

Research Paper

Older patients with *EGFR* mutation-positive non-small cell lung cancer treated with afatinib in clinical practice: A subset analysis of the non-interventional GIDEON study

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ABSTRACT

Introduction: Lung cancer is most common in older patients; despite this, older patients are historically under-represented in clinical studies. Here we present data from GIDEON, a study undertaken in Germany in patients with epidermal growth factor receptor mutation-positive (*EGFR*m+) non-small cell lung cancer (NSCLC) receiving first-line afatinib. GIDEON enrolled a high proportion of patients aged ≥ 70 years, providing an opportunity to study afatinib use in older patients. **Materials and Methods:** In GIDEON (NCT02047903), a prospective non-interventional study, patients with *EGFR*m+ NSCLC received first-line afatinib in routine clinical practice until disease progression, death or intolerable adverse events. Key objectives were twelve-month progression-free survival (PFS) rate and objective response rate (ORR). Overall survival (OS) and safety were also assessed. This post hoc analysis explores outcomes of patients grouped by age (≥ 70 and < 70 years).

Results: In the 152 patients enrolled in GIDEON (69.7% female, 64.5%/22.4%/13.2% with Del19/L858R/other exon 18–21 mutations, 33.6% with brain metastases), the median age was 67 years (range 38–89) and 43.4% were aged ≥ 70 years. In the ≥ 70 years age group and the < 70 years age group, twelve-month PFS rate was 58.9% and 43.9%, median PFS was 17.2 months and 10.6 months, ORR was 72.0% and 76.5%, twelve-month OS rate was 79.1% and 79.2%, 24-month OS rate was 52.0% and 61.7%, and median OS was 30.4 months and 27.4 months, respectively. In the ≥ 70 years age group and the < 70 years age group, grade ≥ 3 adverse drug reactions (ADRs) were observed in 34.8% and 40.7% of patients, respectively; the most common were diarrhea (13.6% and 14.0%), acneiform dermatitis (7.6% and 7.0%), stomatitis (1.5% and 4.7%) and maculopapular rash (1.5% and 4.7%).

Discussion: Patients with *EGFR*m+ NSCLC aged ≥ 70 years showed clinical benefit from first-line afatinib with no unexpected safety signals, supporting the use of afatinib in this setting.

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1. Introduction

Approximately 70% of patients newly diagnosed with lung cancer are aged ≥ 65 years [1]. The risk of developing lung cancer increases with age, peaking in Germany between 65 and 74 years for women, and 65–85 years for men [2]. In oncology, 70 years of age may be considered the threshold of old age and is an important cut-off when considering treatment strategies [3,4]. However, older patients were often underrepresented in registrational trials of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) [5]; generally fewer than half of enrolled patients were aged ≥ 65 years and very few were aged over 75 years [6–8].

Afatinib, an irreversible ErbB family blocker, is approved for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations in the *EGFR* gene [9,10]. In the pivotal LUX-Lung series of clinical trials, afatinib treatment significantly improved efficacy outcomes versus chemotherapy [11,12] or gefitinib [13] in patients with *EGFR* mutation positive (*EGFRm+*) NSCLC. In sub-analyses of the LUX-Lung studies, median progression-free survival (PFS) and overall survival (OS) in older patients were similar to those observed in younger patients, with no unexpected toxicities. Rates of discontinuation due to treatment-related adverse events (AEs) in older patients were generally low (9–14%), indicating that AEs could be managed on treatment with dose adjustments and supportive care [6]. Other studies support the activity and tolerability of afatinib in older patients with NSCLC [14–17].

Additional factors need to be acknowledged when considering treatment with afatinib in older patients. Firstly, the likely presence and severity of comorbidities, assessed by tests such as the Charlson Comorbidity Index (CCI) [18,19], and administration of comedication necessitates consideration of the potential for drug–drug interactions (although drug–drug interactions with afatinib via cytochrome P450 are unlikely) [20,21]. Secondly, tolerability concerns may prompt physicians to choose a starting dose below the approved dose of 40 mg daily in frail patients [15,16].

GIDEON (NCT02047903), a prospective, non-interventional study, was undertaken to investigate first-line afatinib treatment in routine clinical practice in Germany [22]. Data on the overall population have been published previously [23]; the high proportion of enrolled patients aged ≥ 70 years provided an opportunity to further study afatinib use in older people.

2. Materials and Methods

2.1. Patients

The methodology of GIDEON has been previously described [23]. In brief, GIDEON enrolled EGFR-TKI naïve patients aged ≥ 18 years, who had been diagnosed with locally advanced and/or metastatic *EGFRm+* NSCLC, and had received afatinib as a first-line treatment. *EGFR* mutation status was determined by local laboratories; any activating *EGFR* mutation was permitted.

The study was approved by the ethics committee of the Technical University of Dresden.

2.2. Study Design

Patients received afatinib in routine clinical practice until disease progression, death or intolerable AEs. Patients were followed-up for 24 months. Each patient underwent a maximum observation period of three years from the date of study enrollment. Treatment decisions were made independently of study participation by the attending physician. Electronic case report forms (eCRFs) were used to record baseline patient characteristics, treatment details, and AEs, as previously described [23]. Patient characteristics, including comorbidities, concomitant medication, Eastern Cooperative Oncology Group performance status (ECOG

PS), histology, tumor, node and metastasis (TNM) status, and *EGFR* mutation analysis (testing methodology and biomarker analyses), were collected. Tumor staging was performed according to the International Association for the Study of Lung Cancer version 7.

2.3. Patient Evaluation

The primary objective was PFS rate at twelve months. Secondary objectives included: objective response rate (ORR), defined as the proportion of patients with complete response (CR) or partial response (PR) as best response according to investigator review (unconfirmed), and disease control rate (DCR), defined as the proportion of patients with CR, PR, or stable disease (SD) as best response according to investigator review. PFS, treatment-emergent AEs, serious AEs, and adverse drug reactions (ADRs), defined as AEs causally related to the study drug according to the investigator, were also assessed. Other objectives included median OS (from start of therapy until death), and one- and two-year survival rates. CCI scores (Supplemental Table 1) [18], afatinib dose modifications, and subsequent therapies were also recorded.

Quality of life (QoL) and tumor-related symptom control were evaluated every eight weeks as previously described [23], using the self-administered European Organisation for Research and Treatment of Cancer (EORTC) questionnaires (Core Quality of Life Questionnaire [QLQ-C30] [24] and Quality of Life Questionnaire: Lung Cancer [QLQ-LC13]) [25].

2.4. Statistical Analyses

No formal hypothesis testing was performed. Exploratory/descriptive post hoc analyses according to age group (<70 years, ≥ 70 years) were undertaken; testing for statistical significance between and within patient groups was not performed. Analyses of safety endpoints and demographic/baseline characteristics were performed on the treated set (defined as all patients who received at least one dose of afatinib). Patients in the treated set who did not violate any inclusion or exclusion criteria were included in the per-protocol set (PPS). The analyses for the primary objective and secondary efficacy objectives were performed on the PPS.

PFS rate at twelve months was calculated via Kaplan–Meier (K–M) methodology; 95% confidence intervals [CIs] were calculated using Greenwood's variance estimator. Patient-reported QoL responses were transformed to a 0–100 scale and analyzed in line with EORTC scoring algorithms [24]. Time-to-symptom worsening was estimated via K–M methodology. Alcedis GmbH was contracted for the development of the electronic data capture system, data analysis, and transfer of data to Boehringer Ingelheim Pharma GmbH & Co.KG. Statistical analyses were performed by Alcedis and Syneos Health.

3. Results

3.1. Patients

One hundred sixty-one patients were enrolled from 41 sites in Germany between March 24, 2014 and December 30, 2016 (database lock: March 14, 2019), of whom nine patients were ineligible for treatment. Of the 152 patients in the treated set, six did not meet inclusion/exclusion criteria. Therefore, 146 patients were included in the PPS [23]. Median follow-up (from first treatment until death/last contact) was 20.6 months (interquartile range: 8.0–32.7 months).

In the ≥ 70 years age group ($n = 66$, 43.4%), 44 (66.7%) were female, and median age was 76 years (range 70–89 years, Table 1). In the <70 years age group ($n = 86$, 56.6%), 62 (72.1%) patients were female, and median age was 60 years (range 38–68 years). There was a higher proportion of patients with ECOG PS ≥ 2 (9.1% versus 1.2%) or a CCI of ≥ 1 (62.1% versus 25.6%) in the ≥ 70 years age group than the <70 years age group. The median CCI score was 1 (range: 0–7) in the ≥ 70 years age

group and 0 (range 0–3) in the <70 years age group.

A higher proportion of patients in the ≥70 years age group was reported to be receiving medications for pre-existing comorbidities than in the <70 years age group (71.2% and 64.0%, respectively). There were 72 medications documented for the ≥70 years age group and 46 medications documented for the <70 years group. Hypertension was the most common comorbidity not assessed as part of the CCI (53.0% and 26.7% of patients in the ≥70 and <70 years age groups, respectively). There were 52 different medications documented for hypertension. In the treated set, the most commonly administered were beta blockers (n = 30, 19.7%), angiotensin type-1 receptor antagonists (n = 21, 13.8%), calcium channel blockers (n = 21, 13.8%), and angiotensin-converting enzyme inhibitors (n = 20, 13.2%). Reported hypertension drugs with known cytochrome P450 or P-glycoprotein interactions are listed in Supplemental Table 2.

At baseline, all patients aged <70 years, and all but one aged ≥70 years (98.5%), had distant metastases. Fewer patients in the ≥70 years age group had brain metastases than in the <70 years group (21.2% and 43.0%, respectively) (Table 1). The rates of *EGFR* Del19, L858R, and exon18–21 mutations are presented in Table 1.

3.2. Treatment Exposure

More patients in the ≥70 years age group received a starting dose of <40 mg afatinib than in the <70 years age group (37.9% and 16.3%, respectively, Table 2). Overall, patients who received a starting dose of 40 mg afatinib tended to have better ECOG PS (ECOG PS 0/1/>1: 53.1%/38.9%/5.3%) than those who received a starting dose <40 mg afatinib (ECOG PS 0/1/>1: 33.3%/53.9%/2.6%).

Table 1
Patient characteristics.

	Aged <70 years (n = 86)	Aged ≥70 years (n = 66)	Treated set (n = 152)
Sex, n (%)			
Male	24 (27.9)	22 (33.3)	46 (30.3)
Female	62 (72.1)	44 (66.7)	106 (69.7)
Median age, years (range)	60 (38–68)	76 (70–89)	67 (38–89)
<i>EGFR</i> mutation status, n (%)			
Del19	56 (65.1)	42 (63.6)	98 (64.5)
L858R	22 (25.6)	12 (18.2)	34 (22.4)
Exon 18–21 mutations ^a	8 (9.3)	12 (18.2)	20 (13.2)
Brain metastases, n (%)			
Yes	37 (43.0)	14 (21.2)	51 (33.6)
No	49 (57.0)	52 (78.8)	101 (66.4)
ECOG PS, n (%)			
0	46 (53.5)	27 (40.9)	73 (48.0)
1	35 (40.7)	30 (45.5)	65 (42.8)
2	0	4 (6.1)	4 (2.6)
3	1 (1.2)	2 (3.0)	3 (2.0)
Missing	4 (4.7)	3 (4.6)	7 (4.6)
Charlson Comorbidity Index, n (%)			
0	64 (74.4)	25 (37.9)	89 (58.6)
1	14 (16.3)	17 (25.8)	31 (20.4)
>1	8 (9.3)	24 (36.4)	32 (21.1)
Receiving medication for pre-existing comorbidities, n (%)	55 (64.0)	47 (71.2)	102 (67.1)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor. ^aNot including T790M.

The frequency of dose reductions (57.6% and 61.6%) and dose escalations (15.2% and 18.6%) were similar in the ≥70 and <70 years age groups. Reasons for dose modifications are shown in Table 2. In the group aged ≥70 years, there were 36 dose reductions due to AEs/serious AEs, and 53 in the group aged <70 years. Of patients who received a starting dose of 30 mg, dose reduction to 20 mg was required in 57.1% and 25.0% of patients in the ≥70 and <70 years age groups, respectively. Of patients in the ≥70 years age group who received a starting dose of 40 mg, dose reduction to 30 mg and 20 mg was required in 24.4% and 31.7%, respectively. Of patients in the <70 years age group who received a starting dose of 40 mg, dose reduction to 30 mg and 20 mg was required in 48.6% and 15.3%, respectively. At the time of the last recorded dose administration, more patients in the ≥70 years age group received a final dose of <40 mg than in the <70 years age group (71.2% and 64.0%, respectively). Fewer patients in the ≥70 years age group discontinued treatment due to disease progression than in the <70 years age group, especially due to central nervous system (CNS) progression (n = 2 versus n = 10; Supplementary Table 3).

3.3. Effectiveness

Of evaluable patients (n = 145), median PFS was 12.2 months (Fig. 1Ai) and median OS was 30.4 months (Fig. 1Bi) [23]. In the ≥70 years age group, the twelve-month PFS rate was 58.9%, median PFS was 17.2 months (Fig. 1Aii) and median OS was 30.4 months (Fig. 1Bii, Table 3). In the <70 years age group, the twelve-month PFS rate was 43.9%, median PFS was 10.6 months and median OS was 27.4 months. DCR and ORR were similar in ≥70 years and <70 years age groups (Table 3).

Table 2
Starting dose and treatment modifications.

	Age <70 years (n = 86)	Age ≥70 years (n = 66)	Treated set (n = 152)
Dose at first administration, n (%)			
40 mg daily	72 (83.7)	41 (62.1)	113 (74.3)
<40 mg daily	14 (16.3)	25 (37.9)	39 (25.7)
30 mg daily	12 (14.0)	21 (31.8)	33 (21.7)
20 mg daily	2 (2.3)	4 (6.1)	6 (3.9)
Final dose, n (%)			
40 mg daily	31 (36.0)	19 (28.8)	50 (32.9)
<40 mg daily	55 (64.0)	47 (71.2)	102 (67.1)
30 mg daily	43 (50.0)	20 (30.3)	63 (41.4)
20 mg daily	12 (14.0)	27 (40.9)	39 (25.7)
Patients with change in dose, n (%)			
Dose reduction	53 (61.6)	38 (57.6)	91 (59.9)
Dose increase	16 (18.6)	10 (15.2)	26 (17.1)
Number of patients with any modifications, n (%)	55 (64.0)	39 (59.1)	94 (61.8)
Number of dose modifications	69	54	123
Reason for dose modification, n (%)			
Adverse event	50 (72.5)	30 (55.6)	80 (65.0)
Serious adverse event	3 (4.3)	6 (11.1)	9 (7.3)
Dose increased to good tolerance	10 (14.5)	7 (13.0)	17 (13.8)
Patient's wish	3 (4.3)	1 (1.9)	4 (3.3)
Tumor progression	1 (1.4)	1 (1.9)	2 (1.6)
Complete remission	0	1 (1.9)	1 (0.8)
Other	2 (2.9)	8 (14.8)	10 (8.1)

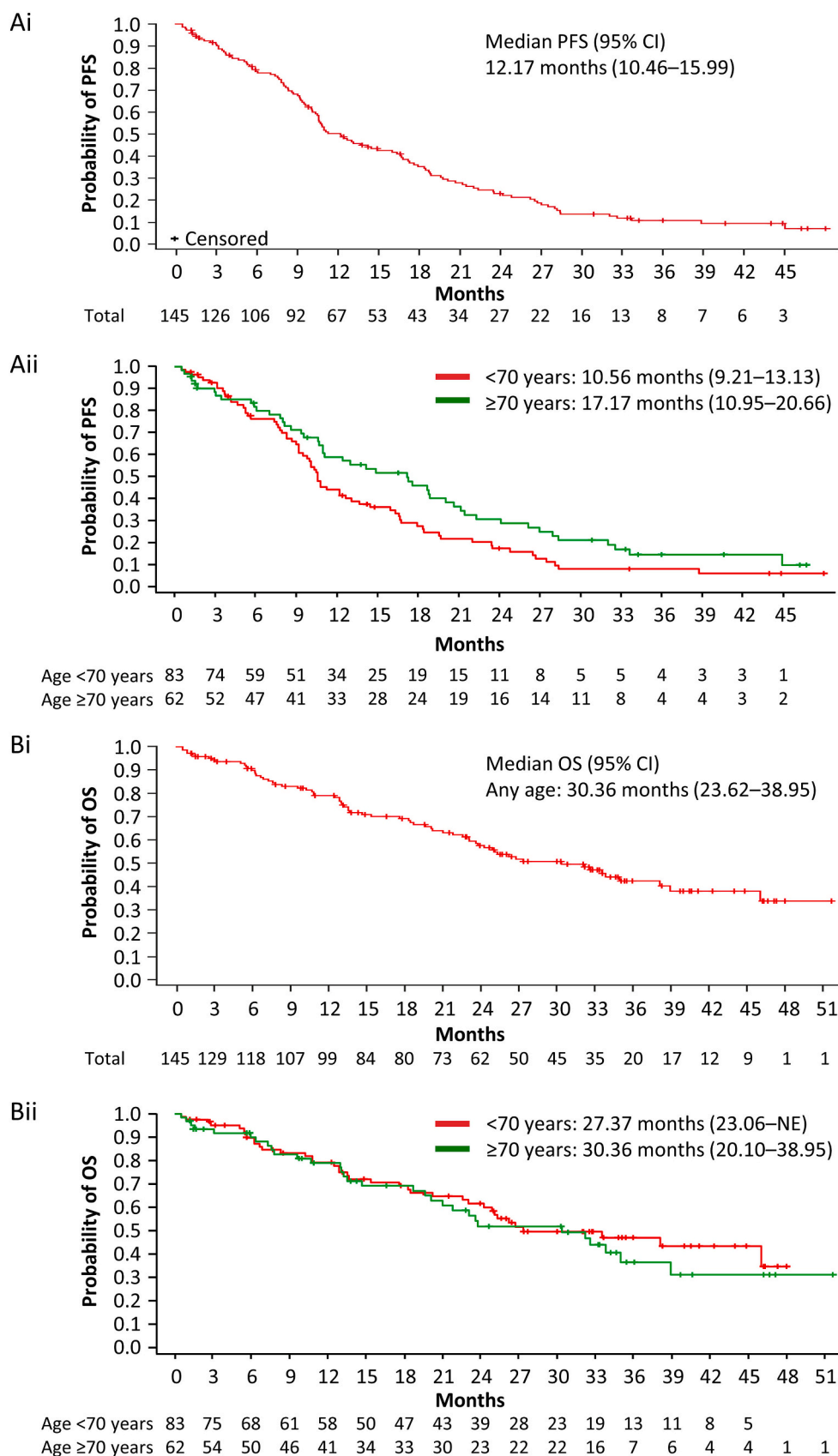


Fig. 1. Per-protocol treated set; progression-free survival in overall population (Ai) and according to age group (Aii). Overall survival in overall population (Bi) and according to age group (Bii). Abbreviations: CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Table 3
Effectiveness.

	Age <70 years (n = 86)	Age ≥70 years (n = 66)
12-month PFS rate, % (95% CI)	43.9 (32.8–54.5)	58.9 (45.1–70.3)
Median PFS, months (95% CI)	10.6 (9.2–13.1)	17.2 (11.0–20.7)
12-month OS rate, % (95% CI)	79.2 (68.2–86.7)	79.1 (66.1–87.6)
24-month OS rate, % (95% CI)	61.7 (49.5–71.9)	52.0 (37.4–64.8)
Median OS, months (95% CI)	27.4 (23.1–NE)	30.4 (20.1–39.0)
	Age <70 years (n = 68)	Age ≥70 years (n = 50)
DCR, % (95% CI)	88.2 (78.1–94.8)	96.0 (86.3–99.5)
ORR, % (95% CI)	76.5 (64.6–85.9)	72.0 (57.5–83.8)

Abbreviations: CI, confidence interval; DCR, disease control rate; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

3.4. Safety

In the ≥70 years age group and <70 years age group, respectively, AEs were reported in 100% and 97.7% of patients, serious AEs were reported in 53.0% and 34.9% of patients, and fatal AEs were reported in 9.1% (death [unrelated to tumor], lung infection, pneumonia, malignant neoplasm progression, dyspnea, and respiratory failure) and 2.3% of patients (death [tumor dependence not evaluable] and cerebrovascular accident). ADRs and grade ≥3 ADRs were experienced by 95.5% and 34.8% of patients, respectively, in the ≥70 years age group and 96.5% and 40.7%, respectively, in the <70 years age group (Table 4). In the ≥70 years age group and <70 years age group, respectively, the most common ADRs were diarrhea (84.8% and 81.4%), acneiform dermatitis (33.3% and 40.7%), paronychia (22.7% and 27.9%) and stomatitis (15.2% and 20.9%; Table 4). ADRs leading to treatment discontinuation were experienced by thirteen (19.7%) patients in the ≥70 years age group and twelve (14.0%) in the <70 years age group (Supplemental Table 4). In the ≥70 years age group, the most common ADRs leading to discontinuation were diarrhea (n = 5, 7.6%), vomiting, nausea, and maculopapular rash (n = 2, 3.0% each). In the <70 years age group, the most common ADRs leading to discontinuation were vomiting (n = 3, 3.5%) and diarrhea (n = 2, 2.3%).

3.5. Quality of Life and Symptom Status Change

The median time to worsening of cough was 22.4 months (95% CI, 12.4 months–non-estimable [NE]) in the ≥70 years age group (n = 52) but was not estimable in the <70 years age group (n = 67; 95% CI, 23.3 months–NE). The median time to worsening of dyspnea was 18.6 months (95% CI, 6.9–NE) in the ≥70 years age group (n = 51) and 20.8 months (95% CI, 13.7–NE) in the <70 years age group (n = 67). The median time to deterioration for pain was 15.0 months (95% CI, 5.8–23.7) in the ≥70 years age group (n = 52) and 18.3 months (95% CI, 7.8–27.7) in the <70 years age group (n = 67). QoL/Global health status was also monitored for change. In the ≥70 years (n = 13) and <70 years

(n = 22) age groups, respectively, ten (76.9%) and fifteen (68.2%) patients reported stable or improved QoL/Global health status.

3.6. Subsequent Therapy

In the ≥70 years age group, 38 patients (57.6%) had no further documented therapy or were no longer subject to follow-up after discontinuation of afatinib, whereas for 28 patients (42.4%), subsequent therapies were documented. These included: chemotherapy (n = 11, 16.7%); radiotherapy (n = 6, 9.1%); and first, second, or third generation EGFR-TKI therapy (n = 6, 9.1%; n = 7, 10.6%; and n = 7, 10.6%, respectively). In the <70 years age group, 40 patients (46.5%) had no further documented therapy or were no longer subject to follow-up, whereas 46 patients (53.5%) had documented subsequent therapy. Subsequent therapies included: chemotherapy (n = 30, 34.9%); radiotherapy (n = 13, 15.1%); and first, second, or third generation EGFR-TKI therapy (n = 13, 15.1%; n = 9, 10.5%; and n = 24, 27.9%, respectively).

Following disease progression, ten patients (15.2%) in the ≥70 years age group, and seventeen patients (19.8%) in the <70 years age group were documented as having undergone tumor rebiopsy during follow-up. Overall, the T790M mutation was detected in six patients (60.0%) from the ≥70 years age group and eleven patients (64.7%) from the <70 years age group.

4. Discussion

Here we assessed efficacy and safety of afatinib with respect to age in a real-world clinical setting. Overall, ORR and OS were similar in the ≥70 and <70 years age groups, with comparable tolerability profiles and low rates of treatment discontinuations due to ADRs. Of note, median PFS was higher in the ≥70 years age group than in the <70 years age group.

The antitumor effectiveness observed in the older population in this study was consistent with previous prospective studies. Here, median PFS and OS of patients aged ≥70 years (17.2 months and 30.4 months,

Table 4
Most common adverse drug-reactions (at least 10% incidence overall in at least one subgroup).

CTCAE grade:	Patients aged <70 years (n = 86)						Patients aged ≥70 years (n = 66)					
	1	2	3	4	5	Any grade	1	2	3	4	5	Any grade
Patients, n (%)	14 (16.3)	34 (39.5)	33 (38.4)	1 (1.2) ^a	1 (1.2) ^b	83 (96.5)	10 (15.2)	30 (45.5)	21 (31.8)	1 (1.5) ^c	1 (1.5) ^d	63 (95.5)
Diarrhea	38 (44.2)	20 (23.3)	12 (14.0)	–	–	70 (81.4)	26 (39.4)	21 (31.8)	9 (13.6)	–	–	56 (84.8)
Acneiform dermatitis	16 (18.6)	13 (15.1)	6 (7.0)	–	–	35 (40.7)	11 (16.7)	6 (9.1)	5 (7.6)	–	–	22 (33.3)
Paronychia	11 (12.8)	12 (14.0)	1 (1.2)	–	–	24 (27.9)	6 (9.1)	9 (13.6)	–	–	–	15 (22.7)
Stomatitis	8 (9.3)	6 (7.0)	4 (4.7)	–	–	18 (20.9)	5 (7.6)	4 (6.1)	1 (1.5)	–	–	10 (15.2)
Maculopapular rash	9 (10.5)	2 (2.3)	4 (4.7)	–	–	15 (17.4)	6 (9.1)	5 (7.6)	1 (1.5)	–	–	12 (18.2)
Dry skin	13 (15.1)	5 (5.8)	–	–	–	18 (20.9)	5 (7.6)	2 (3.0)	–	–	–	7 (10.6)
Nausea	5 (5.8)	3 (3.5)	3 (3.5)	–	–	11 (12.8)	4 (6.1)	2 (3.0)	2 (3.0)	–	–	8 (12.1)
Pruritus	5 (5.8)	5 (5.8)	–	–	–	10 (11.6)	4 (6.1)	2 (3.0)	–	–	–	6 (9.1)
Alopecia	6 (7.0)	3 (3.5)	–	–	–	9 (10.5)	8 (12.1)	–	–	–	–	8 (12.1)
Fatigue	4 (4.7)	–	–	–	–	4 (4.7)	6 (9.1)	2 (3.0)	1 (1.5)	–	–	9 (13.6)
Vomiting	3 (3.5)	2 (2.3)	1 (1.2)	–	–	6 (7.0)	3 (4.5)	3 (4.5)	1 (1.5)	–	–	7 (10.6)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events. ^aGrade 4 amylase increase and lipase increase were both reported in one patient. ^bDeath was reported as an adverse drug reaction in one patient. ^cStevens–Johnson syndrome. ^dPneumonia.

respectively) were similar to those reported in patients aged ≥ 65 years in LUX-Lung 3 and 6 (PFS: 13.7 months, OS: 23.2–31.6 months in patients with common *EGFR* mutations), and in patients aged ≥ 75 years in LUX-Lung 7 (PFS: 14.7 months, OS: 27.9 months) [6]. Furthermore, the ORR in the ≥ 70 years group (72%) was similar to those observed in the overall LUX-Lung 3, 6, and 7 populations (56%–70%) [11–13]. Two observational studies have recently assessed osimertinib in older (≥ 75 years old) patients with *EGFR* + NSCLC. In these studies, median PFS was numerically higher (19.4–22.1 months) than in the current study, and median OS was not reached in the one study that reported OS data [26,27]. However, differences in patient populations preclude cross trial comparisons.

Brain metastases are frequently observed in patients with advanced lung cancer (around 25%), with highest rates among younger patients [28–30]. In the present study, a lower proportion of patients in the ≥ 70 years age group had brain metastases than in the < 70 years age group (21.2% and 43.0%, respectively). Presence of brain metastases is a negative prognostic factor; therefore, the higher rate of brain metastases observed in the < 70 years age group represents a potential confounding factor that may have contributed to the disparity in PFS. The small number of patients with brain metastases in the ≥ 70 years age group precluded meaningful analysis of efficacy in this subgroup. However, previous analysis of the GIDEON population as a whole demonstrated that afatinib was effective in patients with brain metastases. In patients with brain metastases ($n = 48$), the twelve-month PFS rate was 39.4%, median PFS was 10.5 months (95% CI 9.1–12.7) and the ORR and DCR were 77.3% and 93.2% ($n = 44$ evaluable patients), respectively. In patients without brain metastases ($n = 97$), the twelve-month PFS rate was 55.9%, median PFS was 14.9 months (95% CI 10.6–18.4), and the ORR and DCR were 73.0% and 90.5% ($n = 74$ evaluable patients), respectively [23]. Few ($n = 2$) patients in the ≥ 70 years age group had CNS progression at the end of treatment.

Despite similar median OS, the OS K–M curves diverged after around 33 months in favor of the younger patient group. This could reflect a higher uptake of subsequent therapy relative to the older group. From the data available, fewer older patients went on to receive chemotherapy or third generation TKIs following discontinuation of afatinib compared with the younger patient group. Documented rebiopsy rates were low ($< 20\%$) and few patients were reportedly tested for T790M and went on to receive the third generation TKI osimertinib, which has been shown to be a promising treatment option post-afatinib [31]. Reasons for the low uptake of osimertinib reported here likely include its limited availability in Germany during the first half of the study [32,33]; importantly, T790M testing was not recommended as standard in German guidelines until April 2017 [34].

The median OS of 30.4 months observed in patients ≥ 70 years in this study is encouraging. At present, the first-line treatment of choice for *EGFR* + NSCLC has not been fully established, particularly among older patients. Of note, while first-line osimertinib has demonstrated significant OS benefit versus first generation TKIs in the phase III FLAURA trial (hazard ratio [HR]: 0.79; 95% CI, 0.63–0.98), the improvement was less pronounced in patients aged ≥ 65 years (HR: 0.87; 95% CI, 0.63–1.22) [35]. Moreover, while several recent observational studies have indicated that osimertinib is an effective first-line treatment option in older patients, potential development of pneumonitis or interstitial lung disease (ILD) is a concern, occurring in 17–19% of patients [26,27].

In this non-interventional study, ADRs (all/grade ≥ 3) occurred in 96%/38% of patients, similar to rates reported in a previous real-world study (94%/25%) [16]. AEs were consistent with the known tolerability profile of afatinib, with diarrhea and acneiform dermatitis being the most frequent [6]. Rates of ADRs and grade ≥ 3 ADRs in older patients were similar to those seen in the younger subgroup, and no new safety concerns were identified. ADRs leading to treatment discontinuation

were observed in 19.7% and 14.0% of patients in the ≥ 70 years and < 70 years age groups, respectively, similar to rates observed in a previous real-world study (20.8% and 14.3% among patients aged ≥ 70 and < 70 years, respectively) [36].

Consistent with previous real-world findings, older patients more commonly received a < 40 mg starting dose than younger patients [15,16]. Furthermore, a higher proportion of patients who received a starting dose of 40 mg afatinib had an ECOG PS of 0 than among patients who received a starting dose of < 40 mg afatinib. Previously reported reasons for employing a 30 mg starting dose include patient age, body weight [16], and renal failure [10]. Other real-world studies of afatinib treatment found efficacy outcomes were similar for patients receiving a starting dose of < 40 mg and ≥ 40 mg, irrespective of age [15,16].

Comorbidities and polypharmacy are likely in older patients with cancer, increasing the risk of drug–drug interactions [37–40]. In the present study, the median CCI score was higher in the ≥ 70 years age group than in the < 70 years age group (1 [range: 0–7] and 0 [range: 0–3], respectively) and many of the older patients in this study were receiving hypertension drugs. The documented potential for drug–drug interactions with the anti-hypertensive regimens used in this study are listed in the supplementary materials. All calcium channel inhibitors, 50% of beta-blockers, 20% of angiotensin type 1-receptor antagonists, and 20% of combination preparations identified in this study are known to have potential drug–drug interactions via the cytochrome P450 system. While interactions via the cytochrome P450 system are not expected with afatinib [41], three of the documented hypertension drugs are known P-glycoprotein substrates. Afatinib is both a substrate and inhibitor of P-glycoprotein and therefore could be influenced by these drugs [42]. There are reports of limiting interactions by spacing the time of administration of different drugs, and afatinib exposure may be managed by dose alterations [7,38,43]. Nevertheless, the promising activity of afatinib observed in older patients in this study suggests that neither drug–drug interactions nor higher CCI scores compromised clinical activity in this real-world clinical practice setting.

Generally, treatment with *EGFR*-TKIs is associated with improvement in patient-reported QoL and control of NSCLC-related symptoms [44–47]. Few reports have specifically examined QoL among older patients with NSCLC. In a phase II study of Japanese patients with *EGFR* + NSCLC aged ≥ 75 years, there was no significant change of QoL reported in the first twelve weeks of receiving treatment with afatinib [48]. In the present study, QoL and symptom questionnaire data indicated durable benefit for patients in both age groups. In the ≥ 70 years age group, the median time to worsening of symptoms tended to be shorter than in the < 70 years age group. However, a higher proportion of patients in the ≥ 70 years age group reported stable or improved QoL, compared with the < 70 years age group. Further study of health-related QoL and patient-reported symptom control in older patient groups is required.

Real-world studies have inherent weaknesses, including those relating to completeness of data collection compared with randomized controlled trials. All study sites were located in Germany, therefore the results of this study may not reflect outcomes obtained in other regions. The patient population was relatively small and there were differences in patient characteristics between this analysis and previous studies that could potentially have influenced the results. For example, the proportions of patients with Del19 (64%) and L858R (22%) mutations differed from those reported in a combined analysis of the LUX-Lung 3 and LUX-Lung 6 studies (Del19: 50%, L858R: 39%) [49]. Furthermore, some patient characteristics (e.g., mutation type, brain metastases, ECOG PS) differed between age groups. Non-documented factors influencing physicians' decisions may have played a role in patient selection and therapy guidance. A starting dose of 40 mg was received by 74% of patients, higher than the 50–68% reported in other observational studies [16,50]. A further limitation was that the study was not designed to

comprehensively assess outcomes of patients receiving subsequent therapies, including outcomes of patients who received osimertinib following progression on first-line afatinib. Further studies are ongoing that aim to assess this treatment strategy, including in older patients [51,52].

In conclusion, older patients were well represented in this non-interventional study, providing important information on the routine clinical use of afatinib in this patient group. PFS, OS and rates of ADRs in the ≥ 70 years age group were generally similar to those in the < 70 years age group. These findings support the consideration of afatinib as a first-line treatment option in older patients with *EGFR*m+ NSCLC. While osimertinib is also an option in this setting [26,27], and is generally well tolerated and has good activity against brain metastases [53], afatinib might be an attractive option in some instances, e.g., in patients with tumors harboring uncommon mutations, where afatinib has demonstrated relatively broad activity [54], and in cases where a sequential EGFR TKI strategy is pursued [55].

Ethics approval and consent to participate

The study was approved by the ethics committee of the Technical University of Dresden. The study was conducted in accordance with the principles of the International Conference on Harmonisation E6 guideline for Good Clinical Practice and the Declaration of Helsinki, and was performed in compliance with relevant German law and recommendations. All patients provided written consent for study participation. External monitoring was undertaken as previously described [23].

Consent for publication

All patients provided written consent for publication.

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The GIDEON non-interventional study was funded by Boehringer Ingelheim. The sponsor was involved in the study design and the collection, analysis and interpretation of the data. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations, and was involved in the decision to submit the article for publication.

Author Contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment related to the development of the manuscript and have approved the final version.

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Declaration of Competing Interest

Wolfgang M. Brueckl reports receiving lecture and educational event (personal) fees from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Pfizer, Roche Pharmaceuticals, and Takeda; receiving congress (personal) fees from Boehringer Ingelheim, AstraZeneca, and Roche Pharmaceuticals; and receiving advisory board fees (personal) from AstraZeneca, Boehringer Ingelheim, Novartis, Merck Sharp & Dohme, Lilly Pharma, Bristol Myers Squibb, and Roche. Martin Reck reports serving on advisory councils or committees and receiving consulting fees from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Lilly, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Sanofi; and receiving speaker honoraria from AbbVie, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Lilly, Merck, Merck Sharp & Dohme, Novartis, Pfizer, and Roche. Kai Neben reports receiving honoraria (personal fees) from Roche, Takeda, Amgen, Janssen, Pfizer, Bayer, Merck Sharp & Dohme, Bristol Myers Squibb, and Chugai. Frank Griesinger reports receiving support for scientific research from ASTRA, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Siemens, Amgen, GlaxoSmithKline, and Janssen; receiving honoraria for presentations from ASTRA, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens, Amgen, GlaxoSmithKline, Janssen, and Sanofi; and advisory board participation for ASTRA, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens, GlaxoSmithKline, Janssen, and Sanofi. Justyna Rawluk reports serving on advisory councils or committees for AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Boehringer Ingelheim, Roche, and Takeda; and receiving consulting fees from AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Boehringer Ingelheim, Roche, and Takeda. Stefan Krüger reports receiving honoraria and grants or funds from Boehringer Ingelheim. Joachim H. Ficker reports receiving speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi Aventis, and Bristol Myers Squibb. Miriam Möller reports receiving consulting fees (consulting or advisory role) from Boehringer Ingelheim and Roche; and receiving payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Boehringer Ingelheim, Roche, AstraZeneca, and Merck Sharp & Dohme. Andrea Schueler is an employee of Boehringer Ingelheim Pharma GmbH & Co KG. Eckart Laack, Konrad Kokowski and Harald Schäfer report no potential conflict of interest.

Data availability

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use the <https://vivli.org/link> to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

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Appendix A. Supplementary data

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