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Literature Review: EGFR Inhibitor Therapy and Acneiform Rash

Tumour Team: Supportive Care

Cancer Care Alberta

Research Questions:

- What is the evidence for the relationship between rash and response to treatment in adult cancer patients treated with EGFR inhibitor therapy? Table 1
- What is the evidence for the prevention of rash associated with EGFR inhibitor therapy in adult cancer patients? Table 2
- What is the evidence for the management of rash associated with EGFR inhibitor therapy in adult cancer patients? Table 3
- What clinical practice guideline recommendations exist to guide the prevention and management of rash associated with EGFR inhibitor therapy? Table 4

Table 1: What is the evidence for the ***relationship between rash and response to treatment*** in adult cancer patients treated with EGFR inhibitor therapy?

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Methods	Outcomes
Liu, 2013	Systematic review and meta-analysis ***(Level I)***	NSCLS	Gefitinib, erlotinib	6798	Articles investigating association b/n rash and efficacy of EGFR-TKIs and prognosis of pts w NSCLC	• Identified 33 eligible trials (N=6,798) • Used 2 different standards 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] • 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 significantly longer than control group, and same results observed in subgroup analysis
Petrelli, 2013	Systematic review and metal-analysis ***(Level I)***	Advanced Colorectal	Cetuximab panitumumab	3833	Articles reporting correlation of skin rash w survival and/or response rate	• 14 publications (N=3,833) included in meta-analysis • Occurrence of skin toxicity represents predictive factor for survival (HR 0.51; p<0.00001) and progression (HR 0.58; p<0.00001) • Similarly, pts who developed moderate or severe rash had increased chance of response (35 vs 13%; RR 2.23, p<0.00001)
Petrelli, 2012	Literature-based meta-analysis ***(Level I)***	NSCLC	Erlotinib gefitinib	3312	Articles reporting correlation of skin rash w survival, progression and response rate	• Meta-analysis included 24 publications (17 prospective trials and 7 retrospective case series) • Skin rash found to be independent predictive factor for survival (HR: 0.30; p<0.00001) and progression (HR: 0.50; p<0.00001) • Pts who developed Gd2-4 rash more likely to respond to Tx vs pts w no rash (42% vs 7%) • Result for survival meta-analysis appears to be similar for gefitinib and erlotinib

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Methods	Outcomes
Rubovszky, 2018	Phase 2a, open-label, investigator-initiated, single-center ***(Level II)***	Advanced biliary tract	Cetuximab	57	Explore possible predictive factors: 3-wk. cycles w cetuximab (250 mg/m^2 /wk., loading dose: 400 mg/m^2), gemcitabine (1000 mg/m^2 on day 1 and 8), and capecitabine (1300 mg/m^2/day on days 1–14)	• ORR = 21% • Median PFS and OS = 34 (95% CI: 24–40) and 54 (43–67) wks., respectively • Most frequent AEs were skin toxicities • In univariate analysis performance status, previous stent implantation, thrombocyte count at start of therapy, early neutropenia and skin rash statistically significantly influenced ORR, PFS and/or OS • In multivariate Cox regression analysis, only normal thrombocyte count at Tx start and early acneiform rash independent markers of longer survival • In pts showing early skin rash compared to others median PFS was 39 vs. 13 wks. and median OS was 67 vs. 26 weeks, respectively
Aranda, 2012	Nonrandomized phase II open-label ***(Level II)***	Advanced/ metastatic pancreatic cancer	Erlotinib	153	Pts given gemcitabine (1000 mg/m^2/wk., 3 wks. q 4 wks.) + erlotinib (100 mg/day orally continuously) until disease progression/ unacceptable toxicity	• Pts = Gd≥2 rash, 25%; Gd<2 rash, 75% • OS longer in pts w Gd≥2 rash vs Gd<2 (11 vs 5 months; P<0.001) • PFS longer in pts w Gd≥2 rash vs Gd<2 (6 vs 3 months; P<0.001) and shorter in those w/o rash vs grade 1 (2 vs 4 months; P=0.005) or grade≥2 (2 vs 6 months; P<0.001) • Pts w Gd≥2 rash showed higher rates of overall response (21% vs 7%; P<0.05) and disease control (84% vs 43%; P<0.05) vs Gd<2
Fleming, 2012	Randomized phase II ***(Level II)***	Metastatic castration-resistant prostate	Cetuximab	115	Pts w progression after receiving docetaxel, randomized 2:1 to CMP or MP. Mitoxantrone 12 mg/m^2 IV on day 1, PO prednisone 10 mg qd in both arms, and cetuximab 250 mg/m^2 IV (400 mg/m^2 day 1, cycle 1) on days 1, 8, and 15 in CMP arm. Cycles repeated q 21 days. Radiologic Ax of disease and PSA occurred q 4 cycles	• N=75 in CMP and N=40 in MP arm: median TTP was 4.9 and 6.6 months, respectively; measurable disease response rate was 2% and 4%, PSA response rate 7.7% and 17.6%, and median survival 11.9 and 15.7 mos, respectively • Key Gd3-4 toxicities were neutropenia 44% and 25.6%, anemia 6.7% and 7.7%, thrombocytopenia 6.7% and 2.6%, and fatigue 8% in both arms • In unplanned exploratory analysis, median TTP w (n=24) and w/o rash (n=51) in CMP arm was 10.3 mos vs. 2.8 mos (P=0.004) • On multivariable analysis, rash significantly associated w TTP (HR=0.43; P=0.01)
Van Cutsem, 2012	Open-label, phase I/II RCT (EVEREST) ***(Level II)***	Metastatic colorectal	Cetuximab	157	After 21 days of standard-dose cetuximab (400 mg/m^2 initial dose, then 250 mg/m^2/ week) + irinotecan, patients with ≤ grade 1 skin	• Pharmacokinetic profiles reflected dose increase and predictable across dose range investigated • Weekly cetuximab doses of up to 500 mg/m^2 well tolerated, and grade 3 and 4 adverse events generally comparable b/n Tx groups • Dose escalation (n=44) associated w increase in skin reactions grade 2 compared w standard (n=45) dosing (59% vs 38%, respectively)

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					reactions randomly assigned to standard-dose (group A) or dose-escalated (to 500 mg/m^2/week; group B) cetuximab. Pts w grade 2 skin reactions continued on standard-dose cetuximab + irinotecan (group C)	• Dose escalation, compared w standard dosing, showed some evidence for improved response rate (30% vs 16%, respectively) and disease control rate (70% vs 58%, respectively) but no indication of benefit in relation to OS • In exploratory analysis, dose escalation seemed to increase response rate compared w standard dosing in pts w KRAS wild-type but not KRAS mutant tumors
Holch, 2020	Unplanned analysis of phase III FIRE-3 (AIO KRK0306) ***(Level III)***	Metastatic colorectal w *RAS*-WT tumors (i.e. wild-type in *KRAS* and *NRAS* exons 2–4)	Cetuximab	199	First-line FOLFIRI + cetuximab (FOLFIRI/Cet) vs FOLFIRI plus bevacizumab (FOLFIRI/Bev) Retrospective data on cetuximab-induced skin toxicity occurring during cycles 1–3 of Tx correlated w efficacy endpoints, including early tumour shrinkage To control for guarantee-time bias, only pts who completed ≥3 Tx cycles considered	• Of 199 pts treated wFOLFIRI/Cet, 181 (91.0%) completed ≥3 Tx cycles • Significant survival benefit of FOLFIRI/Cet over FOLFIRI/Bev only evident in pts developing cetuximab-induced skin toxicity grade 2–3 [41.0 vs 26.6 mos; HR=0.73; 95% CI: 0.61–0.87; P<0.001] compared w cetuximab-induced skin toxicity grade 0–1 (HR=0.90; 95% CI: 0.67–1.20; P=0.48) • Regarding prognosis, cetuximab-induced skin toxicity grade 2–3 (n=75; 41.4%), compared w cetuximab-induced skin toxicity grade 0–1 (*n*=106; 58.6%), associated w prolonged OS; HR=0.62; 95% CI: 0.42–0.91; *P*=0.01) • In multivariate analysis, both cetuximab-induced skin toxicity (HR=0.66; 95% CI: 0.50–0.87; P=0.003) and early tumour shrinkage (HR = 0.55; 95% CI: 0.41–0.74; P<0.0001) independently prognostic for OS • Absence of both cetuximab-induced skin toxicity grade ≥2 and early tumour shrinkage identified subgroup of pts w very poor prognosis (median OS 15.1 mos)
Sonnenblick, 2016	Unplanned analysis of phase III randomized trial ***(Level III)***	Breast	Lapatinib	1389	Pts w HER2+ early breast cancer randomized to adjuvant trastuzumab, lapatinib, their sequence, or their combination for 1 yr. Evaluated whether development of early lapatinib-related rash (i.e. w/n 6 wks.) associated w DFS and OS	• 3973/6098 lapatinib-treated pts (65.2%) included in analysis, of whom 1389 (35.0%) developed early rash • After median follow-up of 4.5 yrs., development of early rash associated w trend of improved DFS (multivariable: HR=0.87, 95% CI=0.73 to 1.03, P=0.10) and statistically significantly improved OS (multivariable: HR=0.63, 95% CI=0.48 to 0.82, P <0.001) compared w subjects w/o early rash • Compared w pts randomly assigned to trastuzumab (n=2051), pts randomly assigned to trastuzumab/lapatinib combination and developed early rash (n=692) had superior DFS (multivariable: HR=0.72, 95% CI=0.55 to 0.92, P=0.01) and OS (multivariable: HR=0.59, 95% CI=0.39 to 0.90, P=0.01) • Time-dependent analysis suggests occurrence of rash predictive of lapatinib benefit, both when given in combination or sequential to trastuzumab

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Sommeijer, 2014	Unplanned analysis of phase III randomized trial ***(Level III)***	Advanced colorectal	Cetuximab	198	Analysis of NCIC CTG/AGITG CO.17 performed by excluding pts who died/dropped out w/n 28 days and then grouping by worst grade of rash experienced by day 28. Multivariate Cox models conducted separately for pts w KRAS wild-type (n=117) and KRAS mutated tumours (n=81)	• Development of Gd≥2 rash on cetuximab associated w trend towards increased OS (HR 0.61 w 95% CI 0.36–1.02 and p=0.06) and PFS (HR 0.68 w 95% CI 0.45–1.03 and p=0.07) as compared to Gd0/1 rash in pts w wild-type tumours • In pts w wild-type tumours on cetuximab both Gd0/1 and Gd≥2 rash associated w increased PFS (HR 0.57 95% CI 0.38–0.86; p=0.008; and HR 0.32 95% CI 0.21–0.49; p<0.0001) respectively, in comparison w best supportive care • Only development of grade ≥2 rash on cetuximab associated w increased OS (HR 0.52 w 95% CI 0.34–0.80 and p=0.003) in comparison w best supportive care • No significant difference found in OS or PFS among pts on cetuximab w mutated tumours w either rash grade as compared to best supportive care • No consistent trend observed for association of severity of rash and QoL
Azim, 2013	Unplanned analysis of phase III randomized trial ***(Level III)***	Breast	Lapatinib	306	From NeoALLTO investigated frequency and time to develop each AE according to age (≤ 50 vs > 50) and association w pCR in logistic regression model adjusted for age, hormone receptors, tumour size, nodal status, planned breast surgery, completion of lapatinib admin, and Tx arm	• Only pts randomly assigned to arms A and C eligible (n=306) • Younger pts (≤ 50 years) experienced significantly more rash compared w older pts (74.4% vs 47.9%; P<0.0001) • Diarrhea and hepatic AEs observed in 78.8% and 41.2% of pts, respectively, w no differences in rate or severity or time of onset according to age • Early rash (i.e. before starting paclitaxel) independently associated w higher chance of pathologic complete response, mainly in pts > 50 yrs. (OR=3.76; 95% CI, 1.69 to 8.34) but not in those ≤ 50 yrs. (OR=0.92; 95% CI, 0.45 to 1.88; P for interaction=0.01) • No significant association observed b/n pathologic complete response and diarrhea or hepatic AEs
Fiala, 2013	Prospective ***(Level III)***	Advanced stage NSCLC (IIIB, IV) harboring wild-type EGFR and wild-type KRAS genes	Erlotinib	184	Observation of pts w rash (n=90) vs. no rash (n=92) at one month after beginning of Tx	• Median of PFS in pts who observed w rash during Tx was 3.0 vs 1.2 months in pts w no rash (p<0.001) • Median of OS in pts observed w rash during Tx was 13.9 vs 5.8 months in pts w no rash (p<0.001) • ORR in pts observed w rash during Tx was 17.4% vs 3.3% in pts w no rash (p=0.001) • Median of PFS after 1 month of Tx in pts who were observed w rash during 1st month was 2.9 vs 1.1 months in pts w no rash (p=0.027) • Median of OS after 1 month of Tx in pts observed w rash during 1st month was 13.8 vs 9.9 months in pts w no rash (p=0.082)
Parma, 2013	Phase II sub analysis ***(Level III)***	Breast	Labatinib	47	Tx-naïve pts w HER 2+ locally advanced breast cancer, treated w neoadjuvant	• 33 (67%) developed rash of any type, and 26 (55%) had acneiform rash • Of 26 evaluable pts w acneiform rash (55%), 19 (73%) responded to lapatinib and 7 (27%) did not • Of 21 evaluable pts w/o acneiform rash, 11 (67%) responded to Tx and 7 (33%) did not

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					lapatinib monotherapy for 6 wks.	• Thus, no association found b/n occurrence of acneiform rash and response to lapatinib monotherapy
Stintzing, 2013	Unplanned analysis of phase II (GERMAN AIO CRC) ***(Level III)***	Metastatic colorectal	Cetuximab	149	analyzed the value of Cet-ST for treatment efficacy in a randomized trial comparing cetuximab plus capecitabine/irinotecan to cetuximab plus capecitabine/oxaliplatin as first-line treatment of metastatic colorectal cancer analyzed the value of Cet-ST for treatment efficacy in a randomized trial comparing cetuximab plus capecitabine/irinotecan to cetuximab plus capecitabine/oxaliplatin as first-line treatment of metastatic colorectal cancer analyzed the value of Cet-ST for treatment efficacy in a randomized trial comparing cetuximab plus capecitabine/irinotecan to cetuximab plus capecitabine/oxaliplatin as first-line treatment of metastatic colorectal cancer analyzed the value of Cet-ST for treatment efficacy in a randomized trial comparing cetuximab plus capecitabine/irinotecan	• Outcome favoured pts w Gd2-3 cetuximab-induced skin toxicity w regard to ORR (62 vs 41%), PFS (7.8 vs 5.2 months) and OS (30.3 vs 18.0 months) • First-cycle rash observed in 66% of pts and corresponded w longer survival (30.7 vs 20.2 months, p=0.007) • Pts w/o cetuximab-induced skin toxicity had poor outcome (PFS, 1.9 months; OS, 11 months) • Correlation of cetuximab-induced skin toxicity w survival specifically evident in pts w KRAS codon-12-mutated tumours assumed to be cetuximab resistant • In multivariate analysis of pt characteristics, male gender and younger age significantly correlated w cetuximab-induced skin toxicity • Among molecular parameters, no significant correlation w cetuximab-induced skin toxicity found

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					to cetuximab plus capecitabine/oxaliplatin as first line treatment of metastatic colorectal cancer Analyzed value of cetuximab-induced skin toxicity for Tx efficacy in randomized trial comparing: 1) cetuximab + capecitabine/ irinotecan, n=78 2) cetuximab + capecitabine/ oxaliplatin as first-line Tx, n=71	
Gatzemeier, 2011	Subgroup analysis of phase III ***(Level III)***	NSCLC	Cetuximab	1058	Subgroup analysis of pts in FLEX study. Landmark analysis assessed if development of acne-like rash in first 21 days of Tx (first-cycle rash) associated w clinical outcome, on basis of pts in intention-to-treat population alive on day 21	• 518 pts in chemo + cetuximab group (290 of whom had first-cycle rash) and 540 pts in chemo alone group alive on day 21 • Pts in chemo + cetuximab group w first-cycle rash had significantly prolonged OS compared w pts in same Tx group w/o first-cycle rash (median 15.0 mos [95% CI 12.8-16.4] vs 8.8 mos [7.6-11.1]; HR 0.631 [0.515-0.774]; p<0.0001) • Corresponding significant associations also noted for PFS (median 5.4 mos [5.2-5.7] vs 4.3 mos [4.1-5.3]; HR 0.741 [0·607-0.905]; p=0.0031) and response (rate 44.8% [39.0-50.8] vs 32.0% [26.0-38.5]; odds ratio 1.703 [1.186-2.448]; p=0.0039) • OS for pts w/o first-cycle rash similar to that of pts that received chemo alone (median 8.8 mos [7.6-11.1] vs 10.3 mos [9.6-11.3]; HR 1·085 [0.910-1.293]; p=0.36) • Significant OS benefit for pts w first-cycle rash vs w/o seen in all histology subgroups: adenocarcinoma (median 16.9 mos, [14.1-20.6] vs 9.3 mos [7.7-13.2]; HR 0.614 [0.453-0.832]; p=0.0015), squamous-cell carcinoma (median 13.2 months [10.6-16.0] vs 8.1 months [6.7-12.6]; HR 0.659 [0.472-0.921]; p=0.014), and carcinomas of other histology (median 12.6 mos [9.2-16.4] vs 6.9 mos [5.2-11.0]; HR 0.616 [0.392-0.966]; p=0.033)
Wacker, 2007	Unplanned analysis of two phase III (NCIC CTG Study BR.21 and PA.3) ***(Level III)***	NSCLC (n=673) Pancreas (n=499)	Erlotinib	1172	OS, PFS, and tumor response compared b/n pts in rash-evaluable subset who did or did not develop rash	• Presence of rash strongly correlated w OS in both studies • In BR.21, these correlations increased w rash severity grade: grade 1 vs. no rash (HR, 0.41, P<0.001] and grade≥2 vs no rash (HR, 0.29, P<0.001) • Similar results observed for PFS • Disease control (complete response + partial response + stable disease) seemed to increase w presence and severity of rash • In Study PA.3, grade ≥2 rash (but not grade 1) strongly correlated w OS improvement: grade ≥2 vs no rash (HR, 0.47, P<0.001)

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						• Similarly, grade ≥2 rash strongly correlated w improvements in PFS and disease control
Bar-Ad, 2016	Retrospective ***(Level IV)***	Head neck	Cetuximab	602	Loading dose and ≥1 cetuximab dose concurrent w definitive chemoRT (70 Gy + cisplatin) (n=940) or postop chemoRT (60-66 Gy + docetaxel or cisplatin) (n=238)	• 383/602 pts (63.6%) developed Gd2-4 cetuximab rash • Pts manifesting Gd2-4 rash had younger age (P<0.001), fewer pack-yrs. smoking history (P<0.001), more likely to be males (P=0.04), and had p16-negative (P=0.04) oropharyngeal tumors (P=0.003) • In univariate analysis, Gd2-4 rash associated w better OS (HR 0.58, P<0.001) and PFS (HR 0.75, P=0.02), and reduced distant metastasis rate (HR 0.61, P=0.03), but not local-regional failure (HR 0.79, P=0.16) relative to Gd0-1 rash • In multivariable analysis, HRs for OS, PFS, distant metastasis, and local-regional failure, respectively, 0.68 (P=0.008), 0.85 (P=0.21), 0.64 (P=0.06), and 0.89 (P=0.48) • Gd≥2 rash associated w improved survival in p16-negative pts (HR 0.28 [95% CI 0.11-0.74]) but not in p16-positive pts (HR 1.10 [0.42-2.89]) (P=0.05 for interaction) • 25% of pts w Gd2-4 acute in-field radiation dermatitis experienced Gd2-4 late skin fibrosis, vs 14% of pts w Gd0-1 acute in-field radiation dermatitis (P=0.002)
Dascalu, 2015	Retrospective ***(Level IV)***	KRAS wild-type metastatic colorectal	Cetuximab Panitumumab	119	Describe patterns of use of oral antibiotics and steroid creams. Using Cox regression, relationship b/n prophylactic vs reactive rash mgmt. and OS characterized	• Rash occurred in >90% of pts, and reactive favored over prophylactic Tx (66 vs 34%) • Older pts and those w ECOG performance status 0/1 more likely to receive prophylactic creams (44 vs 20% for age <60, p=0.01) and oral antibiotics (62 vs 12% for ECOG ≥2, p=0.01), respectively • Median OS = 7.0 mos • Number of Tx cycles and OS similar in both prophylactic and reactive groups (both p>0.05) • In Cox regression, ECOG >2 correlated w worse survival (HR 22.01, 95% CI 5.25-92.30, p<0.01). However, survival outcomes similar b/n pts prescribed antibiotics prophylactically vs reactively (HR=1.10, 95 % CI 0.43-2.80, p=0.85), and steroid creams prophylactically vs reactively (HR=2.00, 95% CI 0.58-6.92, p=0.27)
Jaka, 2015	Retrospective ***(Level IV)***	Metastatic colorectal	Cetuximab Panitumumab	116	Retrospective study at single institute	• 81.9% of pts developed papulopustular rash • Pts who received most cycles of Tx w EGFR inhibitor were at highest risk of developing rash, and these pts also had most severe rash reactions (P=0.03) • All pts who exhibited complete tumor response had rash, and incidence of rash lower in pts w poor tumor response (P=0.03)
Stepanski, 2013	Retrospective ***(Level IV)***	Pancreatic	Erlotinib	174	Rash severity classified as High (moderate/severe), Low (absent/mild) based on medical record review. Kaplan-	• High Severity group (n=34) had longer median OS from landmark than Low Severity group (n=134; 7.58 mos vs 5.03 mos, P=0.0339) • Cox regression analysis (n=174) confirmed reduced risk of death w High Rash Severity (HR=0.67, P=0.0389) • PFS results showed similar pattern (median PFS 2.37 mos from landmark vs 2.04 mos for High vs Low Severity groups, P=0.0485)

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					Meier analysis assessed PFS and OS by rash status from landmark of 42 days after Tx initiation	

AE=adverse event; DFS=disease free survival; DSS=disease specific survival; Eastern Cooperative Oncology Group=ECOG; HR=hazard ratio; LRF=loco-regional failure; OR=odds ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PFS=prostate-specific antigen; RR=risk ratio; TTP= time to progression

Table 2: What is the evidence for the ***prevention*** of rash associated with EGFR inhibitor therapy in adult cancer patients?

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
Petrelli, 2016	Systematic review and meta-analysis ***(Level I)***	NSCLC, GI	Various agents	1073	Tetracycline, n=3 studies Doxycycline, n=4 studies Minocycline, n=6 studies	• 13 studies included in analysis (randomized and retrospective) • In 12 studies, pts in prophylactic antibiotic arms had lower risk of developing skin rash (OR 0.53, 95% CI 0.39–0.72, P<0.01) than pts w/o antibiotic prophylaxis • In particular, moderate-to-severe toxicities (Gd2–4) reduced by nearly 2/3rds (OR 0.36, 95% CI 0.22–0.60, P<0.01) in 13 studies. Translated to 26% absolute difference of high-grade skin rash compared w control arms (from 50% to 24%) • Results of meta-analysis show that risk of skin rash after Tx w anti-EGFR agents for solid tumours significantly lower in pts taking prophylaxis w antibiotics than in those who were not. Therefore, taking preemptive tetracyclines for several wks. at start of anti-EGFR Tx can significantly reduce incidence and severity of cutaneous acneiform rash
Bachet, 2012	Systematic review and meta-analysis ***(Level I)***	Colorectal, lung, others	Various agents	351	Doxycycline, n=2 studies Minocycline, n=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
Melosky, 2016	Randomized, phase III ***(Level I)***	Advanced NSCLC	Erlotinib	149	Minocycline (100 mg BID for 4 wks.) (n=49) Reactive Tx (after rash developed, per grade of rash) (n=50) No treatment unless severe (Gd3) (n=50)	• Overall incidence of rash (all grades) similar in all Tx groups, at 82% to 84%. No statistically significant difference observed in overall incidence of rash b/n Tx arm 1 and arms 2 and 3 combined (P 5.8769) • Incidence of Gd3 rash was significantly different between arms 1 (prophylactic) and 3 (control; 12% and 28%, respectively; P=0.0455) and b/n arms 2 (reactive) and 3 (control; 8% and 28%, respectively; P=0.0092) • Mean time to max. rash experienced (all grades) significantly longer in arm 1 at 17.4 days vs arms 2 (13.3 days) and 3 (12.0 days; P=0.0147). This was an exploratory analysis and was not specified in statistical analysis plan • For pts w max. severity of rash of Gd1, 2a, or 2b, median duration from onset of rash until resolution was 133.0 days in arm 1, 92.0 days in arm 2, and 98.0 days in arm 3

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						• For pts w max. severity of Gd3 rash, median duration from onset of rash until resolution was 201.0 days in arm 1, 76.0 days in arm 2, and 54.0 days in arm 3 • No pts in any arm that experienced rash had complete resolution to Gd0
Arrieta, 2015	Open-label, RCT ***(Level I)***	NSCLC	Afatinib	90	Tetracycline 250 mg q12 h for 4 wks (n=45) or nothing (n=45) Reactive Tx included general dermatological recommendations (e.g. skin moisturizers, sunscreen, topical steroids, according to toxicity severity)	• No differences found in clinical and dermatological baseline characteristics • Rash incidence of any grade, and Gd ≥2 less frequent in pre-emptive arm vs control arm (44.5 vs 75.6%, RR 0.4 [95% CI 0.17–0.99], p=0.046 and 15.6 vs 35.6%, RR 0.35 [95% CI, 0.12–0.91], p=0.030, respectively) • No difference found in paronychia, xerosis, mucositis, folliculitis, and skin fissure • No AE associated w tetracycline • Neither rash nor pre-emptive tetracycline impacted on response rate, PFS or OS
Jatoi, 2011	Randomized, double-blinded ***(Level I)***	Various cancer types	Various agents	65	Tetracycline 500 mg PO TID (n=33) for 28 days or placebo (n=32)	• Groups balanced on baseline characteristics • During 1st 4 wks., healthcare provider-reported data found that 27 tetracycline-treated pts (82%) and 24 placebo-exposed pts (75%) developed rash • Rash was Gd2+ in 17 (52%) and 14 (44%), respectively (p=0.62) • Comparable Gd2+ rash rates observed during wks. 5 through 8 as well as w pt-reported rash data throughout study period • QoL comparable across study arms, and tetracycline well tolerated
Jatoi, 2010	Double-blind RCT ***(Level I)***	Lung, GI, other	Erlotinib Cetuximab	110	Prophylactic sunscreen (SPF 60: 7.5% titanium dioxide + 7.5% zinc oxide) BID x 28 days, n=54 placebo cream BID x 28 days, n=56	• Physician-reported rash during 4 wks of Tx = 78% sunscreen group vs 80% placebo group (p=1.00) • No significant differences in rash rates over 4 additional wks. post-Tx
Jatoi, 2008	Phase III, double-blind RCT ***(Level I)***	Lung, GI, Other	Cetuximab Gefitinib Other	59	Tetracycline 500 mg BID PO x 28 days, n=30 Placebo, n=29	• N=16 tetracycline group vs N=22 placebo group developed rash (p=0.61) • Gd2 rash=17% tetracycline group vs.= 55% placebo group (p=0.009) at wk. 4 • Tetracycline group reported less itching, burning, stinging, and irritation compared w placebo group
Scope, 2007	Randmized, double-blind ***(Level I)***	GI	Cetuximab	48	Minocycline 100 mg daily + open-label 0.05% tazarotene cream	• At wk. 4, 20% of minocycline pts reported moderate to severe itch vs. 50% of placebo pts (p=0.05)

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
					BID to one side of face x 8 wks., n=24 Oral placebo daily + open-label 0.05% tazarotene cream BID to one side of face x 8 wks., n=24	• Significant overall difference in number of lesions b/n groups, in favour of minocycline group, at wks. 1, 2, and 4 (p=0.05, p=0.0025, p=0.008, respectively) • No differences in total facial lesion counts and subjectively assessed itch by wk. 8 • Cetuximab temporarily stopped due to Gd3 skin rash in N=4 in placebo group vs. none in minocycline group • Tazarotene had no clinical benefit and associated w significant irritation
Shacham Shmueli, 2019	Exploratory phase 2, randomized, double-blind clinical study ***(Level II)***	Metastatic colorectal	Cetuximab Panitumumab	20	BID topical FDX104 4% on one side of face and vehicle foam on other for 5 wks.) initiated 7 ± 3 days prior to EGFRI therapy	• Mean maximal rash grade lower w FDX104 4% vs vehicle, and fewer subjects developed moderate-to-severe (Gd2-3) rash • On Global Severity Score scale, statistically significant difference favored FDX104 4% over vehicle (P=0.047) • AEs (n=68) occurred in 20 subjects; most mild or moderate • Most common AEs were oral mucositis, nausea, and vomiting, common to chemo and EGFRI Tx • Study-drug-related AEs experienced by 5 subjects and consisted of mild, local skin reactions • No study-drug-related systemic side effects reported
Hofheinz, 2018	Double-blind, vehicle-controlled randomized phase II ***(Level II)***	Metastatic colorectal	Cetuximab	126	Doxyclyin + vehicle n=66 Doxycylin + vitamin K1 cream, n=60	• Incidence of skin rash Gd≥2 comparable b/n arms: 42 (63.6%) in vehicle group and 44 (73.3%) in vitamin K group (P=0.28) • Likewise, no difference seen in tripartite skin toxicity score (WoMo) w respect to percentage of skin affected. Mean values for WoMo score during skin Tx period were 18.0 (SD 13.05) for the vehicle and 18.0 (SD 13.37) for vitamin K • However, starting in wk 5 and increasing over time pts treated w vitamin K1 cream had less severe rash and fewer fissures • QoL as well as efficacy and compliance w study medication and anticancer Tx comparable in both arms
Belum, 2017	Prospective, randomized, double-blinded ***(Level II)***	Metastatic colorectal or HNSCC	Cetuximab	11	Pts randomized to: 1 mL of topical dapsone 5% gel (50 mg dapsone/g) to either right or left side of face and chest BID and moisturizer (Vanicream Lite Lotion) to contralateral side (control)	• Overall, 8/11 completed primary outcome evaluation time point • At day 28, avg. decrease in lesion counts b/n dapsone- and moisturizer treated sides of face was 30.5%; a 36.7% reduction in lesion counts observed on day 14 • 9/11 (82%) participants completed both questionnaires at baseline, 6/9 (66.7%) completed at day 14, and 4 of 8 (50%) completed at day 28 • Application-site AEs mild and included xerosis (n=5); burning (n=2); skin tightness, pain, or oiliness (n=1 each); and lacerations (n=1, unrelated) • Other AEs included metallic taste, dry palms, and fingertip fissures (n=1 each). • Overall but not statistically significant reduction in lesion counts observed on dapsone-treated sides, which is consistent w previous studies using oral antibiotics

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
					All pts received oral minocycline 100 mg QD	• Enrollment ended prematurely limiting power of study to observe statistically significant difference
Kripp, 2017	Multicenter, randomized, open-label phase II ***(Level II)***	(K)Ras-wildtype colorectal	Panitumumab	88	Standard arm: doxycycline 100 mg BID, n=40 Erythromycin ointment 2% followed by doxycycline in case of insufficient activity, n=39	• In erythromycin arm, 69% suffered from skin toxicity Gd ≥ 2 (95% CI: 52%-83%; primary endpoint) • In standard arm w doxycycline toxicity rate w Gd ≥ 2 amounted to 63% (95% CI: 47-78%). Thus, primary endpoint not met • Skin related and overall QoL comparable b/n arms
Deplanque, 2016	Open-label, randomized, prospective, phase II ***(Level II)***	NSCLC	Erlotinib	147	Erlotinib alone 150 mg/d PO (control arm), n=74 Erlotinib + doxycycline 100 mg/d (doxycycline arm), n=73	• Baseline characteristics of pts well balanced in intent-to-treat population • Folliculitis occurred in 71% of pts in doxycycline arm and 81% in control arm (*P*=0.175) • Severity of folliculitis and other skin lesions lower in doxycycline arm compared w control arm • Other AEs reported at similar frequency across arms • No significant difference in survival b/n Tx arms
Grande, 2013	Phase II ***(Level II)***	Metastatic colorectal and lung	Erlotinib Cetuximab Panitumumab	51	Oil-free skin moisturizer w sunscreen applied to face and neck BID after cleaning, skin moisturizer w salicylic acid and sulfur applied to back and chest QD at bedtime after cleaning, hand and feet cream w hyaluronic acid and phytosterols applied BID, and lymecycline 300 mg QD	• Metastatic colorectal (60.8%) and metastatic lung cancer (39.2%) • Anticancer drugs were erlotinib/cetuximab/panitumumab 20:30:1 • At 3-mo evaluation, 27.4% pts had =Gd2 skin toxicity • Skin toxicity not related w age (p=0.67), sex (p=0.65), previous chemo regimens (p=0.41), and current anti-EGFR Tx (p=0.22) • No GI or hematological toxicities related to lymecycline observed • Only 6 pts required further drugs • QoL analysis did not show significant difference from beginning and end of Tx
Lacouture, 2010	Phase II, open-label RCT ***(Level II)***	GI	Panitumumab	95	Daily skin moisturizer in AM + sunscreen before going outdoors + 1% topical	• Incidence of ≥Gd2 skin toxicities = 29% pre-emptive group vs 62% reactive group (OR= 0.3, 95% CI 0.1 to 0.6) • Gd2 skin toxicities = 23% pre-emptive group vs 40% reactive group • Gd3 skin toxicities = 6% pre-emptive group vs 21% reactive group • Median time to first occurrence of skin toxicities not reached in pre-emptive group vs 2.1 wks. (95% CI 2.1 to 6.3) in reactive group

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
					hydrocortisone cream in PM + doxycycline 100 mg BID x 6 wks., n=48 Reactive Tx: any treatments investigator deemed necessary for mgmt. of emergent skin toxicity; administered at any time during wks. 1-6; pts not prohibited from using moisturizer or sunscreen, n=47	• Panitumumab dose delays = 1% pre-emptive group vs 6% reactive group
Schimankski, 2017	National, multicenter, phase IV ***(Level IV)***	Various cancer types	Various agents	54	Reconval K1 ointment (0.1%) on face, chest, and fingers once QD + doxycycline 100 mg PO BID	• Recruitment started Q1 2011 and ended Q3 2013 due to slow accrual • Distribution of all exanthema grades (Rash and Dermatitis acneiform) was: Gd0 11.1%; Gd1 46.3%; Gd2 27.8%; Gd3 14.8% • An exanthema Gd2+ occurred in 42.6% • Exanthema of Gd4 not observed • Median time to occurrence of an exanthema Gd2+ was 4.0 wks. (95% CI 3.4–9.3) • Adherence to skin Tx protocol recommendations reduced exanthema to lower grades under continued anti-EGFR Tx up to last Tx: Gd0=48.1%; Gd1=38.9%; Gd2=13.0%; Gd3=0% • Paronychia Gd2+occurred in 22.2% of cases (Gd0=51.9%, Gd1=25.9%, Gd2=20.4%, Gd3=1.9%) w median time to onset of 15.4 wks. • Due to escalating protocol measures, paronychia at time of last pt exam had decreased to lower grades under continued anti-EGFR Tx: Gd0=83.4%; Gd1=14.8%; Gd2=1.9%; Gd3=0% • Skin fissures Gd2+occurred in 31.5% of cases (Gd0=24.1%; Gd1=44.4%; Gd2=29.6%; Gd3=1.9%; Gd4=0%) with a median time to onset of 19.9 weeks • Skin fissures at last Tx had decreased to lower grades under Tx: Gd0=69.5%; Gd1=27.8%; Gd2=3.7%; Gd3=0% • 4 pts (7%) had to prematurely stop anti-EGFR Tx due to toxicity. The incidence of Tx-related serious AEs was 8.0%
Shinohara, 2015	Retrospective ***(Level IV)***	Advanced pancreatic	Erlotinib	99	Efficacy of prophylactic vs	• Incidence rate of acneiform rash and xerosis of any grade during 1st 6 weeks of Tx significantly reduced in prophylactic minocycline group (n=44)

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
					deferred minocycline for skin toxicities Prophylactic group = 200 mg/day oral minocycline from day 1 of chemo and continued Deferred minocycline = 200 mg/day oral initiated after emergence of Gd2 or 3 skin toxicities	compared w deferred minocycline treatment group (n=52) (47.7 vs. 80.8%, p<0.001; 2.3 vs. 19.2%, p=0.01) • Multivariate analysis identified prophylactic minocycline as significant independent factor associated w incidence of acneiform rash and xerosis of any severity (OR 0.16, 95% CI 0.06-0.46, p<0.001; OR 0.11, 95% CI 0.01-0.90, p=0.04)
Yamada, 2015	Retrospective ***(Level IV)***	Metastatic colorectal	Panitumumab	38	Pts received oral minocycline (100 mg qd) + standard skin care using skin moisturizer for prevention and reactive topical steroid (pre-emptive group) or remedy (reactive group) of skin disorders Reactive topical steroid could be administered any time when investigator deemed necessary for mgmt. of emergent skin toxicity	• Occurrence of acneiform rash (grade ≥2) significantly lower in pre-emptive group (n=25) than in reactive group (n=13) (44.0% vs. 84.6%, p=0.04) • No significant differences in occurrence of other adverse events observed b/n groups • Tumor response not significantly different b/n groups (36.0% vs 7.7%, OR, 6.75; 95% CI=0.75-60.76, p=0.12 • Mean time to Tx failure was 149.7 days and 110.2 days in pre-emptive group and reactive Tx group, respectively (HR=0.58; 95% CI= 0.26-1.28, p=0.18)
Pinta, 2017	Case series ***(Level V)***	Metastatic colorectal	Cetuximab	41	Vigorskin cream w 0.1% vitamin K1 (phytomenadione), urea, Triticum volgare germ oil, hydrolyzed wheat protein,	• Application of cream well tolerated • No Gd4 rash reported • Proportion of Gd3 skin rash in 1st 8 wks. of Tx in this population was 15%, at lower limit of values reported in literature, and proportion of pts w Gd2 rash reduced (22.5%)

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
					ceramides-1, -3, and -6 II, and phytosphingosine applied BID in am and pm, on face and trunk after washing/taking bath and after shaving	

AE=adverse event; BID=twice a day; Gd=grade; NA=not applicable; NCI-CTCAE=National Cancer Institute's Common Terminology Criteria for Adverse Events; NR=not reported; NSCLC=non-small cell lung cancer, OR=odds ratio; OS=overall survival; PC=pancreatic cancer, QD, once a day; QoL=quality of life; TTP=time to progression

Table 3: What is the evidence for the ***management*** of rash associated with EGFR inhibitor therapy in adult cancer patients?

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
Kim, 2020	Placebo-controlled, double-blind, multicenter, pilot phase III ***(Level I)***	Pancreatic, NSCLC, Colorectal	Gefitinib Erlotinib, Afatinib, Cetuximab	80	Arm 1=placebo Arm 2=1 ppm of epidermal growth factor (EGF) ointment Arm 3=20 ppm of EGF ointment. Pts applied ointment to skin lesions BID	• Efficacy evaluation available for 80 pts • Responses were 44.4% in arm 1, 61.5% in arm 2, and 77.8% in arm 3 • Linear correlation b/n EGF concentrations and responses (p=0.012) • QoL assessed for 74 pts. Max changes in composite scores by Skindex-16 after Tx significantly different among arms (mean ± SD: -5.2 ± 8.6 for arm 1, -11.7 ± 14.2 for arm 2, and - 18.6 ± 17.7 for arm 3; p=0.008) • EGF arms showed significant improvement in emotions (p=0.005) and functioning (p=0.044) scores over placebo arm
Scope, 2009	Prospective, randomized trial ***(Level I)***	GI	Cetuximab	24	1% pimecrolimus cream BID to left side of face x 5 wks., n=12 1% pimecrolimus cream BID to right side of face x 5 wks., n=12	• Tx side had greater decreases in lesion counts than observation side of face at wk. 2 (p<0.001) & wk. 5 (p=0.02) • No significant difference in pts' Ax of symptoms or blind review of photographs for rash severity b/n Tx and observation sides • Authors concluded that pimecrolimus use did not translate into clinically meaningful benefit for pts
Eriksen, 2017	Double-blinded placebo-controlled phase II ***(Level II)***	Metastatic colorectal	Cetuximab	18	In each pt, vitamin K3 cream and placebo applied BID on 2 separate areas of skin of	• Application of vitamin K3 cream BID during Tx w cetuximab did not reduce number of papulopustular eruptions, and this was independent of use of systemic tetracycline; at wk. 4 (primary endpoint) = 6.1 (placebo) vs 6.3 (vitamin K3) • No significant changes in staining of EGFR or pEGFR observed in skin of vitamin K3-treated area compared to placebo area

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
					min. 10 × 10 cm for ≤ 2 mos	
Hwang, 2016	Open-label, non-comparative, multicentre, phase II ***(Level II)***	NSCLC Pancreatic	Erlotinib	46	EGF ointment (Daewoong Pharmaceuticals Co. Ltd.) containing 1 ppm of nepidermin evenly applied to skin lesions BID	• According to definition of effectiveness, EGF ointment effective in 36 (69.2%) intention to treat pts • Note: Effectiveness of ointment defined as: ○ (1) Gd2, 3, or 4 erlotinib-related skin effects (ERSEs) downgraded to ≤Gd1, or ○ (2) Gd3 or 4 ERSEs downgraded to Gd2 and persisted for ≥ 2 wks. • No statistically significant differences in effectiveness of EGF ointment by gender (p=0.465), age (p=0.547), tumor type (p=0.085), erlotinib dosage (p=0.117), and number of prior chemo sessions (p=0.547) • Grading for average NCI-CTCAE rating of rash/acne and itching improved from 2.02 ± 0.83 to 1.13 ± 0.89 and 1.52 ± 0.84 to 0.67 ± 0.90, respectively (p<0.001) • Most common reason for discontinuing study was cancer progression cancer (37%)
Tastekin, 2014	Open-labeled phase II ***(Level II)***	Metastatic colorectal	Cetuximab	15	Pts who developed Gd2 or 3 skin toxicity treated BID w soap made of oil extracted from Pistacia terebinthus	• 60% of pts (n=9) had Gd3 skin toxicity • Complete response rates in pts w Gd2 and Gd3 skin toxicities were 100 and 33%, respectively • In remaining pts w Gd3 toxicity, skin toxicity regressed to Gd1 • Objective response rate was 100%, and no delay, dose reduction or discontinuation of cetuximab Tx due to skin toxicity necessary • Skin toxicity reoccurred in all pts when pts stopped administering soap and therefore they used it throughout cetuximab Tx
Ke, 2017	1-group pretest-post-test design ***(Level III)***	Colorectal (n=19), breast (n=2), lung (n=4), multiple sites (n=5)	Cetuximab (n=24), Gefitinib (n=4),	30	Topical colloidal oatmeal lotion (COL) 3 to 5 times/day for 4 consecutive wks.	• Significant differences found b/n pretest and all post-tests after using COL w regard to severity, body surface area affected, and level of pruritus in participants who developed EGFRI-induced dermatologic toxicities (p<0.05) • No significant differences in demographics or disease characteristics on EGFRI-induced dermatologic toxicities
Santini, 2012	Single-group, prospective ***(Level III)***	Various cancer types	Various agents	45	Refractory pts: Aprepitant (125 mg on day 1; 80 mg on day 3; 80 mg on day 5) after ≥ 1 wk of standard systemic Tx, n=24 Naive pts: aprepitant given in same schedule as refractory pts, after first onset of	• Median visual analogue scale (VAS) in refractory group was 8.00 (95% CI 7.93-8.57) at baseline and 1.00 (0.00-2.00) after 1 wk of Tx aprepitant (p<0.0001) • In naive group, VAS score was 8.00 (7.43-8.37) at baseline and 0.00 (0.06-1.08) after 1 wk of Tx (p<0.0001) • 41 (91%) pts responded to aprepitant (i.e. had >50% reduction in intensity of pruritis) and pruritus recurred in only 6 (13%) pts • No AEs related to aprepitant occurred

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
					severe pruritus, n=21	
Yamazaki, 2016	Phase IV observational ***(Level IV)***	Recurrent/ advanced NSCLC	Erlotinib	9909	Topical steroids	• Rash occurred in 67.4% of pts; Gd1, 2, and 3 rash observed in 26.8%, 32.4%, and 7.2% of pts, respectively • Most common mgmt. strategy was topical steroids in 75.0% of pts w rash • Regardless of rash grade, earlier initiation of steroids resulted in quicker recovery • In those for whom topical steroids initiated >21 days after rash onset, median recovery time >100 days regardless of rash grade, compared w those treated before rash onset, whose median time to recovery was 35–51 days, depending on rash grade • Median time to recovery of rash in group initiated on medium-rank steroids then changed to strong-rank steroids was 47, 98, and 103 days for those w Gd1, 2, and 3 rash, respectively, compared w 39, 53, and 73 days median recovery for Gd 1, 2, and 3 rash, respectively, in pts initiated on strong-rank steroids
Gerber, 2012	Retrospective, uncontrolled, comparative study ***(Level IV)***	NR	Cetuximab Erlotinib	49	(1) Mometason furoate cream BID, n=21 (ERSS 10.3-77.9) (2) Nadifloxacin 1% cream (QD) + prednicarbate 0.25% cream (1x/d), n=23 (ERSS 12.5-67.1) (3) Nadifloxacin 1% cream (QD) + prednicarbate 0.25% cream (QD) + systemic isotretinoin (10-20 mg/d), n=5 (ERSS >50)	• (1) Mometason furoate cream: Ax of ERSS prior to therapy initiation and after 3 wks. revealed that mean rash severity improved significantly (P=0.00009) from 45.9-27.0 and demonstrated efficacy of our approach • (2) Nadifloxacin 1% cream + prednicarbate 0.25% cream: Ax of ERSS revealed that mean rash severity improved significantly (P=0.03) from 30.9-24.8 after 3 wks., demonstrating efficacy of our approach • (3) Nadifloxacin 1% cream + prednicarbate 0.25% cream + systemic isotretinoin (10 to 20 mg/day): severely affected pts significantly improved during isotretinoin Tx (P=0.015) and demonstrated on avg., reduction of ERSS from 59.2-43.8 after 3 wks., of therapy *ERSS = combined score of severity of 5 different aspects of EGFRI-rash (colour of erythema, distribution of erythema, papulation, pustulation and scaling/ crusts), combined w score based on extent of affected facial area and total body area involved. ERSSs range from 0 (no skin affection), 1 to 20 (mild), b/n 20 and 40 (moderate), up to scores >40 points, indicating severe cases
Wallner, 2016	Systematic review of all types of articles and research designs **(*Level V*)**	Various cancer types	Various agents	17 pubs.	Nursing mgmt. strategies for EGFRI-related cutaneous toxicities	• Nurses essential to mgmt. of EGFRI-related cutaneous toxicities and in ideal position to provide supportive care throughout course of EGFRI Tx • Aim of nursing mgmt. to maintain pts' Tx adherence and QoL by employing pre-emptive and proactive approach • Pt education = most frequently reported mgmt. strategy • Tx options and mgmt. strategies largely anecdotal and based on individual reports and expert opinions

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
						• Although no evidence-based mgmt. strategies exist, nurses can rely on existing Ax tools and guidelines to provide pts w symptom mgmt. and supportive care
Vaccaro, 2016	Uncontrolled, open-label follow-up ***(Level V)***	Metastatic colorectal	Cetuximab	12	Clindamycin phosphate 1.2%–benzoyl peroxide 5% gel once daily, at evening, for 8 wks.	• Significant clinical improvements occurred after 2 wks. of Tx and even more evident after 8 wks. (mean Skin-Score 20.54 ± 7.83, $p=1.37 \times 10^{-6}$ vs. second wk. visit, $p=1.26 \times 10^{-7}$ vs. before Tx) • Dermatology Life Quality Index values decreased from 13.64 ± 2.01 before Tx to 6.45 ± 1.37 after 8 wks. ($p=1.12 \times 10^{-5}$)
Katzer, 2010	Uncontrolled, open label follow-up ***(Level V)***	NR	Cetuximab	29	1% nadifloxacin cream once daily + 0.25% prednicarbate cream once daily x 6 weeks	• Most striking improvements seen after 1 wk. of Tx; additional significant decreases in Skin Score at wks. 2 & 6 • Significant improvement of subjective symptoms (pain, tenderness, pruritis)
Nicolaou, 2010	Prospective case series ***(Level V)***	Lung, HNC, GI	Erlotinib Cetuximab Panitumumab	20	1% pimecrolimus cream BID x 2-6 weeks Pts w Gd2 eruptions also received systemic minocycline 100mg daily	Gd1 pts: • 4/9=CR by wk. 2 • 4/9 = PR (>50%) by wk. 2 Gd2 pts: • 1/11=CR by wk. 2 5/11=PR (>50%) by wk. 2
Ocvirk, 2010	Prospective case series ***(Level V)***	GI	Cetuximab	30	0.1% vitamin K1 cream w urea BID Topical 1% clindamycin or erythromycin added for N=5 pts w Gd2 rash and N=2 pts w Gd3 rash Systemic antibiotics added for N=4 pts w Gd3 rash	• Median time to improvement=8 days • Median time to down-staging one grade=18 days • Decrease in cetuximab dose required for N=3/6 patients with Grade III rash
de Noronha e Menezes, 2009	Prospective case series ***(Level V)***	Lung, GI	Erolitib Cetuximab	19	Doxycycline 100mg/day + topical antibiotics + benzoyl peroxide, n=17	• 8/19=complete response by wk. 4 • 10/19=partial response by wk. 4 • 1/19=no response (pt w Gd3 eruptions; switched to low-dose isotretinoin, but died of disease complications)

Author, date	Study Design	Disease Site	EGFR Inhibitor(s)	N	Treatments or Comparisons	Outcomes
					Minocycline 100mg/day + topical antibiotics + benzoyl peroxide, n=2 All pts used sunscreen + mild skin cleanser + oatmeal cream daily	
Jacot, 2004	Retrospective case series ***(Level V)***	Lung, gyne, GI, head and neck	Gefitinib Cetuximab	29	Gefitinib-group: QD topical antiseptics (hexamidine, povidone iodine), fusidic acid cream, econazole cream, benzoyl peroxide gel, n=20 Cetuximab- group: daily fusidic acid cream, 4% erythromycin solution + betamethasone dipropionate cream, systemic fusidic acid, prophylactic 4% erythromycin emulsion + oral fusidic acid, n=9	• 11/20 in gefitinib-treated group and 6/9 in cetuximab-treated group developed skin toxicity • Topical benzoyl peroxide seemed to give partial improvement • Prophylactic 4% erythromycin solution associated w erythema in N=2 pts • No clear preventive or curative Tx identified in series

AE=adverse event; BID=twice a day; Gd=grade; NA=not applicable; NCI-CTCAE=National Cancer Institute's Common Terminology Criteria for Adverse Events; NR=not reported; NSCLC=non-small cell lung cancer, PC=pancreatic cancer, QD, once a day; QoL=quality of life

Table 4: What ***clinical practice guideline recommendations*** exist to guide the ***prevention and management*** of rash associated with EGFR inhibitor therapy?

Reference	Recommendations
UpToDate, Apr 2020	**Acneiform eruptions secondary to EGFR – Summary and Recommendations** • Acneiform (papulopustular) eruption is prototypical cutaneous adverse reaction to Tx w EGFR inhibitors. Occurs in >80% of pts and more frequent in older pts and in pts w light skin phototypes

Reference	Recommendations
	• Eruption develops mainly in areas rich in sebaceous glands (e.g. scalp, face, upper trunk) w/n 1st 2 wks. of therapy. Erythematous papules and pustules evolve to crusted lesions and eventually resolve leaving persistent erythema, telangiectasias, and skin dryness. Bacterial superinfection may occur • Diagnosis of acneiform eruption in pts receiving EGFR inhibitor therapy usually straightforward, based upon morphology and distribution of skin lesions (e.g. erythematous and follicular papules or pustules in areas rich in sebaceous glands w sparing of palmoplantar surfaces). Severity graded according to NCI CTCAE, version 5.0 • Suggest prophylactic oral tetracyclines in conjunction w topical corticosteroids for pts initiating Tx w EGFR inhibitors. Tx started on same day as EGFR inhibitor therapy. Typically use doxycycline 100 mg BID or minocycline 100 mg QD for 6-8 wks.; low-potency corticosteroids such as hydrocortisone 2.5% or alclometasone 0.05% cream applied BID • For pts w Gd1 rash, suggest topical corticosteroids w or w/o topical antibiotics. Use low potency topical corticosteroids BID for 4 wks. and clindamycin 1% gel BID for 4 wks. • For pts w Gd2 rash who are not taking prophylactic tetracyclines, suggest topical corticosteroids and oral tetracycline antibiotics. Use low potency topical corticosteroids BID for 4 wks. and either doxycycline 100 mg or minocycline 100 mg PO BID for 4 wks. First-generation oral cephalosporins (e.g. cephalexin, cefadroxil) or trimethoprim-sulfamethoxazole can be used as alternative antibiotics for pts taking prophylactic tetracyclines or do not benefit from tetracyclines • For pts w Gd≥3 rash not taking prophylactic tetracyclines, suggest Tx w oral tetracyclines plus short course of systemic corticosteroids in addition to EGFR inhibitor dose modification. Use either doxycycline 100 mg or minocycline 100 mg PO BID for ≥ 4 wks. and prednisone 0.5 mg/kg PO QD for 7 days. First-generation oral cephalosporins (e.g. cephalexin, cefadroxil) or trimethoprim-sulfamethoxazole can be used as alternative antibiotics for pts taking prophylactic tetracyclines or do not benefit from tetracyclines
BC Cancer, 2016	**Definition of rash (acneiform rash on face, scalp or chest):** erythema, edema, papulopustular eruptions followed by crusting and dryness of the skin. **Physical Ax** *Vital Signs* • Frequency – as clinically indicated *Skin Ax* • Ensure adequate light source and gloves if handling non-intact skin • Assess all aspect face, torso, arms, scalp, areas of cutaneous pressure/friction and intertriginous areas – Color Degree of erythema – patchy or uniformly deeply red and any signs of pallor in areas of intense erythema. Hyperpigmentation in non-white pts – Thickening Hyperkeratosis of soles of feet and palmar surfaces – Moisture Any accumulation of fluid under skin – Integrity Any presence and size of flaking, peeling, rash, ulcers and /or blisters – Desquamation Any associated bleeding – Swelling Degree of swelling – Sensory changes Tingling, numbness, pain, pruritus or burning **Symptom Ax** *Normal* • Refer to preTx nursing or oncology Ax *Onset*

Reference	Recommendations
	• When did changes start? • How are changes progressing? • When was your last Tx? *Provoking / Palliating* • What makes the symptoms better? Worse? *Quality* • What symptoms do you have? • When did symptoms begin? • Can you describe nature of symptom? *Region / Radiation* • Where are changes happening? Face, torso, arms, scalp? *Severity / Other Symptoms* • How bothersome is this to you? (0-10 scale, w 0 not at all – 10 being worst imaginable) • Have you been experiencing any other symptoms? Pruritus? Edema? Fever? - possible infection Discharge from pustules? – possible infection Persistent bleeding? – possible thrombocytopenia *Tx* • Strategies used to avoid irritants, heat, and mechanical irritation? • Using any creams or ointments? If so, what type? Effective? • Using any pain meds? If so, what type (topical, systemic)? Effective? • Any other meds or treatments? (e.g. Vitamin B6) *Understanding / Impact on You* • Are these symptoms affecting your daily life? *Value* • What is your comfort goal or acceptable level for this symptom (0 – 10 scale)? **Acneiform rash grading scale – Adapted from NCI CTCAE (Version 4.03)** **Normal** – normal skin **Grade 1 (mild)** - Papules and/or pustules covering **Grade 2 (moderate)** - Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated w symptoms of pruritus or tenderness; associated w psychosocial impact; limiting instrumental ADL **Grade 3 (severe)** - Papules and/or pustules covering >30% BSA, which may or may not be associated w symptoms of pruritus or tenderness; limiting self-care ADL; associated w local superinfection w oral antibiotics indicated **Grade 4 (life-threatening)** - 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

Reference	Recommendations
	***Step-Up Approach to Symptom Mgmt.: Interventions Should Be Based On Current Grade Level and Include Lower Level Grade Interventions As Appropriate** **NORMAL– GRADE 2** **NON – URGENT: Prevention, support, teaching & follow-up care as required** **Pt Care and Ax** • Screen for skin changes at first visit; re-assess at each visit and at peak times for onset (at q 2 wk. appt w Medical Oncology) • Timing of onset, appearance, distribution and skin changes varies with each type of treatment *Pt Self-Ax:* • Assess skin daily. Notify oncologist at next scheduled visit or earlier if symptoms worsen • Assess for early signs of acneiform rash including: - Redness, papulopustules - Tenderness of affected areas (often first sign) - Dry, furrowed skin that becomes reddened or darker (in non-Caucasian pts) **Skin Care and Hygiene** *Skin Care and Hygiene:* • In collaboration w physician or nurse practitioner, use of Topical Agents: Refer to Drug Specific Protocol • Wash and clean skin w lukewarm water; gently pat dry • Wash sweat from skin • Avoid hot water (e.g. while bathing, cleaning dishes) • Apply moisturizing creams or lotions (avoid alcohol and/or perfume-based creams, other recommendations). Apply on intact skin-liberally, gently, and often. • Avoid sun exposure during Tx-use sun block (see protocol specific handout for sun safety resources) *Prevent Constriction of Skin:* • Tight-fitting clothes or harsh fabrics in contact w torso, head and neck e.g. belts and jewelry • Tight bandages, dressings or adhesive tape to skin *Avoid Abrasive Conditions and Mechanical Stress:* • Avoid popping acne pustules, do not use abrasive chemicals (i.e. Benzoyl peroxide or alcohols) to rash-affected areas • Avoid topical anti-acne or anti-rosacea agents *Regulate Temperature:* • Avoid situations that raise body temp (e.g. steam, saunas, hot baths, heating pads, vigorous exercise) **Dietary Mgmt.** • Promote adequate hydration/nutrition during Tx to help prevent skin dryness/ desquamation • Recommend daily fluid intake of 8-12 cups (unless contraindicated) to help keep skin intact • Promote well-balanced and healthy diet (refer to Canada Food Guide) **Pharmacological Mgmt.** • For medical mgmt. of acneiform rash, refer to drug specific protocol and collaborate w Physician or Nurse Practitioner • Avoid using topical anesthetics or diphenhydramine containing creams during Tx as these may exacerbate skin toxicity • Avoid use of OTC acne meds and alcohol containing topical products

Reference	Recommendations
	Pt Education and Follow-up • Reinforce when to seek immediate medical attention: – Temp. ≥ to 38°C and/or presence of redness, discharge or odor from any open areas – possible infection – Unable to perform ADL – reflects deteriorating patient status and severity of acneiform rash – Uncontrolled or increasing pain/discomfort to rash areas • Instruct pt/family to call back if symptoms worsen or do not improve • If indicated, arrange for nurse-initiated telephone follow – up or physician follow-up for further Ax **GRADE 3** **URGENT: Requires medical attention w/n 24 h** **Patient Care and Assessment** • Collaborate w physician or nurse practitioner; temporary drug delay or further assessment • Arrange for further evaluation and Ax in ambulatory setting • Arrange for specific skin care and dressings as necessary • If superinfection concern, see practitioner w/n 24 h **Mgmt. of Skin Complications** *Pain:* • Anticipate need for pain mgmt.; systemic or topical analgesics and/or topical steroids *Local infection:* • Review recent lab tests, culture any suspect areas, assess temp • Review prescribed meds w pt and consider antibiotic Tx and/or topical steroids *Minor bleeding with trauma (stops after 2 mins):* • Review CBC and assess WBC, platelets and hemoglobin • Apply pressure to control bleeding • For prolonged bleeding, collaborate w physician or nurse practitioner for intervention *Alteration in skin integrity:* • May need to apply dressing to prevent infection to altered area, consider hydrocolloid dressings **Pt Education and Follow-Up** • Review correct technique and timing of application of prescribed skin care products • Instruct pt/family to call back if symptoms worsen or do not improve. Arrange for further Ax if indicated **GRADE 4 Presence of following: Temperature ≥ 38°C, uncontrolled pain** **EMERGENT: Requires IMMEDIATE medical attention** **Pt Care and Ax** • Notify physician or nurse practitioner immediately of Ax, facilitate care arrangements as necessary w local emergency dept of hospital and anticipate dose delay. See Chemotherapy Protocols in Resources & Referrals Section below for direction • Tx usually ordered to restart on incremental dose basis when symptoms resolve • Nursing Support: - Monitor vital signs as clinically indicated - Frequent skin assessments and dressings as indicated - Pain and symptom Ax and mgmt. as appropriate **Mgmt. of Skin Complications**

Reference	Recommendations
	Pain: • Increase dose and frequency (i.e. around the clock) of analgesics may be indicated *Local or systemic infection may require treating facility to perform following:* • Review recent lab tests • Culture: Blood and any suspect areas • Assess vital signs, temperature as clinically indicated • Administer topical and/or IV anti-infective medications as prescribed (e.g. antibiotics, antifungals, antiviral agents)
Pinto, 2016	**Mgmt. of Skin Reactions During Cetuximab Tx in Association w Chemo or RT Update of Italian Expert Recommendations** **General Prophylactic Measures** • Measures include both careful Ax of pt for presence of pre-existing dermatological diseases that could worsen consequences of exposure to anti-EGFR therapy, and early interventions aimed at reducing severity of adverse events. • Main skin conditions to be looked for before starting cetuximab Tx are psoriasis, acne vulgaris, rosacea, atopic dermatitis, severe xerosis, ichthyosis, and eczema. • Proactive interventions include wide range of measures intended to prevent or reduce intensity of dermatological adverse events. • Pts should be advised to: o avoid tight footwear; o avoid excessive pressure from clothes, such as shirts, sweaters, etc.; o avoid exposure to direct sunlight w/o protection; o avoid habits/products that can cause dry skin (e.g. hot water, alcohol-based cosmetics); o avoid excessive beard growth, shaving regularly using sharp multiblade razor, applying shaving cream beforehand, and emollients and moisturizing aftershave afterward; o avoid electric shavers and alcohol-based aftershave lotions; o avoid depilatory wax and plucking; o use sunscreens; o regularly use fluid, additive-free and alcohol-free creams and bath oils; o limit use of cosmetics; o remove any make-up w cleansing milk followed by lukewarm water; o cut moustaches and beards before shaving; o cut nails correctly. • Provision of exhaustive info crucial in helping pts to cope w skin reactions. Clear explanations should be provided at each phase of Tx and messages given should be regularly reinforced. **Strategies for Single Types of Skin Reaction** • Papulopustular Rash. CTCAEv4.0 contains different terms referring to skin rash. Classification differentiates b/n conditions on basis of presence/absence of local or systemic infections, impact on ADL, and whether or not they demand intensive Tx. • Grade 1 (G1): No dose modification or Tx interruption indicated. No specific treatments should be started, but adequate time should be devoted to recommending and explaining general measures, as previously outlined. • Grade 2 (G2): No dose modification or Tx interruption indicated. Topical antibiotic Tx should be administered BID until regression to G1. For scalp lesions, erythromycin or clindamycin lotion can be applied. Oral semisynthetic tetracyclines can be used for ≤4 weeks, while rash symptomatic. Medium potency (class III) topical corticosteroids in cream and lotion/foam form considered appropriate for skin and scalp lesions, respectively. Topical corticosteroid Tx should be short lasting, that is, up to 10 days (Fig 1). Oral corticosteroids potentially useful, but not always considered appropriate and safe for this grade of reaction (Fig 1).

Reference	Recommendations
	• Grade 3 (G3): Interrupt anti-EGFR Tx for ≤21 days, until regression to ≤G2 and resume according to Figure 2. Topical antibiotic and corticosteroid Tx, as for G2, considered potentially useful for skin lesions. However, agreement on their utility not as complete as for G2 reactions. Similar lack of agreement over use of topical erythromycin 3% lotion in G3 scalp lesions, whereas topical medium potency corticosteroids in lotion/foam form indicated. Oral antibiotics, as for G2, can be administered. In nonresponding, intensely symptomatic pts pustule culture should also be done, even when no signs of systemic infection. Pending results of antibiogram, in these pts failing to respond to oral semisynthetic tetracyclines, second-line oral antibiotic Tx can be considered together w short course of oral corticosteroids for up to 10 days. In pts w highly symptomatic/nonresponsive G3 lesions and no signs of systemic infection, oral retinoids considered to be of uncertain utility, due to insufficient experience w this Tx. Furthermore, fear of liver toxicity prevents widespread use. In contrast, analgesics considered useful option in this subgroup of pts (Fig. 3). • Grade 4 (G4): Interrupt anti-EGFR Tx immediately and definitively. An antibiogram culture of exudate mandatory and topical Tx should be administered as indicated for G2. IV antibiotic Tx should be started, to be confirmed or modified after antibiogram. IV betamethasone should be considered. Furthermore, these pts should be admitted to hospital **Vitamin K1 Cream** • Despite heterogeneity of available studies, results reported seem to show advantages to be derived from use of vitamin K1 in prophylaxis and Tx **Antibiotic Prophylaxis** • As most trials in prophylactic setting have been conducted in small groups, Italian experts unable to reach agreement on actual role of antibiotic prophylaxis. Main conclusion drawn was that use of pre-emptive antibiotics cannot be recommended routinely; however, as some pts can benefit clinically from Tx w tetracyclines, these can be offered on individual basis in attempt to reduce severity of rash and improve QoL. At present, both minocycline 100 mg/day and doxycycline 200 mg BID are widely used options.
Califano, 2015	**Mgmt. of skin adverse events in pts taking EGFR-TKIs (UK practice)** 1. Provide pt education about prevention and mgmt. of skin AEs before EGFR TKI Tx starts. Explain that rash is not acne. 2. Prevention: moisturize regularly; protect against excessive exposure to sunlight; use SPF 30 UVA and UVB protective sunscreen appropriately; use emollients or soap substitutes 3. Grade 1 toxicity: continue EGFR TKI at current dose; continue to moisturize regularly (check compliance and change emollient if necessary); consider topical antibiotics in alcohol-free formulation until resolved (may take 14 days before improvement); use recommended appropriate shampoos. 4. Grade 2 toxicity: continue EGFR TKI at current dose unless rash is prolonged or intolerable or there are other intolerable AEs (refer to Summary of Product Characteristics [SPC]); continue to moisturize regularly and intensify emollient use (check compliance again and advise about appropriate amount to use per week); apply short term topical steroids; continue topical antibiotics during and after oral antibiotic course (tetracycline 2 weeks); antihistamines can be considered (usually given at night for their potential sedative effect but be aware of impact on driving/using machinery). 5. Grade 3 toxicity: discontinue EGFR TKI and only reinstate (at reduced dose) when skin AE has resolved to Grade 2 (refer to SPC); manage as for Grade 2; oral antibiotics and topical steroids as appropriate: refer pt to dermatologist who specializes in drug related cutaneous AEs; investigate for cause(s) of infection. **Prevention of Rash** • To reduce risk of cutaneous AEs, pts should be advised to moisturize skin intensively and to protect skin from excessive exposure to sunshine. • Pts should use emollient several times day. Ointments generally more effective for dry, irritable rashes b/c they have hydrating effect by improving skin's lipid barrier. By contrast, water-based creams can further dry skin and very greasy emollients may increase risk of folliculitis • Although limited evidence that EGFR-TKIs trigger photosensitive reaction, encouraging pts to cover skin and to wear SPF 30 UVA/UVB non-occlusive sunscreen, especially in strong sunshine, is pragmatic approach • For personal hygiene, aqueous emollients and soap substitutes are less dehydrating for skin than normal soaps; shampoos that reduce risk of scalp folliculitis, e.g. ketoconazole, betadine and ceanel, should be recommended **Mgmt of Rash**

Reference	Recommendations
	• Pts w grade 1 rash should continue their EGFR-TKI therapy and apply emollient regularly • If there are signs of superadded infection, application of topical antibiotics in alcohol-free formulations, as recommended in local guidelines, should be considered for ≥14 days. • If rash has progressed to grade 2, EGFR-TKI can be continued at current dose as rash improves w/n 2 weeks in majority of cases. Dose reduction or interruption of EGFR-TKI might be appropriate if grade 2 rash prolonged or intolerable. Physicians should refer to current EGFR-TKI summary of product characteristics (SPC) for prescribing advice • If chronic grade 2 rash develops, dermatologist should be consulted as rash can have deleterious effect on pt's QOL. Moisturizing should be intensified and topical steroids (e.g. 1–2.5 % hydrocortisone or eumovate ointment to face; betnovate, elocon or dermovate ointment to body) can be applied on short-term basis (i.e. for 2–3 weeks), and then pt's condition should be reviewed. Topical antibiotics (as alcohol-free formulations), in accordance w local guidelines, and/or course of oral antibiotics (e.g. tetracycline C2 weeks) may be indicated. Oral antihistamines sometimes prescribed for pts w grade 2 itchy rash, but only limited proportion of pts derive symptomatic benefit. Pts should be advised about possible sedative effects of antihistamines on ability to drive or operate machinery • In case of grade 3 rash, EGFR-TKI therapy should be temporarily interrupted and treating physician should refer to current SPC for each EGFR-TKI for prescribing advice. We recommend restarting EGFR-TKI therapy only when rash has improved to grade B2. Dose reductions recommended in SPCs for erlotinib and afatinib, but not for gefitinib*. Not uncommon in clinical practice to restart gefitinib on alternate days but not recommended in SPC. Rash should be managed as recommended for grade 2 rash, w oral antibiotics and topical corticosteroids as appropriate and referral to dermatologist who specializes in drug-related cutaneous AEs. Any potential infection associated w rash should be identified and appropriately treated, as recommended in local guidelines. *Please note that SPC for gefitinib does not recommend dose reductions. SPC should be consulted for full information
Gutzmer, 2011	Advice for preventive skin care procedures for all patients receiving therapy with EGFR inhibitors Avoidance of frequent hand washing, daily, long showers or frequent, long baths • Use of mild bath or shower oils or syndets (no soap) • Use of moisturizers and/or urea-containing skin care products (ointment, cream) without fragrances or other skin irritants (no lotion or gel) • Avoidance of sun tanning parlors, consistent use of sun protection products (light protection factor > 20) and/or use of clothing with protection from UV radiation • Avoidance of skin contact with skin irritants such as solvents, disinfectants, polishes • Avoidance of activities which mechanically stress the skin (e. g. garden work, carrying heavy objects, hot hair drying) • Adequate treatment of pre-existing skin diseases (referral to dermatologist) • Adequate Tx of pre-existing skin disease (referral to dermatologist) Consensus recommendations on mgmt. of cutaneous side effects of EGFR inhibitors • Recommendations envision 3-step concept that ranges from general measures/preventive measures (step 1) over measures that can be performed by primary treating physician (step 2) up to advanced therapy by an experienced dermatologist (step 3). Recommendations step 1 and 2 are addressed to primary treating physician responsible for tumor therapy. Detailed recommendations for escalated therapy by specialized dermatologists (step 3) will be presented in a separate publication. Step 1: General measures/preventive measures • Before start of treatment, patient should be informed of various cutaneous side effects, usual time points of manifestation but also about positive correlation b/n early occurring papulopustular exanthems and therapy success and general measures should be discussed. Here pre-existing skin diseases such as rosacea or seborrheic dermatitis should be diagnosed and adequate therapy initiated, if needed. • No reliable recommendations can be made re. medicinal prophylaxis of EGFR-induced cutaneous lesions. Therapy of papulopustular exanthems on face and trunk.

Reference	Recommendations
	Step 2: Basic therapy (by primary treating physician) • At appearance of 1st papulopustular lesions, primary treating physician should initiate combined therapy w topical metronidazole- or nadifloxacin-containing ointment and systemic tetracycline (either doxycycline: 2 x 50 or 100 mg daily, minocycline: 2 x 50 mg daily or tetracycline: 2-4 x 250 mg daily) • In case of inadequate response, pts should be referred as quickly as possible to experienced dermatologist for advanced diagnostics and therapy
Lacouture, 2011	Papulopustular (acneiform) rash recommendations Preventive (wks. 1-6 and 8 or EGFRI initiation) • Topical ○ Recommended: hydrocortisone 1% cream w moisturizer and sunscreen BID ○ Not recommended: pimecrolimus 1% cream; tazarotene 0.05% cream; sunscreen as single agent • Systemic ○ Recommended: minocycline 100 mg daily; doxycycline 100 mg BID (note: doxycycline preferred in pts w renal impairment. Minocycline less photosensitizing) ○ Not recommended: tetracycline 500 mg BID Tx • Topical ○ Recommended: alclometasone 0.05% cream; fluocinonide 0.05% cream BID; clindamycin 1% ○ Not recommended: vitamin K1 cream • Systemic ○ Recommended: doxycycline 100 mg BID; minocycline 100 mg daily; isotretinoin at low doses (20-30 mg/d) ○ Not recommended: acitretin ○ Comment: photosensitizing agents
Pinto, 2011	Mgmt. of skin toxicity associated w cetuximab Tx in combination w chemo or RT Mgmt. of Gd1 skin rash • Skin lesions and symptoms – papules, pustules or symptom-free erythema • Cetuximab dose modifications – No • Topical Tx – No • Systemic Tx – No • intervention – General educational and prophylactic measures Mgmt. of Gd2 skin rash • Skin lesions and symptoms – Eruption w papules (Gd2A) or pustules (Gd2B) covering <50% of body surface, w moderate symptoms, and that does not interfere w daily activities • Cetuximab dose modifications – No • Topical Tx – Antibiotics: clindamycin 1% gel, erythromycin 3% gel/cream, metronidazole 0.75%-1% cream/gel, BID until regression to Gd1 (avoid benzoyl peroxide products). Lesions of scalp: erythromycin 2% lotion • Systemic Tx ○ Prevalence of papules (Gd2A) No ○ Prevalence of pustules (Gd2B): Antibiotics: minocycline 100 mg per os QD, doxycycline 100 mg per os QD for ≥4 wks. and until rash is symptomatic Mgmt. of Gd3 skin rash

Reference	Recommendations

	• Skin lesions and symptoms – Eruption w papules (Gd3A) or pustules (Gd3B) covering 50% of body surface; severe symptoms that interfere w daily activities
	• Cetuximab dose modifications
	  ○ First occurrence: delay cetuximab infusion for ≤21 days until skin rash improves to ≤Gd2. If improvement, continue at 250 mg/m^2. If no improvement, discontinue therapy
	  ○ Second occurrence: delay cetuximab infusion for ≤21 days until skin rash improves to ≤Gd2. If improvement, continue at reduced dose of 200 mg/m^2. If no improvement, discontinue therapy
	  ○ Third occurrence: delay cetuximab infusion for ≤21 days until skin rash improves to ≤Gd2. If improvement, continue at reduced dose of 150 mg/m^2. If no improvement, discontinue therapy
	  ○ Fourth occurrence: discontinue therapy definitively
	• Topical Tx – Antibiotics: clindamycin 1% gel, erythromycin 3% gel/cream, metronidazole 0.75–1% cream/gel, BID until regression to Gd1 (avoid benzoyl peroxide products). Lesions of scalp: erythromycin 2% lotion
	• Systemic Tx
	  ○ Antibiotics: minocycline 100 mg per os QD, doxycycline 100 mg per os QD for ≥4 wks. and until rash symptomatic
	  ○ Corticosteroids: methylprednisolone 0.4 mg/kg per os, prednisone 0.5 mg/ kg per os, for up to 10 days
	• Systemic Tx in highly symptomatic/nonresponsive pts
	  ○ Retinoids: isotretinoin 0.3–0.5 mg/kg per os
	  ○ Corticosteroids: methylprednisolone or dexamethasone IV
	  ○ Antihistamines: clorfenamine IM/IV
	  ○ Antibiotics: amoxicillin/clavulanic acid, gentamicin IV
	  ○ IV hydration
	
	Mgmt. of Gd4 skin rash
	• Skin lesions and symptoms – Generalized rash; severe symptoms that require emergency Tx
	• Cetuximab dose modifications – Discontinue therapy immediately and definitively
	• Topical Tx - Antibiotics: clindamycin 1% gel, erythromycin 3% gel/cream, metronidazole 0.75%–1% cream/gel, BID until regression to Gd1 (avoid benzoyl peroxide products). Lesions of scalp: erythromycin 2% lotion
	• Systemic Tx
	  ○ Retinoids: isotretinoin 0.3–0.5 mg/kg per os
	  ○ Corticosteroids: methylprednisolone, dexamethasone IV
	  ○ Antihistamines: clorfenamine IM/IV
	  ○ Antibiotics: amoxicillin/clavulanic acid, gentamicin IV
	  ○ IV hydration
	  ○ Hospitalization

Balagula, 2010	Gd0: • Prophylactic therapy w sunscreen (SPF ≥ 30); moisturizing creams; gentle skin care instructions given Gd1: • Continue chemo at current dose and monitor for change in severity • Treat w 2.5% hydrocortisone cream and 1% clindamycin gel daily • Reassess after 2 wks.: if reaction worsens or does not improve, proceed to mgmt. of Gd2 lesions Gd2: • Continue chemo at current dose and monitor for change in severity • Treat w 2.5% hydrocortisone cream and doxycycline 100mg daily or minocycline 100mg BID

Reference	Recommendations
	• Reassess after 2 wks.: if reaction worsens or does not improve, proceed to mgmt. of Gd3/4 lesions Gd 3/4: • Modify dose per package insert • Obtain bacterial/viral cultures if infection suspected • Continue Tx w 2.5% hydrocortisone cream and doxycycline 100mg daily or minocycline 100mg BID + prednisone 0.5mg/kg for 5 days • Reassess after 2 wks.: if reaction worsens or does not improve, dose interruption or discontinuation may be necessary

Potthoff, 2010
 	
German Expert Panel
	Mild (Gd1):
	• Continue EGFR inhibitor therapy; monitor for change in severity
	• Consider topical antibiotics (e.g.,2% clindamycin, 1% erythromycin cream, 0.75% metronidazole, 1% nadifloxacin)
	  ○ Isolated scattered lesions: cream preferred
	  ○ Multiple scattered areas: lotion preferred
	• Reassess after ≥ 2 wks. or at any worsening of symptoms; if worsening or no improvement, see recommendations for Gd2 toxicity; consider referral to dermatologist
	
	Moderate (Gd2):
	• Continue EGFR inhibitor therapy; monitor for change in severity
	• Skin-type-adjusted moisturizer
	• Topical Tx as per Gd1 + short-term topical steroid (e.g. 0.02% prednicarbate cream) + oral antibiotic for ≥ 2 wks.
	• Doxycycline 100mg BID or minocycline hydrochloride 100mg BID
	• Reassess after ≥ 2 wks. or at any worsening of symptoms; if worsening or no improvement, see recommendations for Gd3 toxicity; refer to dermatologist
	
	Severe (Gd3):
	• Reduce EGFR inhibitor dose as per label; monitor for change in severity
	• Skin-type-adjusted moisturizer
	• Topical and systemic Tx, as per Gd2
	• Refer to dermatologist
	• Consider oral isotretinoin (no combination w oral tetracyclines b/c of possible increase in intracranial pressure) or systemic steroids
	• Reassess after ≥2 wks. or at any worsening of symptoms; if worsening or no improvement, see recommendations for Gd4 toxicity
	
	Life-Threatening (Gd4):
	• Dose interruption or permanent discontinuation of EGFR inhibitor, as per label
	• Individual Tx concept
	• Systemic steroids are additionally recommended

Melosky, 2009 *Canadian Recommendations*	• Topical 2% clindamycin lotion BID recommended for mild-to-severe skin rash • Use of low- to medium-potency topical steroid such as 1% hydrocortisone lotion BID further enhances Tx of mild-to-severe rash by inhibiting inflammation • For moderate-to-severe skin toxicity, oral semisynthetic tetracycline antibiotics minocycline (100mg BID) or doxycycline (100mg QD or BID) recommended for min. of 4 wks. in addition to topical steroids • Overall, mgmt. of skin rash should be individualized for each pt, depending on type, severity, and location of skin toxicity caused by anti-EGFR therapy • Clinicians may wish to refer pt to dermatologist if skin toxicity does not improve w/n 1–2 wks. of Tx; referral also recommended if pt severely symptomatic (necrosis, blistering, or petechial or purpuric lesions), if multiple hair, nail, and skin issues emerge, or if skin toxicity has uncharacteristic appearance or distribution

Reference	Recommendations

Burtness, 2009
 	
NCCN Task Force Report
	• Topical steroids and antibiotics (e.g. clindamycin, erythromycin) may be useful for treating papulopustular skin rash
	  ○ Some task force members routinely use low-strength topical steroids on face, or medium-strength topical steroids on body, if pt symptomatic; however, based on expert preference and clinical experience rather than data from RCTs
	• Systemic therapy option for skin rash associated w EGFR inhibitors in certain settings, including severe rash, rash shown to be or looks infected, rash refractory to topical agents, and rash recurrent despite dose modification
	  ○ Prophylactic/mitigating treatments: tetracycline, minocycline, doxycycline
	  ○ Reactive treatments
	  ▪ Tetracyclines: minocycline, doxycycline, tetracycline
	  ▪ Retinoids: isotretinoin, acitretin
	  ○ Reactive treatment for infection
	  ▪ Importance of bacterial culture, esp. around nose, abscesses, pustules on body
	  ▪ Anti-staphylococcal antibiotics: cephalexin, dicloxacillin
	  ▪ Anti–methicillin-resistant staphylococcus aureus antibiotics: sulfamethoxazole/ trimethoprim, linezolid

Gridelli, 2008 *Italian Oncologists & Dermatologists Consensus Statement (erlotinib-specific)*	Gd1: • Topical Tx optional (sulfosalicylic creams, topical antibiotics) • No dose reduction or Tx interruption Gd2: • Topical Tx; if necessary, add systemic tetracyclines and steroids; systemic antihistamines to palliate pruritus • No dose reduction or Tx interruption • In cases of very distressing symptoms affecting QoL if no response to rash Tx, consider interruption of erlotinib Tx for 3–5 days and then re-start at full-dose; if AEs re-occur w/n15 days, consider dose reduction Gd3: • In addition to topical treatments, add systemic tetracyclines + systemic corticosteroids; antihistamines to palliate pruritus • At resolution, consider prevention w short courses of tetracyclines • If no resolution or recurrence, interrupt Tx until improvement to ≥Gd2; re-start erlotinib at 100mg daily Gd4: • interrupt definitive erlotinib therapy w/o trying dose-reduction • Refer to burn-wound unit for intensive care
Bianchini, 2008	Gd1: • Consider topical therapy w emollient cream or ointment (Diprobase cream, Dermol 500 lotion, Aveeno oatmeal cream) • No delay in EGFR inhibitor admin Gd2: • Continue w local therapy as for Gd1 • Start systemic antibiotic therapy w lymecycline 408mg QD x 6-8 wks. • If new lesions develop or steady, double the dose (BID) • If further new lesions develop or steady, continue lymecycline 408mg daily and add 1% clindamycin (nonalcoholic) lotion BID • If uncommon skin lesions occur, refer to dermatologist • No delay in EGFR inhibitor administration Gd3: • If already treated as per Gd2, add minocycline 100mg QD x 6-8 wks. + 1% clindamycin (nonalcoholic) lotion BID • If rash presented as Gd3 from beginning, start Tx as for Gd2 • If rash persists, refer to dermatologist • Dose reductions, as per package inserts, may be required Gd4: • Stop EGFR inhibitor Tx; refer urgently to dermatologist

Reference	Recommendations
	General Measures: • Bath or shower w oil instead of soap. Use lukewarm water • Avoid sun exposure and use good sunscreen • Nail hygiene, nail manicure and pedicure, nail polish to harden nails • Avoid friction and pressure on nail fold by wearing wide shoes; use antiseptic bath • Remove make up w hypoallergenic liquid cleanser • Avoid alcoholic lotions or gels

Eaby, 2008; Lynch, 2007
 	
US Interdisciplinary HER1/EGFR-Inhibitor Dermatologic Toxicity Forum
	General Measures:
	• Employ proactive approach in managing skin reactions
	• Suggest pts use thick, alcohol-free emollient cream
	• Suggest pts use sunscreen of ≥SPF 15, preferably containing zinc oxide or titanium dioxide
	• If pt presents w rash, verify appropriate admin and follow algorithm below in stepwise manner:
	Mild:
	• Continue EGFR inhibitor at current dose and monitor for change in severity
	• No Tx or topical 1% hydrocortisone 1% or 2.5% cream and/or 1% clindamycin gel
	• Reassess after 2 wks.; if reactions worsen or do not improve, proceed to next step
	Moderate:
	• Continue EGFR inhibitor at current dose and monitor for change in severity; continue Tx of skin reaction w following:
	  ○ 2.5% hydrocortisone cream or 1% clindamycin gel or 1% pimecrolimus cream PLUS doxycycline 100mg BID or minocycline 100mg BID
	• Reassess after 2 wks.; if reactions worsen or do not improve, proceed to next step
	Severe:
	• Reduce EGFR-inhibitor dose as per label and monitor for change in severity; continue Tx of skin reaction w following:
	  ○ 2.5% hydrocortisone cream or 1% clindamycin gel or 1% pimecrolimus cream + doxycycline 100mg BID or minocycline 100mg BID plus medrol dose pack
	  ○ Reassess after 2 wks.; if reactions worsen, dose interruption or discontinuation may be necessary

Lacouture, 2006
 	
SERIES Clinic, Chicago
	Mild/Moderate:
	• Doxycycline or minocycline 50mg BID + topical pimecrolimus BID and reassess at 2 wks.
	  ○ If improvement, continue and reassess q 2-4 wks.
	  ○ If no improvement/worsening of symptoms, increase dose of doxycycline or minocycline and continue pimecrolimus; reassess in 2-4 wks.
	Severe:
	• Doxycycline or minocycline 100mg BID + topical pimecrolimus BID and reassess at 2 wks.
	  ○ If improvement, continue and reassess q 2-4 wks.
	  ○ If no improvement/worsening of symptoms, add oral steroids (prednisone or methylprednisolone); reassess q 2-4 wks.
	  ○ If no improvement w oral steroids, consider reduction or interruption of EGFR inhibitor
	• Add moisturizers, lactic acid, and/or antihistamines, as appropriate

Rhee, 2005 *MD Anderson Cancer Center*	Gd1: • Clindamycin gel for isolated scattered lesions, or • Clindamycin lotion for multiple scattered areas Gd2: • Minocycline hydrochloride 200mg BID on day 1, then 100mg BID, or • Trimethoprim/ sulfamethoxazole BID Gd3: • Minocycline hydrochloride 200mg BID on day 1, then 100mg BID, or • Trimethoprim/ sulfamethoxazole BID

Reference	Recommendations
Segaert & van Cutsem, 2005	Gd1: • No Tx or Tx w topical anti-acne or anti-rosacea agents w anti-inflammatory properties can be started (e.g. metronidazole gel or cream, erythromycin or clindamycin gel or lotion, benzoyl peroxide gel or cream on face or salicylic acid in alcoholic lotion on chest/back) • When acneiform eruption fading or becoming scaly, switch topical Tx to cream bases instead of alcoholic lotions/ gels Gd2: • Topical Tx as for Gd1 can be used together w topical menthol cream or oral antihistamine (cetirizine, loratadine, hydroxyzine) when itch present and oral tetracycline (minocycline 100mg daily or lymecycline 300mg daily or doxycycline 100mg daily) Gd3: • Delay of therapy w EGFR inhibitors should be taken into consideration • In addition to aforementioned topicals, compresses w physiologic solution can be applied in case of acute inflammation • Oral antihistamines and oral tetracyclines at high (maximal anti-inflammatory) doses (minocycline 100mg BID or lymecycline 300mg BID or doxycycline 100mg BID complete Tx; dose can be tapered as soon as acute inflammation has faded Gd4: • Should be treated in specialized burn care units and EGFR inhibitors should be immediately stopped

BID=twice a day; CTCAE=Common Terminology Criteria for Adverse Events; HER=human epidermal growth factor; NCCN=National Comprehensive Cancer Network; NCI=National Cancer Institute; QD=once daily; SPF=sun protection factor

Appendix A: Levels of Evidence

- Level I – evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias or meta-analyses of RCTs without heterogeneity
- Level II – small RCTs, large RCTs with potential bias, meta-analyses including such trials, or RCTs with heterogeneity
- Level III – prospective cohort studies
- Level IV – retrospective cohort studies or case-control studies
- Level V – studies without a control group, case reports, or expert opinions