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# Use of Pre-emptive Vs. Reactive Management Strategies for Skin Toxicities Among mCRC Patients Treated with Panitumumab in the US

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**Abstract:** Background: The study aimed to assess oncologist's opinions and perceptions regarding the management of dermatologic toxicity among the patients they treat with panitumumab, with specific emphasis on the timing of rash management. Methods: A survey was developed in September 2016 based on the current literature and expert opinions regarding the management of dermatologic toxicities. Eligible oncologists were board certified and had treated at least five new or continuing patients with mCRC in the last three months, with at least three patients who received or were currently receiving panitumumab. Pre-emptive treaters were defined as those who reported treating≥50% of their panitumumab-treated patients prior to the onset of rash. The remaining oncologists were categorized as reactive treaters. Results: Among the 250 oncologists who completed the survey, 139 (56%) participants were categorized as pre-emptive treaters. A higher proportion of pre-emptive treaters than reactive treaters recommended every one of the specific management strategies that were assessed in the survey, including: skin moisturizer (78% vs. 58%; p<0.001), sunscreen (75% vs. 57%; p=0.002), over-the-counter (OTC) topical steroids (42% vs. 37%; p=0.27), prescription strength topical steroids (30% vs 30%; p=0.95), topical antibiotics (37% vs. 26%; p=0.001), oral antibiotics (39% vs. 26%; 0.006), and UV protective garments (61% vs. 47%; p=0.008). Conclusions: Our results clearly illustrate the urgent need for heightened education among oncologists who treat mCRC patients with panitumumab. Several management strategies, such as moisturizer, sunscreen, and UV protective garments, are easily implemented and should be recommended to 100% of mCRC patients who receive panitumumab.

**Keywords:** Anti-EGFR, Panitumumab, Dermatologic Toxicity, Anceniform Rash, Metastatic Colorectal Cancer (mCRC)

## 1. Introduction

Metastatic colorectal cancer (mCRC) is a grave illness that is confirmed in approximately 20%-25% of patients at the time of their colorectal cancer (CRC) diagnosis in the United States (U.S.). Of the remaining CRC patients, as many as 50% will eventually develop mCRC during the course of their disease. During the last decade, improvements in the treatment of mCRC patients have increased median survival time from 12 months to more than 30 months, and there is evidence of survival increasing to more than 40 months. [1-5] Therapies that target the epidermal growth factor receptor (EGFR), namely panitumumab (Vectibix, Amgen Inc) and

cetuximab (Erbitux) are among the treatments contributing to this increased survival. [6]

EGFR-Inhibitors are associated with both acute (early) and chronic (later) skin toxicities. Acneiform rash is the most common form of acute dermatologic toxicity. The acneiform rash occurs in approximately 75-85% of patients who are treated with an anti-EGFR and is usually grade 1-2, with 15-20% of patients experiencing grade 3 or higher acute toxicity. [7-9] The rash typically occurs early in the course of panitumumab therapy. The rash is associated with pruritus and pain, which can impair quality of life, and may result in dose reduction or treatment cessation in approximately one third of patients [7, 9, 10].

There are currently no clinical standards for the management of dermatologic toxicities for mCRC patients who are treated with panitumumab. Clinical trial data suggests that select pre-emptive management strategies can reduce the incidence of rash. Specifically, the Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) and the Japan Skin Toxicity Evaluation Protocol with Panitumumab (J-STEPP) studies were open-label, randomized trials designed and implemented to evaluate differences in pre-emptive versus reactive management of panitumumab-associated dermatologic toxicities among patients with mCRC. [11, 12] The pre-emptive skin treatment regimen began one day before the first panitumumab dose and continued through weeks one to six. The regimen consisted of skin moisturizer, sunscreen, 1% hydrocortisone cream and doxycycline 100mg twice per day in the STEPP study, and skin moisturizer, sunscreen, 0.5% hydrocortisone cream and minocycline 100mg once per day in the J-STEPP study. Both studies demonstrated reduced severity in panitumumab-associated dermatologic toxicities through the implementation of pre-emptive vs. reactive skin management. The efficacy of oral tetracyclines for the prevention of the acneiform eruption has been evaluated in a recent meta-analysis. This 2016 meta-analysis was based on nine randomized trials and four observational studies (n=1073 patients). [13] This study reported prophylactic treatment with doxycycline or minocycline reduced by approximately 50 percent the risk of developing a skin rash of any grade (odd ratio [OR]=0.54; 95% confidence interval [CI]=0.40-0.73) and by approximately 70 percent the risk of grade 2 or 3 rash (OR=0.36, 95% CI=0.22-0.60). Restricting the analysis to randomized trials resulted in similar findings.

There is a paucity of real world data regarding the management of dermatologic toxicity among mCRC patients treated with panitumumab in the U.S. The objective of this study was to utilize a survey tool to assess oncologist's opinions and perceptions of skin rash management among the patients they treat with panitumumab. This information may inform clinical management strategies that could prevent and reduce the incidence or severity of skin toxicity in mCRC patients who are treated with panitumumab.

# 2. Methods

This is a cross-sectional study that utilized an online survey tool distributed in September 2016.

## 2.1. Survey Tool

The novel survey tool was developed based on the current literature and expert opinions. It was designed to be completed online in approximately 30 minutes and included the following sections (A) Treatment Background with five questions, (B) Skin Toxicity Management Strategy with nine questions, (C) Specifics of Skin Toxicity Management Strategy with nineteen questions, and (D) Therapy Adjustment with eleven questions. The survey underwent two rounds of pilot testing with treating clinicians to ensure readability, sensibility and content validity. The survey included questions on demographic characteristics of the physicians, opinions on how dermatologic toxicities are typically managed among mCRC patients, as well as specific management strategies they recommend to their panitumumab-treated patients (i.e. moisturizers, sunscreen, UV protective garments, over-the-counter topical steroids, prescription steroids, topical antibiotics, and oral antibiotics) and the timing of their recommendation relative to the onset of rash.

## 2.2. Participants

Oncologists were recruited from a national database through a third party panel provider, M3 Global Research®. M3 Global Research® has access to over two million physicians and one million health care professionals globally for participation in both qualitative and quantitative studies. The oncologists were sampled at random and then stratified by size of institution, type of institution (academic cancer centers and community hospitals) and region within the United States (West, South, Midwest and Northeast). Eligible physicians were board certified oncologists who have treated at least five new or continuing patients with mCRC in the last three months, and with at least three patients who received or is receiving panitumumab, and consented to participate in the survey. Physicians were excluded if they spend less than 60% of their time in clinical practice and if they were not allowed to be compensated for participation in survey research (i.e. those who are licensed in Vermont and those who treat patients in Government or VA settings).

## 2.3. Treatment Strategy Classification: Defining Pre-emptive Vs. Reactive Treaters

Our analyses were conducted by categorizing the oncologists as either pre-emptive or reactive treaters based on the manner in which they answered specific survey questions. Pre-emptive treaters were defined as those who reported treating≥50% of their panitumumab-treated patients prior to the onset of rash. The remaining oncologists were categorized as reactive treaters.

### 2.4. Data Analysis

Data analysis was performed using STATA statistical software (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP). Descriptive statistics were used to characterize the demographics of the sampled population. Responses to the survey questions were cross-tabulated and compared across pre-emptive vs. reactive treaters. The Fisher exact test was used in cross-tabulations to compare binary and categorical data across the two treatment groups and the Student's T-tests were used to assess differences in means between the two treatment groups. In this descriptive study, we considered p-values to be statistically significant if they were less than 0.05.

## 3. Results

Table 1 summarizes the demographic and clinical expertise of the 250 oncologists who completed the survey. Approximately 139 (56%) participants were categorized as a pre-emptive treater based on the timing of their self-reported management strategies and the remaining 111 (44%) participants were categorized as reactive treaters. Regardless of treatment classification, all participants were well-seasoned clinicians in terms of number of years practicing oncology (mean=15 years for pre-emptive treaters and 13 years for reactive treaters) and number of new or continuing mCRC patients they personally treated in the last three months (mean=43 patients for pre-emptive treaters and 48 patients for reactive treaters). The majority of participants were community-based clinicians (65% in each treatment strategy group) and most were in a practice with 6-20 other doctors (30% in each treatment strategy group). The practice locations of the participants were evenly distributed across the U.S. Familiarity of the STEPP and J-STEPP strategies used to manage skin toxicities varied across the two treatment groups, with a higher proportion of reactive treaters than pre-emptive treaters reporting that they were not familiar with the strategies outlined in those two studies (54% vs 35%, p=0.01).

***Table 1.*** *Participant demographics and clinical experience by pre-emptive vs. reactive treater.*

| Physician Demographic | Preemptive Treater* (n=139) | Reactive Treater* (n=111) | p-value |
|---|---|---|---|
| Number of Years Practicing Oncology-mean (SD) | 15 yrs (7.4) | 13 yrs (7.5) | 0.06 |
| Primary Hospital Affiliation-n (%) | | | |
| Academic/University hospital | 50 (36%) | 40 (36%) | 0.9 |
| Community-based | 89 (64%) | 71 (64%) | |
| Size of practice setting - n (%) | | | |
| Group practice≥20 doctors | 15 (11%) | 14 (13%) | 0.6 |
| Group practice 6-20 doctors | 41 (30%) | 33 (30%) | |
| Group practice≤5 doctors | 29 (21%) | 17 (15%) | |
| Solo practice | 4 (3%) | 7 (6%) | |
| No response | 50 (35%) | 40 (36%) | |
| Practice Location**-n (%) | | | |
| West | 29 (21%) | 22 (20% | 0.2 |
| Midwest | 22 (16%) | 28 (25%) | |
| South | 50 (36%) | 29 (26%) | |
| Northeast | 38 (27%) | 32 (29%) | |
| New or continuing mCRC patients oncologist personally treated in the past 3 months - mean (SD) | 43 (24) | 48 (26) | 0.1 |
| Familiar and follow STEPP or J-STEPP strategies to manage EGFR-related skin toxicities - n (%) | | | |
| Yes | 52 (37%) | 27 (24%) | 0.01 |
| Familiar but do not follow their management strategies | 38 (27%) | 24 (22%) | |
| Not familiar | 49 (35%) | 60 (54%) | |

* The oncologists were defined as a preemptive treater if they reported initiating skin management strategies in at least 50% of patients prior to the onset of rash. The reactive treaters reported initiating skin management strategies in<50% of patients prior to the onset of rash.

** West (WA, OR, CA, NV, AZ, CO, HI), Midwest (NE, MN, IA, MO, WI, IL, MI, IN, OH), South (OK, TX, AR, LA, MD, DC, VA, KY, TN, AL, NC, GA, FL), Northeast (NH, NY, MA, CT, RI, PA, NJ).

*Informing Patients about Skin Toxicity Treatment and Management*

When asked what method they used to inform patients about skin toxicity treatment and management, a higher proportion of pre-emptive treaters than reactive treaters reported that they speak directly with patients and also provide written materials about skin toxicity treatment and management (26% vs. 20%; p=0.01) (Table 2). Providing written materials only was the most commonly selected answer to this question among pre-emptive treaters (43%), while speaking directly with each patient was the most commonly selected answer to this question among reactive treaters (40%). Few participants in either treatment group reported providing no information on this topic to patients.

***Table 2.*** *Method for informing patient about skin toxicity and management.*

| | Preemptive Treaters n=139 n (%) | Reactive Treaters n=111 n (%) | p-value |
|---|---|---|---|
| No – do not provide materials or talk with the patient | 2 (2%) | 12 (11%) | 0.01 |
| Yes – provide written materials | 60 (43%) | 32 (29%) | |

| | Preemptive Treaters n=139 n (%) | Reactive Treaters n=111 n (%) | p-value |
|---|---|---|---|
| Yes – we speak directly with each patient | 40 (29%) | 44 (40%) | |
| Yes – we speak directly with the patient and provide written materials | 36 (26%) | 23 (20%) | |

*Skin Toxicity Treatment Management Strategies and Timing*

A higher proportion of pre-emptive treaters than reactive treaters recommended all of the specific management strategies that were assessed in the survey (Figure 1). Specifically, the proportion of patients recommended to receive each agent was as follows for pre-emptive vs. reactive treaters, respectively: skin moisturizer (78% vs. 58%; p<0.001), sunscreen (75% vs. 57%; p=0.002), over-the-counter (OTC) topical steroids (42% vs. 37%; p=0.27), prescription strength topical steroids (30% vs 30%; p=0.95), topical antibiotics (37% vs. 26%; p=0.001), oral antibiotics (39% vs. 26%; 0.006), and UV protective garments (61% vs. 47%; p=0.008).

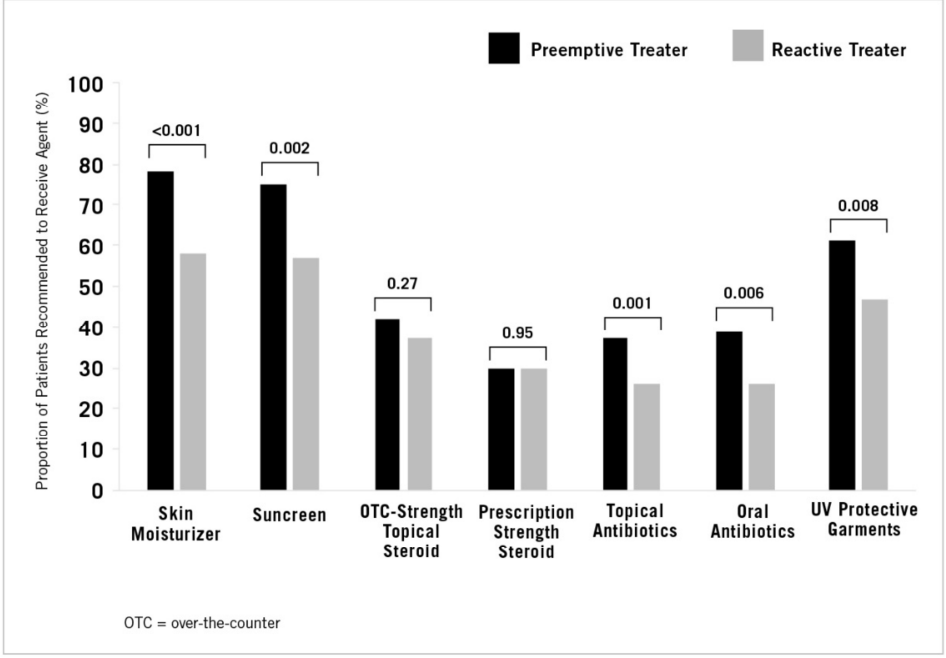


***Figure 1.*** *The proportion of patients recommended to receive each dermatologic toxicity management strategy.*

Study participants were asked to describe the timing of their initiation of skin management strategies (Table 3). A higher proportion of pre-emptive treaters than reactive treaters were more likely to initiate the use of specific treatments prior to starting panitumumab than at other times during the course of therapy. Specifically, the proportion of participants who reported starting each treatment before panitumumab was as follows for pre-emptive vs. reactive treaters, respectively: skin moisturizer (49% vs 25%, p<0.001), sunscreen (50% vs 36%; p=0.01), OTC topical steroids (19% vs 7%; p=0.01), prescription strength topical steroids (14% vs. 4%; <0.001), topical antibiotics (14% vs. 6%; p=0.09), oral antibiotics (17% vs 5%; 0.001), and UV protective garments (37% vs. 26%; 0.17). Table 3 illustrates a trend in reactive treaters being more likely than pre-emptive treaters to start skin toxicity management at the sign of first rash or after grade 2 rash was present. This was especially true for management strategies that required a prescription, such as prescription strength topical steroids or oral antibiotics.

***Table 3.*** *Timing of Skin Management Treatment Initiation.*

| Skin Management Strategies | Preemptive Treaters n=139 n (%) | Reactive Treaters n=111 n (%) | p-value |
|---|---|---|---|
| Skin moisturizer | | | |
| Prior to starting Pmab | 69 (49%) | 28 (25%) | |
| At the same time that treatment with Pmab starts | 62 (45%) | 45 (41%) | <0.001 |
| At the first sign of any rash | 4 (3%) | 35 (32%) | |
| Other | 4 (3%) | 3 (3%) | |
| Sunscreen | | | |
| Prior to starting Pmab | 69 (50%) | 40 (36%) | |
| At the same time that treatment with Pmab starts | 60 (43%) | 49 (44%) | 0.0132 |
| At the first sign of any rash | 5 (4%) | 14 (13%) | |
| Other | 5 (4%) | 8 (7%) | |
| OTC strength topical steroids | | | |
| Prior to starting Pmab | 26 (19%) | 8 (7%) | 0.014 |

| Skin Management Strategies | Preemptive Treaters n=139 n (%) | Reactive Treaters n=111 n (%) | p-value |
|---|---|---|---|
| At the same time that treatment with Pmab starts | 40 (29%) | 31 (28%) | |
| At the first sign of any rash | 38 (27%) | 50 (45%) | |
| At grade 2 rash or higher | 15 (11%) | 11 (9%) | |
| Other | 20 (14%) | 11 (9%) | |
| Prescription strength topical steroids | | | |
| Prior to starting Pmab | 20 (14%) | 4 (4%) | |
| At the same time that treatment with Pmab starts | 30 (22%) | 22 (20%) | |
| At the first sign of any rash | 28 (20%) | 25 (23%) | |
| At grade 2 rash or higher | 24 (17%) | 45 (40%) | <0.001 |
| At grade 3 rash or higher | 13 (9%) | 6 (5%) | |
| Other | 24 (17%) | 9 (8%) | |
| Topical antibiotics | | | |
| Prior to starting Pmab | 20 (14%) | 7 (6%) | |
| At the same time that treatment with Pmab starts | 34 (24%) | 19 (17%) | |
| At the first sign of any rash | 31 (22%) | 32 (29%) | 0.09 |
| At grade 2 rash or higher | 37 (27%) | 33 (30%) | |
| Other | 17 (12%) | 20 (18%) | |
| Oral antibiotics | | | |
| Prior to starting Pmab | 23 (17%) | 5 (5%) | |
| At the same time that treatment with Pmab starts | 34 (24%) | 15 (14%) | |
| At the first sign of any rash | 20 (14%) | 15 (14%) | 0.001 |
| At grade 2 rash or higher | 23 (17%) | 29 (26%) | |
| At grade 3 rash or higher | 27 (19%) | 29 (26%) | |
| Other | 12 (9%) | 18 (16%) | |
| UV protective garments | | | |
| Prior to starting Pmab | 52 (37%) | 29 (26%) | |
| At the same time that treatment with Pmab starts | 51 (37%) | 36 (32%) | |
| At the first sign of any rash | 11 (8%) | 17 (15%) | 0.17 |
| At grade 2 rash or higher | 5 (4%) | 5 (5%) | |
| Other | 20 (14%) | 24 (22%) | |

*Utilization of Nursing Support and Dermatology*

It was common for both pre-emptive and reactive treaters to utilize nursing support in many activities that are associated with managing skin toxicity in panitumumab-treated mCRC patients (Table 4). However, the utilization of nursing support was consistently higher for pre-emptive treaters than reactive treaters, respectively, including: educating on the importance of wearing protective garments (70% vs. 59%), educating on increased sensitivity to the sun while on treatment (75% vs. 59%), advising patients on OTC treatments (64% vs. 51%), prescribing treatments before rash occurs (50% vs. 33%), advising patients on treatment options after rash occurs (63% vs 56%), and prescribing treatments after rash occurs (53% vs. 48%). The utilization of dermatologic support was similar for pre-emptive and reactive treaters, with 40% in both groups reporting that they occasionally consult with a dermatologist (Table 4). A slightly higher proportion of pre-emptive treaters than reactive treaters reported that they never consult with a dermatologist (8% vs 3%).

***Table 4.*** *Utilization of nursing support or dermatology to minimize or manage EGFR rash.*

| | Preemptive Treaters (n=139) n (%) | Reactive Treaters (n=111) n (%) |
|---|---|---|
| Frequency of Nursing Support Activities | | |
| Educating on the importance of wearing protective garments | 97 (70%) | 65 (59%) |
| Educating on increased sensitivity to the sun while on treatment | 104 (75%) | 66 (59%) |
| Monitoring for skin toxicity during treatment | 100 (72%) | 82 (74%) |
| Advising patients on OTC treatments | 89 (64%) | 57 (51%) |
| Prescribing treatments before rash occurs | 69 (50%) | 37 (33%) |
| Advising patients on treatment options after rash occurs | 87 (63%) | 62 (56%) |
| Prescribing treatments after rash occurs | 73 (53%) | 53 (48%) |
| Other | 139 (100%) | 111 (100%) |
| Utilization of Dermatologic Support | | |
| I *always* consult with a dermatologist | 6 (4%) | 6 (5%) |
| I *frequently* consult with a dermatologist | 33 (24%) | 22 (20%) |
| I *occasionally* consult with a dermatologist | 55 (40%) | 44 (40%) |
| I *rarely* consult with a dermatologist | 34 (24%) | 35 (31%) |
| I *never* consult with a dermatologist | 11 (8%) | 4 (3%) |

## 4. Discussion

Dermatologic toxicities are common among mCRC patients who are treated with anti-EGFR therapies. While they are not life threatening, they can have a tremendous negative impact on a patient's quality of life. [7, 14, 15] Furthermore, dermatologic toxicities are known to lead to

reductions or cessation of anti-EGFR therapy, with studies reporting approximately 30% of patients discontinued treatment due to skin toxicity. [7, 15] Results from clinical studies, such as STEPP and JSTEPP have highlighted the utility of managing dermatologic toxicities in a pre-emptive manner. [11, 12] To our knowledge, this is the first study to utilize real world data to assess the timing of rash management among oncologists in U.S. who treat mCRC patients with anti-EGFR therapies. Our results illustrate that the number of patients who receive pre-emptive management of rash can be greatly improved, with just over half of the participants reporting that they implement pre-emptive management strategies (and even then clearly not implementing therapy that is truly pre-emptive).

While clinical standards do not exist for the management of dermatologic toxicities associated with anti-EGFR treatments, The Multinational Association for Supportive Care in Cancer (MASCC) Skin Toxicity Study Group has developed clinical guidelines for the prevention and treatment of dermatologic toxicities associated with anti-EGFR therapies. [16] These guidelines have yet to be incorporated as the standard of care, leaving wide discrepancies in the management of rash before and after it occurs. The MASCC guidelines include preventive recommendations consisting of topical 1% hydrocortisone cream with moisturizer and sunscreen and systemic treatment with 100 mg of minocycline or doxycycline daily. Treatment recommendations include topical 1% clindamycin or 0.05% alcometasone or flucinonide creams, and systemic treatments of 20-30mg isotretinoin or 100 mg of doxycycline or minocycline. These preventive recommendations are based on regimens found to be effective in the STEPP and JSTEPP studies. [11, 12] The STEPP study reported the incidence of ≥ grade 2 skin toxicities was reduced by more than 50% in the pre-emptive group compared with the reactive group during the 6-week skin treatment period. [11] The quality of life measure was also reported to be less impaired relative to patients in the reactive group. [11] Similarly, JSTEPP reported a 66% reduction in the incidence of≥grade 2 skin toxicities between the groups. [12]

Despite the positive results from STEPP and JSTEPP, few oncologists in our study followed these strategies and a high proportion of physicians were not familiar with them. A multinational expert panel recently reviewed evidence related to how non-pharmaceutical skin care products can be used to prevent and manage skin toxicity following oncology therapies. [17] This panel suggested that skin barrier dysfunction may be linked to adverse events in the skin following therapy. They identified moisturizers as a key component to improve barrier function and skin hydration, thereby reducing pruritus and preventing secondary infection due to scratching. Likewise, the authors note the issue of photosensitivity whereby sun exposure can exacerbate rash resulting from anti-EGFR therapies and recommend the application of a broad-spectrum sunscreen daily. The study further reports on cosmetics and non-pharmaceutical skin care products that may further irritate and thus worsen skin toxicities. Our study found that moisturizers were the most commonly recommended therapy in among both pre-emptive and reactive treaters 78% vs. 58%, respectively). However, it was still far below being recommended to 100% of the patients which is unacceptable given the accessibility, simplicity and affordability relative to other pharmaceutical agents. Similar results were found for sunscreen among pre-emptive vs reactive treaters (75% vs. 57%) and UV protective garments (61% vs 47%), which are also therapies that are likewise relatively simple to recommend.

Our data also identified a large gap in the proportion of patients receiving information on rash either verbally or in written form. Ideally, patients would receive both verbal and written information about rash, however, our study suggests only 26% of pre-emptive treaters and 20% of reactive treaters provide both to their patients. These results illustrate the urgent need to educate oncologists on the importance of educating patients on how it can be managed. Our study also found that consulting a dermatologist is not common practice. Collaborations between oncologists and dermatologists are thought to maximize the management of adverse cutaneous reactions while minimizing changes to therapy. [17-19] Boone et al. conducted an in-person survey among 110 practitioners of US oncology practices using a questionnaire with 51 open-ended questions pertaining to incidence of rash, treatment practices, patient perceptions and outcome in treating the rash. [7] The underuse of dermatologists was similar between this study (8%) and our study (6%). [7] Peuvrel et al conducted a survey among 67 French practitioners related to prophylactic and curative management of EGFR skin toxicities based on a questionnaire with 31 questions covering 11 clinical situations. [19] This study also identified the underutilization of dermatologists for managing anti-EGFR skin toxicities. The authors reported 97% of respondents did not consider a routine dermatology consultation at the time of anti-EGFR initiation, 76% declared they had never sent their patients to a dermatologist prior to the appearance of skin lesions. Dermatologists were utilized by 76% of respondents if a patient's rash persisted for more than 2 weeks. A final survey was identified among 149 German oncologists (106 medical and 43 dermatological), only 9% of the medical oncologists reported that they would have referred the patient to a dermatologist. [18]

This study has several strengths. First, it includes a randomly selected sample of practicing U.S. oncologists derived from a national database that has access to over 2 million physicians. The participants were obtained from all areas of the U.S., represented both academic and community cancer centers, and were experienced oncologists with many years of practice and robust patient loads. Therefore, we believe our results are generalizable to U.S. oncologists who treat mCRC patients with panitumumab. Second, we implemented a rigorous survey development process to ensure limited measurement error. This included two rounds of pilot testing prior to implementation. Finally, the survey captured real world data on current practices and opinions of oncologists for managing anti-EGFR skin toxicity and is the

first of its kind to ask questions about pre-emptive and reactive treatment strategies in the U.S. This type of information is urgently needed in the clinical community to improve patient care. The study also has several limitations. The survey sought to capture 'usual' practices of oncologists, the extent to which patient-level characteristics influence treating decisions were not available in this study. The survey included physicians treating mCRC patients within the last 3 months which leads to the potential for recall bias among those providers on the outer limits of these inclusion criteria. However, given the mean number of patients treated in the last 3 months in both groups was greater than 40 patients, recall bias is likely to be minimal. Social desirability bias could also affect the results. If for example, physicians felt compelled to respond in accordance with MASCC or other clinical guidelines then the results may over-estimate the amount of pre-emptive treatments provided. The survey categorized providers as pre-emptive treaters based on a≥50% portion of patients they treated pre-emptively. This categorization may have under-estimated or biased the distribution of responses. However, post-hoc analyses showed that only 38 participants reported that they treat 100% of their patients pre-emptively, which further highlights the lack of understanding for this important patient management strategy.

## 5. Conclusions

These data highlight important gaps in the provision of pre-emptive management strategies related to anti-EGFR skin toxicities. Specifically, the pre-emptive provision of sunscreen, moisturizers, over-the-counter topical steroids and oral antibiotics could all be dramatically improved, ideally with the patient receiving all of these strategies in agreement with the MASCC recommendations. Such improvements could be made through the use of continuing medical education opportunities for health care providers in oncology. Opportunities also exist to improve patient education through avenues other than the health care provider, such as patient advocacy groups. Among patients with rash, improvements in integrating care with dermatologists are needed. Future research should aim to understand barriers to provision of these management strategies among oncologists and barriers to uptake of these strategies among patients.

## Declarations

### Ethics Approval and Consent to Participate

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Ethical review: This study utilized data from the third-party M3 Global Research® which does not require review by an ethical review committee.

### Consent for Publication

Not applicable.

### Availity of Data and Material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing Interests

KL is a compensated employee of Amgen Inc as an Epidemiology Senior Manager and a stockholder in Amgen Inc.

GK is a compensated employee of Amgen Ltd as an Observational Research Senior Manager and a stockholder in Amgen Ltd.

KH was a compensated employee of Amgen Inc as a Senior Medical Scientist during the development of this study and a stockholder in Amgen Inc. and holds a Provisional Patent from UCLA.

TG is a compensated employee of Amgen Inc as the Oncology Platform Leader and a stockholder in Amgen Inc.

MM is an employee of Adelphi Research, work contracted through Amgen, Inc.

RB is an employee of Adelphi Research, work contracted through Amgen, Inc.

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## Authors Contributions

All authors were involved in, and contributed to, the drafting and critical review of this manuscript.

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