Topical corticosteroid therapy for facial acneiform eruption due to EGFR inhibitors in metastatic colorectal cancer patients: a randomized controlled trial comparing starting with a very strong or a weak topical corticosteroid (FAEISS study, NCCH1512, colorectal part)

Katsuko Kikuchi1,2 · Naoya Yamazaki3 · Keiko Nozawa4,5 · Haruhiko Fukuda6 · Taro Shibata7 · Ryunosuke Machida7 · Tetsuya Hamaguchi8 · Atsuo Takashima9 · Hirokazu Shoji9 · Narikazu Boku9 · Sumiko Takatsuka10 · Tatsuya Takenouchi10 · Tomohiro Nishina11 · Shusuke Yoshikawa12 · Masanobu Takahashi13 · Akiko Hasegawa14 · Akihito Kawazoe15 · Toshiki Masuishi16 · Hitoshi Mizutani17 · Yoshio Kiyohara12

Received: 13 August 2021 / Accepted: 27 January 2022 / Published online: 3 February 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

Background Although pre-emptive therapy with oral tetracycline, moisturizer, sunscreen, and topical corticosteroid is useful for preventing acneiform eruption (AfE) due to epidermal growth factor receptor (EGFR) inhibitors, no studies have examined the efficacy of topical corticosteroids themselves, or investigated the optimal potency of corticosteroid for treating facial AfE (FAfE).

Patients and methods Screened patients with RAS wild-type colorectal cancer started pre-emptive therapy with oral minocycline and moisturizer on initiation of cetuximab or panitumumab therapy. Patients who developed grade 1 or 2 FAfE were randomly allocated to two groups: a ranking-down (RD) group that started with a very strong corticosteroid and serially ranked down every 2 weeks unless FAfE exacerbated; and a ranking-up (RU) group that started with a weak corticosteroid and serially ranked up at exacerbation. FAfE grade, patient quality of life, and adverse events (AEs) with topical corticosteroid were evaluated every 2 weeks. The primary endpoint was the total number of times grade 2 or higher FAfE was identified in the central review of the 8-week treatment period.

Results No significant differences in total numbers of grade 2 or higher FAfE or in AEs caused by topical corticosteroids were observed between groups during the 8 weeks. Incidence of grade 2 or higher FAfE tended to be lower in the RD group during the first 2 weeks.

Conclusion Considering the long-term care of FAfE, the RU regimen appears suitable and should be considered the standard treatment for FAfE due to EGFR inhibitor therapy.

Trial registration UMIN Clinical Trials Registry (UMIN000024113).

Keywords Epidermal growth factor receptor (EGFR) · Anti-EGFR antibody · Colorectal cancer · Skin toxicity · Acneiform eruption · Topical corticosteroid

Introduction

Epidermal growth factor receptor (EGFR) inhibitors including monoclonal antibodies (mAbs) for EGFR and tyrosine kinase inhibitors (TKIs) are effective therapeutic options for patients with colorectal cancer (CRC), non-small cell lung cancer (NSCLC), and squamous cell carcinoma of head and neck (SCCHN). Anti-EGFR mAbs such as cetuximab and panitumumab have been used for metastatic CRC as monotherapies or in combination with other anticancer agents. Patients receiving EGFR inhibitors commonly present with skin toxicities, including acneiform eruption (AfE), which sometimes cause discontinuation of the therapy. AfE develops as early as weeks 1–3 after initiating the therapy and reaches peak frequency by weeks 3–5 [1]. In particular,
Facial AEs (FAEs) can cause psychological distress and impair patient quality of life (QOL). In the STEPP [2] and J-STEPP [3] studies, pre-emptive therapy with oral doxycycline or minocycline, weak topical corticosteroid, and skin moisturizer were shown to exert favorable effects in preventing AEs with panitumumab therapy, although the effects of topical corticosteroid monotherapy on AEs remain unclear. Because of concerns regarding steroid-induced dermatitis (SID) [4] due to topical corticosteroid for facial lesions, weak- or medium-potency corticosteroids have been used for FAE in clinical practice. However, the efficacy of weak topical corticosteroids controlling FAE activity is sometimes unsatisfactory. Recently, rapid effects have been reported from starting topical therapy with a very strong corticosteroid [5]. In addition, distinguishing between SID and FAE due to EGFR inhibitors is not easy for oncologists treating CRC patients without consulting dermatologists.

The present study was designed to compare two regimens of topical corticosteroid therapy for AEs due to EGFR inhibitors among patients with CRC or NSCLC, with a focus on facial lesions (a phase III, open-label, randomized trial evaluating topical corticosteroid for Facial Acneiform dermatitis by EGFR Inhibitors: Stepwise rank down from potent corticosteroid; FAEISS study; NCCH1512). The regimens comprised one with serial ranking down from a very strong corticosteroid, and one with serial ranking up from a weak corticosteroid. Here, we present the primary analysis of metastatic CRC patients who received cetuximab or panitumumab. The results in NSCLC patients have been published in a separate paper [6].

Materials and methods

Patients

Eligible patients were those with RAS wild-type metastatic CRC who received anti-EGFR antibody drugs (cetuximab or panitumumab). Other eligibility criteria included age, 20–79 years; Eastern Cooperative Oncology Group Performance Status [7] score 0 or 1; absence of active bacterial, fungal, and viral infections; and absence of any facial lesions influencing the evaluation of facial lesions. Informed consent for participation in this prospective study was obtained prior to enrolment. Patients with a history of previous anti-EGFR therapy were excluded.

Study design

This study was an open-label, multicenter, randomized controlled trial. As the first registration for screening before randomization, eligible patients started pre-emptive therapy with oral minocycline at 100 mg or 200 mg daily, and application of skin moisturizer containing heparinoid to the face twice daily from the date of starting anti-EGFR antibody therapy. All screened patients were instructed to avoid solar ultraviolet radiation, and use of sunscreen was recommended. Patients were instructed to apply topical 0.5% prednisolone cream when they developed FAE. Patients who developed FAE grade 1 or 2 within 8 weeks were randomly assigned to one of two groups: a ranking-up (RU) group or a ranking-down (RD) group. The topical corticosteroids used in this study are listed in Supplementary Table S1. The RU group started topical therapy with 0.5% prednisolone cream. When the grade of FAE was exacerbated as judged by the attending physician, the topical corticosteroid was ranked up to one class higher. In contrast, the RD regimen started with a topical very strong corticosteroid, and then corticosteroid was changed to one rank lower every 2 weeks. If the grade of FAE exacerbated, the class of topical corticosteroid was maintained without ranking down (Fig. 1). In both groups, topical corticosteroids of strong or very strong class were used for FAE on non-face areas. If grade 3 or higher FAE affecting the whole body according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0-JCOG (Japan Clinical Oncology Group) was observed, protocol treatment was terminated.

Evaluations

Efficacy variables were FAE grade and patient QOL. For the assessment of endpoints, FAE was graded after the end of the 8-week treatment by three trained dermatologists (central review) based on digital photographs of the face taken under a pre-determined, standardized method on each evaluation date. According to the qualitative scheme described by Scope et al. [8], with the following minor modification, FAE was classified as grade 0, no symptoms; grade 1, less than one-third of the face involved; grade 2, more than one-third but less than two-thirds of the face involved; or grade 3, more than two-thirds of the face involved. QOL was assessed using the Dermatology Life Quality Index (DLQI) questionnaire immediately before and after completing 8 weeks of topical corticosteroid therapy.

Safety variables were specified as topical corticosteroid- and EGFR inhibitor-induced adverse events (AEs). AEs due to topical corticosteroid were also assessed by 3 dermatologists based on the digital photographs of the face according to the following criteria for SID and topical (bacterial/fungal/viral) infection. SID was assessed as grade 0, no symptoms; grade 1, mild symptom, not interfering with daily life; grade 2, moderate symptom, partially interfering with daily life; or grade 3, severe symptom, severely interfering with daily life. Topical infection was assessed as grade 0, no infection; grade 1, involved lesion affects less than one-third of the area of
face receiving topical treatment; grade 2, involved lesion affects more than one-third and less than two-thirds of the area of the face receiving topical treatment, and requires use of antibacterial medication; or grade 3, involved lesion affects more than two-thirds of the area of the face receiving topical treatment, and requires use of intravenous antimicrobial agents. The severity of EGFR inhibitor-induced AEs of the skin (i.e., pruritus, paronychia, and xerosis) and AfE of the whole body were assessed according to CTCAE version 4.0-JCOG by an attending physician.

Efficacy and safety variables were evaluated at the time of randomization (i.e., on the start date) and at 2, 4, 6, and 8 weeks after starting randomized topical corticosteroid therapy, with the exception of the aforementioned QOL assessments.

**Study objectives (endpoints)**

On central review, presence or absence of FAfE grade 2 or higher at every evaluation date during the 8-week study period was checked, and the total number of times FAfE grade 2 or higher occurred during the 8-week study period was determined as the primary endpoint. Secondary endpoints were the incidences of FAfE of grade 2 or higher, FAfE of grade 3 or higher, and AEs due to topical corticosteroid during the study period. The numbers of patients who continued EGFR therapy, with FAfE of grade 1 or higher and with non-lowered QOL scores at the end of the study period, were also evaluated.

**Statistical analyses**

A superiority test design was applied to determine whether the duration of grade 2 or higher FAfE during the study period was shorter in the RD group compared to the RU group. The total number of times FAfE grade 2 or higher was observed in the 8-week study (5 evaluation points) was compared between groups using the stratified Wilcoxon rank-sum test, with drug and sex as stratification factors. To test the null hypothesis (i.e., that there are no differences between groups in terms of the primary endpoint) using the stratified Wilcoxon rank-sum test with a one-sided alpha of 0.05 and 80% power, 94 patients were required for the primary analysis. Assuming the incident proportion of FAfE (grade 1 or higher) as 85%, a sample size of 120 patients was planned for the first registration. Although this study was initially planned to include NSCLC patients, due to the low incidence of FAfE from EGFR-TKI treatment, registration of NSCLC patients was closed early and the results of that subgroup were published independently [6]. The incidences of FAfE of grade 2 or higher, and of FAfE grade 3 or higher, and the proportions of continued EGFR therapy, FAfE grade 1 or higher, and non-lowered QOL scores at the end of the study were evaluated using Fisher’s exact test. Incidences of AEs due to topical CS during the 8-week study period were compared between the RU and RD groups using Fisher’s exact test. In addition, subgroup analyses for drug (cetuximab or panitumumab), additional anticancer drugs, sex, and age (less than vs. greater than or equal to the median) were performed. One-sided $p < 0.05$ was considered statistically significant for analysis of the primary endpoint. Statistical analyses were performed using SAS® version 9.4 software (SAS Institute, Cary, NC).

**Results**

**Patients**

Between October 2016 and December 2018, a total of 172 patients with metastatic CRC were enrolled at the first
registration and received pre-emptive therapy. All 106 patients who developed grade 1 or 2 facial AfE were randomized to the RU group \((n = 53)\) or RD group \((n = 53)\). Baseline characteristics were well balanced between groups (Table 1) and the proportion of grade 2 or higher FAE was also similar between the RU group \((11.3\%)\) and RD group \((9.8\%)\). Two patients in the RD group terminated EGFR inhibitor therapy due to progression of the primary disease (untreated patients in Fig. 2). In the RD group, 1 patient judged as grade 3 by central review was ineligible. In the RU group, the potency of corticosteroid was ranked up to medium class in 2 patients before randomization within 2 weeks after initiating EGFR inhibitor therapy because of exacerbated FAE.

In the RD group, 16 patients failed to achieve stepwise ranking down due to exacerbation of FAE at the 8-week evaluation (Table 2). The potency of corticosteroid was ranked up to medium in 10 patients and to strong in 2 patients at the 8-week evaluation in the RU group (Table 2).

### Efficacy

As the primary endpoint, no significant difference in the total number of observation of grade 2 or higher FAE was seen between groups, using anticancer agents and sex as stratification factors \((p = 0.86)\) (Table 3). The incidence of FAE grade 2 or higher increased in a time-dependent manner. In the RU group, 11.3%, 26.1%, 32.6%, 35.0%, and 35.7% of patients had developed FAE grade 2 or higher at weeks 0 (second registration), 2, 4, 6, and 8 of the study, respectively. In the RD group, 9.8%, 15.7%, 34.1%, 39%, and 53.8% developed FAE grade 2 or higher at the corresponding weeks (Table 4). Incidences of grade 2 or higher FAE and grade 3 or higher FAE during the 8 weeks, continuation of EGFR therapy, and grade 1 or higher FAE at the end of protocol treatment showed no differences between groups (Supplementary Table S2).

### QOL

The number of patients with no worsening of QOL score was low in both groups, at 2.0% in the RU group and 6.4% in the RD group, and no significant difference was apparent between groups (Supplementary Table S2).

### Safety

Before randomization, 2 patients discontinued the pre-emptive therapy because of pruritus or liver dysfunction, probably caused by minocycline. After randomization, 2 patients in the RU group terminated protocol treatment due to grade 3 diarrhea and grade 3 anorexia, caused by oral minocycline. One patient in the RD group terminated treatment due to local infection of the face, which was suspected to be due to topical corticosteroid. However, no differences in incidences of AEs caused by topical corticosteroid (i.e., SID and local infection) were seen between groups (Supplementary Table S3).

### Discussion

In the present study, pre-emptive therapy with oral minocycline and skin moisturizer on the face were started simultaneously with EGFR inhibitors, and topical 0.5% prednisolone cream, as a weak corticosteroid, was permitted for use against FAE that developed before randomization. Grade 1 or 2 FAE developed in 106 of 172 subjects \((61.6\%)\) before randomization. This incidence is lower than those of previous reports without pre-emptive therapy, in which 90% with panitumumab and 80–86% with cetuximab developed AfE at some site on the body [9]. Favorable effects from the pre-emptive therapy on FAE were suggested.

The duration of grade 2 or higher FAE during the 8-week study period was assessed as the number of observations among the 5 observation time points for the primary

| Table 1 Patient characteristics | First registration alone \((n = 66)\) | RU group \((n = 53)\) | RD group \((n = 53)\) |
|---------------------------------|----------------------------------|----------------|----------------|
| Age \(\text{Median (range) year}\) | 65 \((26–79)\) | 62 \((36–76)\) | 58 \((26–78)\) |
| Sex \(\text{no. (%)}\) | | | |
| Male | 33 \((50.0)\) | 36 \((67.9)\) | 35 \((66.0)\) |
| Female | 33 \((50.0)\) | 17 \((32.1)\) | 18 \((34.0)\) |
| EGFR inhibitors and other anticancer agents \(\text{no. (%)}\) | | | |
| Cetuximab | NA | 0 | 2 \((3.9)\) |
| Cetuximab plus other agents | NA | 10 \((18.9)\) | 9 \((17.6)\) |
| Panitumumab | NA | 3 \((5.7)\) | 3 \((5.9)\) |
| Panitumumab plus other agents | NA | 40 \((75.5)\) | 37 \((72.5)\) |
endpoint. The results showed no significant difference between RU and RD groups, and we could not identify any advantage of starting with a very strong corticosteroid. Moreover, no significant differences were seen between regimens in secondary endpoints, as the incidence of grade 2 or higher or grade 3 or higher FAfE during the study period, proportions with continuation of EGFR inhibitors, grade 1 or higher FAfE, or the percentage of patients with no worsening of QOL at the end of the study.

The RD regimen showed more favorable effects during the first 2 weeks but could not maintain control later and more than 50% of patients showed grade 2 or higher FAfE by the end of the study. The severity of FAfE could potentially have increased over time in some patients, probably because of the initial pre-emptive treatment with oral minocycline, and FAfE failed to maintain control in the RD group later in the treatment period, because the potency of topical corticosteroid was weakened in accordance with the protocol. This also suggested that topical corticosteroids offering strong potency or above are effective in controlling FAfE, whereas topical corticosteroids of medium potency or below might be inadequate to control FAfE in some severe cases.

Long-term use of stronger topical corticosteroids on the face carries a risk of AEs including SID and secondary

| Table 2 | Topical corticosteroid used during the course of protocol treatment |
|---------|---------------------------------------------------------------|
|         | RU group, treated patients (n = 53)                          | RD group, treated patients (n = 51) |
|         | Weak  | Medium | Strong | Very strong | Weak  | Medium | Strong | Very strong |
| 0 to 2 weeks | 46    | 2*     | 0      | 0           | 1**   | 0      | 0      | 50          |
| 2 to 4 weeks | 39    | 5      | 0      | 0           | 0     | 0      | 40     | 8           |
| 4 to 6 weeks | 33    | 9      | 0      | 0           | 0     | 29     | 15     | 2           |
| 6 to 8 weeks | 31    | 10     | 2      | 0           | 26    | 12     | 3      | 1           |

One * out of 2 patients in the RU group and one ** in the RD group were assessed as ineligible. Because of disappearance of AfE, some patients stopped using topical CS.
infection, so we used a stepwise ranking down every 2 weeks from a very strong corticosteroid to a weak corticosteroid unless exacerbation developed. Grade 1 SID was observed in 1 patient in the RU regimen. Grade 1 SID in 2 patients and grade 2 local infection in 1 patient were observed in the RD regimen, but no marked differences were seen between regimens.

These results were based on an evaluation that lasted only 8 weeks. However, some patients resistant to strong topical corticosteroid for FAfE were present, particularly in the RD group, and these cases require careful attention to avoid SID. With the RU regimen, FAfE increased over time, but was limited to around 35% with some increase in corticosteroid potency by the end of the study.

Table 3  Number of episodes of grade 2 or higher facial acneiform eruption observed

| Primary analysis | Number of observation times of grade 2 or higher facial AIE (%) | Subgroup analysis |
|------------------|---------------------------------------------------------------|------------------|
| RU group         | N 0 1 2 3 4 5                                                | EGFR inhibitors cetuximab |
| RD group         | 53 32 (60.4) 5 (9.4) 6 (11.3) 5 (9.4) 2 (3.8)               | Number of observation times of grade 2 or higher facial AIE (%) |
|                  |                                                              |     |
| EGFR inhibitors panitumumab | N 0 1 2 3 4 5                                                |     |
| Concomitant medications with other anticancer agents | Number of observation times of grade 2 or higher facial AIE (%) |     |
| Concomitant medications without other anticancer agents | Number of observation times of grade 2 or higher facial AIE (%) |     |
| Gender           | Number of observation times of grade 2 or higher facial AIE (%) |     |

Table 4  Changes in the incidence of grade 2 or higher and grade 3 or higher facial AIE

|        | RU group, treated patients | RD group, treated patients |
|--------|---------------------------|---------------------------|
|        | Grade 2 or higher | Grade 3 or higher | Grade 2 or higher | Grade 3 or higher |
| At 2nd registration | 11.3% (6/53) | 0% (0/53) | 9.8% (5/51) | 2.0% (1/51) |
| 2 weeks after | 26.1% (12/46) | 2.2% (1/43) | 15.7% (8/51) | 2.0% (1/51) |
| 4 weeks after | 32.6% (14/43) | 7.0% (3/43) | 34.1% (16/47) | 12.8% (6/47) |
| 6 weeks after | 35.0% (14/40) | 7.5% (3/40) | 39.5% (17/43) | 11.6% (5/43) |
| 8 weeks after | 35.7% (15/42) | 11.9% (5/42) | 53.8% (21/39) | 10.3% (4/39) |

Missing or unevaluable cases were excluded from the denominator.
Conclusion

Pre-emptive therapy with oral minocycline and skin moisturizer showed some promise for reducing the risk of grade 2 FAfE. Stepwise down-ranking from a very strong topical corticosteroid for FAfE worked during the first 2 weeks, but failed to show significant advantages over the RU regimen from a weak corticosteroid through the 8 weeks of the study. Short-term use of a very strong corticosteroid may have some merit for suppressing initial FAfE, but a standard RU regimen from a weak corticosteroid appears suitable in long-term care for FAfE and should be considered the standard treatment for FAfE due to EGFR inhibitor therapy.

Limitations

The duration of protocol treatment was only 8 weeks and no follow-up period was provided afterward. Long-term observation of the duration and severity of FAfE, the potency of topical corticosteroid needed, and the AEs of topical corticosteroids on the face are necessary. We chose a central review using only photographs of the face to eliminate differences in evaluations by board-certified dermatologists and non-dermatologists, because not all hospitals have an attending dermatologist to evaluate skin symptoms.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-022-06874-1.

Acknowledgements The authors are grateful to their patients and the staff of all participating institutions. The authors also wish to thank Ms. Kaoru Koike, Mr. Tomoaki Yamada, and Ms. Keiko Ohata for assistance with data management, and Ms. Harumi Kaba for designing the case report forms and electronic data-capture system.

Author contribution Study conceptualization and design: Katsuko Kikuchi, Yoshio Kiyohara, Naoya Yamazaki, Tetsuya Hamaguchi, Keiko Nozawa, Haruhiko Fukuda, and Hitoshi Mizutani. Formal analysis and investigation: Taro Shibata, Ryunosuke Machida, and Haruhiko Fukuda. Funding acquisition: Keiko Nozawa. Material preparation and data collection: Katsuko Kikuchi, Naoya Yamazaki, Keiko Nozawa, Tetsuya Hamaguchi, Atsuo Takashima, Hirokazu Shoji, Narikazu Boku, Sumiko Takatsuka, Tatsuya Takenouchi, Tomohiro Nishina, Shusuke Yoshikawa, Masanobu Takahashi, Akiko Hasegawa, Akihito Kawazoe, Toshiki Masuishi, and Yoshio Kiyohara. The first draft of the manuscript was written by Katsuko Kikuchi. All authors contributed comments and helped revise previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This study was supported by Japan Agency for Medical Research and Development (AMED) under Grant Number JP17ck0106326.

Data availability All data generated or analyzed during this study are included in this published article.

Code availability Not applicable.

Declarations

Ethics approval This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics review board of each participating institution. Research ethics boards at all participating institutions approved the study protocol.

Consent to participate Each enrolled patient provided written informed consent.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

References

1. Agero AL, Dusza SW, Benvenuto-Andrade C et al (2006) Dermatologic side effects associated with the epidermal growth factor receptor inhibitors. J Am Acad Dermatol 55:657–670
2. Lacouture ME, Mitchell EP, Piperdi B et al (2010) Skin toxicity evaluation protocol with panitumumab (STEPPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 28:1351–1357
3. Kobayashi Y, Komatsu Y, Yuki S et al (2015) Randomized controlled trial on the skin toxicity of panitumumab in Japanese patients with metastatic colorectal cancer: HGC3G1001 study. J-STEPP Future Oncol 11:617–627
4. Ljubojevica S, Basta-Juzbasiae A, Lipozeneiae J (2002) Steroid dermatitis resembling rosacea: aetiopathogenesis and treatment. J Eur Acad Dermatol Venerol 16:121–126
5. Yamazaki N, Kiyohara Y, Kudoh S et al (2016) Optimal strength and timing of steroids in the management of erlotinib-related skin toxicities in a post-marketing surveillance study (Polarstar) of 9909 non-small-cell lung cancer patients. Int J Clin Oncol 21:248–253
6. Nishino K, Fujiwara Y, Ohe Y et al (2020) Results of the non-small cell lung cancer part of a phase III, open-label, randomized trial evaluating topical corticosteroid therapy for facial acniform dermatitis induced by EGFR inhibitors: stepwise rank down from potent corticosteroid (FAElSS study, NCCH-1512). Support Care Cancer 29:2327–2334
7. Oken MM, Creech RH, Tormey DC et al (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649–655
8. Scope A, Lieb JA, Dusza SW et al (2009) A prospective randomized trial of topical pimecrolimus for cetuximab-associated acne-like eruption. J Am Acad Dermatol 61:614–620
9. Overman MJ, Hoff PM (2007) EGFR-targeted therapies in colorectal cancer. Dis Colon Rectum 50:1259–1270

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
Authors and Affiliations

Katsuko Kikuchi1,2 · Naoya Yamazaki3 · Keiko Nozawa4,5 · Haruhiko Fukuda6 · Taro Shibata7 · Ryunosuke Machida7 ·
Tetsuya Hamaguchi8 · Atsuo Takashima9 · Hirokazu Shoji9 · Narikazu Boku9 · Sumiko Takatsuka10 ·
Tatsuya Takenouchi10 · Tomohiro Nishina11 · Shusuke Yoshikawa12 · Masanobu Takahashi13 · Akiko Hasegawa14 ·
Akihito Kawazoe15 · Toshiki Masuishi16 · Hitoshi Mizutani17 · Yoshio Kiyohara12

1 Tohoku University School of Medicine, Sendai, Japan
2 Sendai Taihaku Dermatology Clinic, AEON Supercenter 2F, 1-21-1 Kagitori Honcho, Taihaku Ku, Sendai, Miyagi 982-0805, Japan
3 Department of Dermatologic Oncology, National Cancer Center Hospital, Tokyo, Japan
4 Department of Nursing, Faculty of Nursing, Mejiro University, Saitama, Japan
5 Appearance Support Center, National Cancer Center Hospital, Tokyo, Japan
6 Data Management Division, National Cancer Center Hospital, Tokyo, Japan
7 Biostatistics Section, Research Management Division, National Cancer Center Hospital, Tokyo, Japan
8 Department of Medical Oncology, Saitama Medical University International Medical Center, Saitama, Japan
9 Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan
10 Department of Dermatology, Niigata Cancer Center Hospital, Niigata, Japan
11 Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan
12 Dermatology Division, Shizuoka Cancer Center Hospital, Sunto-gun, Japan
13 Department of Medical Oncology, Tohoku University Hospital, Sendai, Japan
14 Department of Medical Oncology, Osaka International Cancer Institute, Osaka, Japan
15 Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
16 Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan
17 Department of Dermatology, Mie University Hospital, Tsu, Japan