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# Impact of afatinib dose modification on safety and effectiveness in patients with *EGFR* mutation-positive advanced NSCLC: Results from a global real-world study (RealGiDo)

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ABSTRACT

*Objectives:* In the LUX-Lung clinical trials of afatinib in *EGFR* mutation-positive NSCLC, tolerability-guided dose adjustment reduced the incidence and severity of adverse events while maintaining efficacy. The RealGiDo study evaluated the impact of afatinib dose adjustment in a real-world setting.

*Materials and methods:* This non-interventional, observational study used medical records of *EGFR* mutation-positive NSCLC patients treated with first-line afatinib. Primary outcomes were adverse drug reaction (ADR) incidence and severity, time to treatment failure (TTF), and time to progression (TTP), relative to LUX-Lung 3 (LL3).

*Results:* 228 patients were enrolled from 13 countries. Baseline characteristics were in line with LL3 but with more Del19 patients (78.1% vs. 49.0%) and fewer Asian patients (43.9% vs. 72.2%); 11.8% had ECOG performance status 2–3. A total of 71 (31.1%) received a modified starting dose of ≤30 mg. Of patients who started with 40 mg, 67.1% underwent dose reductions, 86.5% of which were in the first 6 months. Dose reductions were mainly due to ADRs and were more common in female, East Asian, and low body-weight patients. There were no new safety signals and fewer ≥grade 3 ADRs (28.4% vs. 48.9%) and serious adverse events (5.2% vs. 14.0%) than in LL3. Median TTF and TTP were 18.7 and 20.8 months, respectively, and were not impacted by reduced starting dose or dose modification.

*Conclusion:* Real-world data show that afatinib dose adjustments reduced the frequency and intensity of ADRs

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without compromising effectiveness, highlighting the benefit of tailoring afatinib dose to optimise treatment outcomes and supporting clinical decision-making.

The study is registered at clinicaltrials.gov (NCT02751879).

## 1. Introduction

Randomised controlled trials (RCTs) are conducted to assess the efficacy and safety of study drugs under well-defined, controlled clinical conditions and in selected patient populations; however, trial outcomes may not always reflect real-world experience as patients may not be representative of the general patient population in a clinical practice setting [1]. For example, in the real-world setting, patients may have higher rates of poor prognostic factors and/or more co-morbidities, patient compliance may be poorer, and routine medical practice may differ from clinical trial protocol-specified patient care [1,2]. Consequently, the importance of assessing whether clinical trial outcomes are reflected in the real-world setting, among a broader patient population, is increasingly recognised, with real-world evidence valued by regulatory authorities such as the US Food and Drug Administration (FDA) [1].

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are standard first-line treatment for patients with *EGFR* mutation-positive non-small cell lung cancer (NSCLC) [3,4]. The second-generation ErbB family blocker afatinib was approved in this setting based on two large, randomised phase 3 trials. In the global LUX-Lung 3 trial, afatinib significantly improved progression-free survival (PFS; median 13.6 vs. 6.9 months; hazard ratio 0.47, 95% confidence interval [CI] 0.34–0.65) in patients (26% of whom were Caucasian) with *EGFR* mutation-positive (Del19/L858R) NSCLC vs. cisplatin/pemetrexed [5]. Similar data were observed in the Asian LUX-Lung 6 trial, which compared afatinib vs. gemcitabine/cisplatin [6]. In both studies, afatinib significantly improved overall survival (OS) vs. chemotherapy in a prespecified analysis of patients with Del19 *EGFR* mutations [7]. A subsequent randomised phase 2B trial, LUX-Lung 7, in patients with *EGFR* mutation-positive (Del19/L858R) NSCLC, showed that afatinib prolonged PFS and time to treatment failure (TTF) vs. the first-generation EGFR TKI gefitinib [8]; there was also a non-significant trend towards improved OS with afatinib [9].

Afatinib has a predictable adverse event (AE) profile, consistent with its inhibition of EGFR. Key treatment-related AEs include gastrointestinal effects (such as diarrhoea) and skin toxicity (such as rash/acne and paronychia). These AEs have been shown to be manageable with supportive care and tolerability-guided dose adjustment [5,6,10,11]. Per the label, the recommended starting dose of afatinib is 40 mg/day; however, in the case of grade ≥3 or certain prolonged grade 2 treatment-related AEs, afatinib treatment should be withheld until the AE has recovered to grade 1 or baseline levels. Afatinib treatment can then be re-started at a reduced dose of 30 mg/day, and further decreased to 20 mg/day, if required [12]. Post-hoc analysis of LUX-Lung 3 showed that dose reductions occurred in 53.3% of afatinib-treated patients [13], with the majority occurring within the first 6 months of treatment. As would be expected, dose reduction resulted in decreases in the incidence and severity of treatment-related AEs. Importantly, dose adjustment did not affect therapeutic efficacy, with median PFS in patients whose dose was reduced in the first 6 months similar to those whose dose was not reduced (11.3 vs. 11.0 months) [13]. Similarly, post-hoc analysis of LUX-Lung 6 and LUX-Lung 7 showed that tolerability-guided dose adjustment of afatinib reduced the frequency and intensity of treatment-related AEs without affecting efficacy [13,14].

However, it was unknown if such tolerability-guided dose adjustment of afatinib in the real-world setting had a similar impact as observed in the global LUX-Lung 3 trial. We therefore conducted a non-interventional, retrospective study (Real World Data on Gi[l]Otrif® Dose Adjustment; RealGiDo) to determine if dose modifications in the real-world setting were similar to those observed in the global LUX-Lung 3 trial, with a similar impact on safety without compromising effectiveness. Secondly, the impact of a modified starting dose on safety and effectiveness was analysed.

## 2. Materials and methods

### 2.1. Study design and patients

RealGiDo was a global, non-interventional, observational study conducted at 29 sites across 13 countries (Austria, Canada, France, Germany, Italy, Japan, South Korea, Mexico, Poland, Singapore, Spain, Taiwan and the United States; NCT02751879). Sites were included based on the commercial availability of afatinib prior to 1 January 2015 and the use of afatinib having been adopted as routine care for patients with *EGFR* mutations. Medical records of consecutive patients who met the following criteria were retrospectively reviewed: aged ≥18 years with *EGFR*-mutated (Del19/L858R) TKI-naïve advanced NSCLC who were treated first-line with afatinib within the approved label, and who provided written informed consent where required (in some countries this requirement was exempt for retrospective observational studies based on local regulations and legal requirements).

Patients were excluded if they had any contraindications to afatinib based on the label, had NSCLC with uncommon mutations (as the US FDA-approved label did not cover first-line approval of these patients at the time the study was initiated), or had been treated within a clinical trial. Furthermore, inclusion was restricted to patients with treatment initiation ≥6 months prior to enrolment to avoid early censoring and enable collection of mature adverse drug reaction (ADR) data; patients who had discontinued afatinib treatment < 6 months (for example, due to toxicity or progressive disease) were allowed to prevent selection bias. A maximum of 15 patients were enrolled per site. Investigators used patient medical records to collect details of baseline demographics, afatinib treatment dose and duration (along with dose modifications and reasons), ADRs, concomitant medication, and the date and type of progression from patient medical records. For quality assurance of the documented patient observations, source data verification was performed on 30% of included patients.

### 2.2. Outcomes and assessments

The primary safety outcome was the percentage of patients with ADRs by severity. ADRs were assessed by the investigator and defined as an adverse reaction that had at least a reasonable possibility of a causal relationship with the medicinal product; the incidence and severity of all ADRs were documented according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0). The primary efficacy outcomes were time to treatment failure (TTF; synonymous to time on treatment, defined as the time from the first dose of afatinib to that of the last dose of afatinib), and time to progression (TTP; defined as the time from the first dose of afatinib to the earliest occurrence of documented progression or death). Secondary outcomes were the percentage of patients receiving a modified starting dose of afatinib, and reasons for modifying the starting dose.

### 2.3. Statistical analysis

The sample size of 200 patients was chosen to be in the same range as LUX-Lung 3 (in which 230 patients were included in the afatinib

arm) [13]. Based on physician feedback, it was anticipated that 25–30% of patients would receive a modified starting dose. As such, it was estimated that about 50 patients would receive a modified starting dose, which was expected to be sufficient to gain an overview of the reasons for using a modified starting dose in the real-world setting.

All patients treated with afatinib were included in the safety and effectiveness analyses. Analyses of the incidence and severity of ADRs were descriptive. For patients with afatinib dose modifications in the first 6 months of treatment, the frequency and severity of common ADRs pre- and post-dose modification were analysed (≥40 mg vs. < 40 mg and ≥30 mg vs. < 30 mg). TTF and TTP were estimated using the Kaplan-Meier method and were compared between patients with and without dose modifications using the log-rank test.

## 3. Results

### 3.1. Patients and treatment

A total of 228 patients were included (Table 1), the majority of whom received the recommended starting dose of 40 mg/day (155 patients; 68.0%). Baseline characteristics of these 155 patients were generally consistent with those reported for afatinib-treated patients in the LUX-Lung 3 trial (Table 1); however, in RealGiDo patients were older, there were more patients with *EGFR* Del19 mutations, and patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) 2–3 were included (19/155; 12.3%). A total of 73 (32.0%) patients received a modified starting dose of afatinib: 2 (0.9%) started with 50 mg/day (this was the standard starting dose at the site); 69 (30.3%) started with 30 mg/day, and 2 (0.9%) with 20 mg/day (Fig. 1A). The reasons given for starting with ≤30 mg/day were broad but were most commonly related to patient characteristics and included factors such as patient age, gender and body weight (30 patients); other reasons reported on medical records included investigator's decision (23 patients) and institutional standards (11 patients) (Fig. 1B). Female and Caucasian patients tended to be more likely to start with ≤30 mg/day (Table 1).

Overall, 177 (77.6%) patients had a dose modification; of these, 149 had dose reductions only, 4 had dose escalations only, and 24 had both dose reductions and escalations. Of the 155 patients who received afatinib 40 mg/day as their starting dose, 104 patients (67.1%) had a dose reduction; of these, 90 (86.5%) had a dose reduction during the first 6 months (Fig. 2). In LUX-Lung 3, 53% of patients had a dose reduction, 86% of which occurred within the first 6 months. Consistent with LUX-Lung 3, dose reductions tended to be more common among female patients, Asian patients and those with lower body weight (Fig. 2; Supplementary Table 1). The most common reason for dose reductions was safety/tolerability (accounted for 86.0% of dose reductions in patients who started on ≥40 mg/day); other reasons included patient's wish (2.5%), investigator's decision (7.4%) and other reasons (4.1%). Reasons for dose reductions were similar for those who started with ≤30 mg/day; 14/71 (20%) patients who started on ≤30 mg/day subsequently dose-escalated.

At the time of documentation, 122 (53.5%) patients were still on treatment. Among the 105 patients who had discontinued afatinib treatment, the main reason was progressive disease (74 [70.5%] patients). Other reasons included ADRs (17 [16.2%]), death (8 [7.6%]), loss to follow-up (1 [0.9%]), and refusal to continue taking afatinib (1 [0.9%]).

**Table 1**
Baseline demographics of patients in RealGiDo and afatinib-treated patients in LUX-Lung 3.

| | RealGiDo overall population (N = 228) | RealGiDo by starting dose | | Patients who received afatinib 40 mg | |
|---|---|---|---|---|---|
| | | ≥40 mg (N = 157)[a] | ≤30 mg (N = 71) | RealGiDo (N = 155) | LUX-Lung 3 afatinib-treated patients (N = 230) |
| Female, N (%) | 138 (60.5) | 90 (57.3) | 48 (67.6) | 89 (57.4) | 147 (63.9) |
| Median age, years (range) | 67.0 (32.0–90.0) | 67.0 (32.0–90.0) | 69.0 (35.0–85.0) | 67.0 (32.0–90.0) | 62.0 (28.0–86.0) |
| Median weight, kg (range) | 65.0 (37.0–118.0) | 65.0 (37.0–118.0) | 65.0 (40.0–93.0) | 65.0 (37.0–118.0)[b] | 61.1 (12.9)[c] |
| Median BMI, kg/m$^2$ (range) | 24.2 (13.9–47.3) | 24.6 (13.9–47.3) | 23.0 (18.6–31.6) | 24.6 (13.9–47.3)[b] | 23.9 (4.1)[c] |
| Race, N (%) | | | | | |
| Asian | 100 (43.9) | 74 (47.1) | 26 (36.6) | 74 (47.7) | 166 (72.2) |
| Caucasian | 96 (42.1) | 59 (37.6) | 37 (52.1) | 57 (36.8) | 61 (26.5) |
| Other | 3 (1.3) | 2 (1.3) | 1 (1.4) | 2 (1.3) | 3 (1.3) |
| Missing | 29 (12.7) | 22 (14.0) | 7 (9.9) | 22 (14.2) | 0 |
| ECOG PS, N (%) | | | | | |
| 0 | 90 (39.5) | 65 (41.4) | 25 (35.2) | 63 (40.7) | 92 (40.0) |
| 1 | 102 (44.7) | 71 (45.2) | 31 (43.7) | 71 (45.8) | 138 (60.0) |
| 2 | 20 (8.8) | 12 (7.6) | 8 (11.3) | 12 (7.7) | 0 |
| 3 | 7 (3.1) | 7 (4.5) | 0 | 7 (4.5) | 0 |
| Missing | 9 (4.0) | 2 (1.3) | 7 (9.9) | 2 (1.3) | 0 |
| Clinical stage at screening, N (%) | | | | | |
| IIIB | 12 (5.3) | 7 (4.5) | 5 (7.0) | 6 (3.9) | 20 (8.7) |
| IV | 216 (94.7) | 150 (95.5) | 66 (93.0) | 149 (96.1) | 210 (91.3) |
| Histology, N (%) | | | | | |
| Adenocarcinoma (predominantly) | 226 (99.1) | 155 (98.7) | 71 (100.0) | 155 (100.0) | 230 (100.0) |
| Squamous cell carcinoma (predominantly) | 1 (0.4) | 1 (0.6) | 0 | 0 | 0 |
| NOS | 1 (0.4) | 1 (0.6) | 0 | 0 | 0 |
| *EGFR* mutation type, N (%) | | | | | |
| Del19 | 178 (78.1) | 119 (75.8) | 59 (83.1) | 117 (75.5) | 112 (48.7) |
| L858R | 49 (21.5) | 37 (23.6) | 12 (16.9) | 37 (23.9) | 91 (39.6) |
| Other | 0 | 0 | 0 | 0 | 27 (11.7) |
| Unknown/missing | 1 (0.4) | 1 (0.6) | 0 | 1 (0.7) | 0 |

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; NOS = not otherwise specified.

[a] Two patients received a starting dose of afatinib > 40 mg; these patients were not included in the comparison with LUX-Lung 3.

[b] Data shown are for the 157 patients who received afatinib ≥40 mg.

[c] Mean ( ± standard deviation).

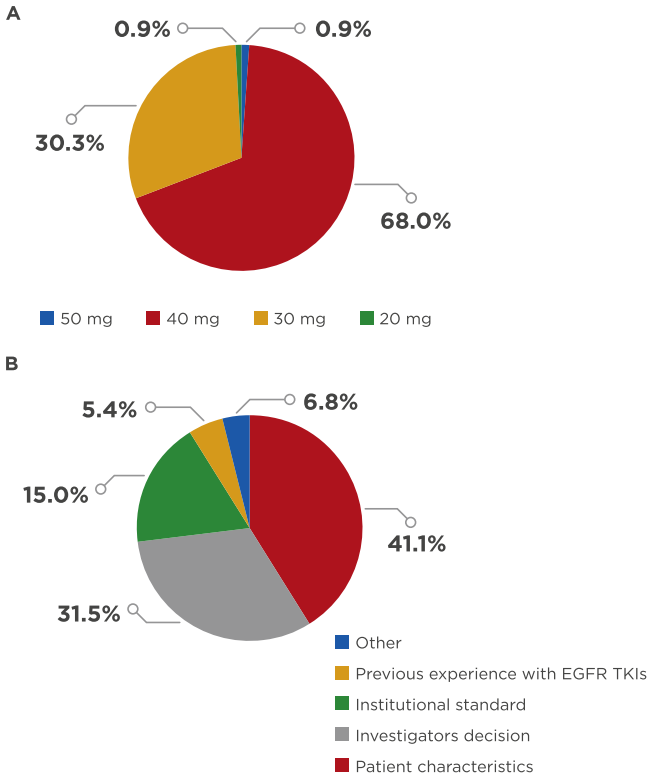



**Fig. 1.** Afatinib starting dose in RealGiDo (A) and the reasons given for a modified starting dose (B).
Abbreviations: EGFR = epidermal growth factor receptor; TKIs = tyrosine kinase inhibitors.

### 3.2. Safety

#### 3.2.1. Overall safety profile and comparison to LUX-Lung 3

In RealGiDo, the overall safety profile of afatinib was similar in the overall population and in the group of patients who received a starting dose of afatinib 40 mg/day (Table 2). ADRs were experienced by 215/228 (94.3%) patients in the overall RealGiDo population, with 56 (24.6%) experiencing grade ≥3 ADRs. Among patients receiving a starting dose of afatinib 40 mg/day (n = 155), 146 (94.2%) experienced an ADR, with 44 (28.4%) experiencing a grade ≥3 ADR; 8 (5.2%) patients had a serious AE (Table 2). There were fewer grade ≥3 ADRs (28.4% vs. 48.9%) and serious AEs (5.2% vs. 14.0%) in patients treated with afatinib 40 mg/day in RealGiDo than in the LUX-Lung 3 trial.

The most common ADRs, both overall and in patients who received a 40 mg/day starting dose, were diarrhoea (75%/77%), rash/acne (63%/61%), paronychia/nail effect (49%/47%) and stomatitis/mucositis (34%/37%), and were mainly of grade 1/2 intensity; this profile was consistent regardless of patient age (Supplementary Table 2). The incidences of these individual ADRs were generally lower than in LUX-Lung 3 (Table 2). Overall median time to first onset of diarrhoea, rash/acne, paronychia and stomatitis/mucositis was 0.4 months, 0.8 months, 2.5 months and 0.5 months, respectively (Supplementary Fig. 1). Time to onset was in general delayed in patients who started with ≤30 mg. Overall, 144 (63.2%), 158 (69.3%) and 51 (22.4%) patients received concomitant medication to manage diarrhoea, skin reactions and stomatitis/mucositis, respectively. Co-medication use was generally similar across patient subgroups regardless of dose modification and/or starting dose (Supplementary Fig. 2).

#### 3.2.2. Safety profile in patients who received a modified afatinib dose

Among patients who received a starting dose of afatinib 40 mg/day and had a dose modification within the first 6 months, 72 (98.6%) experienced an ADR prior to dose modification and 52 (71.2%) after dose modification. As seen in LUX-Lung 3, the severity of ADRs was reduced following dose modification; pre- and post-dose modification incidences of grade 1, 2, 3, and 4 ADRs were 11.0% and 20.6%, 57.5% and 37.0%, 27.4% and 12.3%, and 2.7% and 1.4%, respectively (Fig. 3A). Dose reductions also led to decreases in the incidence and severity of the most commonly reported ADRs (Fig. 3B); for example, the overall (grade ≥3) incidences of diarrhoea, oral mucositis, and rash acneiform were 82.2% (13.7%), 42.5% (8.2%) and 46.6% (9.6%) pre-dose modification, reducing to 32.9% (1.4%), 8.2% (1.4%) and 19.2% (2.7%) post-dose modification. The exception was paronychia, the incidence of which was not reduced following dose modification; however, most events were grade 1/2 in severity.

Among the 71 patients who started on ≤30 mg/day afatinib, 68 (95.8%) patients had an ADR; 12 (16.9%) had a grade 3 ADR and there were no grade 4 ADRs (Fig. 3C). Common ADRs by starting dose are shown in Fig. 3D.

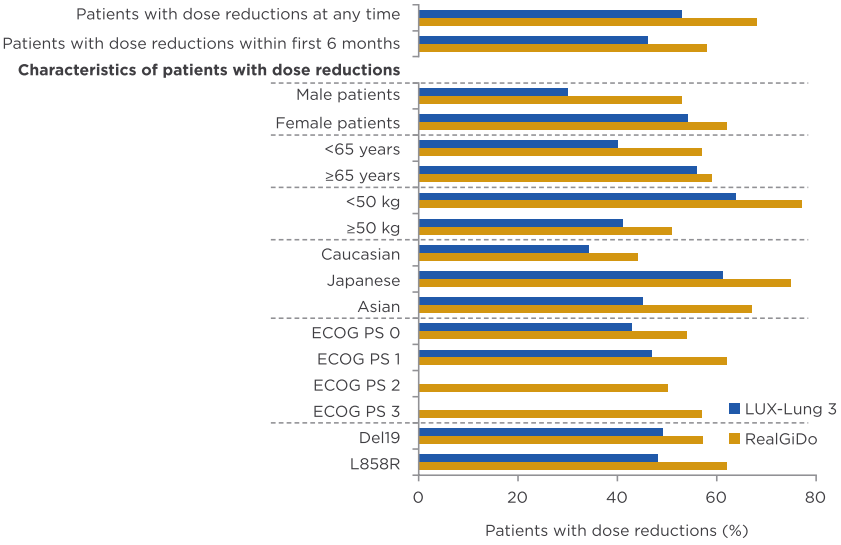



**Fig. 2.** Proportion of patients in RealGiDo and LUX-Lung 3 who started on afatinib 40 mg and who had a dose reduction within the first 6 months of treatment, overall and by patient subgroup. Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status.

**Table 2**
Overall safety profile of afatinib in RealGiDo and in LUX-Lung 3.

| N (%) | RealGiDo overall population (N = 228) | RealGiDo afatinib 40 mg/day starting dose (N = 155) | Lux-Lung 3 afatinib-treated patients (N = 229)[a] |
|---|---|---|---|
| Drug-related AEs | 215 (94.3) | 146 (94.2) | 229 (100.0) |
| Drug-related grade ≥3 AEs | 56 (24.6) | 44 (28.4) | 112 (48.9) |
| Drug-related AEs leading to discontinuation | 17 (7.5) | 13 (8.4) | 18 (7.9) |
| Discontinued due to rash | 2 (0.9) | 2 (1.3) | 0 |
| Discontinued due to diarrhoea | 8 (3.5) | 5 (3.2) | 3 (1.3) |
| Drug-related SAE | 15 (6.6) | 8 (5.2) | 32 (14.0) |
| Drug-related SAE leading to death | 0 | 0 | 4 (1.7) |
| Most frequent treatment-related ADRs/AEs (> 10% occurrence in RealGiDo or Lux-Lung 3) | | | |
| Rash/acne[b] | 143 (62.7) | 95 (61.3) | 204 (89.1) |
| Diarrhoea | 171 (75.0) | 120 (77.4) | 219 (95.2) |
| Paronychia/nail effect | 111 (48.7) | 73 (47.1) | 130 (56.8) |
| Stomatitis/mucositis | 78 (34.2) | 58 (37.4) | 165 (72.1) |
| Decreased appetite | 0 | 0 | 47 (20.5) |
| Vomiting | 2 (0.9) | 1 (0.7) | 39 (17.0) |
| Fatigue | 7 (3.1) | 6 (3.9) | 40 (17.5) |
| Nausea | 8 (3.5) | 3 (1.9) | 41 (17.9) |
| Dry skin/pruritus | 60 (26.3) | 32 (20.7) | 67 (29.3) |

Abbreviations: AE = adverse event; ADRs = adverse drug reactions; SAE = serious adverse event.
[a] One patient was not included in the safety population in LUX-Lung 3 as they did not receive afatinib.
[b] Includes rash maculo-papular and rash acneiform.

#### 3.2.3. Effectiveness

For the overall population, the median TTF was 18.7 months (95% CI 15.1–21.5) (Fig. 4A). Median TTF was 19.5 months (95% CI 13.4–not evaluable [NE]) in patients who remained on ≥40 mg/day for the first 6 months (N = 66), 17.7 months (95% CI 14.5–21.5) in patients who dose reduced to < 40 mg/day within the first 6 months (N = 91), and 19.4 months (95% CI 12.9–NE) in patients who started with afatinib ≤30 mg/day (N = 71; p = 0.543). The Kaplan-Meier estimate of the proportion of patients remaining on treatment at 12 months was 70% in the patients who remained on ≥40 mg/day for the first 6 months, 74% in the patients who dose reduced to < 40 mg/day within the first 6 months, and 66% in patients who started with afatinib ≤30 mg/day; respective rates at 18 months were 53%, 50%, and 53%.

A total of 75 patients had experienced a progressive disease event at the time of data analysis. Of these, 43 (57.3%) had experienced radiological progression, 3 (4.0%) patients had clinical progression only, and 29 (38.7%) had both clinical and radiological progression. There was no difference in type of progression based on reduced starting dose or dose reduction during the first 6 months of treatment (data not shown). In the overall population, median TTP was 20.8 months (95% CI 19.1–25.9) (Fig. 4B). Median TTP was 29.0 months (95% CI 17.9–NE) for those who remained on ≥40 mg/day, 20.0 months (95% CI 14.7–23.0) among patients who had a dose reduction to < 40 mg/day within the first 6 months, and 25.9 months (95% CI 17.3–NE) among patients with a starting dose ≤30 mg/day (p = 0.392). The Kaplan-Meier estimate of the proportion of patients without progressive disease or tumour-related death at 12 months was 79% in the patients who remained on ≥40 mg/day for the first 6 months, 84% in the patients who dose reduced to < 40 mg/day within the first 6 months, and 86% in patients who started with afatinib ≤30 mg/day; respective rates at 18 months were 65%, 60% and 64%.

Median TTF and TTP were consistent across patient subgroups, including those grouped according to *EGFR* mutational status (Del19 vs. L858R) and age (< 75 years vs. ≥ 75 years) (Supplementary Fig. 3). In patients with Del19 vs. L858R, respectively, median TTF was 18.2 vs. 20.0 months and median TTP was 20.5 months vs. not reached. In patients aged < 75 years vs. ≥ 75 years, median TTF was 17.8 vs. 24.9 months and median TTP was 20.5 vs. 25.7 months. Both median TTF and median TTP were significantly longer in patients with ECOG PS 0/1 vs. those with ECOG PS 2/3 (20.0 vs. 11.3 months and 22.4 vs. 12.2 months, respectively).

## 4. Discussion

With several treatment options available for *EGFR* mutation-positive NSCLC, data on outcomes and tolerability, not only from RCTs but also real-world evidence, are important for making decisions on first-line therapies and sequencing of treatments. The RealGiDo results reported here support those of the phase 3 LUX-Lung 3 clinical trial, demonstrating that tolerability-guided afatinib dose adjustment in the real-world setting reduced the frequency and intensity of ADRs, without impacting effectiveness, with similar TTF and TTP reported. Furthermore, the results demonstrate no adverse impact on effectiveness in the selected patients that received a modified starting dose. The observed median TTF and TTP of 18.7 and 20.8 months, respectively, are reassuring.

The baseline demographics of patients in RealGiDo were generally consistent with those observed in the LUX-Lung 3 trial [5], although patients were older and more patients had *EGFR* Del19 mutations in the RealGiDo non-interventional study, likely reflecting treatment guidelines and local practice patterns, together with physicians' positive perception of the OS benefit of afatinib in these patients [7,9]. In addition, in contrast to LUX-Lung 3, which excluded patients with ECOG PS 2/3, patients with a poorer performance status were included in RealGiDo, reflective of the real-world setting of the study.

The overall safety profile of afatinib in RealGiDo was generally consistent with that observed in LUX-Lung 3 (as well as LUX-Lung 6 and 7), and no new safety signals were reported [5,6,8]. Consistent with results from afatinib clinical trials, the key treatment-related ADRs in RealGiDo were diarrhoea, rash/acne, paronychia and stomatitis/mucositis. The frequency of these ADRs was lower in the RealGiDo population than in LUX-Lung 3, and there were overall fewer treatment-related grade ≥3 ADRs and serious AEs in RealGiDo than in LUX-Lung 3. These differences are most likely related to physicians' increased familiarity with afatinib and prophylactic AE management. In RealGiDo, participating sites recruited a median of 8 patients, whereas in LUX-Lung 3 the median was 2, suggesting that physicians participating in RealGiDo may have had more experience with afatinib. However, it should also be noted that, owing to differences in study design, fewer side effects might be documented in the real-world setting vs. clinical trials. Interestingly, the incidence of ADRs that can be prophylactically managed with medication and management strategies (e.g. diarrhoea, skin toxicity) were lower in this real-world setting than in the LUX-Lung

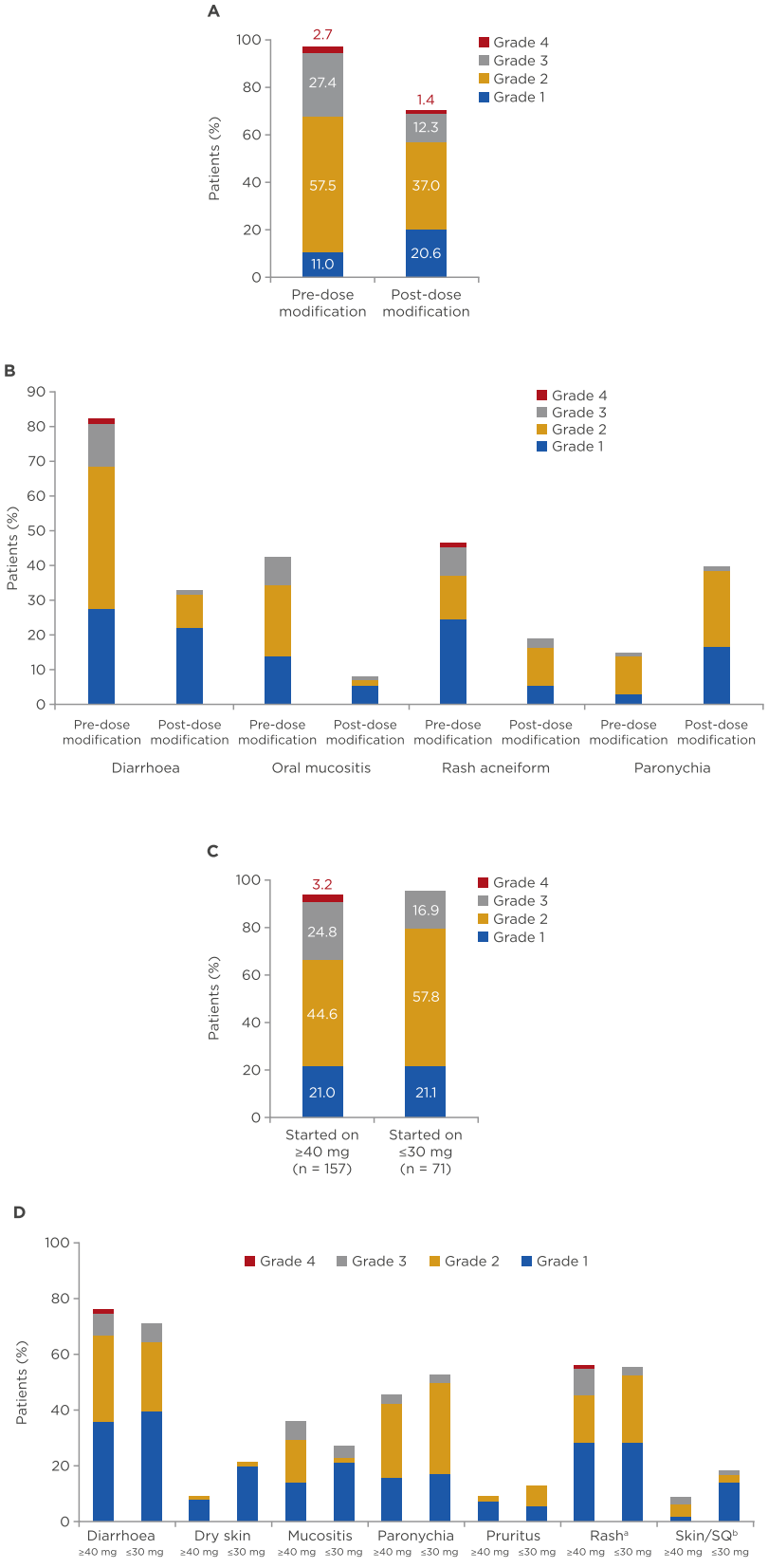


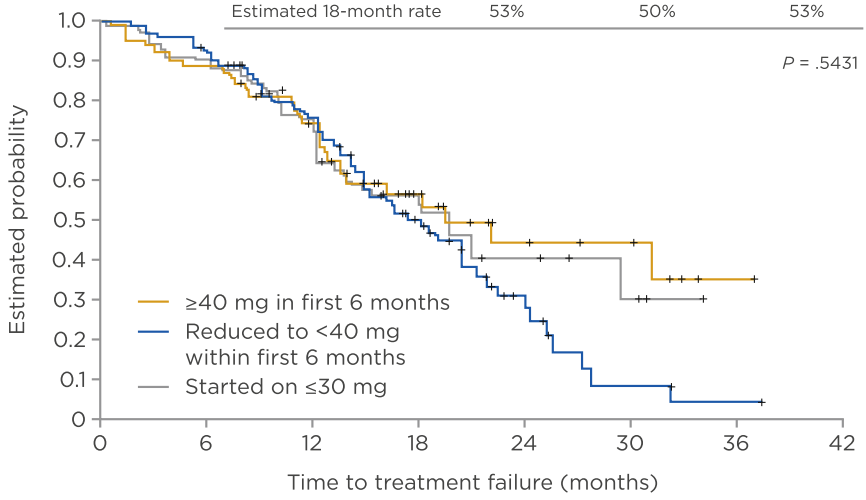

**Fig. 3.** Afatinib safety profile in patients who had a dose reduction or received a modified starting dose of afatinib. (A) Overall safety profile pre- and post-dose reduction in patients who had a dose reduction within the first 6 months after starting on afatinib 40 mg/day. (B) common ADRs (> 10% incidence) pre- and post-dose reduction in patients who had a dose reduction within the first 6 months after starting on afatinib 40 mg/day (N = 91). (C) Overall safety profile in patients by starting dose. (D) Incidences of the most common ADRs by starting dose.
[a]Grouped term includes the preferred terms 'rash maculo-papular' and 'rash acneiform'.
[b]Skin and subcutaneous tissue disorders, other.
Abbreviations: ADRs = adverse drug reactions; SQ = subcutaneous skin disorders.

trials, further supporting the awareness and effectiveness of management strategies.

Among patients who started on afatinib 40 mg/day in RealGiDo, 67% of patients had a dose reduction. This is a higher percentage than observed in LUX-Lung 3, 6 and 7 (53.3%, 28.0% and 39.4%, respectively) [5,6,14]. The greater percentage of dose reductions in RealGiDo may reflect an increasing awareness and understanding among physicians that tolerability-guided afatinib dose adjustment utilising this strategy does not compromise outcomes. Further, criteria for dose reductions were strictly defined in the LUX-Lung 3 protocol.

A

| | ≥40 mg in first 6 months (n = 66) | Reduced to <40 mg within first 6 months (n = 91) | Started on ≤30 mg (n = 71) |
|---|---|---|---|
| Events | 25 | 51 | 30 |
| Median (months), 95% CI | 19.5 (13.4–NR) | 17.7 (14.5–21.5) | 19.4 (12.9–NR) |
| Total population | | 18.7 (15.1–21.5) | |
| Estimated 12-month rate | 70% | 74% | 66% |
| Estimated 18-month rate | 53% | 50% | 53% |




B

| | ≥40 mg in first 6 months (n = 66) | Reduced to <40 mg within first 6 months (n = 91) | Started on ≤30 mg (n = 71) |
|---|---|---|---|
| Events | 18 | 39 | 20 |
| Median (months), 95% CI | 29.0 (17.9–NR) | 20.0 (14.7–23.0) | 25.9 (17.3–NR) |
| Total population | | 20.8 (19.1–25.9) | |
| Estimated 12-month rate | 79% | 84% | 86% |
| Estimated 18-month rate | 65% | 60% | 64% |

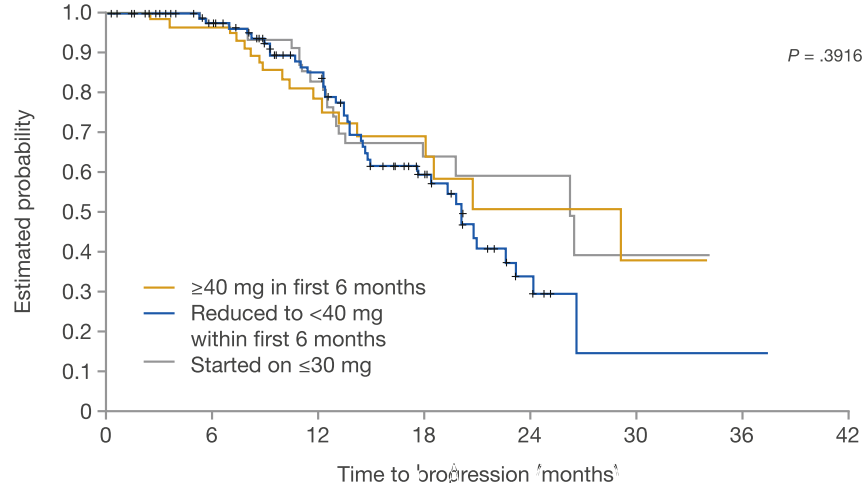



**Fig. 4.** Time to treatment failure (A) and time to progression (B) among patients in RealGiDo, overall and by dose received. Abbreviations: CI = confidence interval; NR = no response.

Consistent with LUX-Lung 3, the majority of dose reductions took place within the first 6 months of afatinib treatment in RealGiDo. The main reason for dose reductions was the occurrence of treatment-related ADRs. Overall, consistent with the LUX-Lung 3, 6 and 7 trials [13,14], dose reduction lowered the intensity and frequency of AEs (overall ADR incidence of 98.6% and 71.2% before and after dose reduction). The individual incidences of diarrhoea, mucositis and rash were all reduced with dose modification, but there was no impact on the incidence of paronychia, possibly because paronychia appears to be a time-dependent rather than dose-dependent ADR.

Around one-third of patients started with a modified afatinib dose (predominantly 30 mg/day). The main reason for starting with a modified dose was related to patient characteristics, including diverse factors such as age, gender and body weight, followed by investigator's decision. There was no clear pattern for the selection of patients to receive a lower starting dose, although it appeared to be more commonplace in females and Caucasians. Among those who received a lower starting dose, the frequency of ADRs was similar to those who started with afatinib 40 mg/day (95.8% and 94.2%, respectively); however, the intensity of ADRs was lower in these selected patients (the incidence of grade ≥3 ADRs was 16.9% vs. 28.4%, and there were no grade 4 AEs). Of note, approximately 20% of patients who received a modified starting dose had a dose escalation. Consistent with results from the LUX-Lung clinical studies [13,14], dose adjustment of afatinib did not appear to compromise its clinical activity. This is further supported by results from a recent real-world study of 44 patients with *EGFR* mutation-positive NSCLC in the United Kingdom in which first-line afatinib dose reductions had no impact on effectiveness; of note, dose adjustment had no impact on median PFS or median OS [15].

There was also no indication that *EGFR* mutational status affected TTF or TTP, suggesting that the high proportion of Del19-positive patients may not have substantially affected the effectiveness outcomes. However, the relatively small number of patients with L858R prevents any firm conclusions being drawn. Unsurprisingly, patients with poor performance status at study start had shorter TTF and TTP vs. those with ECOG PS 0/1, likely reflecting the poorer prognosis of these patients. However, despite this poorer prognosis, there was a clear benefit in the 27 patients with ECOG PS 2/3. The real-world effectiveness of afatinib across a broad range of patients was further demonstrated by subgroup analysis showing that effectiveness was not impacted by patient age, which is consistent with previous results from general clinical practice in Japan [16]. While TTP is not the same as, and cannot be directly compared with, PFS in a clinical trial, the effectiveness data reported here are in line with other real-world data [17,18] and demonstrate afatinib to be an effective first-line treatment for patients with *EGFR*-mutation positive NSCLC.

Real-world studies are valuable, and should be considered complementary to clinical trials. The importance of real-world data for understanding the use of pharmaceutical agents in a broader patient population, outside of the constraints of clinical trials, is being increasingly recognised [1,19]. While clinical trials can provide robust evidence of efficacy and safety of a particular treatment, there often remains uncertainty about the generalisability and external validity of the results (due to a selected patient population). Furthermore, adherence to treatment may be artificially higher in clinical trials (e.g. intensive follow-up that does not occur in real-world practice). Real-world data can also reflect the influence of the clinical setting and healthcare system factors on treatment outcomes. A recent analysis that aimed to provide empirical evidence for the ASCO Value Framework concluded that real-world data in oncology tend to show less effectiveness than RCTs, especially if the RCTs have used surrogate markers such as PFS as endpoints and if the trial population is directly compared with the overall population [20]. For lung cancer, the analysis estimated that such RCTs overestimate real-world outcomes by an average of 18%; however, it is unknown how these measures compare for specific drugs, tumour types and lines of therapy. It is reassuring to see in the RealGiDo study a better tolerability than in LUX-Lung 3 and effectiveness outcomes (TTF/TTP) of 19–21 months.

A key limitation of the RealGiDo study is the retrospective nature. However, several features of the study design helped to mitigate such limitation. For example, the involvement of multiple sites across 13 countries, and the broad inclusion criteria (for example, including patients with poorer performance status), increased the relevance of the results to global real-world practice. Further, the restriction to patients with treatment initiation ≥6 months prior to enrolment avoided early censoring and enabled collection of mature ADR data, while the inclusion of patients who had discontinued afatinib treatment < 6 months prevented selection bias. Selection bias was further limited through the enrolment of consecutive patients who met the inclusion criteria and provided written informed consent as necessary. The involvement of only sites that prescribed afatinib regularly could lead to a potential bias, as patients treated by physicians who are less experienced with management of afatinib might experience more ADRs during treatment; however, any such potential bias was limited by restricting each site to the enrolment of a maximum of 15 patients.

In conclusion, the RealGiDo data demonstrate that the afatinib safety profile in the real-world setting is consistent with that reported in clinical trials, with no new safety signals and fewer grade ≥3 ADRs and serious AEs than in LUX-Lung 3. Consistent with clinical trial evidence, tolerability-guided afatinib dose adjustment in the real-world setting reduced the frequency and intensity of ADRs without compromising effectiveness, and there was also no indication of effectiveness being affected in the selected patients that received a modified starting dose. These results confirm afatinib as an effective first-line treatment for patients with *EGFR*-mutation positive NSCLC and highlight that tailoring the afatinib dose based on individual patient characteristics and the occurrence of treatment-related AEs can help to optimise treatment outcomes.

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## Role of the funding source

The trial was designed by the coordinating investigator (BH) in collaboration with Boehringer Ingelheim. Data were collected by the investigators and analysed by the sponsor and the Alcedis GmbH study team. All authors, including those from Boehringer Ingelheim, were responsible for data interpretation and critical review of the article and approved the final version. BH had full access to all data in the study and had final responsibility for the decision to submit for publication. The datasets generated and analysed during the study are available from BH on reasonable request.

## Disclosure

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.10.028.

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