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ORIGINAL ARTICLE

A systematic review of patient-reported outcome instruments of dermatologic adverse events associated with targeted cancer therapies

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Abstract
Purpose Dermatologic adverse events (dAEs) in cancer treatment are frequent with the use of targeted therapies. These dAEs have been shown to have significant impact on health-related quality of life (HRQoL). While standardized assessment tools have been developed for physicians to assess severity of dAEs, there is a discord between objective and subjective measures. The

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identification of patient-reported outcome (PRO) instruments useful in the context of targeted cancer therapies is therefore important in both the clinical and research settings for the overall evaluation of dAEs and their impact on HRQoL.

Methods A comprehensive, systematic literature search of published articles was conducted by two independent reviewers in order to identify PRO instruments previously utilized in patient populations with dAEs from targeted cancer therapies. The identified PRO instruments were studied to determine which HRQoL issues relevant to dAEs were addressed, as well as the process of development and validation of these instruments.

Results Thirteen articles identifying six PRO instruments met the inclusion criteria. Four instruments were general dermatology (Skindex-16©, Skindex-29©, Dermatology Life Quality Index (DLQI), and DIELH-24) and two were symptom-specific (functional assessment of cancer therapy-epidermal growth factor receptor inhibitor-18 (FACT-EGFRI-18) and hand-foot syndrome 14 (HFS-14)).

Conclusions While there are several PRO instruments that have been tested in the context of targeted cancer therapy, additional work is needed to develop new instruments and to further validate the instruments identified in this study in patients receiving targeted therapies.

Keywords Targeted cancer therapy · Dermatologic adverse events · Patient-reported outcomes · Health-related quality of life

Introduction

Over the last decade, as multiple targeted anticancer agents have been introduced, the dermatologic adverse events (dAEs) that accompanied them have become more prevalent and a growing concern in the treatment of patients with cancer [1]. The increased incidence and severity of dAEs with novel therapies, such as acneiform rash, pruritus, xerosis, hair changes and hand-foot skin reaction (palmar-plantar erythrodysesthesia syndrome), have underscored the significance of dermatologic evaluation and treatment of these dAEs in patients with cancer. The range of dAEs from cancer therapy has a profound impact on the health-related quality of life (HRQoL) of the patient, which includes the emotional, psychosocial and physical well-being of patients [2].

For healthcare providers managing patients receiving targeted therapies, the severity of patient's skin condition is not easily assessed and communicated. Additionally, the visible degree of the disease often does not correlate with patient distress and impact on quality of life (QoL). The severity of the dAE is therefore related to both its clinical extent and its effects on a patient's HRQoL. The Common Terminology Criteria for Adverse Events (NCI CTCAE) is a standardized tool used in oncology trials to document and grade toxic effects of anticancer therapies; [3] however, there are inconsistencies in the severity grading between patients and physicians [4]. Hence, supplementing healthcare provider-graded dAEs with patient self-report of symptoms can help to improve dAE reporting and treatment in both research and clinical settings [5]. Close monitoring, early recognition and early intervention of dAEs may relieve symptoms and reduce their duration, ultimately leading to improvements in patients' HRQoL [6].

Patient-reported outcome (PRO) instruments that evaluate HRQoL of cancer patients with dAEs are, therefore, increasingly important in the evaluation of novel therapies in clinical trials. PRO instruments can be categorized as generic, disease-specific, or symptom-specific instruments. Generic instruments evaluate across different diseases and patient populations, while disease- or symptom-specific instruments assess the HRQoL effects of a particular disease or its therapies, respectively. To select the proper PRO instrument, one should consider the instrument content, quality and its development and validation [7] and the intended use (e.g. clinical care or research purposes). To identify available PRO instruments in the treatment of oncology patients with dAEs from targeted cancer therapy, we conducted a systematic review of the literature. The objectives were the following: (1) identify PRO instruments designed to measure HRQoL in patients with dAEs from targeted cancer therapy and (2) evaluate the development, content and psychometric properties of these instruments.

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Materials and methods

A comprehensive electronic literature search of published articles was conducted in the following databases: MEDLINE via PubMED, PsychINFO (Psychological Abstracts) via OVID, Cochrane via Wiley, EMBASE via Elsevier, CINAHL via EBSCO and HAPI (Health and Psychosocial Instruments) via OVID. There was no date restriction, and each database was searched in its entirety. Grey literature sources were also searched and reviewed to include SCOPUS and BIOSIS Previews® for conference proceedings and meeting abstracts. There were no limits placed on language or publication type. Controlled vocabulary (MeSH, PsychINFO subject headings, CINAHL headings, EMTREE) and keywords were used with the strategy including keywords and Medical Subject Headings (MeSH) terms (Appendix 1). Further manual search of the reference lists of the relevant studies was also performed. Four broad concept categories were searched, and results were combined using the appropriate Boolean operators (AND, OR). The broad categories included the following: patient-reported outcomes, QoL, skin conditions and targeted cancer therapies.

Two independent reviewers examined the titles and abstracts of all articles. The full text of any potentially relevant article was examined using the inclusion criteria: (1) patient population with dAEs from targeted anticancer agents and (2) study describing a PRO instrument measuring HRQoL or patient satisfaction. Exclusion criteria were as follows: (1) articles that did not include a PRO instrument of HRQoL or patient satisfaction, (2) articles that used generic or ad hoc questionnaires (i.e. without published evidence of a development or validation process) and (3) no PRO outcomes of interest related to our patient population.

The identified PRO instruments were studied to determine which HRQoL issues relevant to dAEs were addressed. All instruments were investigated to obtain information on the original development and validation process. The instruments were assessed for adherence to guidelines of the Scientific Advisory Committee of the Medical Outcomes Trust and US Food and Drug Administration [8].

Results

The search identified 1124 articles (Fig. 1). The full text of 73 articles was reviewed in detail for eligibility. Four additional articles were identified via manual search. Thirteen articles

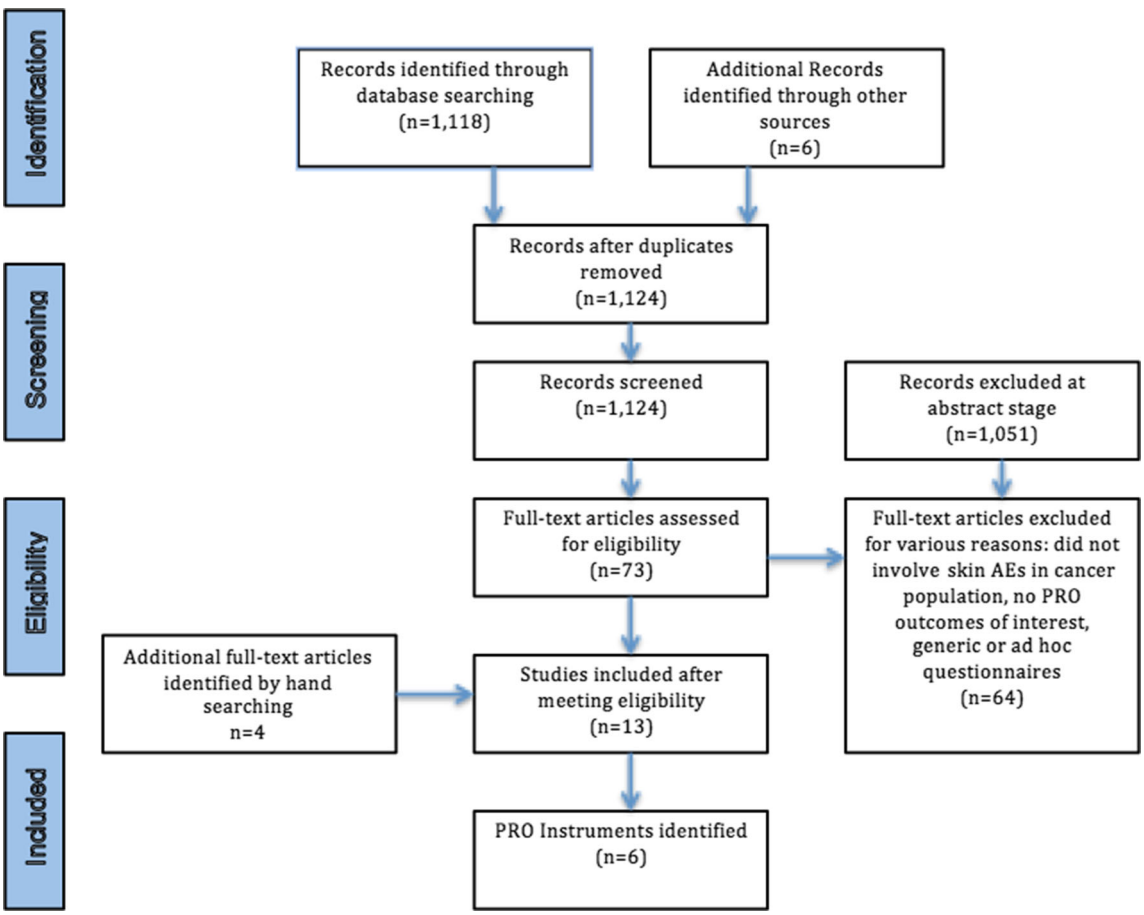

Fig. 1 Flow diagram of search strategy

(Table 1) identifying six instruments (Table 2) met the inclusion criteria. Four instruments were generic (Skindex-16© [2, 9–11], Skindex-29© [12], Dermatology Life Quality Index (DLQI) [6, 13], Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen (DIELH-24) [14]), and two were symptom-specific (Functional Assessment of Cancer Therapy Epidermal-Growth Factor Receptor Inhibitor 18 (FACT-EGFRI-18) [15, 16] and Hand-Foot Syndrome 14 (HFS-14) [17–19]).

The Skindex-29© is a validated, self-administered, 29-item questionnaire (Appendix 2). The instrument uses open-ended questions to assess how bothered a patient is by his/her skin condition on a 5-point scale (1–5) from 'never' (1) to 'all the time' (5). Results of the Skindex-29© are reported as 3-scale scores assessing emotions, physical symptoms and functioning. Scale scores are the means of responses to the items included in the scale, ranging from 29 to 116, and higher scores indicate worse HRQoL. An Italian version of the instrument was previously utilized to measure the impact of EGFRI skin toxicity on HRQoL in colon cancer patients [12]. More comprehensive than the later developed Skindex-16©, the Skindex-29© is more useful in understanding detailed effects of a condition on HRQoL [20]. Since it has been available for clinical researchers for longer than the Skindex-16©, the Skindex-29© also has a more expansive database of typical scores for a variety of skin conditions [20]. However, this increased detail comes with the disadvantage of a longer survey, which may be a disadvantage in studies where respondent burden is a concern. Another disadvantage of the Skindex-29© is the lack of questions pertaining to the hair, nails or mucous membranes, which are common sites of toxicity for targeted cancer therapies [15].

Developed from the Skindex-29© questions with the best performance characteristics, the Skindex-16© is a 16-question survey that has been validated to accurately and sensitively measure how much a patient is bothered by a skin condition

Table 1 Previous studies with PRO instruments in targeted cancer therapy

Publication	PRO Instrument	Population	Targeted therapies	Findings
Joshi SS. Cancer, 2010 [2]	Skindex-16©	67	EGFRI	• Lower overall QoL for patients <50 years old • High concordance between QoL score and grading severity related to papulopustular rash • Greater impact on emotion>symptom>functioning domains
Nardone B. J Drugs Dermatol, 2012 [9]	Skindex-16©	23	Sorafenib, Sunitinib	• Significant correlation between CTCAE grading and QoL scores for hand-foot syndrome
Rosen AC. Am J Clin Dermatol, 2013 [10]	Skindex-16©	163 (targeted therapy), 120 (nontargeted therapy	EGFRI, mTOR, TKIs	• Significantly greater number of dAEs and QoL scores for targeted therapy subgroup
Jatoi A. Cancer, 2008 [11]	Skindex-16©	61	EGFRI	• Validated instrument • Assessed QoL difference for patients receiving tetracycline to alleviate EGFRI toxicity • No significant difference in QoL seen
Andreis F. Health Qual Life Outcomes, 2010 [12]	Skindex-29©	45	EGFRI	• Validated instrument in Italian • Symptom domain had most QoL impact
Lacouture ME. J Clin Oncol, 2010 [6]	DLQI	95	EGFRI	• Compared QoL in patients receiving reactive versus proactive skin toxicity treatment •Less QoL decrease for proactive treatment group
Osio A. Br J Dermatol, 2009 [13]	DLQI	15	EGFRI	• Moderate to strong impact on QoL in four patients
Unger K. Z Gastroenterol, 2013 [14]	DIELH-24	20 (Chemotherapy+anti-EGFR), 20 (chemotherapy)	EGFRI	• No significant difference in QoL between targeted vs. nontargeted therapy groups • Severity of skin rash significantly correlated to QoL in both groups
Wagner LI. Support Care Cancer, 2013 [15]	FACT-EGFRI-18	20	EGFRI	• Validation of instrument
Boers-Doets CB. Support Care Cancer, 2013 [16]	FACT-EGFRI-18	10 (patients with dAEs due to anti-EGFR therapy)	EGFRI	• Physical discomfort has most QoL impact • Significant correlations between intensity of dAEs and QoL
Sibaud V. Oncologist, 2011 [17]	HFS-14	43 (with hand-foot syndrome)	Sorafenib, sunitinib	• Validation of instrument • Positive correlation between HFS-14, CTCAE grading, Skindex-16
Taieb C. Value in Health, 2009 [18]	HFS-14	20 (with hand-foot syndrome)	Sorafenib, sunitinib	• Details development of instrument
Teo YL. Cancer Chemother Pharmacol 2014 [19]	HFS-14	24	Sunitinib	• HFS-14 and pain scale scores strongly correlate • HFS-14 score and pain scale scores were moderately correlated with HFSR grade

CTCAE Common Terminology Criteria for Adverse Events, *EGFRI* epidermal growth factor receptor inhibitor, *HFSR* hand-foot skin reaction, *QoL* quality of life

Table 2 Comparison of PRO instruments previously tested in targeted cancer therapy

PRO instrument	Type of instrument	Number of questions	Validation status for targeted therapies
Skindex-16©	Generic	16	Validated
Skindex-29©	Generic	29	Validated
DLQI	Generic	10	Validated
DIELH-24	Generic	24	Not validated
FACT-EGFRI-18	Symptom-specific	18	In process
HFS-14	Symptom-specific	14	Validated

(Appendix 3). It uses questions to assess how bothered a patient is by his/her skin condition on a seven-point scale (0–6) from 'never bothered' (0) to 'always bothered' (6) and assesses HRQoL as it pertains to three domains of life: symptoms, emotions and functioning. The Skindex-16© has been shown to have good reproducibility (r=0.88–0.90) [21]. The survey has been tested with several targeted therapies, including EGFRIs and tyrosine kinase inhibitors (Table 1). These studies showed significant correlation between survey's HRQoL scores and other outcome measures, including severity grading and NCI CTCAE scores [2, 9–11]. Because the Skindex-16© assesses how much a side effect 'bothers' the respondent rather than 'how often' such a side effect occurs (as in the Skindex-29©), the instrument may more directly assess side effects on HRQoL [20]. In addition, the single-page length of this survey is helpful in studies where respondent burden may be troublesome [20]. However, similar to the Skindex-29©, the Skindex-16© does not specifically address toxicities of the hair, nails or mucous membranes.

The DLQI was the first dermatology-specific HRQoL instrument [22]. It is a 10-question survey assessing symptoms and feelings, daily activities, leisure, work/school, personal relationships and treatment within the last week (Appendix 4). It has been validated and found to be reliable in adult patients (>18 years old) with different skin diseases. Each question has four alternative responses scored from 0 to 3: 'not at all' (0), 'a little' (1), 'a lot' (2) or 'very much' (3). The scores are summed, and overall scores range from 0 (no impairment) to 30 (maximum impairment). In five studies that looked at internal consistency for the DLQI, Cronbach's α scores ranged from 0.83 to 0.93 [22, 23]. The instrument was previously utilized to examine differences in decrease in HRQoL from panitumumab-related skin toxicities in patients receiving pre-emptive skin dermatologic treatment compared to reactive dermatologic treatment [6]. The DLQI has also been used to measure impact of long-term EGFRI side effects on HRQoL [13]. As the first dermatology-specific HRQoL instrument, a major strength of the DLQI is its vast amount of available clinical research data. In addition, the DLQI was purposefully designed to be very simple to use and score [24]. Score interpretation is also relatively easy (e.g. greater than ten generally implies a very severe impact) [24]. However, like the Skindex instruments, the DLQI does not address the hair, nail or mucous membrane toxicities.

The Deutsches Instrument zur Erfassung der Lebensqualität bei Hauterkrankungen (DIELH-24), or German Instrument for Recording Quality of Life in Skin Diseases, is a HRQoL instrument previously shown to possess internal consistency, reliability and validity in the German language for general skin complaints and atopic dermatitis [25]. Recently, it was used in the setting of cetuximab therapy for metastatic colorectal cancer [14]. A major disadvantage of this instrument is its current availability only in German.

The FACT-EGFRI-18 is an 18-question survey that assesses the physical, emotional, social and functional impact of the skin, nail and hair toxicities from EGFRI treatment on patients' HRQoL (Appendix 5). It uses statements and asks patients to use a 5-point scale, from 'not at all' (0) to 'very much' (4), to indicate how that statement applies to them. Instrument development was accomplished by interviewing patients and providers, and there is currently a trial through Southwest Oncology Group (SWOG) that has FACT-EGFRI-18 validation as a secondary objective. To date, patient and expert input has been solicited for item generation, selection and refinement with further validation underway [15, 16]. The major strength of the FACT-EGFRI-18 is its incorporation of questions related to the hair, nails and mucous membrane toxicities [15]. One weakness of this instrument is the lack of substantial clinical research data for comparison since the survey has just recently been developed. Another limitation of the FACT-EGFRI-18 is its application to only EGFRI side effects.

The Hand-Foot Syndrome 14 (HFS-14) is a QoL scale for patients experiencing chemotherapy-associated hand-foot syndrome (HFS) and targeted therapy-associated hand-foot skin reaction (HFSR). This instrument measures severity and impact on patients. The HFS-14 is a 14-item questionnaire that has been validated to measure how HFS impairs a patient's HRQoL (Appendix 6). It uses statements that may be true for patients with HFS, and each item is scored on a three-point Likert scale: 0, 'no, never'; 1, 'yes, from time to

time'; 2, 'yes, always'. Patients are also asked if their HFS affects their hands, feet or both and to assess their overall level of pain (not painful, moderately painful and very painful). While Skindex-16© and FACT-EGFRI-18 focus on patient's experiences with dAEs in the past week, the HFS-14 asks patients to base their answers on experiences within the past day. This tool demonstrated good internal consistency (Cronbach's $\alpha > 0.9$) and had good correlation with other validated tools (DLQI, Skindex-16© and NCI CTCAE clinical grading) [17]. A primary weakness of HFS-14 is its limitation to only HFS toxicities. In addition, there is limited published data related to HFS-14 survey results at this time.

Discussion

With the increased use of novel chemotherapeutic agents, dAEs are increasingly more common [1]. Historically, alopecia and mucositis were the most common dAEs associated with chemotherapy. With newer target-specific therapies, other dAEs including papulopustular (acneiform) rash, hand-foot skin reaction, xerosis, pruritus, hair changes (including trichomegaly, hypertrichosis, hair curling), pigmentary changes, mucosal toxicities, fissures of fingertips and toes and nail changes (paronychia, onycholysis) have become more prominent [26]. Such dAEs can often necessitate treatment interruption or dose modification and may also significantly impact HRQoL [27]. A recent survey study showed that target-specific cancer therapies are associated with a poorer HRQoL compared to traditional nontargeted cancer therapies [10]. In an interview study of patients receiving EGFRIs, patients identified physical discomfort—specifically, the sensations of pain, burning, skin sensitivity—as having the largest impact on HRQoL, resulting in worry, frustration and depression [28]. In particular, younger patients with dAEs from cancer treatment appear to have a significantly greater decrease in HRQoL compared to older patients who experience similar toxicities [2].

The previous lack of systematic grading systems for dAEs has led to the recent development of standardized systems to evaluate these toxicities in both the research and clinical settings. In particular, the NCI CTCAE was developed as a standardized tool used in oncology trials to document and grade toxic effects of anticancer therapies [26]. However, patients and physicians often disagree as to the severity of dAEs [16]. It is also difficult for healthcare providers to objectively measure the effect of a particular dAE on a patient's HRQoL. Therefore, it is crucial to develop a strategy to capture patient's understanding of the severity of dAEs and their effects on HRQoL.

In this study, we have reviewed the PRO instruments that can be utilized in research and clinical settings to objectively assess the effects of dAEs on patient HRQoL. Our systematic review of the literature identified six available PRO instruments that have been used to measure HRQoL in patients with dAEs from targeted cancer therapy. PRO instruments are useful as a means to acknowledge the discrepancy between patient and clinicians' understanding of dAEs and as a supplement to grading systems, such as NCI CTCAE, in evaluating the overall effect of dAEs on patient wellbeing. Furthermore, patients with cancer are generally receptive to repeated HRQoL assessment, making implementation of PRO instruments feasible [29]. Routine use of these instruments may encourage patients to address how dAEs affect their physical, emotional and psychosocial wellbeing. In doing so, clinicians can intervene earlier to improve symptoms and reduce the length of dAEs, ideally leading to improvements in patients' HRQoL and avoid unnecessary modifications in or cessation of cancer treatment [6]. Future research is required to assess whether the incorporation of HRQoL tools in routine clinical practice would lead to less dAEs. In another study, the investigators evaluated the differences in plasma sunitinib and metabolite concentrations between patients with and without dAEs. [19] In this study, hand and feet complaints were assessed utilizing HFS-14. This demonstrates another utility of PRO instruments: to correlate clinical outcomes with biochemical findings.

There are several limitations to be acknowledged in this review. While our search was only limited to targeted therapies, there are other PRO instruments developed for the measurement of HRQoL in dermatologic patients [30]. Although these PRO instruments have not been tested specifically in targeted cancer therapy, they are additional resources that the clinician or scientific investigator may consider for application and further validation in the context of targeted cancer therapy.

Targeted therapies are gaining popularity in the management of cancers ranging from chronic myeloid leukemia to renal cell carcinoma. Much evidence suggests that patients' HRQoL may be affected by the dAEs of these agents. As there is often a discord between objective and subjective measures of dAEs in clinical practice, there may be a need to incorporate appropriate PRO instruments to accurately assess these dAEs from patient's perspective. This study has reviewed the PRO instruments that can currently be utilized in research and clinical settings to objectively assess the effects of dAEs on patient HRQoL.

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Conflict of interest Dr. Roeland has a consultant role with Cellulitix.

Dr. Choi has received remuneration from Onyx Pharmaceuticals and has a consultant role with Biotest AG.

Dr. Bryce has a consultant role with AstraZeneca and Roche.

Dr. Gerber has a consultant role with Galderma International. He is also receiving research funding from Hoffman La Roche.

Dr. Lacouture has a consultant role with AstraZeneca, Roche, Bayer, Janssen, Exelixis, Advancell, BMS, Amgen and Genentech. He is also receiving research funding from Berg, Roche and BMS.

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Appendix 1

Table 3 Search strategies and terms used

Medical subject headings (MeSH)	Keyword terms
("Questionnaires" [Mesh] OR "Weights and Measures" [Mesh] OR "Health Care Surveys" [Mesh] AND ("Quality of Life" [Mesh] OR "Quality-Adjusted Life Years" [Mesh] OR "Health Status" [Mesh] OR "Personal Satisfaction" [Mesh] OR "Patient Satisfaction" [Mesh] OR "Patient Compliance" [Mesh] OR "Pain" [Mesh] OR "Body Image" [Mesh] OR "Social Adjustment" [Mesh] OR "Social Behavior" [Mesh] OR "Shyness" [Mesh] OR "Social Distance" [Mesh] OR "Social Isolation" [Mesh] OR "Fear" [Mesh] OR "Frustration" [Mesh] OR "Personal Autonomy" [Mesh] OR "Self Concept" [Mesh] OR "Adaptation, Psychological" [Mesh] OR "Stress, Psychological" [Mesh] OR "Emotions" [Mesh]) AND "Skin Diseases" [Mesh] OR "Epidermal Necrolysis, Toxic" [Mesh] AND ("Molecular Targeted Therapy" [Mesh] OR "temsirolimus" [Supplementary Concept] OR "lenalidomide" [Supplementary Concept] OR "Aromatase Inhibitors" [Mesh] OR "anastrozole" [Supplementary Concept] OR "exemestane" [Supplementary Concept] OR "letrozole" [Supplementary Concept] OR "dasatinib" [Supplementary Concept] OR "4-methyl-N-(3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-((4-pyridin-3-ylpyrimidin-2-yl)amino)benzamide" [Supplementary Concept] OR "bosutinib" [Supplementary Concept] OR "trastuzumab" [Supplementary Concept] OR "pertuzumab" [Supplementary Concept] OR "lapatinib" [Supplementary Concept] OR "gefitinib" [Supplementary Concept] OR "erlotinib" [Supplementary Concept] OR "cetuximab" [Supplementary Concept] OR "panitumumab" [Supplementary Concept] OR "everolimus" [Supplementary Concept] OR "N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine" [Supplementary Concept] OR "PLX4032" [Supplementary Concept] OR "crizotinib" [Supplementary Concept] OR "vorinostat" [Supplementary Concept] OR "romidepsin" [Supplementary Concept] OR "bexarotene" [Supplementary Concept] OR "alitretinoin" [Supplementary Concept] OR "Tretinoin" [Mesh] OR "bortezomib" [Supplementary Concept] OR "carfilzomib" [Supplementary Concept] OR "10-propargyl-10-deazaaminopterin" [Supplementary Concept] OR "sunitinib" [Supplementary Concept] OR "pazopanib" [Supplementary Concept] OR "regorafenib" [Supplementary Concept] OR "cabozantinib" [Supplementary Concept] OR "rituximab" [Supplementary Concept] OR "alemtuzumab" [Supplementary Concept] OR "ofatumumab" [Supplementary Concept] OR "ipilimumab" [Supplementary Concept] OR "iodine-131 anti-B1 antibody" [Supplementary Concept] OR "ibritumomab tiuxetan" [Supplementary Concept] OR "denileukin diftitox" [Supplementary Concept] OR "cAC10-vcMMAE" [Supplementary Concept])	(patient-reported outcomes OR PROM OR PROMs OR PRO OR PROs OR patient-reported outcomes OR questionnaire OR instrument OR instruments OR measure OR measures OR scale OR scales OR survey OR surveys) AND (quality of life OR QOL OR HRQL OR HRQOL OR quality adjusted life years OR QALY OR health status OR functional status OR well-being OR personal satisfaction OR patient satisfaction OR patient compliance OR pain OR disability OR disabilities OR disabled OR body image OR social function OR social behavior OR social behaviour OR shyness OR social distance OR social isolation OR fear OR frustration OR autonomy OR self-concept OR adaptation OR adjustment OR coping OR stress OR emotion) AND (skin conditions OR skin side effects OR skin irritation OR skin reactions) AND (targeted cancer therapies OR molecularly targeted drugs OR molecularly targeted therapies OR EGFR inhibitors OR temsirolimus OR lenalidomide OR Aromatase inhibitors OR Anastrozole OR Arimidex OR Exemestane OR Aromasin OR Letrozole OR Femara OR Dasatinib OR Sprycel OR Nilotinib OR Tasigna OR Bosutinib OR Bosulif OR Trastuzumab OR Herceptin OR Pertuzumab OR Perjeta OR Lapatinib OR Tykerb OR Gefitinib OR Iressa OR Erlotinib OR Tarceva OR Cetuximab OR Erbitux OR Panitumumab OR Vectibix OR Torisel OR Everolimus OR Afinitor OR Vandetanib OR Caprelsa OR Vemurafenib OR Zelboraf OR Crizotinib OR Xalkori OR Vorinostat OR Zolinza OR Romidepsin OR Istodax OR Bexarotene OR Targretin OR Alitretinoin OR Panretin OR Tretinoin OR Vesanoid OR Bortezomib OR Velcade OR Carfilzomib OR Kyprolis OR Pralatrexate OR Folotyn OR Bevacizumab OR Avastin OR Ziv-aflibercept OR Zaltrap OR Sorafenib OR Nexavar OR Sunitinib OR Sutent OR Pazopanib OR Votrient OR Regorafenib OR Stivarga OR Cabozantinib OR Cometriq OR Rituximab OR Rituxan OR Alemtuzumab OR Campath OR Ofatumumab OR Arzerra OR Ipilimumab OR Yervoy OR cTositumomab OR 131I-tositumomab OR Bexxar OR Ibritumomab tiuxetan OR Zevalin OR Denileukin diftitox OR Ontak OR Brentuximab vedotin OR Adcetris)

Appendix 2. Skindex-29© [21]

Skindex29
©MMChren,1996

These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My skin hurts	☐1	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5
21. I am embarrassed by my skin condition	☐1	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐5

Appendix 3. Skindex-16© [21]

kindex16
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THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓			•			Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐

Skindex16 - United States/English - Mapi Institute.
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Appendix 4. Dermatology Life Quality Index (DLQI) [22]

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	 Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒

Please check you have answered EVERY question. Thank you.

Appendix 5. Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitors-18 (FACT-EGFRI-18) [15]

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
ST4	My skin or scalp feels irritated	0	1	2	3	4
ST5	My skin or scalp is dry or "flaky"	0	1	2	3	4
ST6	My skin or scalp itches	0	1	2	3	4
ST7	My skin bleeds easily	0	1	2	3	4
ST9	I am bothered by a change in my skin's sensitivity to the sun	0	1	2	3	4
ST32	My skin condition interferes with my ability to sleep	0	1	2	3	4
ST22	My skin condition affects my mood	0	1	2	3	4
ST17	My skin condition interferes with my social life	0	1	2	3	4
ST24	I am embarrassed by my skin condition	0	1	2	3	4
ST37	I avoid going out in public because of how my skin looks	0	1	2	3	4
ST26	I feel unattractive because of how my skin looks	0	1	2	3	4
ST34	Changes in my skin condition make daily life difficult	0	1	2	3	4
ST38	The skin side effects from treatment have interfered with household tasks	0	1	2	3	4
ST16	My eyes are dry	0	1	2	3	4
ST15	I am bothered by sensitivity around my fingernails or toenails	0	1	2	3	4
ST29	Sensitivity around my fingernails makes it difficult to perform household tasks	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
ST11	I am bothered by increased facial hair	0	1	2	3	4

Appendix 6. Hand-Foot Syndrome 14 [HFS 14] [17]

Hand–Foot Syndrome (HFS)-14

Please respond to the following statements as spontaneously as possible. There is no right or wrong answer, just whatever corresponds to what you experience on a daily basis.

Specify the area affected by your hand-foot syndrome: ☐Hands ☐Feet ☐Both

Would you say your hand-foot syndrome tends to be: ☐Very painful ☐Moderately painful ☐Not painful

	Yes, always	Yes, from time to time	No, never	Not relevant to me
1. I find it hard to turn the key in my door because of my hand–foot syndrome	☐	☐	☐	
2. I find it hard to prepare my meals because of my hand-foot syndrome	☐	☐	☐	
3. I have difficulty performing everyday actions because of my hand-foot syndrome	☐	☐	☐	
4. I have difficulty washing myself, putting on makeup (or shaving) because of my hand-foot syndrome	☐	☐	☐	
5. I find it hard to drive my car because of my hand-foot syndrome	☐	☐	☐	☐
6. I find it hard to put on my stockings/tights (or my socks) because of my hand-foot syndrome	☐	☐	☐	
7. I take longer than usual to get dressed because of my hand-foot syndrome	☐	☐	☐	
8. I have difficulty putting on my shoes because of my hand-foot syndrome	☐	☐	☐	
9. It is hard for me to stand because of my hand-foot syndrome	☐	☐	☐	
10. I have difficulty walking, even over quite short distances, because of my hand-foot syndrome	☐	☐	☐	
11. I tend to stay seated or lying down because of my hand-foot syndrome	☐	☐	☐	
12. I find it hard to fall asleep because of my hand-foot syndrome	☐	☐	☐	
13. My work is suffering because of my hand-foot syndrome	☐	☐	☐	☐
14. My relationships with others are less amicable because of my hand-foot syndrome	☐	☐	☐	

Patient Signature_____ Date*_____ Time*_____ (* indicates required)

Signature_____Title*_____ Date*_____ Time*_____ (* indicates required)

☐ Initial Visit ☐ Follow Up Visit

XX-XXXXX XXX CIMC Approval Date: xx/xx/xx Rev: XX/XX.XXX.xx

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