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Impact of a planned dose interruption of dacomitinib in the treatment of advanced non-small-cell lung cancer (ARCHER 1042)

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Abstract

Objectives—Dacomitinib is a pan-HER inhibitor for advanced non-small-cell lung cancer (NSCLC). We explored the impact of a planned 4-day dacomitinib dose interruption on plasma exposure of dacomitinib and adverse events (AEs) of interest in Cohort III of the ARCHER 1042 study.

Materials and methods—Patients, treatment-naïve for advanced NSCLC with *EGFR* activating mutations, received oral dacomitinib 45 mg QD (once daily). A planned dose interruption occurred in Cycle 1 from Days 11 through 14. The primary endpoint was the pharmacokinetic (PK) characteristics of dacomitinib in Cycle 1 Day 10 and during dose interruption. Secondary endpoints included safety and concomitant medications used to treat AEs of interest.

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Conflict of interest

D-WK, SS, and BCC have no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.lungcan.2017.01.021>.

Results—Cohort III enrolled 25 patients. Median plasma $C_{\max}$ of dacomitinib in Cycle 1 Day 10 was 83.40 ng/mL. Average median plasma dacomitinib concentration during the 4-day dose interruption was 42.63 ng/mL. In the first 8 weeks of treatment 1) 80% of patients used concomitant medications for dermatologic AEs, 76% for diarrhea, and 44% for stomatitis, and 2) all patients experienced treatment-emergent AEs and 28% had all-causality Grade 3 AEs.

Conclusion—At 45 mg QD dosing, PK parameters of plasma dacomitinib in Cycle 1 Day 10 were comparable to that obtained in Cycle 1 Day 14 from other dacomitinib studies. Average median plasma dacomitinib concentration during the 4-day dose interruption was approximately half of the median plasma $C_{\max}$ of dacomitinib observed prior to dose interruption. The toxicity profile was consistent with that from other studies of dacomitinib.

Keywords

Dacomitinib; Non-small-cell lung cancer; Dose interruption; Pharmacokinetic; Supportive care

1. Introduction

Dacomitinib (PF-00299804) is an orally administered, irreversible, small-molecule pan-HER inhibitor in development for the treatment of advanced non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) activating mutations [1–3]. Acneiform rash, diarrhea, stomatitis, dry skin, and paronychia [1–4] are frequent adverse events (AEs) associated with dacomitinib and other *EGFR* tyrosine kinase inhibitors (TKIs) [5,6]. These AEs can lead to reduced treatment adherence, dose reductions, or permanent discontinuation of therapy, and may have a negative impact on treatment efficacy. ARCHER 1042, a triple cohort phase II study, explored prophylactic measures in dacomitinib treatment for patients with advanced NSCLC [7]. Cohorts I and II consisted of patients who received dacomitinib in the second-line setting. Data on these two cohorts showed that 1) doxycycline reduced the incidence of all causality, grade > 2 select dermatologic adverse events of interest (SDAEI) by 50% ($p = 0.016$); 2) doxycycline, as well as topical alclometasone dipropionate cream, alleviated patient-reported Quality of Life (QoL) on dermatologic symptoms; and 3) a probiotic, VSL#3, did not reduce the incidence of diarrhea and stomatitis/oral mucositis and did not have a positive impact on patient-reported QoL on diarrhea or stomatitis symptoms [7].

In the current report, we present data on Cohort III of the ARCHER 1042 study. Patients in this cohort were treatment-naïve for advanced NSCLC with known *EGFR* activating mutations. We explored the impact of a planned 4-day dacomitinib dose interruption on plasma exposure of dacomitinib and the effects of this dose interruption on AEs of interest. The reasons for the dose interruption were 1) to allow for the assessment of dacomitinib pharmacokinetics during the dose interruption and 2) to allow normal tissue-level repair and adaptation and to improve tolerance of skin and gastrointestinal mucosa.

2. Materials and methods

2.1. Patients

Patients had to meet the following inclusion criteria: 1) age ≥ 18 years; 2) evidence of measurable or non-measurable advanced (Stage IIIB/IV) NSCLC for which there was no curative therapy; 3) known *EGFR* mutation; 4) no prior systemic chemotherapy for advanced NSCLC; 5) no prior EGFR-targeted therapy; 6) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and 7) adequate renal and hepatic function.

Patients with any of the following were excluded from the study: 1) surgery, chemotherapy, radiotherapy, or biological/investigational agents within two weeks of study registration; 2) leptomeningeal or symptomatic brain metastases; 3) clinically significant gastrointestinal abnormalities; 4) known diffuse interstitial lung disease; and 4) uncontrolled or significant cardiovascular disease.

The study was done in accordance with the International Conference on Harmonisation and Good Clinical Practice standards. Approval from institutional review board/ethics committee at each participating institution was obtained. Patients provided written informed consent before the start of study-specific procedures. The study is registered with ClinicalTrials.gov (NCT01465802).

2.2. Study design and treatment schedule

All patients in Cohort III received open-label oral dacomitinib 45 mg QD (once-daily) from Day 1 of Cycle 1 (each cycle was defined as 28 days). Dacomitinib was withheld on Days 11, 12, 13 and 14 of Cycle 1. Dosing resumed from Day 15 of Cycle 1 until patients experienced unacceptable toxicity, tumor progression, or death. Further details on the treatment schedule are in the supplementary material.

2.3. Pharmacokinetic sampling and analysis

Blood samples for pharmacokinetic analysis of dacomitinib and its metabolite, PF-05199265, were collected at pre-specified intervals: pre-dose on Cycle 1 Day 10 and 2, 4, 6, 24, 48, 72, 96 and 120 h post-dose; and pre-dose on Day 1 of Cycle 3 through Cycle 10. Plasma concentrations of dacomitinib and PF-05199265 were analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

Pharmacokinetic (PK) parameters were derived using non-compartmental methods for dacomitinib and PF-05199265. The PK parameters were maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration-time curve from 0 to 24 h (AUC₂₄) on Day 10 of Cycle 1, and area under the plasma concentration-time curve, AUC₁₂₀, from Day 10 of Cycle 1 through Day 14 of Cycle 1 (dacomitinib was withheld on Days 11, 12, 13 and 14 of Cycle 1).

2.4. Study assessments

Adverse event and treatment assessments are described in the supplementary material. For the purposes of this study, we use the term “stomatitis”, rather than “mucositis” to describe

treatment-associated, clinically relevant oral damage including ulceration. Such terminology is consistent with the preferred use of stomatitis to describe oral mucosal injury with other non-cytotoxic treatment regimens and reflects differences in the underlying pathogenesis and clinical course and presentation of the conditions [8].

Patient-Reported Outcomes (PRO) of health-related QoL and disease/treatment-related symptoms were assessed using the Skindex-16 survey [9] and the modified-Oral Mucositis Daily Questionnaire (OMDQ) [10] as described previously [7].

2.5. Endpoints

The primary endpoint for Cohort III was the PK of dacomitinib and its metabolite, PF-05199265—specifically 1) area under the plasma concentration-time curve, AUC_{120} , from Day 10 of Cycle 1 through Day 14 of Cycle 1; 2) area under the plasma concentration-time curve from 0 to 24 h (AUC_{24}) on Day 10 of Cycle 1; 3) maximum observed concentration obtained by inspection of the data (C_{max}); and 4) time of occurrence of C_{max} (T_{max}).

The secondary endpoints were 1) the relative dose intensity (RDI) of dacomitinib in the first 8 weeks of treatment; 2) concomitant medication (both prescription and non-prescription) used for SDAEI, diarrhea, and stomatitis; and 3) overall safety profile as characterized by type, frequency, severity of adverse events as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4 (CTCAE v4). SDAEI were defined as acneiform dermatitis, dry skin, exfoliative rash, nail discoloration, nail disorder, paronychia, pruritus, rash, skin exfoliation, skin fissures, skin infection, skin laceration, and skin ulcer. Exploratory endpoints were patient-reported outcomes of QoL on dermatologic, diarrhea, and stomatitis symptoms.

2.6. Statistical analysis

Sample size was determined based on the observed inter-patient variability (30–40%) by the minimum number of patients required to provide good point estimates of plasma PK parameters. Further details are in the supplementary material.

3. Results

3.1. Patients

A total of 25 patients from two centers in the Republic of Korea and five centers in the USA were enrolled in Cohort III. Median age was 64 years; 72% of the patients were women; 60% of the patients were Korean (Table 1).

The median duration of dacomitinib treatment was 52.9 weeks (range: 2.9–164.1 weeks). The median number of cycles started per treated patient was 13.

3.2. Primary endpoint

Following 45 mg QD dosing for 10 days, the observed median plasma C_{max} was 83.40 ng/mL for dacomitinib and 12.20 ng/mL for PF-05199265 (Table 2). The observed median T_{max} was 5.85 h for dacomitinib and 5.98 h for PF-05199265. The observed median

exposure up to 24 h post-dose (AUC_{24}) on Day 10 of Cycle 1 for dacomitinib and PF-05199265 was 1620 ng·h/mL and 254 ng·h/mL, respectively.

The median plasma concentration-time plot for dacomitinib from the start of Day 10 to the end of Day 14 of Cycle 1 (Fig. 1A) showed that withholding dacomitinib from Days 11 through 14 resulted in a gradual decrease in plasma dacomitinib concentration, consistent with reported plasma half-life for dacomitinib. The median plasma dacomitinib concentration at the start of the dose interruption on Day 11 of Cycle 1 was 66.8 ng/mL and decreased to 26.3 ng/mL at the end of Day 14 of Cycle 1 (Fig. 1A). The average median plasma dacomitinib concentration on Day 11 was 59.03 ng/mL, on Day 12 was 46.53 ng/mL, on Day 13 was 36.35 ng/mL, and on Day 14 was 28.6 ng/mL (Fig. 1A). The average median plasma dacomitinib concentration during the dose interruption from the start of Day 11 through the end of Day 14 of Cycle 1 was 42.63 ng/mL.

The median plasma concentration-time plot for PF-05199265 from the start of Day 10 to the end of Day 14 of Cycle 1 showed a decrease in plasma PF-05199265 concentration (Fig. 1B). The average median plasma PF-05199265 concentration on Day 11 was 9.32 ng/mL, on Day 12 was 7.92 ng/mL, on Day 13 was 7.1 ng/mL, and on Day 14 was 6.5 ng/mL (Fig. 1B). The average median plasma PF-05199265 concentration from the start of Day 11 through the end of Day 14 of Cycle 1 was 7.71 ng/mL.

3.3. Secondary endpoints

3.3.1. Relative dose intensity (RDI) of dacomitinib—The RDI of dacomitinib during the first 8 weeks of treatment was 125 to >100% in two patients (the RDI in each of these two patients was 101.9%; this was because Cycle 1 for them lasted 29 days instead of 28 days), 100 to >90% in 14 patients, 90 to >75% in five patients, and 75% in four patients (Table 3). The RDI of dacomitinib for the first three treatment cycles is shown in Supplementary Table 1.

3.3.2. Concomitant medication for SDAEI, diarrhea, and stomatitis—During the first 8 weeks of treatment, 20 patients (80%) used concomitant medications for SDAEIs (Table 3), the most common treatment being topical clindamycin and hydrocortisone. Nineteen patients (76%) used concomitant medications for diarrhea, the most common treatment being loperamide hydrochloride. Eleven patients (44%) used concomitant medications for stomatitis, the most common treatment being topical dexamethasone.

3.3.3. Safety—Patients were followed up 28 days after the last dose of dacomitinib treatment and, if they were alive at that time, were deemed to have completed the study. There were no deaths due to study 28 days after or >28 days after the last dacomitinib dose. There was one death due to disease progression 28 days after the last dacomitinib dose and one death due to a thromboembolic event >28 days after the last dacomitinib dose.

All patients in the as-treated population experienced at least one treatment-emergent adverse event (TEAE) in the first 8 weeks of treatment (Table 3). One patient (4%) experienced grade 3 treatment-emergent serious adverse events (SAEs) (diarrhea, nausea, vomiting). Seven patients (28%) experienced all-causality grade 3 TEAEs; five of these patients had

dacomitinib-related grade 3 AEs (gastrointestinal disorders). No patient experienced all-causality grade 4 AEs or grade 5 AEs. Two patients (8%) permanently discontinued dacomitinib treatment because of AEs: one was dacomitinib-related (pruritus), the other was not (hyponatremia). Three patients (12%) had temporary interruptions because of AEs (diarrhea that was dacomitinib-related in two patients and acneiform dermatitis that was dacomitinib-related in one patient). Seven patients (28%) had dose reductions due to AEs that were dacomitinib-related (diarrhea, skin toxicities, stomatitis).

A summary of all-causality TEAEs across *all cycles* is shown in Supplementary Table 2. As expected, the incidences of SAEs, grade 3/4/5 AEs, dacomitinib discontinuations, and dose reductions were higher during this longer time period than in the first 8 weeks.

The most common all-causality any grade TEAEs in the first 8 weeks of treatment (Table 4) were diarrhea (92%), stomatitis (64%), acneiform dermatitis (60%), dry skin (56%), and paronychia (56%). The most common all-causality grade 2 TEAEs in the first 8 weeks of treatment (Table 4) were diarrhea (40%) and paronychia (36%). All-causality grade 3 TEAEs in the first 8 weeks included diarrhea (20%), nausea (4%), and vomiting (4%). The most common all-causality TEAEs across *all cycles* are shown in Supplementary Table 3.

3.4. Exploratory endpoints

For the Skindex-16 survey, exceeding the minimum clinically important difference (MCID) of 10 points indicates a clinically relevant sign of deteriorating symptoms [9]. The change in Skindex-16 total scores from baseline showed that there was clinically meaningful deterioration in the scores for all visits (Supplementary Fig. 1). Furthermore, there was clinically meaningful deterioration in the scores for the three Skindex subdomains (Symptoms, Emotion, Functioning) at all visits (Supplementary Fig. 2). For the modified-OMDQ, increasing scores are associated with greater symptom burden. The change in the modified-OMDQ scores for mouth and throat soreness (question 2 in the modified-OMDQ) from baseline showed that the scores worsened (i.e. increased) during dacomitinib treatment (Supplementary Fig. 3A). This trend was also observed for the modified-OMDQ scores for diarrhea (Supplementary Fig. 3B).

4. Discussion

The impact of a planned 4-day interruption in dacomitinib treatment was explored in Cohort III of the ARCHER 1042 study. The median time to first occurrence of diarrhea and rash in patients treated with dacomitinib (45 mg QD) is 10 days and 11 days, respectively (unpublished data from the Investigator's Brochure for dacomitinib, November 2013). Therefore, the dose interruption was scheduled to start at Day 11 of Cycle 1. We chose the duration of the dose interruption to be four days (1) to allow for normal tissue level repair and (2) based on symptom improvement observed after temporary discontinuation of drug in other dacomitinib studies.

Plasma PK parameters of dacomitinib following 14 days of dosing have been reported earlier in the US Phase I ARCHER 1001 trial [11], the South Korea Phase I ARCHER 1003 trial [12], and the Japan Phase I ARCHER 1005 trial [13]. The observed median plasma

$C_{\max}$ value for dacomitinib (83.40 ng/mL) and observed median $T_{\max}$ value (5.85 h) following 45 mg dacomitinib QD dosing for 10 days in Cohort III of ARCHER 1042 were in agreement with the Cycle 1 Day 14 values reported in the aforementioned studies. The observed median dacomitinib exposure over 24 h following 10 days of dosing in Cohort III of ARCHER 1042 (1620 ng·h/mL) was similar to 24-h exposures observed at steady state in other studies [7,12].

As a result of the planned 4-day dose interruption, the average median plasma dacomitinib concentration during Days 11 through 14 of Cycle 1 (42.63 ng/mL) in Cohort III of ARCHER 1042 was approximately 50% of the observed median $C_{\max}$ value of dacomitinib just before dose interruption (i.e. Day 10 of Cycle 1). This was also the case when the average median plasma dacomitinib concentration during the 4-day dose interruption in Cohort III of ARCHER 1042 was compared with the median $C_{\max}$ values following 14 days of dacomitinib dosing at 45 mg QD in other trials. The average median plasma dacomitinib concentration during the 4-day dose interruption was also lower than the median $C_{\max}$ value (59.9 ng/mL) following 14 days of dacomitinib dosing at 30 mg QD in the South Korea Phase I ARCHER 1003 trial [12]. It is difficult to determine if the average median plasma dacomitinib concentration during the 4-day dose interruption (42.63 ng/mL) would have been high enough to inhibit *EGFR* tyrosine kinase with activating mutations in advanced NSCLC since there is limited published data on the efficacy of dacomitinib administered at <30 mg QD: (1) in the US Phase I ARCHER 1001 trial, one patient with advanced NSCLC with an *EGFR* activating mutation had a partial response when administered dacomitinib at 16 mg QD [11]; (2) in the Japan Phase I ARCHER 1005 trial, one patient with NSCLC with an *EGFR* activating mutation had a partial response when administered dacomitinib at 15 mg QD [13]; and (3) no patients were administered dacomitinib at <30 mg QD in the South Korea Phase I ARCHER 1003 trial [12].

Secondary endpoints for Cohort III of the ARCHER 1042 study included concomitant medications used for SDAEI, diarrhea, and stomatitis, and the overall safety profile of dacomitinib. A total of 76% of patients in Cohort III received concomitant medications for diarrhea in the first 8 weeks of treatment, 44% received concomitant medications for stomatitis, and 80% received concomitant medications for SDAEIs. This was in agreement with the safety profile of dacomitinib in Cohort III where 92% of patients experienced any grade diarrhea in the first 8 weeks of treatment, 64% experienced stomatitis, and >55% experienced skin toxicities (60% experienced acneiform dermatitis, 56% experienced dry skin, and 56% experienced paronychia).

Although the safety profile of dacomitinib was a secondary endpoint for Cohort III of the ARCHER 1042 study, a comparison of the safety profile with that from other clinical studies of dacomitinib was not an objective. It is, therefore, difficult to draw firm conclusions about the impact of the 4-day dose interruption on dacomitinib-induced AEs. In the phase II ARCHER 1017 trial, patients were given dacomitinib, without a planned dose interruption, as first-line treatment for advanced NSCLC with *EGFR* activating mutations [3]. Within ARCHER 1017, a cohort of 29 patients received 45 mg dacomitinib QD. Compared with this cohort, Cohort III of the ARCHER 1042 study had a lower incidence of SAEs (24.0% in Cohort III vs 37.9% in the cohort from ARCHER 1017), a lower incidence of temporary

interruption of dacomitinib due to AEs (24.0% vs 72.4% in the cohort from ARCHER 1017), and a lower incidence of grade 3 or 4 AEs (60% vs 69.0% in the cohort from ARCHER 1017). The incidence of grade 5 AEs in Cohort III of ARCHER 1042 (8.0%) was similar to that in the cohort from ARCHER 1017 (6.9%). There are, however, caveats with these comparisons. First, the cohorts are from two separate studies. Second, the mean duration of dacomitinib treatment for the two cohorts was not identical (52.9 weeks [range: 2.9–164.1 weeks] for Cohort III from the ARCHER 1042 study, 71 weeks [range: 4.1–237.6 weeks] for the cohort from the ARCHER 1017 study).

PROs on the Skindex-16 survey for Cohort III patients indicated that there was clinically meaningful deterioration in the scores for all visits compared with the baseline score. In addition, PROs on diarrhea and stomatitis symptoms indicated that modified-OMDQ scores worsened during dacomitinib treatment. The deterioration in scores for the Skindex-16 survey and modified-OMDQ was consistent with the investigator-reported TEAEs on dermal and gastrointestinal toxicities. It is possible that a longer dose interruption or a more frequent dose interruption may have had a positive impact on PROs and improved the safety profile.

In conclusion, data from Cohort III of the ARCHER 1042 study indicated that the average median plasma dacomitinib concentration during the 4-day dose interruption was approximately 50% of the median C_{max} value obtained just before dose interruption. A trend towards a decrease in the incidence of SAEs and temporary interruption of dacomitinib due to AEs was also noted. We have previously reported that data on Cohort I of the ARCHER 1042 study showed that the incidence of dacomitinib-induced grade 2 SDAEI can be reduced with doxycycline [7]. We cannot firmly conclude whether a planned dose interruption would be an optimal strategy for mitigating dacomitinib-induced AEs because of the small sample size of Cohort III in the ARCHER 1042 study and the lack of a control group. However, the results from Cohort III and additional dosing regimens may allow for a better understanding of treatment schedules for dacomitinib and other EGFR TKIs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NSCLC	non-small-cell lung cancer
HER	Human Epidermal Growth Factor Receptor
EGFR	Epidermal Growth Factor Receptor.

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Fig. 1. Median plasma concentration-time plot from the start of Day 10 of Cycle 1 to the end of Day 14 of Cycle 1 for dose-compliant patients; (A) dacomitinib, (B) PF-05199265.

Table 1

Demographics and baseline characteristics of Cohort III (as enrolled population).

	N = 25
Median age (range), years	64 (35–92)
Sex, n (%)	
Men	7 (28.0)
Women	18 (72.0)
Race, n (%)	
White	6 (24.0)
Black	1 (4.0)
Asian	18 (72.0)
Korean	15 (60.0)
Southeast Asian	2 (8.0)
Indian subcontinent	1 (4.0)
ECOG Performance Status, n (%)	
0	18 (72.0)
1	5 (20.0)
2	2 (8.0)

ECOG = Eastern Cooperative Oncology Group.

Table 2

Summary of descriptive statistics for pharmacokinetic parameters of plasma dacomitinib and its metabolite, PF-05199265 – Day 10 through Day 14 of Cycle 1, for dose-compliant patients only.

	Dacomitinib	PF-05199265
N/n	25/23	25/23
C_{max} (ng/mL)		
Median	83.40	12.2
Geometric Mean	79.68	8.5176
Geometric Mean CV(%)	36	137
T_{max} (h)		
Median	5.85	5.98
Geometric Mean	5.127	5.673
Geometric Mean CV(%)	53	126
AUC_{24} (ng.h/mL)		
Median	1620.00	254.00
Geometric Mean	1712.88	184.62
Geometric Mean CV(%)	35	139
AUC_{120} (ng.h/mL)		
Median	6050.00	1000.00
Geometric Mean	5743.60	742.32
Geometric Mean CV(%)	32	129

N is the total number of patients in the treatment group of the indicated population.

n is the total number of patients contributing to the summary statistics.

C_{max} = observed maximum plasma concentration.

CV = coefficient of variation.

AUC_{24} = area under the curve from 0 time to 24 h.

AUC_{120} = area under the curve from 0 time to 120 h.

Table 3

Summary of secondary endpoints (as-treated population).

N = 25	
Overall relative dose intensity (RDI) of dacomitinib in the first 8 weeks of treatment	
125 to >100%, n (%)	2 (8.0)
100 to >90%, n (%)	14 (56.0)
90 to >75%, n (%)	5 (20.0)
75%, n (%)	4 (16.0)
Concomitant drug treatment for adverse events of interest in the first 8 weeks of treatment	
SDAEI, diarrhea, and stomatitis, n (%)	22 (88.0)
SDAEI, n (%)	20 (80.0)
Diarrhea, n (%)	19 (76.0)
Stomatitis, n (%)	11 (44.0)
Treatment-emergent adverse events (all causalities) in the first 8 weeks of treatment	
Patients with adverse events, n (%)	25 (100.0)
Patients with serious adverse events, n (%)	1 (4.0)
Patients with grade 3 or 4 adverse events, n (%)	7 (28.0)
Patients with grade 5 adverse events, n (%)	0 (0.0)
Discontinuations due to adverse events, n (%)	2 (8.0)
Temporary interruptions due to adverse events, n (%)	3 (12.0)
Dose reductions due to adverse events, n (%)	7 (28.0)

Overall RDI is defined as total actual received dose on study divided by (45 mg Dacomitinib * Actual total number of days on treatment), where Actual total number of days on treatment = last Dacomitinib dosing date on study – first Dacomitinib dosing date on study + 1.

First 8 weeks RDI is defined as total actual received dose during first 8 weeks from the date of first Dacomitinib dose divided by (45 mg Dacomitinib * 56 days).

SDAEI = Select Dermatologic Adverse Events of Interest.

Table 4

Treatment-emergent adverse events (all causalities) that occurred in at least 15% of patients in the first 8 weeks of treatment.

Preferred Term	N = 25	
	All Grades n (%)	Grade 2 n (%)
Any AEs	25 (100.0)	22 (88.0)
Diarrhea	23 (92.0)	10 (40.0)
Stomatitis	16 (64.0)	6 (24.0)
Dermatitis acneiform	15 (60.0)	5 (20.0)
Dry skin	14 (56.0)	3 (12.0)
Paronychia	14 (56.0)	9 (36.0)
Pruritus	9 (36.0)	1 (4.0)
Decreased appetite	8 (32.0)	2 (8.0)
Dry mouth	5 (20.0)	0 (0.0)
Epistaxis	5 (20.0)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	5 (20.0)	4 (16.0)
Rhinitis allergic	5 (20.0)	0 (0.0)
Productive cough	4 (16.0)	0 (0.0)
Rash maculo-papular	4 (16.0)	3 (12.0)
Vomiting	4 (16.0)	2 (8.0)
Select Dermatologic Adverse Events of Interest (SDAEI)	24 (96.0)	14 (56.0)

Select Dermatologic Adverse Events of Interest were defined as dermatitis acneiform, dry skin, exfoliative rash, nail discoloration, nail disorder, paronychia, pruritus, rash, skin exfoliation, skin fissures, skin laceration, skin infection, and skin ulcer.