

Original Research

**Randomized, Double-blind, Placebo-controlled Phase II Study on the Efficacy and Safety
of Vitamin K1 Ointment for Cetuximab or Panitumumab-induced Acneiform Eruptions:
VIKTORIA study**

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25

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27 Hashimoto, Takahashi, and Iwasa contributed to the design of the study, and Hashimoto,

28 Takahashi, Iwasa, Honma, K. Kato, Hamaguchi, Yamada, Shimada contributed to conducting

29 the study. Yamazaki independently assessed acneiform eruption by photograph. Hashimoto and

30 Y. Kato wrote the initial draft of the article, and all authors critically reviewed and approved the

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32

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41

ABSTRACT

Purpose: Skin toxicities associated with anti-epidermal growth factor receptor (EGFR) antibodies, have a profound effect on the continuation of treatment. We assessed the efficacy and safety of vitamin K1 (VK1) ointment for acneiform eruptions induced by anti-EGFR antibody treatment.

Methods: The VK1 ointment was applied to one-half of an affected area and placebo ointment was applied to the other half twice a day for 8 weeks, with photography and clinical evaluation being performed every two weeks. The primary endpoint was the change of the VK1/placebo ratio for the number of acneiform eruptions counted by an independent dermatologist between the onset and end of the treatment period.

results: A total of 30 patients were enrolled. The mean VK1/ placebo ratio for the number of acneiform eruptions between the onset and end of the treatment period was -0.158 ± 0.680 and 0.146 ± 0.575 , respectively, which was not statistically significant ($P = 0.069$). The mean number of acneiform eruptions at each treatment period at the VK1 and placebo application sites was gradually decreased according to the treatment period.

57 **conclusion:** VK1 ointment was not effective against acneiform eruptions induced by
58 treatment with cetuximab or panitumumab. Reassessment of the VK1 concentration in the
59 ointment and the endpoint of skin lesions is required before designing further studies.

60

61 **Key words:** acneiform eruptions, cetuximab, panitumumab, vitamin K1, ointment

62 INTRODUCTION

63 Administration of cetuximab or panitumumab, antibodies targeting the epidermal growth factor
64 receptor (EGFR), combined with cytotoxic chemotherapy is the standard regimen for patients
65 with metastatic colorectal cancer of the K-ras wild type.¹ A typical adverse effect induced by
66 the anti-EGFR antibody therapy is skin toxicity because EGFR is not only expressed on tumor
67 cells, but also on various other cells, including keratinocytes, sweat gland cells, basal cells, and
68 the epithelial cells of hair follicles. Cutaneous symptoms occur in 80–90% of patients receiving
69 anti-EGFR antibody treatment and are severe in about 15% of the cases. It has been reported
70 that the onset and severity of cutaneous symptoms are correlated with the tumor response and
71 survival rate.^{2,3} Among the various cutaneous symptoms, acneiform eruptions often occur on
72 the nose, cheek, jaw, forehead, back, and/or chest within 3 weeks of starting the anti-EGFR
73 antibody therapy. These skin lesions cause physical and mental discomfort that can influence
74 both the continuation and intensity of the treatment, thus, having an effect on the clinical
75 outcomes.⁴ The standard management for acneiform eruptions induced by anti-EGFR antibody
76 therapy involves prophylactic administration of tetracycline antibiotics, moisturizing agents,

77 and topical steroids based on the results of several previous randomized-controlled trials^{4–13} and
78 a meta-analysis.¹⁴ However, the therapeutic methods needed for the management of skin
79 toxicity observed in the treatment with anti-EGFR antibody remains an unresolved issue in
80 clinical practice.

81 Vitamin K (VK) is a group of fat-soluble vitamins. Vitamin K1 (VK1) is found in the
82 dietary components, particularly in green leafy vegetables, and is metabolized to vitamin K2
83 via vitamin K3 (VK3) in humans.¹⁵ Beier et al¹⁶ reported EGFR activation and downstream
84 signaling in human keratinocytes exposed to VK3. We, therefore, hypothesized that EGFR
85 activation by short-term exposure to VK could counteract the inhibitory effect of cetuximab or
86 panitumumab on this receptor, resulting in reducing the acneiform eruptions in patients
87 receiving the anti-EGFR antibody therapy. In a clinical setting, topical VK1 ointment showed
88 promising data of pre-emptive intervention before skin toxicity or treatment after the rash
89 appeared, despite pilot studies of small sample size.^{17–19} However, to date, the treatment benefits
90 of topical VK1 application have not been established in any randomized, double-blind, placebo-
91 controlled prospective study. The strength of this study is that there is a reduced bias due to

within-patient comparison.

The present study was, therefore, designed to clarify whether VK1 ointment has the ability to reduce acneiform eruptions induced by anti-EGFR antibody therapy in Japanese patients with metastatic colorectal cancer.

PATIENTS AND METHODS

Patients

Among the Japanese patients aged 20 years or older, receiving treatment with cetuximab or panitumumab, those who developed acneiform eruptions on the face or chest and gave written informed consent were eligible for this study. Patients who were using VK preparations or VK antagonists were ineligible. The study protocol was approved by the Institutional Review Board of the National Cancer Center Hospital (approval number: 2011-196). This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research involving Human Subjects by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare of Japan.

107

108 **Study Design and Objectives**

109 This was a placebo-control, double blind, randomized phase II study in which the efficacy
110 and the safety of a VK1 ointment were evaluated in patients who developed acneiform eruptions
111 during treatment with cetuximab or panitumumab. The study was registered with UMIN-CTR
112 (UMIN000008099).

113

114 **Study Procedures**

115 Cetuximab was administered by intravenous infusion once a week, with the first dose (400
116 mg/m²) being infused over 2 hours and the second and subsequent doses (250 mg/m²) infused
117 over 1 hour. Panitumumab (6 mg/kg) was administered by intravenous infusion over 1 hour
118 every 2 weeks, and it was used concomitantly with anticancer drugs (5-fluorouracil, irinotecan,
119 and/or oxaliplatin) if deemed appropriate by the attending doctor. In those patients who
120 developed acneiform eruptions after the administration of cetuximab or panitumumab and met
121 the inclusion criteria for this study, two matching areas of the face (circle) or the chest

122 (diameter) (at least 10 cm × 10 cm) were marked on the right and left sides of the midline (one
123 on each side). VK1 ointment was applied to right or left area following assignment and the
124 placebo ointment was applied to the other area twice a day for 8 weeks, with photography and
125 clinical evaluation performed every 2 weeks. VK1 and placebo ointment were applied from the
126 evening of the treatment day. The treatment period was set at 8 weeks after the onset of skin
127 eruptions in the study protocol. However, when cetuximab or panitumumab was discontinued
128 before 8 weeks owing to disease progression or other events, the treatment period was modified
129 to run from the onset of acneiform eruptions to the time of discontinuation. During the treatment
130 period, the use of other topical preparations that could potentially influence the acneiform
131 eruptions was not allowed at the sites where the test drug or placebo was being applied. There
132 were no restrictions regarding the use of topical preparations at other sites and no restrictions
133 on oral antibiotics. The use of topical, oral, and parenteral steroids was prohibited during the
134 treatment period, apart from oral and/or parenteral steroids as antiemetic therapy in patients
135 receiving the anticancer drugs.

136

137 **VK1 and Placebo Ointments**

138 The VK1 and placebo ointments used in this study were prepared as follows. The 0.1%
139 VK1 ointment was prepared by thoroughly blending VK1 (100 mg) with white petrolatum (100
140 g). After the coloring fluid was prepared by dissolving the required amount of yellow food-
141 grade coloring agent in purified water (2.5 mL), the placebo ointment was prepared by
142 thoroughly blending the coloring fluid with white petrolatum (100 g).

143 The VK1 ointment was light-sensitive and patients were instructed to store it in a cool and
144 dark place, with the expiration date set at two weeks after the preparation. Stability testing was
145 performed using some randomly selected containers of the VK1 ointment to evaluate whether
146 the VK1 content was maintained over time.

147

148 **Blinding**

149 In this study, the patients, doctors, and pharmacists acting as clinical research coordinators
150 (study pharmacists) were blinded to the treatment assigned. The VK1 and placebo ointments
151 used in this study were indistinguishable with regard to appearance and each ointment was

152 randomly placed into a container labeled “A” or “B”. The study pharmacists instructed the
153 patients to apply the ointment in container “A” at the site on the right side and the ointment in
154 container “B” on the left side (Figure 1). The drug assignment list was sealed and was kept
155 securely by the study drug assignment manager until end of the study.

156

157 **Endpoint**

158 The primary endpoint was the change of the VK1/placebo ratio for the number of
159 acneiform eruptions counted by an independent dermatologist between the onset and end of the
160 treatment period. Patients were given diaries to record the daily application of the study drugs,
161 other ointments used concomitantly (if any), and administration of antibiotics (if any), and these
162 diaries were reviewed to assess the drug use and compliance. For evaluation of acneiform
163 eruptions, a dermatologist who was not involved in the study counted the number of eruptions
164 at the evaluation sites on photographs taken at each time of evaluation. In addition, the patient’s
165 attending doctor evaluated the eruptions by using Common Terminology Criteria for Adverse
166 Events (CTCAE) v4.0 and the Multinational Association of Supportive Care in Cancer

167 (MASCC) scale every 2 weeks as secondary endpoints (Supplemental Table S1). The
168 application of the ointments was checked from the patients' diaries. A compliance rate of 100%
169 was defined as the patient applying the study drugs to the sites twice daily every day throughout
170 the treatment period.

171

172 **Statistical Analysis**

173 The data are shown as means and standard deviation. The ratio of the number of acneiform
174 eruptions at the VK1 site to the number at the placebo site was calculated as follows:
175
$$\text{VK1/placebo ratio} = \frac{\{(\text{number of acneiform eruptions at the placebo site after treatment}) -$$

176
$$(\text{number of acneiform eruptions at the VK1 site after treatment})\}}{(\text{number of acneiform}$$

177
$$\text{eruptions at the placebo site after treatment})}.$$
 The mean VK1/placebo ratio for the number of
178 acneiform eruptions between the onset and end of the treatment period was analyzed by paired
179 *t*-test. In addition, the mean number of acneiform eruptions at 0, 2, 4, 6, and 8 weeks after the
180 treatment at the VK1 and placebo sites was analyzed by one-way analysis of variance (ANOVA)
181 followed by Dunnett's test. On the other hand, the proportion of patients who had eruptions \geq

Grade 2 based on CTCAE v4.0 and \geq Grade 2A based on MASCC scale between at the onset and 8 weeks after the treatment at the VK1 and placebo sites was analyzed by Fisher's exact test. All analyses were performed using JMP software version 14.2.0 (SAS Institute, Tokyo, Japan). All P values were two-tailed, and $P < 0.05$ was considered significant.

The number of patients required for this study was calculated using the following assumptions: the difference between the VK1/placebo ratio at the start of treatment and at the end of treatment was 0.25, the standard deviation of the difference was 0.4, the α error was set at 0.05 (two-sided), and the β error was set at 0.1. Accordingly, the number of patients required was estimated to be 27 patients, and the target number of patients was set at 30.

RESULTS

Patient Characteristics

As shown in Figure 2, 30 patients were enrolled from August 2012 to August 2014. One patient did not receive the treatment as per the protocol because of early progression; the remaining 29 patients were available for analysis. All the participants were examined for the

K-ras status, which was confirmed to be wild type. In eight of the 29 (27.5%) patients, anti-EGFR antibody treatment was terminated before 8 weeks (at 2, 4, and 6 weeks, there were 2, 3, and 3 cases respectively) due to disease progression. The baseline patient characteristics are listed in Table 1.

Primary Endpoint

The mean VK1/placebo ratio for the number of acneiform eruptions between the onset and end of the treatment period is shown in Figure 3. The values at the onset and end of the treatment were -0.158 ± 0.680 and 0.146 ± 0.575 , respectively, and were not statistically significant ($P = 0.069$). The photos at the start and end of protocol treatment are shown in Figure 4.

Secondary Endpoint

The mean number of acneiform eruptions at each treatment period on the VK1 and placebo sites is shown in Figure 5. The mean number of acneiform eruptions in both the groups was gradually decreased according to the treatment period, but there was no statistically significant

difference among all the periods on the VK1 site. On the other hand, there was statistically significant difference between 0 week and 4 and 8 weeks on the placebo site ($P = 0.042$ and $P = 0.011$, respectively). In addition, the proportion of patients who had eruptions \geq Grade 2 based on CTCAE v4.0 between the onset and 8 weeks on the VK1 and placebo site was 34.5% and 19.0%, respectively, which was not statistically significant ($P = 0.341$). In contrast, the proportion of patients who had eruptions \geq Grade 2A based on the MASCC scale between the onset and 8 weeks on the VK1 site was 93.1% and 57.1%, respectively, which was statistically significant ($P = 0.004$). Similar results were obtained for the placebo site, 89.6% and 66.7%, respectively, which was statistically significant ($P = 0.073$).

Compliance with the Study Treatment

The compliance rate exceeded 90% in 19 of the 29 patients (66%), whereas it was 70–90% in six patients (21%) and $< 50\%$ in three patients (10%). There was no difference in the number of ointment applications between the right and left sides in any of the patients. In one patient, data on the use of the ointments were missing. The mean amount of VK1 and placebo ointment

227 used over two weeks was 18.21 g (range: 0.5–100 g) and 18.51 g (range: 0–100 g), respectively.

228

229 **Adverse Effects**

230 No adverse effects that were thought to be caused by the VK1 or placebo ointments were
231 observed. To evaluate the systemic effect of VK1 ointment, prothrombin time- international
232 normalized ratio (PT-INR) was measured in 25 of the 29 patients. The PT-INR values were
233 within the normal range in all the patients before the start of the study treatment and also during
234 the treatment.

235

236 **DISCUSSION**

237 To date, there has been limited information available regarding the therapeutic benefit of
238 supportive therapy for skin toxicity induced by the anti-EGFR antibody therapy in a clinical
239 practice setting. To the best of our knowledge, the present study is the first randomized, double-
240 blind, placebo-controlled phase II design for checking the efficacy and safety of VK1 ointment
241 for cetuximab or panitumumab-induced acneiform eruptions. Furthermore, VK1 ointment was

242 not effective against acneiform eruptions induced by cetuximab or panitumumab. The present
243 findings, therefore, suggest that reassessment of the VK1 concentration in the ointment and the
244 method of evaluating skin lesions is required before designing further studies.

245 Our findings demonstrate that the primary endpoint did not show any significant difference
246 between the VK1 and placebo ointment treatments with regard to the effect on acneiform
247 eruptions induced by cetuximab or panitumumab. The present approach in our hypothesis that
248 EGFR activation by short-term exposure to VK could counteract the inhibitory effect of
249 cetuximab or panitumumab on this receptor completely failed. However, several previous
250 studies reported that topical VK1 ointment had promising efficacy of pre-emptive intervention
251 before skin toxicity or treatment after the rash appeared, despite pilot studies having a small
252 sample size.¹⁷⁻¹⁹ Our data for VK1 efficacy were inconsistent with those of Ocvirk et al,¹⁷ who
253 reported the improvement of skin rash of all grades after a median of 18 days with no adverse
254 effects in 30 metastatic colorectal cancer patients receiving cetuximab. Differences in the nature
255 of the study design and the methodology applied could account for discrepancies between both
256 the results. Ocvirk et al¹⁷ also reported that VK1 cream alone was enough to manage skin

257 toxicity in patients with Grade 1 acneiform eruptions. Taken together, it seems likely that VK1
258 cream may be effective on cetuximab or panitumumab-induced acneiform eruptions of Grade
259 1, but not in the case of severe skin toxicity more than Grade 2.

260 In general, adverse events caused by anticancer drugs are evaluated using CTCAE.
261 However, CTCAE does not appropriately evaluates acneiform eruptions because only the
262 percentage of the body surface area affected by eruptions is assessed, whereas symptoms such
263 as tenderness and pruritus are not considered. Since the effect of acneiform eruptions on the
264 patient is influenced by involvement of visible sites such as the face rather than by the total
265 area, evaluation using CTCAE can not accurately determine the severity of the rash.
266 Accordingly, we evaluated the efficacy of VK1 ointment based on the change in the number of
267 eruptions counted by an independent dermatologist. Each patient's attending doctor also
268 evaluated the acneiform eruptions by using CTCAE, by counting the number of eruptions, and
269 using the MASCC scale, which assesses the presence or absence of symptoms such as
270 tenderness and pruritus. However, none of these evaluations indicated that VK1 ointment could
271 improve cutaneous symptoms compared with the placebo ointment. This study is the first

272 within-patient comparison in which individual patients were randomized for application of the
273 VK1 ointment to the right or left side of an affected site, whereas the placebo ointment was
274 applied to the other side. If the patients are assigned to a test drug or placebo group when
275 evaluating a topical preparation, application of the ointment can vary between patients and it
276 becomes difficult to determine the efficacy of the test drug. In our study, the ointment containers
277 were collected after use to check the amount of ointment applied. Although the amount varied
278 between patients, they were blinded to the assignment of ointment. There was no marked
279 differences between the amounts of VK1 and placebo ointments used on each side by a single
280 patient. We observed that the number of acneiform eruptions decreased in both groups (Fig.4);
281 this could be attributed to the moisturizing effect of white petroleum. This method of blinded
282 within-patient comparison may be useful to reduce bias.

283 The present study has several limitations; the first was the concomitant use of antibiotics. In
284 this study, the use of topical steroids was prohibited so that the efficacy of VK1 ointment could
285 be evaluated more accurately, but antibiotics and moisturizing agents were allowed because it
286 was ethically problematic to compel the patients to only use the VK1 ointment for 8 weeks. As

287 a result, we do not demonstrate any effect of the VK1 ointment on acneiform eruptions. While
288 the number of acneiform eruptions was decreased at 8 weeks after the start of treatment, this
289 might be due to the concomitant use of antibiotics and moisturizing agents, and the petrolatum
290 base of the study drugs also has a moisturizing effect that might have improved the skin lesions
291 over time. Second, the concentration of VK1 in the ointment was 0.1%, based on the previous
292 studies. However, while the present study was underway, it was reported that 1% VK3 ointment
293 was not effective for skin disorders in a study evaluating the effect of topical VK3 preparations.
294 VK1 is found in the natural environment and is metabolized by vitamin-K epoxide reductase to
295 vitamin K2 via vitamin VK3 in humans. There are no detailed data on the absorption rate of
296 topical VK1 administered to the skin surface. VK3 has higher activity than VK1 and the LD₅₀
297 of VK3 is 50-times lower than that of VK1,^{20,21} suggesting that the VK1 concentration should
298 be reconsidered for future studies. Exposure time is important for VK3 to activate EGFR, and the
299 number of administrations of topical VK might have an affect on it¹⁵. Third, the endpoint was the
300 change in the VK1/placebo ratio for the number of acneiform eruptions, CTCAE, and MASCC
301 scale. A recent study evaluating the pre-emptive effect of VK1 on acneiform eruptions also

found no significant difference in the primary endpoint, but VK1 improved the WoMo score, an alternative and more thorough skin toxicity scoring tool for acneiform eruptions from 5 weeks.²² This suggests that the methods that were employed by us to evaluate the acneiform lesions in the present study might not have been sufficiently sensitive.

CONCLUSIONS

VK1 ointment was not effective against acneiform eruptions induced by treatment with cetuximab or panitumumab. Our data provide preliminary information about the Japanese population that can likely be translated to other Asian populations, and further highlights the need for additional research in this field. The reassessment of number of administrations and VK1 concentration in the ointment, as well as the endpoint of skin lesions, are required before designing further studies.

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318 **Role of sponsor**

319 This was an investigator-initiated study. The sponsor of the study had no role in the study design,
320 data collection, data analysis, data interpretation, or writing of the report. The corresponding
321 author had full access to all the data in the study and had final responsibility for the decision to
322 submit for publication.

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388 **Figure legends**

389 **Fig 1. Randomization**

390 A = Vitamin K1, B = Placebo or A = Placebo, B = Vitamin K1 random assignment (envelope
391 method)

392

393 **Fig 2. CONSORT diagram**

394

395 **Fig 3. Mean VK1/placebo ratio for the number of acneiform eruptions**

396 The data are shown as means and standard deviation. The mean VK1/placebo ratio for the
397 number of acneiform eruptions between the onset and end of the treatment period was analyzed
398 by paired *t*-test.

399

400 **Fig 4. The photos at the start and end of protocol treatment**

401 **Fig 5. Mean number of acneiform eruptions at each treatment period**

402 The data are shown as means and standard deviation. The mean number of acneiform eruptions

403 at 0, 2, 4, 6, and 8 weeks after the start of treatment at the VK1 site and at the placebo site was

404 analyzed by ANOVA followed by Dunnett's test.

405

406 **Table 1. Patients' characteristics at the baseline (N = 29). Data are given as number (%)**

407 **of patients unless otherwise mentioned**

Characteristic	Value
Sex	
Male	21 (72.4%)
Female	8 (27.6%)
Age, median (range), years	64 (31–78)
BSA, median (range), m ²	1.63 (1.34–2.05)
ECOG performance status	
0	13 (44.8%)
1	15 (51.7%)
2	1 (3.4%)
Anti-EGFR antibody	
Cetuximab	17 (58.6%)
Panitumumab	12 (41.4%)
Minocycline use	8 (27.6%)
Topical moisture use	19 (65.5%)
Baseline CTCAE at VK1 site	
Grade 1	19 (65.5%)

Grade 2	10 (34.5%)
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Baseline MASCC scale at VK1 site

0	1 (3.4%)
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1A	1 (3.4%)
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2A	17 (58.6%)
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3A	10 (34.5%)
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408 BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal

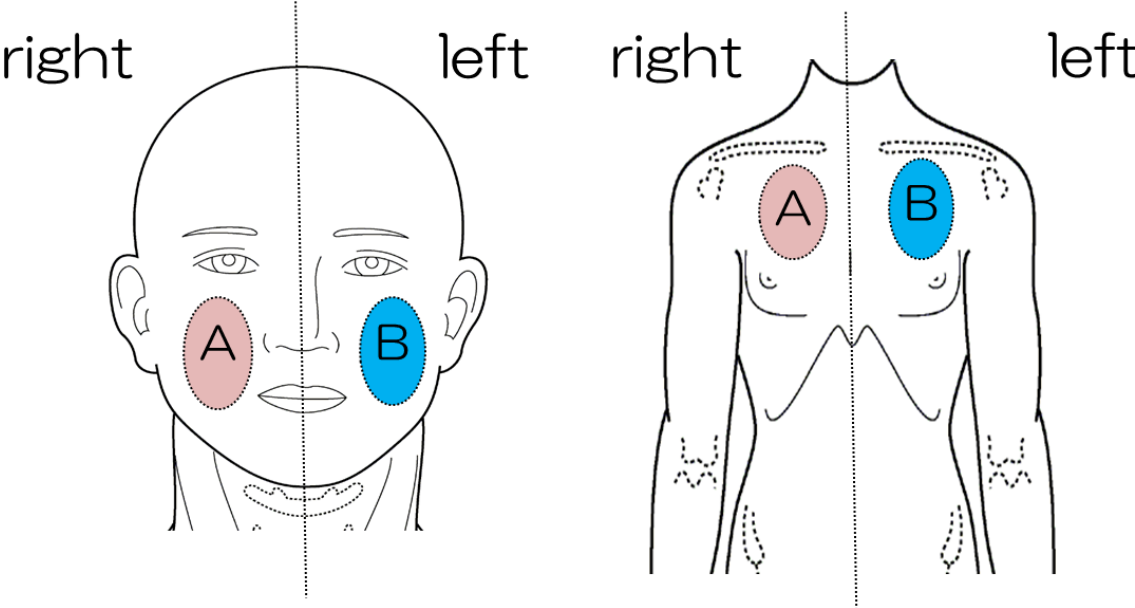
409 growth factor receptor; CTCAE = Common Terminology Criteria for Adverse Events; MASCC

410 = Multinational Association of Supportive Care in Cancer; VK = vitamin K

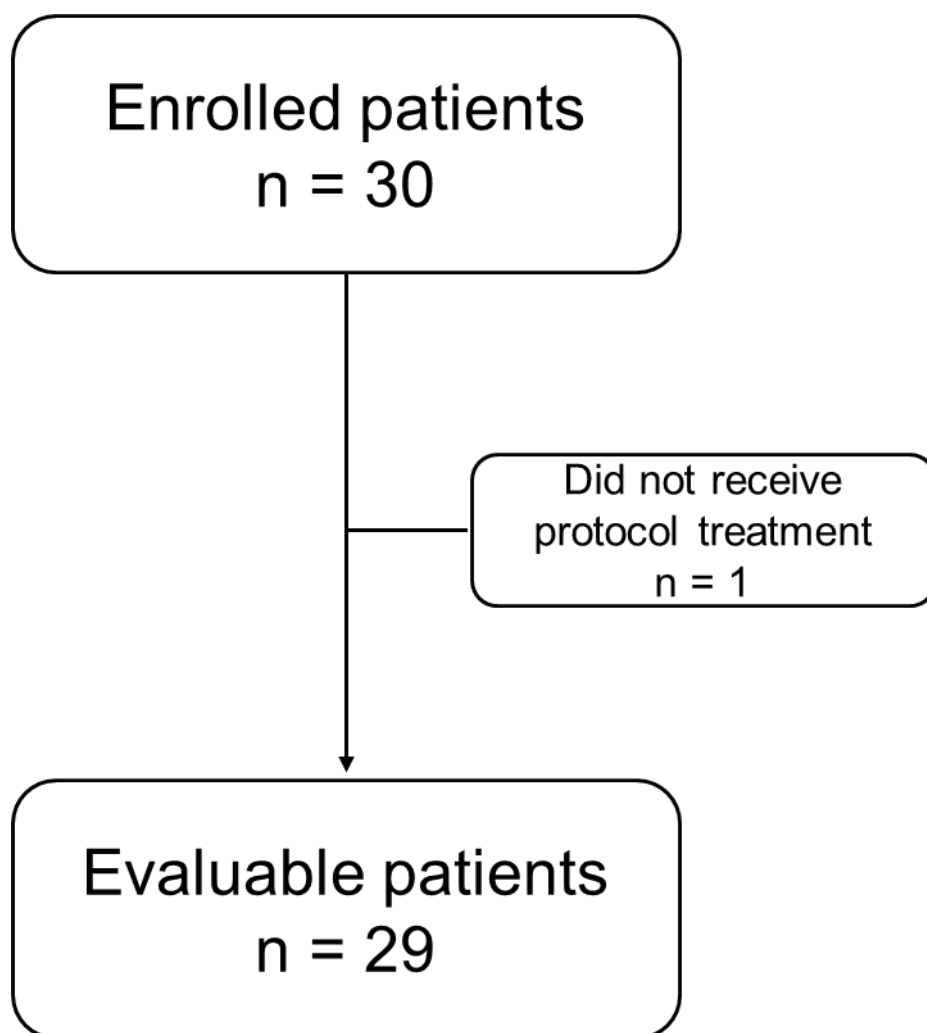
411

412

Fig. 1



413



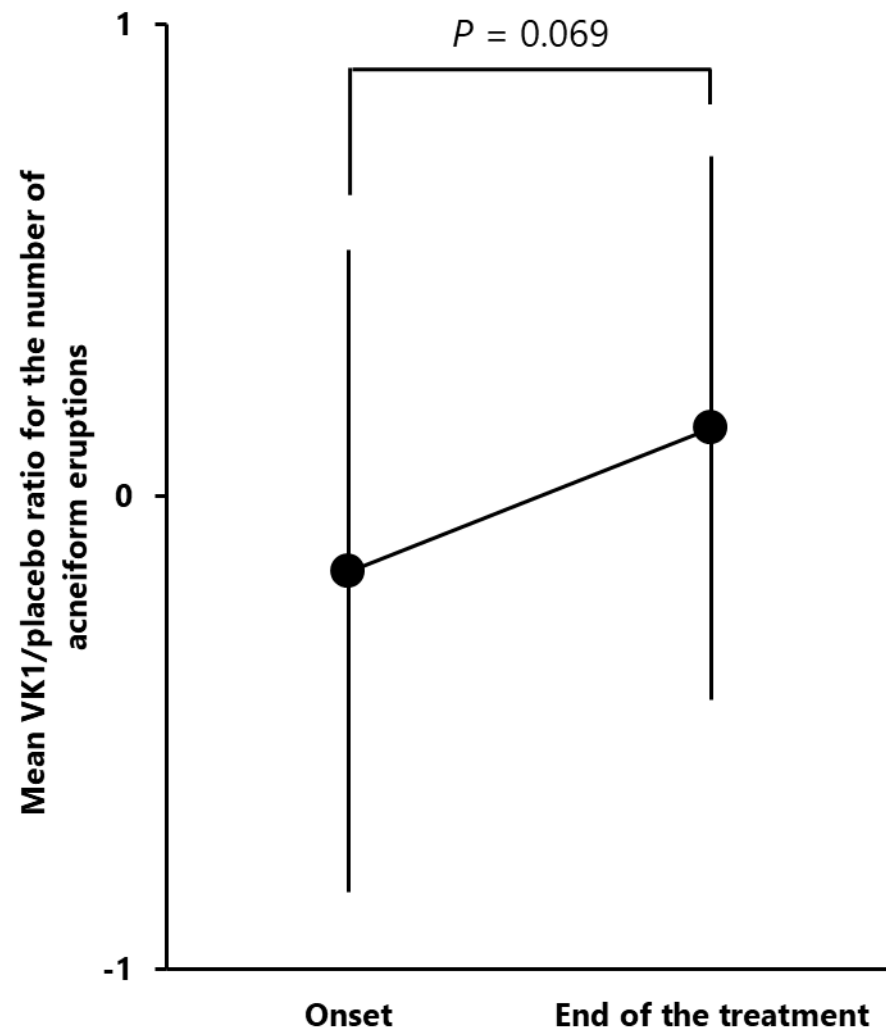


Fig. 3

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Fig 4.



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VK 1 start of treatment

VK 1 end of treatment (8 weeks)

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424

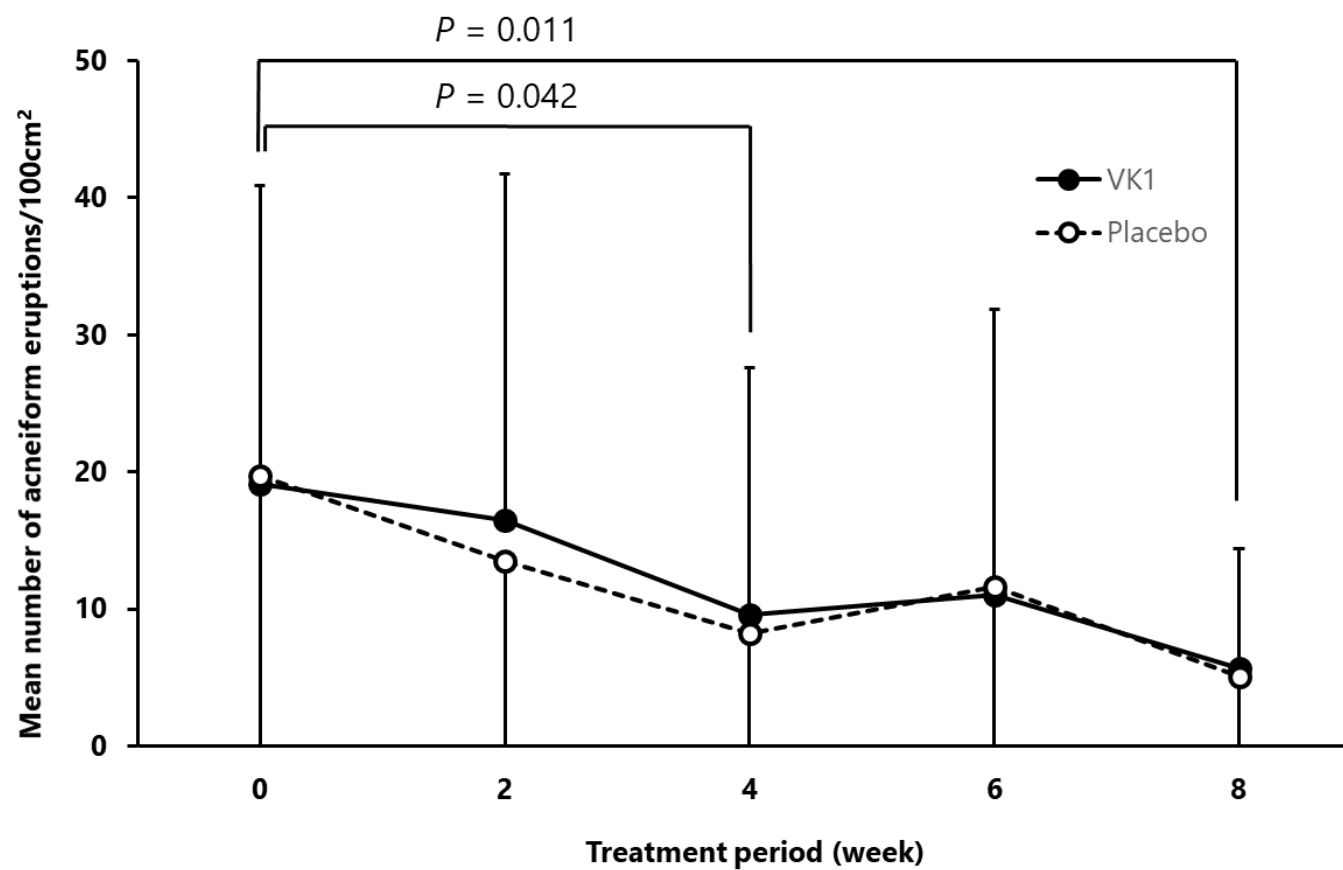
Placebo start of treatment



Placebo end of treatment (8 weeks)

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Fig. 5



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428

429 **Supplementary**

430 **Table S1. MASCC scale**

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Papulopustular eruption (grading individually for face, scalp, chest, or back)	1A Papules or pustules < 5 or 1 area of erythema or edema < 1 cm in size	2A Papules or pustules 6–20 or 2–5 areas of erythema or edema < 1 cm in size	3A Papules or pustules > 20 or More than five areas of erythema or edema < 1 cm in size	-
	1B	2B	3B	-

	<p>Papules or pustules < 5</p> <p>or</p> <p>One area of erythema or edema < 1 cm in size and pain or pruritus</p>	<p>Papules or pustules 6–20</p> <p>or</p> <p>2–5 areas of erythema or edema < 1 cm in size and pain, pruritus, or effect on emotins or functioning</p>	<p>Papules or pustules > 20</p> <p>or</p> <p>More than five areas of erythema or edema < 1 cm in size and pain, pruritus, or effect on emotins or functioning</p>	
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