009;27:2523-2529.
78. Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol*. 2009;27:1864-1871.
79. Goss G, Ferry D, Wierzbicki R, et al. Randomized phase II study of gefitinib compared with placebo in chemotherapy-naive patients with advanced non-small-cell lung cancer and poor performance status. *J Clin Oncol*. 2009; 27:2253-2260.
80. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet*. 2008;372: 1809-1818.
81. Crinò L, Cappuzzo F, Zatloukal P, et al. Gefitinib versus vinorelbine in chemotherapy-naive elderly patients with advanced non-small-cell lung cancer (INVITE): a randomized, phase II study. *J Clin Oncol*. 2008;26:4253-4260.
82. Maruyama R, Nishiwaki Y, Tamura T, et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol*. 2008;26:4244-4252.
83. Tamura K, Okamoto I, Kashii T, et al. Multicentre prospective phase II trial of gefitinib for advanced non-small cell lung cancer with epidermal growth factor receptor mutations: results of the West Japan Thoracic Oncology Group trial (WJTOG0403). *Br J Cancer*. 2008;98:907-914.
84. Oshita F, Yamada K, Saito H, Noda K. Phase II study of nedaplatin and irinotecan followed by gefitinib for elderly patients with unresectable non-small cell lung cancer. *Cancer Chemother Pharmacol*. 2008;62:465-470.
85. Chen YM, Liu JM, Chou TY, Perng RP, Tsai CM, Whang-Peng J. Phase II randomized study of daily gefitinib treatment alone or with vinorelbine every 2 weeks in patients with adenocarcinoma of the lung who failed at least 2 regimens of chemotherapy. *Cancer*. 2007;109:1821-1828.
86. Asahina H, Yamazaki K, Kinoshita I, et al. A phase II trial of gefitinib as first-line therapy for advanced non-small cell lung cancer with epidermal growth factor receptor mutations. *Br J Cancer*. 2006;95:998-1004.
87. Niho S, Kubota K, Goto K, et al. First-line single agent treatment with gefitinib in patients with advanced non-small-cell lung cancer: a phase II study. *J Clin Oncol*. 2006;24:64-69.
88. Rothenberg ML, LaFleur B, Levy DE, et al. Randomized phase II trial of the clinical and biological effects of two dose levels of gefitinib in patients with recurrent colorectal adenocarcinoma. *J Clin Oncol*. 2005;23:9265-9274.
89. Tsuboi M, Kato H, Nagai K, et al. Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer. *Anticancer Drugs*. 2005;16:1123-1128.
90. Polychronis A, Sinnett HD, Hadjiminas D, et al. Preoperative gefitinib versus gefitinib and anastrozole in postmenopausal patients with oestrogen-receptor positive and epidermal-growth-factor-receptor-positive primary breast cancer: a double-blind placebo-controlled phase II randomised trial. *Lancet Oncol*. 2005;6:383-391.
91. Lee DH, Han JY, Lee HG, et al. Gefitinib as a first-line therapy of advanced or metastatic adenocarcinoma of the lung in never-smokers. *Clin Cancer Res*. 2005;11:3032-3037.
92. Canil CM, Moore MJ, Winquist E, et al. Randomized phase II study of two doses of gefitinib in hormone-refractory prostate cancer: a trial of the National Cancer Institute of Canada-Clinical Trials Group. *J Clin Oncol*. 2005;23:455-460.
93. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol*. 2003;21:2237-2246.
94. Cohen MH, Williams GA, Sridhara R, et al. United States Food and Drug Administration Drug Approval summary: Gefitinib (ZD1839; Iressa) tablets. *Clin Cancer Res*. 2004;10:1212-1218.
95. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;373: 1097-1104.
96. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA*. 2012;307: 1265-1272.
97. Carvajal RD, Antonescu CR, Wolchok JD, et al. KIT as a therapeutic target in metastatic melanoma. *JAMA*. 2011;305: 2327-2334.
98. Schlemmer M, Bauer S, Schütte R, et al. Activity and side effects of imatinib in patients with gastrointestinal stromal tumors: data from a German multicenter trial. *Eur J Med Res*. 2011;16:206-212.
99. Rao K, Goodin S, Levitt MJ, et al. A phase II trial of imatinib mesylate in patients with prostate specific antigen progression after local therapy for prostate cancer. *Prostate*. 2005;62: 115-122.
100. Agulnik M, Cohen EW, Cohen RB, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. *J Clin Oncol*. 2007;25:3978-3984.
101. Coombes RC, Tat T, Miller ML, et al. An open-label study of lapatinib in women with HER-2-negative early breast cancer: the lapatinib pre-surgical study (LPS study). *Ann Oncol*. 2013; 24:924-930.
102. Goss PE, Smith IE, O'Shaughnessy J, et al. Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2013;14: 88-96.
103. Toi M, Iwata H, Fujiwara Y, et al. Lapatinib monotherapy in patients with relapsed, advanced, or metastatic breast

cancer: efficacy, safety, and biomarker results from Japanese patients phase II studies. *Br J Cancer*. 2009;101:1676-1682.
104. Sridhar SS, Hotte SJ, Chin JL, et al. A multicenter phase II clinical trial of lapatinib (GW572016) in hormonally untreated advanced prostate cancer. *Am J Clin Oncol*. 2010;33:609-613.
105. Ross HJ, Blumenschein GR Jr, Aisner J, et al. Randomized phase II multicenter trial of two schedules of lapatinib as first- or second-line monotherapy in patients with advanced or metastatic non-small cell lung cancer. *Clin Cancer Res*. 2010; 16:1938-1949.
106. Whang YE, Armstrong AJ, Rathmell WK, et al. A phase II study of lapatinib, a dual EGFR and HER-2 tyrosine kinase inhibitor, in patients with castration-resistant prostate cancer. *Urol Oncol*. 2013;31:82-86.
107. Johnston S, Pippen J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol*. 2009;27:5538-5546.
108. Wadlow RC, Hezel AF, Abrams TA, et al. Panitumumab in patients with KRAS wild-type colorectal cancer after progression on cetuximab. *Oncologist*. 2012;17:14.
109. Muro K, Yoshino T, Doi T, et al. A phase 2 clinical trial of panitumumab monotherapy in Japanese patients with metastatic colorectal cancer. *Jpn J Clin Oncol*. 2009;39: 321-326.
110. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol*. 2007;25:1658-1664.
111. Bible KC, Suman VJ, Molina JR, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol*. 2010;11:962-972.
112. Iwamoto FM, Lamborn KR, Robins HI, et al. Phase II trial of pazopanib (GW786034), an oral multi-targeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North American Brain Tumor Consortium Study 06-02). *Neuro Oncol*. 2010;12:855-861.
113. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:303-312.
114. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*. 2013;14: 552-562.
115. Herzog TJ, Scambia G, Kim BG, et al. A randomized phase II trial of maintenance therapy with Sorafenib in front-line ovarian carcinoma. *Gynecol Oncol*. 2013;130:25-30.
116. Dingemans AM, Mellema WW, Groen HJ, et al. A phase II study of sorafenib in patients with platinum-pretreated, advanced (stage IIIb or IV) non-small cell lung cancer with a KRAS mutation. *Clin Cancer Res*. 2013;19:743-751.
117. Wakelee HA, Lee JW, Hanna NH, Traynor AM, Carbone DP, Schiller JH. A double-blind randomized discontinuation phase-II study of sorafenib (BAY 43-9006) in previously treated non-small-cell lung cancer patients: eastern cooperative oncology group study E2501. *J Thorac Oncol*. 2012;7: 1574-1582.
118. Lam ET, Ringel MD, Kloos RT, et al. Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. *J Clin Oncol*. 2010;28:2323-2330.
119. Pacey S, Ratain MJ, Flaherty KT, et al. Efficacy and safety of sorafenib in a subset of patients with advanced soft tissue sarcoma from a phase II randomized discontinuation trial. *Invest New Drugs*. 2011;29:481-488.
120. Bianchi G, Loibl S, Zamagni C, et al. Phase II multicenter, uncontrolled trial of sorafenib in patients with metastatic breast cancer. *Anticancer Drugs*. 2009;20:616-624.
121. Blumenschein GR Jr, Gatzemeier U, Fossella F, et al. Phase II, multicenter, uncontrolled trial of single-agent sorafenib in patients with relapsed or refractory, advanced non-small-cell lung cancer. *J Clin Oncol*. 2009;27:4274-4280.
122. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol*. 2009;27:3312-3318.
123. Kloos RT, Ringel MD, Knopp MV, et al. Phase II trial of sorafenib in metastatic thyroid cancer. *J Clin Oncol*. 2009;27: 1675-1684.
124. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27:1280-1289.
125. Moreno-Aspitia A, Morton RF, Hillman DW, et al. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. *J Clin Oncol*. 2009;27:11-15.
126. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008; 359:378-390.
127. Dahut WL, Scripture C, Posadas E, et al. A phase II clinical trial of sorafenib in androgen-independent prostate cancer. *Clin Cancer Res*. 2008;14:209-214.
128. Chi KN, Ellard SL, Hotte SJ, et al. A phase II study of sorafenib in patients with chemo-naive castration-resistant prostate cancer. *Ann Oncol*. 2008;19:746-751.
129. Elser C, Siu LL, Winquist E, et al. Phase II trial of sorafenib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or nasopharyngeal carcinoma. *J Clin Oncol*. 2007;25:3766-3773.
130. Kane RC, Farrell AT, Saber H, et al. Sorafenib for the treatment of advanced renal cell carcinoma. *Clin Cancer Res*. 2006;12: 7271-7278.
131. Strosberg JR, Weber JM, Choi J, et al. A phase II clinical trial of sunitinib following hepatic transarterial embolization for metastatic neuroendocrine tumors. *Ann Oncol*. 2012;23: 2335-2341.
132. Chau NG, Hotte SJ, Chen EX, et al. A phase II study of sunitinib in recurrent and/or metastatic adenoid cystic carcinoma (ACC) of the salivary glands: current progress and challenges in evaluating molecularly targeted agents in ACC. *Ann Oncol*. 2012;23:1562-1570.
133. Escudier B, Roigas J, Gillessen S, et al. Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27:4068-4075.
134. Faivre S, Raymond E, Boucher E, et al. Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicentre, phase II study. *Lancet Oncol*. 2009;10:794-800.
135. Zhu AX, Sahani DV, Duda DG, et al. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. *J Clin Oncol*. 2009; 27:3027-3035.

136. Socinski MA, Novello S, Brahmer JR, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. *J Clin Oncol*. 2008;26:650-656.
137. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356:115-124.
138. Kwitkowski VE, Prowell TM, Ibrahim A, et al. FDA approval summary: temsirolimus as treatment for advanced renal cell carcinoma. *Oncologist*. 2010;15:428-435.
139. Duran I, Kortmansky J, Singh D, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. *Br J Cancer*. 2006;95:1148-1154.
140. Oza AM, Elit L, Tsao MS, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol*. 2011;29:3278-3285.
141. Kim KB, Kefford R, Pavlick AC, et al. Phase II study of the MEK1/MEK2 inhibitor Trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. *J Clin Oncol*. 2013;31:482-489.
142. Ahn JS, Lee KH, Sun JM, et al. A randomized, phase II study of vandetanib maintenance for advanced or metastatic non-small-cell lung cancer following first-line platinum-doublet chemotherapy. *Lung Cancer*. 2013;82:455-460.
143. Wells SA Jr, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol*. 2012;30:134-141.
144. Kiura K, Nakagawa K, Shinkai T, et al. A randomized, double-blind, phase IIa dose-finding study of Vandetanib (ZD6474) in Japanese patients with non-small cell lung cancer. *J Thorac Oncol*. 2008;3:386-393.
145. Kirschbaum M, Frankel P, Popplewell L, et al. Phase II study of vorinostat for treatment of relapsed or refractory indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol*. 2011;29:1198-1203.
146. Giusti RM, Shastri KA, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: panitumumab (Vectibix). *Oncologist*. 2007;12:577-583.
147. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28:4697-4705.
148. Thaler J, Karthaus M, Mineur L, et al. Skin toxicity and quality of life in patients with metastatic colorectal cancer during first-line panitumumab plus FOLFIRI treatment in a single-arm phase II study. *BMC Cancer*. 2012;12:438.
149. Bergman H, Walton T, Del Bel R, et al. Managing skin toxicities related to panitumumab. *J Am Acad Dermatol*. 2014;71:754-759.
150. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer*. 2006;6:803-812.
151. Albanell J, Rojo F, Averbuch S, et al. Pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: histopathologic and molecular consequences of receptor inhibition. *J Clin Oncol*. 2002;20:110-124.
152. Lichtenberger BM, Gerber PA, Holcmann M, et al. Epidermal EGFR controls cutaneous host defense an prevents inflammation. *Sci Transl Med*. 2013;5:199ra111.
153. Sugawara T, Iwamoto N, Akashi M, et al. Tight junction dysfunction in the stratum granulosum leads to aberrant stratum corneum barrier function in claudin-1-deficient mice. *J Dermatol Sci*. 2013;70:12-18.
154. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367:107-114.
155. Anforth R, Liu M, Nguyen B, et al. Acneiform eruptions: a common cutaneous toxicity of the MEK inhibitor trametinib. *Australas J Dermatol*. 2014;55:250-254.
156. Lynch T, Kim E, Eaby B, Garey J, West D, Lacouture ME. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist*. 2007;12:610-621.
157. Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen activated protein kinase cascade for the treatment of cancer. *Oncogene*. 2007;26:3291-3310.
158. Folkman J. Role of angiogenesis in tumor growth and metastasis. *Semin Oncol*. 2002;29:15-18.
159. Brown LF, Yeo KT, Berse B, et al. Expression of vascular permeability factor (vascular endothelial growth factor) by epidermal keratinocytes during wound healing. *J Exp Med*. 1992;176:1375-1379.
160. Van Geel RM, Beijnen JH, Schellens JH. Concise drug review: pazopanib and axitinib. *Oncologist*. 2012;17:1081-1089.
161. Eilers R, Gandhi M, Patel J, et al. Dermatologic infections in cancer patients treated with epidermal growth factor receptor inhibitor therapy. *J Natl Cancer Inst*. 2010;102:47-53.
162. Zhang L, Zhou Q, Ma L, Wu Z, Wang Y. Meta-analysis of dermatological toxicities associated with sorafenib. *Clin Exp Dermatol*. 2011;36:344-350.
163. Lipster D, Kragballe K, Saurat JH. Other topical medications. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology*. 1st ed. Philadelphia (PA): Elsevier Limited; 2003. p. 2062.
164. Rawlings AV, Davies A, Carlomusto M, et al. Effect of lactic acid isomers on keratinocyte ceramide synthesis, stratum corneum lipid levels and stratum corneum barrier function. *Arch Dermatol Res*. 1996;288:383-390.
165. Van Scott EJ, Yu RJ. Hyperkeratinization, corneocyte cohesion, and alpha hydroxy acids. *J Am Acad Dermatol*. 1984;11:867-879.
166. Kiyohara Y, Yamazaki N, Kishi A. Erlotinib-related skin toxicities: treatment strategies in patients with metastatic non-small cell lung cancer. *J Am Acad Dermatol*. 2013;69:463-472.