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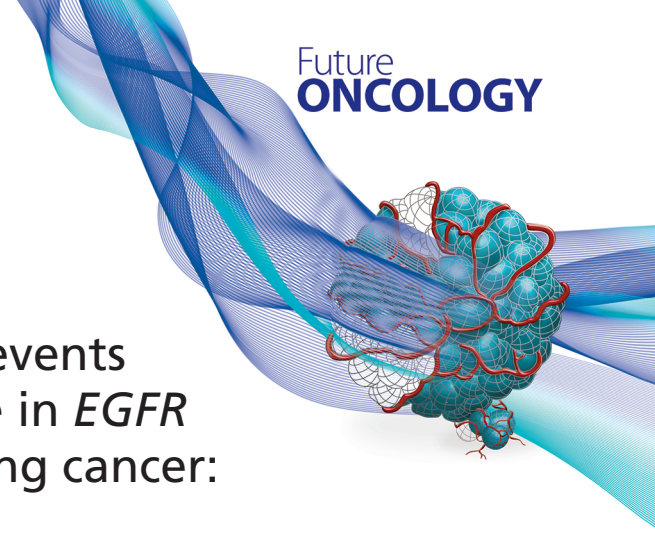

# Management of common adverse events related to first-line dacomitinib use in *EGFR* mutation-positive non-small-cell lung cancer: a pooled safety analysis

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**Aim:** This pooled safety analysis was conducted to analyze incidence and management of key dacomitinib-associated adverse drug reactions (ADRs). **Patients & methods:** Patients with *EGFR* mutation-positive advanced non-small-cell lung cancer who received first-line dacomitinib at the 45 mg/day recommended starting dose were included. ADRs were identified based on reasonable association with EGFR tyrosine kinase inhibitors. **Results:** Overall, 251/255 patients (98%) experienced ADRs. The most common were diarrhea, rash, stomatitis, nail disorder and dry skin. Dose interruptions and dose reductions were reported in 47 and 52% of patients, respectively. Fewer Grade 3 key ADRs were observed following dose reductions. **Conclusion:** Dacomitinib was generally tolerable. Most reported ADRs were known to be associated with EGFR tyrosine kinase inhibitors and were managed with standard medical management and dose modifications.

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**Keywords:** adverse event management • dacomitinib • non-small-cell lung cancer

Dacomitinib, a second-generation EGFR TKI, was investigated in the first-line setting in patients with non-small-cell lung cancer (NSCLC) containing *EGFR*-activating mutations at a starting dose of 45 mg/day in two trials: ARCHER 1050 (ClinicalTrials.gov identifier: NCT01774721) [1], an ongoing, multicenter, randomized, open-label, Phase III study that is no longer recruiting patients, and A7471017 (Cohort A; NCT00818441) [2], a multicenter, noncomparative Phase II study. ARCHER 1050 demonstrated significant improvement with dacomitinib versus gefitinib in both progression-free survival (PFS; hazard ratio [HR]: 0.59 [95% CI: 0.47–0.74]; $p < 0.0001$; median PFS, 14.7 vs 9.2 months) and overall survival (OS; HR: 0.76 [95% CI: 0.58–0.99]; $p = 0.044$; median OS, 34.1 vs 26.8 months) [1,3]. The safety profile of dacomitinib was consistent with prior dacomitinib clinical trial experience and is similar to that of other EGFR TKIs. In the dacomitinib group, the most common Grade 3 adverse events (AEs) were dermatitis acneiform (14%), diarrhea (8%) and paronychia (7%), while Grade 4 AEs occurred in five patients; 9% of patients experienced treatment-related serious AEs and 10% discontinued because of treatment-related AEs, which was similar to the permanent discontinuation rate in the gefitinib arm (7%) [1].

In the patient-reported outcomes (PROs) analysis from ARCHER 1050, global quality of life (QoL) was clinically similar between the two study arms; however, dacomitinib was associated with a greater increase from baseline in treatment-related symptoms of diarrhea and sore mouth compared with gefitinib [1].

A pooled safety analysis of the ARCHER 1050 and A7471017 (Cohort A) trials was performed, with a primary objective of analyzing the incidence and management of key adverse drug reactions (ADRs) and PROs associated with the first-line use of dacomitinib in patients with *EGFR* mutation-positive advanced NSCLC. The most common ADRs were characterized regarding the timing of onset, duration and severity, whereas management of key ADRs was assessed in terms of the use of dose reductions and dose interruptions. A secondary objective was to develop management guidelines for key all-cause ADRs associated with dacomitinib treatment on the basis of experience gained from the conduct of these studies.

## Materials & methods

### Study design, patients & treatment

As previously described [1,2], patients with previously untreated, histologically confirmed advanced Stage IIIB–IV NSCLC with *EGFR*-activating mutations were included in the analysis and received oral dacomitinib as first-line treatment at a starting dose of 45 mg/day. Patients with CNS metastasis were excluded from ARCHER 1050.

### Safety assessments & ADR reporting

Safety assessments were carried out as previously described [1,2]. The severity of all AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. An ADR was identified on the basis of whether it was reasonably associated with dacomitinib treatment, taking into consideration the mechanism of action of EGFR TKIs, temporal relationship to therapy, underlying disease and concomitant medication confounders, available nonclinical toxicity data and the overall assessment of ADRs by the investigators. Serious ADRs were defined as AEs that resulted in death, were life-threatening, required hospitalization, resulted in significant disability/incapacity or resulted in birth defects. To minimize underestimation of the frequency of ADRs, some ADRs were denoted as clusters of preferred terms from the Medical Dictionary for Regulatory Activities version 19.1. Supplementary Table 1 lists preferred terms associated with their cluster terms.

### Criteria for dose reductions & dose interruptions

The criteria for dose reductions and dose interruptions were defined in detail in the study protocols. For treatment-related toxicities of Grade 3, Grade 4 or prolonged Grade 2 severity, dose reductions were permitted to 30 mg/day and then to 15 mg/day. If the reduced dose was tolerated, the dacomitinib dose may have been increased to the previous dose level at the investigator's discretion. If the 15 mg/day dose level was not tolerated, dacomitinib was permanently discontinued.

Dose interruptions of <2 weeks were permitted for Grade 3, Grade 4 or intolerable Grade 2 toxicities. Upon recovery to Grade 2 or baseline, treatment was resumed at the same dose level or reduced to the next dose level (mandated for Grade 4 toxicities) at the investigator's discretion. If the patient did not recover within 2 weeks of interruption, treatment was permanently discontinued.

### Patient-reported outcomes

All PRO data were derived from the ARCHER 1050 trial. To provide information on the experience of patients with ADRs, PROs were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the corresponding lung cancer module (QLQ-LC13) [1]. Mean total scores at each cycle for diarrhea and sore mouth were calculated over the first 30 cycles (where >10 patients were included) and referenced to the four reporting categories of 'not at all', 'a little', 'quite a bit' and 'very much' regarding experience during the week preceding completion of the questionnaire.

## Results

### Patient population & treatment

The pooled safety analysis included 255 patients with *EGFR* mutation-positive advanced NSCLC who received dacomitinib 45 mg/day as first-line therapy (ARCHER 1050, n = 225 [data cutoff of 29 July 2016]; A7471017 [Cohort A]; n = 30). Demographics and baseline characteristics are summarized in Supplementary Table 2. The median duration of treatment for the combined population was 66.7 weeks (range 0.3–296.3 weeks).

Table 1. Incidence, time to onset and duration of the most frequent adverse drug reactions.

| | Dacomitinib (n = 255) | | | | | |
|---|---|---|---|---|---|---|
| | Any grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
| **Any adverse event**† | 251 (98) | 31 (12) | 102 (40) | 112 (44) | 4 (2)‡ | 2 (1)‡ |
| **Diarrhea** | | | | | | |
| Incidence, n (%) | 226 (89) | 130 (51) | 72 (28) | 23 (9) | 0 | 1 (0.4) |
| Median TTO of first episode§, days | 7 | – | – | – | – | – |
| Median TTO of worst episode¶, days | 14 | – | – | – | – | – |
| Median duration, days | 158 | 155 | 12 | 7 | 0 | 1 |
| **Stomatitis**# | | | | | | |
| Incidence, n (%) | 183 (72) | 108 (42) | 63 (25) | 11 (4) | 1 (0.4) | 0 |
| Median TTO of first episode§, days | 8 | – | – | – | – | – |
| Median TTO of worst episode¶, days | 10 | – | – | – | – | – |
| Median duration, days | 125 | 91 | 44 | 19 | 9 | 0 |
| **Rash**†† | | | | | | |
| Incidence, n (%) | 210 (82) | 50 (20) | 93 (37) | 67 (26) | 0 | 0 |
| Median TTO of first episode§, days | 12 | – | – | – | – | – |
| Median TTO of worst episode¶, days | 51 | – | – | – | – | – |
| Median duration, days | 445 | 304 | 100 | 17 | 0 | 0 |
| **Dry skin**‡‡ | | | | | | |
| Incidence, n (%) | 85 (33) | 56 (22) | 25 (10) | 4 (2) | 0 | 0 |
| Median TTO of first episode§, days | 50 | – | – | – | – | – |
| Median TTO of worst episode¶, days | 57 | – | – | – | – | – |
| Median duration, days | 315 | 288 | 118 | 9 | 0 | 0 |
| **Nail disorder**§§ | | | | | | |
| Incidence, n (%) | 167 (66) | 56 (22) | 89 (35) | 22 (9) | 0 | 0 |
| Median TTO of first episode§, days | 48 | – | – | – | – | – |
| Median TTO of worst episode¶, days | 74 | – | – | – | – | – |
| Median duration, days | 354 | 251 | 95 | 16 | 0 | 0 |

†If the same patient had more than one occurrence in the same event category, only the most severe occurrence was taken.
‡Grade 4 ADRs were mucosal inflammation (n = 1) and hypokalemia (n = 3). Grade 5 ADRs were diarrhea (n = 1) and pneumonitis (n = 1).
§Time from the first dose to the first occurrence of an ADR.
¶Time from the first dose to the first occurrence of the maximum Common Terminology Criteria for Adverse Events grade of an ADR.
#Group term comprised of any reported PTs within the HLT stomatitis and ulceration, plus the PTs dry mouth, cheilitis, oral pain, oropharyngeal pain and mucosal inflammation.
††Group term comprised of any reported PTs within the HLT acnes or within the HLT rashes, eruptions and exanthems NEC, plus the PTs erythema, erythema multiforme, palmar–plantar erythrodysesthesia syndrome, pruritus, rash erythematous and rash pruritic.
‡‡Group term comprised of the PTs dry skin and xerosis.
§§Group term comprised of any reported PTs within the HLT nail and nail bed conditions (excluding infections and infestations), plus the PTs paronychia and nail infection.
ADR: Adverse drug reaction; HLT: High-level term; NEC: Not elsewhere classifiable; PT: Preferred term; TTO: Time to onset.

## Overall safety

Of 255 patients in the analysis population, 251 (98%) reported ≥1 ADR. Incidences and grades of all ADRs that occurred in ≥10% of patients are shown in Supplementary Table 3. The most common ADRs with dacomitinib were diarrhea, rash, stomatitis, nail disorder and dry skin. ADRs of Grade 1 and 2 severity occurred in 31 patients (12%) and 102 patients (40%), respectively; Grade 3 events occurred in 112 patients (44%) and Grade 4 events occurred in four patients (2%). Grade 5 events occurred in two patients (0.8%; diarrhea and pneumonitis). Serious ADRs were reported in 17 patients (7%), most frequently diarrhea (n = 5; 2%), interstitial lung disease (n = 3; 1%), rash (n = 3; 1%) and decreased appetite (n = 3; 1%).

Dose interruptions and dose reductions associated with ADRs were reported in 119 patients (47%) and 133 patients (52%), respectively (Supplementary Table 4). Rash, nail disorder and diarrhea were the most common reasons for dose interruptions and dose reductions. 17 patients (7%) permanently discontinued treatment because of ADRs, most commonly rash (n = 6; 2%), interstitial lung disease (n = 5; 2%) and diarrhea (n = 2; 0.8%). Of these 17 patients, six permanently discontinued dacomitinib because of a serious ADR. Incidences, times to onset and median durations of the most common ADRs associated with dacomitinib are shown in Table 1 and further evaluated in detail below.

## Gastrointestinal-related ADRs

### *Diarrhea*

Diarrhea was the most common ADR reported with dacomitinib and occurred in 226 patients (89%). Events were of Grade 1 or 2 severity among most patients (n = 202; 79%); Grade 3 events occurred in 23 patients (9%; Table 1 & Supplementary Figure 1A). One case of Grade 5 diarrhea occurred in a patient who had not sought antidiarrheal management.

The onset of diarrhea occurred during the first cycle of dacomitinib treatment in 189 patients (74%). The median times from the first dose to the onset of the first event and the worst event (maximum CTCAE grade) were 7 and 14 days, respectively (Table 1). The median duration of diarrhea was 7 days among patients with Grade 3 diarrhea. Diarrhea led to dose interruptions in 26 patients (10%) and dose reductions in 19 patients (7%; Supplementary Table 4).

Among all patients who underwent dose reductions due to ADRs, fewer Grade 2 or 3 events of diarrhea were reported in the time intervals following both the first and second dacomitinib dose reductions compared with the number reported in the intervals before the dose reductions (Figure 1A). Two patients (0.8%) permanently discontinued dacomitinib because of diarrhea (Grade 2, n = 1 [0.4%]; Grade 5, n = 1 [0.4%]).

### *Stomatitis*

Stomatitis, comprising the group terms corresponding to stomatitis (Supplementary Table 1), occurred in 183 patients (72%) and was of Grade 1 or 2 severity among most patients (n = 171; 67%; Table 1 and Supplementary Figure 1B). Grade 3 events occurred in 11 patients (4%), and one patient (0.4%) had a Grade 4 event; no Grade 5 events occurred. Two patients (0.8%) had Grade 3 stomatitis events that were classified as serious.

The median times from the first dose to the onset of the first event and the worst event (maximum CTCAE grade) were 8 and 10 days, respectively (Table 1); among patients with Grade 3 events, the median duration was 19 days. One patient had Grade 4 stomatitis lasting 9 days. Stomatitis led to dose interruptions in 22 patients (9%) and dose reductions in 12 patients (5%; Supplementary Table 4).

As noted with diarrhea, among all patients who underwent dose reductions due to ADRs, fewer Grade 2 or 3 stomatitis events were reported in the intervals following dose reductions compared with the number reported before the dose reductions (Figure 1B). One patient (0.4%) permanently discontinued dacomitinib because of Grade 3 stomatitis.

## Cutaneous-related ADRs

### *Rash*

Rash, comprising the group terms corresponding to rash (Supplementary Table 1), was the second most common ADR reported with dacomitinib and occurred in 210 patients (82%; Table 1 and Supplementary Figure 1C). The most frequent ADRs were dermatitis acneiform (n = 127; 50%), pruritus (n = 57; 22%), palmar–plantar erythrodysesthesia syndrome (n = 46; 18%), rash (n = 43; 17%) and acne (n = 32; 13%). Overall, 143 patients (56%) had Grade 1 or 2 ADRs and 67 patients (26%) had Grade 3 ADRs; no Grade 4 or 5 events were reported. Three patients (1%) had rash that was classified as serious (Grade 2, n = 1 [0.4%]; Grade 3, n = 2 [0.8%]).

The median times from the first dose to the onset of the first event and the worst event (maximum CTCAE grade) were 12 and 51 days, respectively. The median duration of rash was 17 days for Grade 3 events (Table 1). Rash led to dose interruptions in 68 patients (27%), of whom 43 (17%) had Grade 3 rash and dose reductions in 84 patients (33%; Supplementary Table 4).

Among all patients who had dose reductions due to ADRs, fewer Grade 3 rash events were observed in the time period after the dacomitinib dose was reduced to 30 mg/day than in the time period before the dose reduction (Figure 1C). Six patients (2%) permanently discontinued dacomitinib because of rash (Grade 2, n = 3 [1%]; Grade 3, n = 3 [1%]).

### *Dry skin*

Dry skin, comprising the group terms corresponding to dry skin (Supplementary Table 1), occurred in 85 patients (33%). Most events were of Grade 1 or 2 severity (n = 81; 32%). Grade 3 events occurred in four patients (2%), and no Grade 4 or 5 events of dry skin were reported (Table 1 & Supplementary Figure 1D).

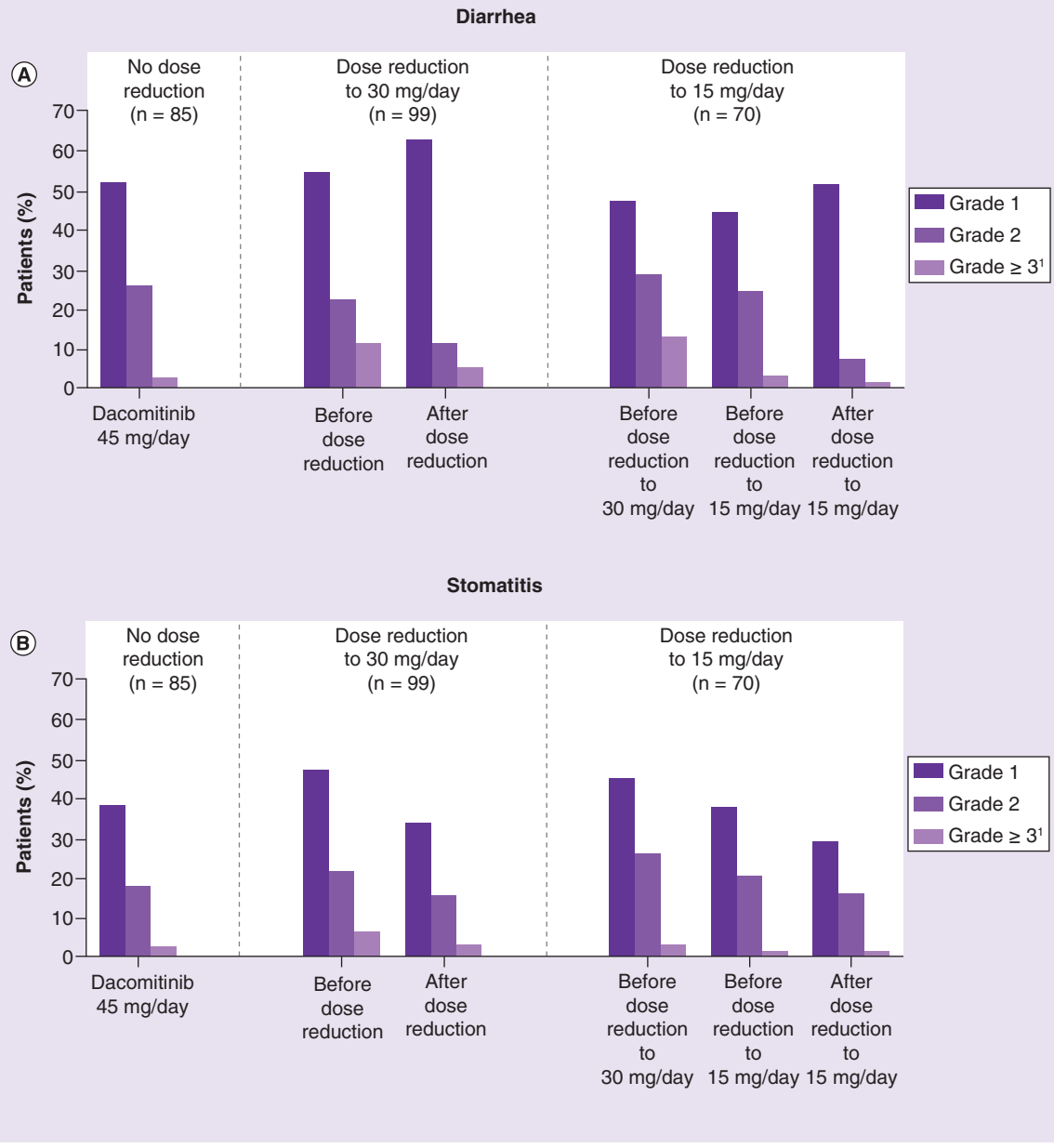


**Figure 1. Incidences and severity of key ADRs before and after dose reduction. (A)** Diarrhea, **(B)** stomatitis, **(C)** rash, **(D)** dry skin and **(E)** nail disorder. The incidences and severity of the most frequent ADRs are summarized in patients who did or did not undergo dose reductions because of adverse events. The frequencies of ADRs in the interval before the dose reductions and in the interval after dose reductions are indicated.
[1]There were no Grade 4 events requiring dose reductions for diarrhea, stomatitis, rash, dry skin or nail disorder.
ADR: Adverse drug reaction.

The median times from the first dose to the onset of the first event and the worst event (maximum CTCAE grade) were 50 and 57 days, respectively. The median duration of dry skin was 9 days among patients with Grade 3 events (Table 1). Dry skin led to dose interruptions in five patients (2%) and dose reductions in eight patients (3%; Supplementary Table 4).

Among all patients who underwent dose reductions due to ADRs, fewer Grade 3 dry skin events were observed during the intervals following dose reductions compared with the time intervals before the dose reductions (Figure 1D). No patients permanently discontinued dacomitinib because of dry skin.


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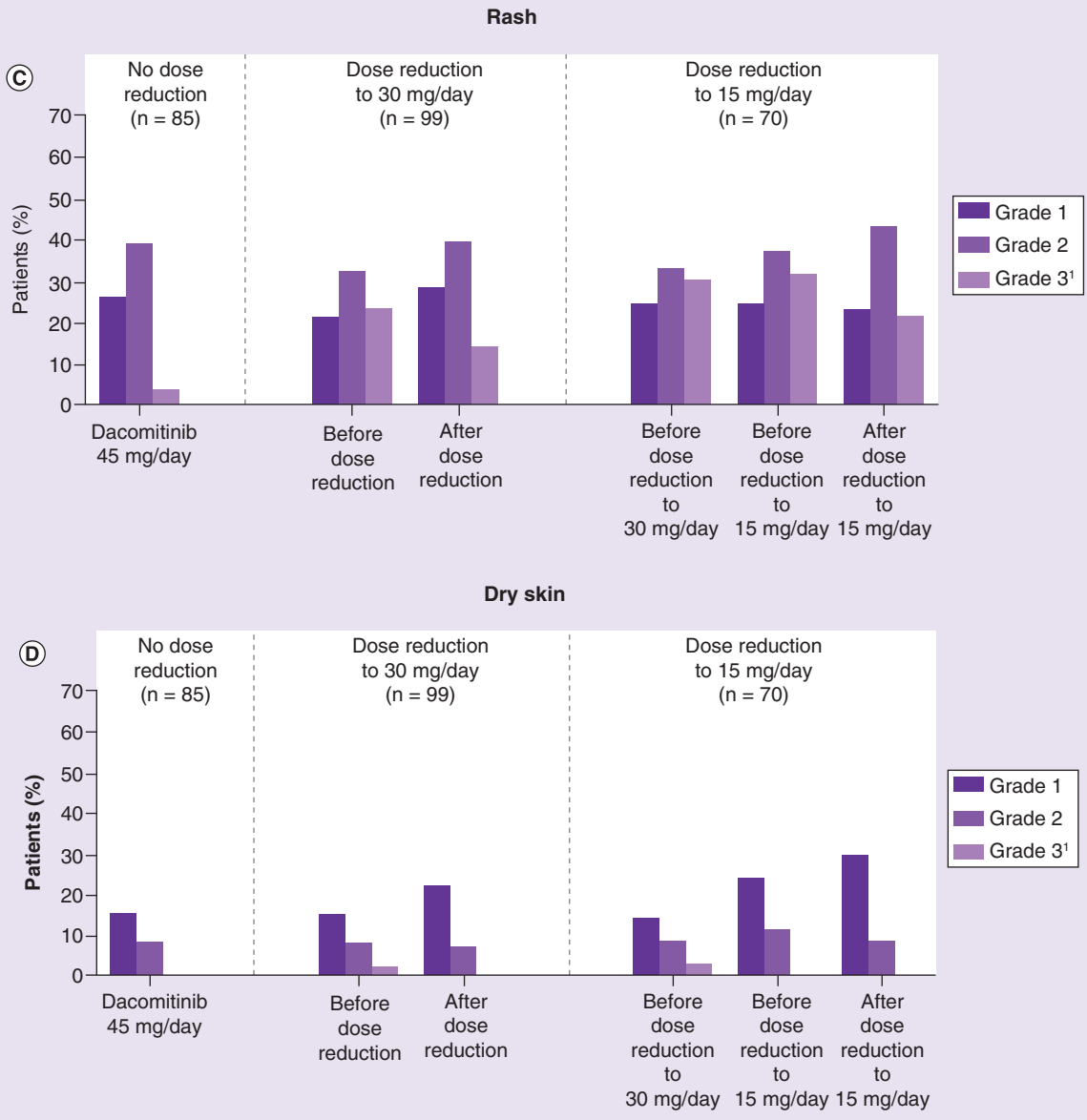


**Figure 1. Incidences and severity of key ADRs before and after dose reduction (cont.). (A)** Diarrhea, **(B)** stomatitis, **(C)** rash, **(D)** dry skin and **(E)** nail disorder. The incidences and severity of the most frequent ADRs are summarized in patients who did or did not undergo dose reductions because of adverse events. The frequencies of ADRs in the interval before the dose reductions and in the interval after dose reductions are indicated.
[1]There were no Grade 4 events requiring dose reductions for diarrhea, stomatitis, rash, dry skin or nail disorder.
ADR: Adverse drug reaction.

### *Nail disorder*

Nail disorder, comprising terms corresponding to nail disorder (Supplementary Table 1), occurred in 167 patients (66%) and was of Grade 1 or 2 severity in most patients (n = 145; 57%). Grade 3 events occurred in 22 patients (9%), and no Grade 4 or 5 events were reported (Table 1 & Supplementary Figure 1E). None of the nail disorder events were classified as serious.

The median times from the first dose to the first event and the worst event (maximum CTCAE grade) were 48 and 74 days, respectively. The median duration of nail disorder was 16 days among patients with Grade 3 events

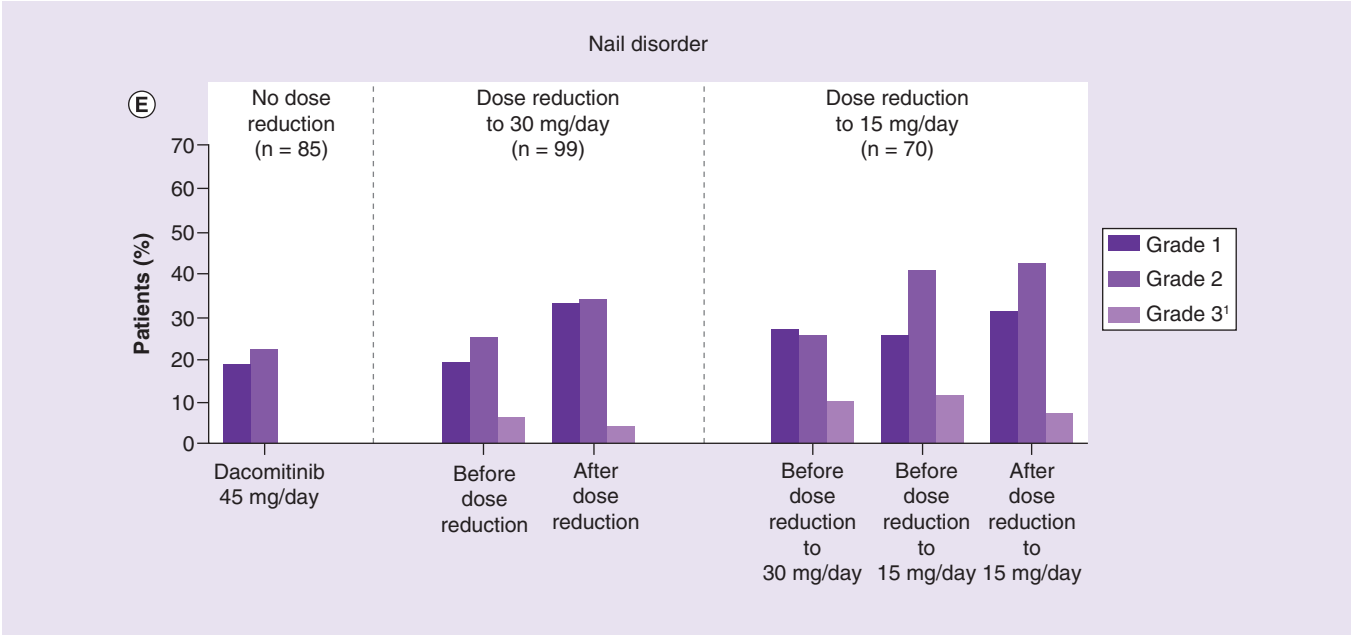


**Figure 1. Incidences and severity of key ADRs before and after dose reduction (cont.). (A)** Diarrhea, **(B)** stomatitis, **(C)** rash, **(D)** dry skin and **(E)** nail disorder. The incidences and severity of the most frequent ADRs are summarized in patients who did or did not undergo dose reductions because of adverse events. The frequencies of ADRs in the interval before the dose reductions and in the interval after dose reductions are indicated.
[1]There were no Grade 4 events requiring dose reductions for diarrhea, stomatitis, rash, dry skin or nail disorder.
ADR: Adverse drug reaction.

(Table 1). Nail disorder led to dose interruptions in 33 patients (13%) and dose reductions in 42 patients (16%; Supplementary Table 4).

Among all patients who had dose reductions due to ADRs, the frequency of Grade 3 nail disorder events decreased slightly in the intervals after dose reductions (Figure 1E). No patients permanently discontinued dacomitinib because of a nail disorder.

### Patient-reported outcomes

In the ARCHER 1050 study, mean PRO scores at each cycle for diarrhea and sore mouth demonstrated symptom worsening that peaked early and declined over the treatment course (Figure 2). These scores fell into the range between 0 ('not at all') and 33.3 ('a little') by cycle 4 for diarrhea (EORTC QLQ-C30) and cycle 3 for sore mouth (EORTC QLQ-LC13).

## Discussion

Dacomitinib at a starting dose of 45 mg/day is an effective first-line therapy for patients with *EGFR* mutation-positive advanced NSCLC, demonstrating significant improvements in PFS and OS compared with gefitinib, while maintaining global QoL [1,3]. The most frequently reported ADRs associated with dacomitinib included diarrhea, stomatitis, rash, dry skin and nail disorder. These ADRs, primarily mediated by the inhibition of epithelial EGFR expression [4,5], were consistent with prior dacomitinib studies [6–8] and studies of other EGFR TKIs including second-generation agents [9–11]. More than half of the ADRs were Grade 1 or 2. ADRs were managed, on the basis of the guidance provided to investigators during the dacomitinib clinical trials, using dose interruptions, dose reductions and concomitant medications (as recommended by the AE management guidelines defined for the ARCHER 1050 study [1]). Only a small proportion of patients (n = 17; 7%) required permanent discontinuation of dacomitinib, with few of these (n = 6) related to serious ADRs. PRO results were consistent with the incidence, degree and duration of ADRs in the study population, suggesting that the PRO instrument aligned well with AE reporting for detecting and reflecting the patient's experience.

Diarrhea – the most common ADR seen with dacomitinib – occurred early (median time to onset of 7 days), similar to observations with afatinib in the LUX-Lung 7 trial [11,12]. The early onset of diarrhea after dacomitinib

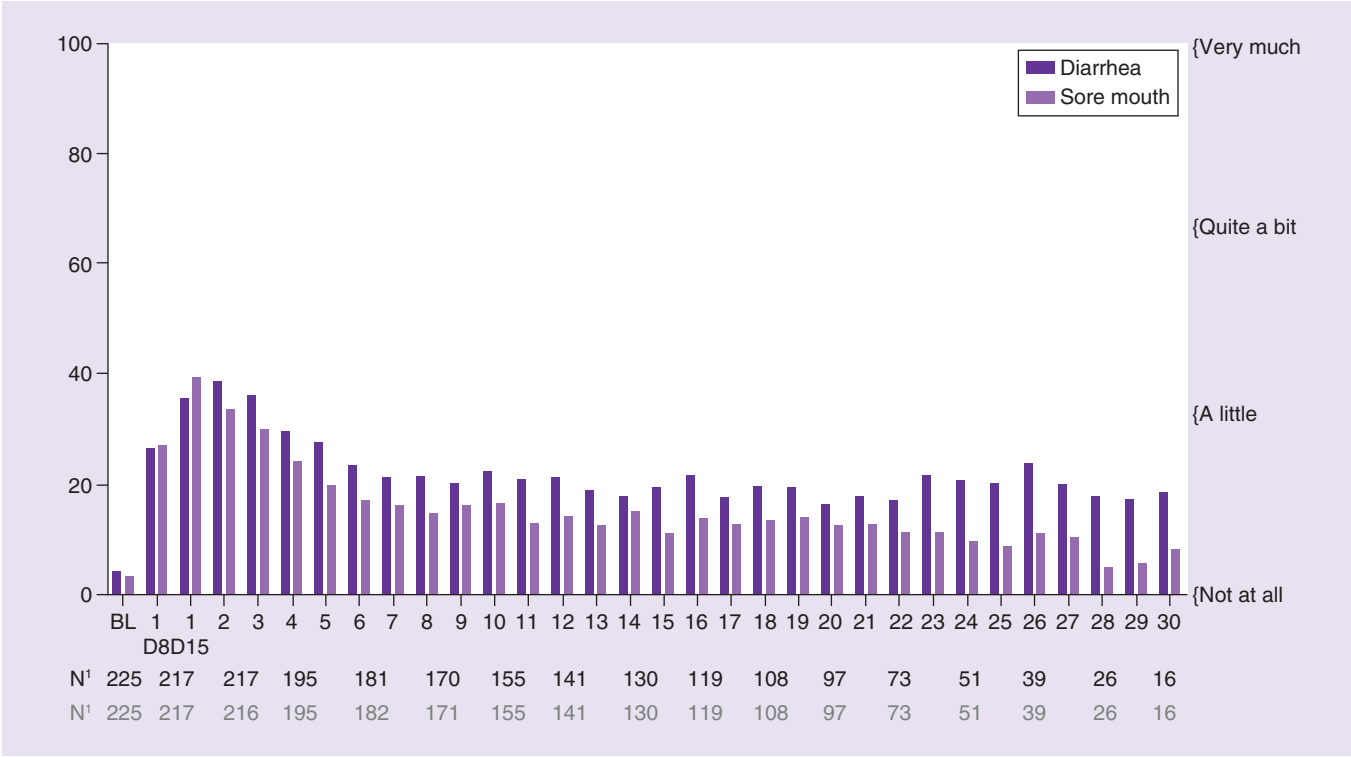


**Figure 2. PRO scores by cycle for diarrhea (assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]) and sore mouth (assessed using the EORTC QLQ lung cancer module [LC13]).** Mean total scores at each cycle for diarrhea and sore mouth were calculated over the first 30 cycles (where >10 patients were included). The labels (1) 'not at all', (2) 'a little', (3) 'quite a bit', and (4) 'very much' were the response options directly chosen by the patients to the questions on whether they had diarrhea or sore mouth and tongue, respectively, during the past week. The numbering on the x-axis represents cycles; the y-axis represents the standardized transformation applied to these choices by the EORTC calculation guidelines. Patients responded in regard to their experience during the week preceding completion of the questionnaire with the following categories: 0–not at all, 33.3–a little; 66.6–quite a bit; 100–very much.
BL: Baseline; D: Day; PRO: Patient-reported outcome; $N^1$: Number of patients who completed ≥1 question at each cycle.

initiation emphasizes the importance of early intervention for prevention of complications [4]. In addition to non-pharmacologic strategies (management of symptoms, dietary intake and fluid management), proactive management of diarrhea with antidiarrheal medications (e.g., loperamide) is recommended [4]. Treatment of diarrhea should begin promptly at the first sign of symptom onset and continue until 12 h after diarrhea cessation. As seen in this analysis, and as previously observed with afatinib [12], dose reductions and interruptions can enable effective management of diarrhea without the need for permanent discontinuation, leading to reduced incidence and lower grade events in the time interval following dose modification. Supplementary Figure 2 details the management of diarrhea with dacomitinib.

Stomatitis was common with dacomitinib and had a median time to onset of 8 days, as seen with afatinib [11]. As previously described for other EGFR TKIs [13,14], management of stomatitis includes guidelines for oral care and dose modifications (Supplementary Figure 3). For Grade ≥3 stomatitis, dacomitinib should be withheld until symptoms resolve to Grade ≤2. Upon recovery, dacomitinib can be resumed with a reduction of one dose level. As with diarrhea, dose reductions were effective in this analysis for management of stomatitis events without the need for treatment discontinuation.

Rash, the second most frequent ADR with dacomitinib, was managed with dose reductions and dose interruptions. Supplementary Figure 4 shows detailed management guidelines, consistent with those previously described for EGFR TKIs [5,13], for patients who develop rash or erythematous and exfoliative skin conditions during dacomitinib treatment. Briefly, for intolerable Grade 2 or ≥3 events, dacomitinib should be withheld; once symptoms resolve to Grade 1 or baseline, treatment may be resumed at the same or next lower dose level (for Grade 2 and 3 events) or resumed at the next lower dose level (for Grade 4 events).

Nail disorder and dry skin events occurred later compared with other key ADRs (median times to onset of 48 and 50 days, respectively) and Grade 1 and 2 events appeared to have increased incidence among patients who received dacomitinib dose reductions. The later time to onset and longer time on therapy may partially account for why changes in incidence of these Grade 1 and 2 ADRs were not apparent following dose reductions (Figure 1E). Management guidelines for dry skin and nail disorder with dacomitinib were developed on the basis of prior EGFR TKI experience [5,15] and are detailed in the Supplementary Appendix and Supplementary Figures 5 and 6.

Oral prophylaxis with tetracycline antibiotics has shown mixed results in treating EGFR TKI-induced dermatologic toxicities. While doxycycline/tetracycline prophylaxis was shown to reduce the incidence of dermatologic AEs with dacomitinib and afatinib [16,17], prophylaxis with oral minocycline did not alter the overall incidence of erlotinib-induced rash (versus reactive treatment) in the Pan Canadian Rash trial [18]. In the Phase II ARCHER 1042 study [17], prophylactic treatment with oral doxycycline (100 mg twice daily for 4 weeks) significantly reduced the incidence of Grade ≥2 select dermatologic AEs (by 50%) versus placebo, reduced concomitant medication use for dermatologic AEs, and was associated with less deterioration in QoL. Prophylactic doxycycline administered for cutaneous events also lowered the incidence of Grade ≥2 diarrhea in dacomitinib-treated patients (n = 56; incidence of 34%) compared with placebo (n = 58; incidence of 41%); however, this difference was not statistically significant [17]. These data suggest that the use of oral prophylaxis with tetracycline antibiotics for patients receiving dacomitinib requires further exploration.

One limitation of this analysis stems from the majority of patients having come from the Phase III ARCHER 1050 study which excluded the enrollment of patients with brain metastases, thus potentially enriching the analysis population for those individuals with better overall prognosis. In addition, the ADRs considered in this analysis were limited to those most frequently associated with EGFR TKI therapy and did not necessarily reflect other less common unique aspects of the dacomitinib safety profile. Finally, this analysis did not specifically evaluate the effect of ADR management strategies beyond dose reductions and dose interruptions.

## Conclusion

In summary, dacomitinib provides a new treatment option for the first-line treatment of patients with *EGFR* mutation-positive advanced NSCLC. Most ADRs related to dacomitinib can be effectively managed with standard medical management or dose modifications. Proactive counseling of patients in conjunction with pre-emptive monitoring and treatment are likewise integral components of patient care. Effective management of dacomitinib therapy can help to improve tolerability and patient experience of treatment-related symptoms, allowing patients to continue treatment.

### Summary points

- Dacomitinib-related adverse events are consistent with those observed with other EGFR inhibitors.
- The key adverse events seen with dacomitinib were diarrhea, rash, stomatitis, nail disorder and dry skin.
- Most dacomitinib-related adverse events were managed by dose modifications and concomitant medications.
- Guidelines are provided for effective management of key adverse events.
- Effective therapy management can improve patient experience and optimize benefit.

### Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2018-0944

### Financial & competing interests disclosure

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### Ethical conduct

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

### Author contributions

All authors contributed to the concept and design of the study, to conducting the analysis, interpretation of the results, writing and revisions of the manuscript and approval of the final version submitted for publication.

### Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is: ClinicalTrials.gov identifier: NCT01774721 and Cohort A; NCT00818441. Upon request, and subject to certain criteria, conditions and exceptions (see www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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