Real-world global data on targeting epidermal growth factor receptor mutations in stage III non-small-cell lung cancer: the results of the KINDLE study

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Abstract

Background: Tyrosine kinase inhibitors (TKIs) are the standard of care for resectable and metastatic non-small-cell lung cancer (NSCLC) harbouring epidermal growth factor receptor (EGFR) mutations (EGFRm). We describe the real-world practice of EGFRm testing, prevalence, treatment and outcomes in EGFRm stage III NSCLC from a multi-country, observational study.

Methods: The KINDLE study retrospectively captured diagnostic information, treatments and survival outcomes in patients with stage III NSCLC from January 2013 to December 2017. Baseline characteristics and treatments were described and real-world outcomes from initial therapy were analysed using Kaplan–Meier methods.

Results: A total of 3151 patients were enrolled across three regions: Asia (n = 1874), Middle East and North Africa (MENA) (n = 1046) and Latin America (LA) (n = 231). Of these, 1114 patients (35%) were tested for EGFRm (46% in Asia, 17% in MENA and 32% in LA) and EGFRm was detected in 32% of tested patients (34.3% in Asia, 20.0% in MENA and 28.4% in LA). In a multi-variate analysis, overall EGFRm patients treated with EGFR-TKI monotherapy as initial treatment, without any irradiation, had twice the risk of dying (hazard ratio: 1.983, 95% confidence interval: 1.079–3.643; p = 0.027) versus any other treatment. Finally, unresectable patients with EGFRm NSCLC who received concurrent chemoradiotherapy (cCRT) as initial therapy had longer overall survival (OS) compared with their counterparts who only received TKI monotherapy without any irradiation (48 months versus 24 months; p < 0.001).

Conclusion: The KINDLE study showed that a minority of stage III NSCLC patients were tested for EGFRm. Patients with EGFRm with unresectable NSCLC had similar outcomes from cCRT as initial therapy compared with EGFR wild type with a trend in OS favouring the EGFRm group. Outcomes with EGFR-TKI monotherapy as initial therapy, without any irradiation, were worse. The ongoing LAURA study (NCT03521154) will help define the role of EGFR-TKIs in EGFRm stage III NSCLC treated with cCRT.

Keywords: epidermal growth factor receptor, non-small-cell lung cancer, stage III, tyrosine kinase inhibitors, unresectable

Introduction

Lung cancer is one of the most common type of cancer diagnosed globally (11.6% of the total cancer cases) and the leading cause of cancer death (18.4% of the total cancer deaths).1,2 About 85% of all lung cancer cases are non-small-cell lung cancer (NSCLC) of which roughly a third are stage III disease at diagnosis3 [sub-classified
Owing to the heterogeneous nature of stage III NSCLC, its management requires a multi-disciplinary, multi-modal approach including surgery, radiotherapy (RT) and systemic therapy, often in a combined fashion. Depending on the expertise, as many as 50% of stage IIIA NSCLC may be amenable to surgical resection either with neoadjuvant and/or adjuvant therapy. However, in many cases deemed as unresectable, concurrent chemoradiotherapy (cCRT) is recommended followed by durvalumab consolidation for up to 12 months for eligible patients.3–7

The discovery of epidermal growth factor receptor (EGFR) gene mutations in NSCLC has led to the development of novel targeted therapies dramatically improving treatment outcomes. EGFR mutations (EGFRm) are common in NSCLC with a global prevalence ranging from 10% to 50%.8 The most common EGFRm are exon 19 deletions and a point mutation in exon 21 (L858R), which account for approximately 45% and 40% of all EGFRm in NSCLC, respectively.9,10 In addition, with the increased usage of next-generation sequencing, the oncogenic role of concurrent genomic alterations and their potential impact on the treatment strategy will be of importance.11 The use of EGFRm testing and the use of EGFR-tyrosine kinase inhibitors (TKIs) have resulted in superior survival outcomes [overall survival (OS) and progression-free survival (PFS)] compared with standard chemotherapy (CT) or SoC.12 The common EGFRm (exon 19 deletion and L858R) are associated with sensitivity to first-generation (erlotinib and gefitinib), second-generation (afatinib and dacomitinib) and third-generation (osimertinib) EGFR-TKIs.9,10 Osimertinib is the preferred EGFR-TKI with a proven OS benefit over first-generation EGFR-TKI and with proven efficacy in the central nervous system.13 In addition, the role of EGFR-TKIs has become established as adjuvant treatment in resectable stage I-III NSCLC but is not yet established in unresectable stage III EGFRm NSCLC post-cCRT. The clinical value of using osimertinib in completely resected EGFRm stage IB-III A NSCLC [hazard ratio (HR) 0.20, 99.12% confidence interval (CI), 0.14–0.30].14 In contrast, how treatment with an EGFR-TKI will affect outcomes in unresectable/inoperable stage I-III EGFRm NSCLC still needs to be investigated. Currently, the LAURA trial (NCT 03521154) is ongoing, using osimertinib in unresectable stage III EGFRm NSCLC as maintenance treatment post-chemoradiotherapy (CRT).15 For medically inoperable stage I-II EGFRm NSCLC, there is now a sub-protocol opened in PACIFIC-4 (NCT03833154) using stereotactic body radiation therapy followed by adjuvant osimertinib for 3 years.16

There is a dearth of data on testing practices in stage III NSCLC for EGFRm and programmed death ligand 1 (PD-L1) status and the treatment patterns adopted in patients with NSCLC having these mutations in a real-world setting, particularly in the low- to middle-income countries. Additionally, there is a knowledge gap on the role, usage and real-world outcomes of EGFR-TKIs in EGFRm unresectable stage III NSCLC. Therefore, we analysed testing practices, the rate of EGFRm testing, treatment patterns and associated survival outcomes in patients with stage III NSCLC. These data were collected as a part of the KINDLE real-world retrospective global study in non-United States and non-European countries.

Methods

Study design

KINDLE was a retrospective, non-interventional, multi-centre study conducted across 19 countries in Asia, Middle East and North Africa (MENA) and Latin America (LA) at 101 centres in patients diagnosed with de novo locally advanced stage III NSCLC (AJCC seventh edition) between January 2013 and December 2017. The study protocol (NCT03725475) was reviewed and approved by the Institutional Review Boards/Independent Ethics Committees of all the participating centres before study initiation. Written informed consents were obtained before the data collection from patients’ medical records, from the patients or their next-to-kin (in case of deceased patients) or the legal representatives. The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization, good clinical practices, good pharmacoepidemiology practices and the applicable legislation on
non-interventional studies and/or observational studies. The reporting of this manuscript has been done in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology checklist. The details of the study design, eligibility criteria and data collection methods have been reported by Jazieh et al.

Data collection and study outcomes
For this analysis, we extracted the data from the main KINDLE dataset on demographic parameters, disease characteristics, treatment patterns and associated outcomes [OS and real-world PFS (rwPFS)] based on the staging and resectability and segregated according to the subsets with and without EGFRm. Molecular testing was done at primary diagnosis. The extracted data for each subset included demography, clinical characteristics and selected treatment patterns with survival outcomes as reported by Jazieh et al. along with type of EGFRm and PD-L1 expression status.

The occurrence of disease progression was ascertained from documentation in the patients' records such as imaging reports, pathology reports and oncologist notes on disease progression. The definitions rwPFS, first progression interval and OS along with documentation of sequential treatment regimens within each progression interval for patients who received treatment are reported by Jazieh et al.

Statistical analyses
Statistical analysis was performed using SAS 9.4 software. Socio-demographic and clinical characteristics for each subset according to EGFRm status were summarized using descriptive statistics and compared between patients with EGFRm and patients without EGFRm; p values were derived to detect statistical significance. EGFRm status was described using descriptive statistics according to country-wise distribution, treatment modalities (initial therapy, first line, second line) and staging and resectability (initial therapy, first line, second line). Initial therapy was defined as NSCLC treatment(s) received on or after the index date (i.e. date of initial diagnosis of primary stage III NSCLC) to the date of first documented disease progression.

The survival outcomes (rwPFS and OS) according to EGFRm status based on different treatment patterns, staging and resection status were determined using median survival estimates and were reported along with the two-sided 95% CI. A multi-variate Cox proportional hazards model and HR along with 95% CI was used to identify the significant effects of EGFRm status on OS by controlling relevant demographic and clinical covariates affecting OS. A p < 0.05 was considered statistically significant.

Results
Testing patterns and prevalence of EGFRm in stage III NSCLC
Of the 3151 patients enrolled (Asia = 1874, MENA = 1046 and LA = 231), EGFRm testing was performed in 1114 (35%) patients, ranging from 17% (n = 175) in the MENA region to 46% (n = 865) in Asia. EGFR mutations were detected in 31.7% (n = 353) of the total population with the highest prevalence in Asia (34.3%) and the lowest in the MENA region (20%). The percentages of EGFRm testing and EGFRm status by region are shown in Figure 1.

The majority of patients had only one EGFRm (89.5%) and the most common EGFRm were the exon 19 deletions (44.2%) and exon 21 L858R mutation (31.9%) (Table 1). Conclusive EGFRm testing was performed in 828 patients with adenocarcinoma: 325 cases (39%) were EGFRm; 503 cases (61%) were EGFRwt. Similarly, a conclusive EGFRm test was performed in 148 patients with epidermoid or squamous cell carcinoma: 17 cases (11.5%) were EGFRm and 131 cases (88.5%) were EGFRwt (Table 2).

Testing for PD-L1 expression was performed for 368 patients (11.7%) of whom 188 patients (51.1%) were found to have PD-L1 expression (i.e. PD-L1 ≥ 1%) (MENA: 27/54, 50%; Asia:147/292, 50.3%; and LA: 14/22, 63.6%) (Supplemental Table 1). Overall, the most commonly used antibodies were Dako22C3 (31.8%) and Ventana SP263 (26.4%) (Supplemental Table 1). Finally, 50 patients (14%) of the EGFRm group (N = 353) had PD-L1 expression and 23 patients (12%) of the PD-L1 (N = 188) were EGFRm positive (data not shown).

Demographic and clinical characteristics
The median age (range) was 63.0 years (21–92 years) and was comparable, irrespective of whether EGFRm testing was performed or not and regardless of EGFRm status. The patients who underwent testing as well as those with
EGFRm included a significantly higher percentage of \((p < 0.001)\) females (Tested: 34% versus Untested 18%; EGFRm: 51% versus EGFRwt 25%), non-smokers (Tested: 34% versus Untested 17%; EGFRm: 58% versus EGFRwt 22%), patients with adenocarcinoma (Tested: 79% versus Untested 39%; EGFRm: 92% versus EGFRwt 73%) compared with their untested or EGFRwt counterparts, respectively. The AJCC staging distribution and Eastern Cooperative Oncology Group (ECOG) performance status were similar for patients with and without EGFRm (Table 2).

Figure 1. Region-wise prevalence of (a) EGFR testing and (b) EGFR mutations. EGFR, epidermal growth factor receptor; EGFRwt, EGFR wild-type.

Treatment patterns and survival outcomes
Treatment patterns and outcomes of initial therapy. Of the 1114 patients tested for EGFRm, clinical outcome data were available in 880 patients and of these, 288 patients had EGFRm. Overall, targeted therapy was included in five different upfront treatment regimens: monotherapy, or in combination with any of the following: RT, CT, sequential chemoradiotherapy (sCRT)/cCRT and immunotherapy. The predominant treatment modalities used as initial therapy for patients with EGFRm were EGFR-TKIs \((n = 69, 24\%)\), cCRT \((n = 48, 16.7\%)\) and CT alone.
The EGFRm patients who received EGFR-targeted therapy only, without any irradiation (n = 69) as initial therapy, showed median rwPFS of 10.9 months (95% CI: 7.46–13.40) and a median (m)OS of 25.4 months (95% CI: 21.62–34.92). All of these patients were treated with a palliative intent. Hence, the outcome of these patients cannot be compared to those amenable for CRT.

**Outcome by EGFRm status in the overall population with stage III disease**

The median rwPFS was similar in the overall population with EGFRm compared with EGFRwt (14.0 months versus 12.2 months; \( p = 0.95 \)) [Figure 2(a)]. However, the median OS was significantly longer in the overall population with EGFRm compared with EGFRwt (50.3 months versus 40.0 months; \( p = 0.00063 \)) [Figure 2(b)]. The results using propensity score matching were similar (Supplemental Table 2 and Supplemental Figure S1A and S1B).

**Outcome by EGFRm status in resectable and unresectable stage III disease**

In resectable patients, both median rwPFS and OS were similar in patients with EGFRm compared with patients with EGFRwt (18.9 months versus 19.9 months; \( p = 0.31 \) and 58.6 months versus 57.9 months; \( p = 0.31 \), respectively) (Supplemental Figure S2A and S2B). In unresectable patients, the median rwPFS was also similar for EGFRm and EGFRwt (12.3 months versus 10.7 months; \( p = 0.93 \)). In contrast, the median OS was significantly longer in unresectable patients with EGFRm compared with EGFRwt (47.5 months versus 32.4 months; \( p = 0.01 \)) (Supplemental Figure S2C and S2D). The results using propensity score matching were similar (Supplemental Table 2 and Supplemental Figure S2E–S2H).

**Outcomes with cCRT by EGFR mutation Status in unresectable stage III disease**

As stage III NSCLC is a heterogeneous disease, the treatment modalities and outcomes vary; hence, we decided to focus on unresectable stage III NSCLC cohort. In the unresectable stage III NSCLC cohort, EGFRm patients treated with cCRT as initial treatment showed a similar median rwPFS compared with those with EGFRwt tumours (10.5 months versus 10.8 months; \( p = 0.65 \)); mOS was also found to be similar between the two groups (48 months versus 36.5 months; \( p = 0.065 \)) with a trend favouring the EGFRm group [Figure 3(a) and (b)]. The
### Table 2. Demographic and clinical characteristics of patients with and without EGFR mutations.

| Characteristic                               | All patients (N=3151) | Tested (N=1114) | Untested (N=2037) | p Value | EGFRm (N=353) | EGFRwt (N=688) | p Value |
|---------------------------------------------|-----------------------|-----------------|-------------------|---------|---------------|---------------|---------|
| Age, median [range] (years)                 | 63.0 [21–92] [n=3084] | 63.0 [24–92] [n=1107] | 62 [21–89] [n=2038] | 0.38    | 64 [25–90] [n=352] | 63 [24–92] [n=682] | 0.07    |
| Gender, n (%)                               |                       |                 |                   |         |               |               |         |
| Female                                      | 740 (24)              | 373 (34)        | 367 (18)          | ***     | 181 (51)      | 172 (25)      | ***     |
| Male                                        | 2411 (77)             | 741 (67)        | 1670 (82)         |         | 172 (49)      | 516 (75)      |         |
| Tobacco smoking, n (%)                      |                       |                 |                   |         |               |               |         |
| Current/ex-smoker                           | 2163 (69)             | 655 (59)        | 1508 (75)         | ***     | 112 (32)      | 491 (71)      | ***     |
| Never smoker                                | 712 (23)              | 375 (34)        | 337 (17)          |         | 204 (58)      | 154 (22)      |         |
| Unknown/missing                             | 276 (9)               | 84 (8)          | 192 (9)           |         | 37 (11)       | 43 (6)        |         |
| AJCC stage seventh edition, n (%)           |                       |                 |                   |         |               |               |         |
| Stage IIIA                                  | 1568 (56)             | 601 (57)        | 967 (55)          | 0.29    | 208 (61)      | 357 (55)      | 0.06    |
| Stage IIIB                                 | 1239 (44)             | 451 (43)        | 788 (45)          |         | 131 (39)      | 291 (45)      |         |
| Histology type, n (%)                       |                       |                 |                   |         |               |               |         |
| Adenocarcinoma                              | 1665 (54)             | 880 (79)        | 785 (39)          | ***     | 325 (92)      | 503 (73)      | ***     |
| Epidermoid or squamous cell carcinoma       | 1134 (37)             | 155 (14)        | 979 (48)          |         | 17 (5)        | 131 (19)      |         |
| Other/unknown                               | 352 (11)              | 79 (7)          | 273 (13)          |         | 11 (3)        | 53 (8)        |         |
| ECOG performance status, n (%)              |                       |                 |                   |         |               |               |         |
| 0–1                                         | 1941 (62)             | 667 (60)        | 1274 (63)         | ***     | 209 (59)      | 409 (59)      | 0.21    |
| ≥2                                          | 246 (8)               | 61 (5)          | 185 (9)           |         | 16 (5)        | 42 (6)        |         |
| Missing                                     | 964 (31)              | 386 (35)        | 578 (28)          |         | 128 (36)      | 237 (34)      |         |
| Resectability, n (%)                        |                       |                 |                   |         |               |               |         |
| Resectable                                  | 667 (30)              | 337 (39)        | 330 (24)          | ***     | 133 (48)      | 193 (35)      | ***     |
| Unresectable                                | 1545 (70)             | 521 (61)        | 1024 (76)         |         | 142 (52)      | 358 (65)      |         |
| PD-L1 testing, n (%)                        |                       |                 |                   |         |               |               |         |
| Yes                                         | 368 (12)              | 263 (24)        | 105 (5)           | ***     | 58 (17)       | 190 (28)      | 0.001   |
| No                                          | 2344 (74)             | 779 (70)        | 1565 (77)         |         | 273 (77)      | 455 (66)      |         |
| Unknown/missing                             | 439 (14)              | 72 (6)          | 367 (18)          |         | 22 (6)        | 43 (6)        |         |
| PD-L1 status, n (%)                         |                       |                 |                   |         |               |               |         |
| Negative                                    | 180 (49)              | 122 (44)        | 58 (55)           | 0.16    | 35 (60)       | 77 (40)       | 0.008   |
| Positive                                    | 188 (51)              | 141 (54)        | 47 (45)           |         | 23 (40)       | 113 (60)      |         |

*Information was missing for 939 (all patients), 256 (tested), 78 (EGFRm), 137 (EGFRwt) and 683 (untested) patients.

**p Value < 0.001.

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EGFRwt, epidermal growth factor receptor wild-type; PD-L1, programmed death ligand 1.
| Initial treatment                  | Total number of patients | Patients with EGFRm n (%) | Median rwPFS (95% CI) (months) | Median OS (95% CI) (months) | Patients with EGFRwt n (%) | Median rwPFS (95% CI) (months) | Median OS (95% CI) (months) |
|----------------------------------|--------------------------|---------------------------|-------------------------------|-----------------------------|----------------------------|-------------------------------|-------------------------------|
| Surgery alone                    | 30                       | 17 [5.9]                  | 17.6 [7.06–44.52]             | 37.1 [21.91–66.73]          | 13 [2.2]                   | 14.4 [7.43–NC]                | NC [20.83–NC]                 |
| Surgery + cCRT                   | 17                       | 5 [1.7]                   | 18.9 [8.28–NC]                | 41.3 [14.42–41.26]          | 12 [2.0]                   | 20.5 [7.39–35.81]             | 41.9 [14.36–NC]              |
| Surgery + sCRT                   | 55                       | 22 [7.6]                  | 20.6 [13.17–42.15]            | NC [38.83–NC]               | 33 [5.6]                   | 48.2 [17.05–NC]               | NC [NC–NC]                   |
| Surgery + CT                     | 67                       | 24 [8.3]                  | 12.3 [8.02–28.19]             | 58.6 [37.82–NC]             | 43 [7.3]                   | 16.4 [13.70–20.67]            | 40.2 [23.75–57.86]            |
| cCRT + Surgery                   | 10                       | 3 [1.0]                   | 22.0 [11.20–NC]               | 44.8 [NC–NC]                | 7 [1.2]                    | 18.0 [4.50–NC]                | 29.4 [28.48–NC]              |
| cCRT                             | 229                      | 48 [16.7]                 | 10.8 [5.75–14.98]             | 50.8 [47.21–NC]             | 181 [30.6]                 | 10.8 [8.94–12.29]             | 32.9 [25.03–49.61]            |
| cCRT + CT                        | 23                       | 3 [1.0]                   | 6.5 [5.32–11.01]              | NC [NC–NC]                  | 20 [3.4]                   | 11.2 [6.64–15.11]             | NC [30.62–NC]                |
| sCRT                             | 69                       | 20 [6.9]                  | 10.0 [5.65–13.77]             | 29.0 [23.29–NC]             | 49 [8.3]                   | 12.4 [9.95–16.00]             | 32.0 [21.88–NC]              |
| CT                               | 152                      | 28 [9.7]                  | 12.3 [3.58–17.25]             | 65.4 [23.69–NC]             | 124 [20.9]                 | 6.9 [5.26–8.38]               | 25.3 [19.55–43.83]            |
| CT + Targeted therapy            | 17                       | 9 [3.1]                   | 18.4 [2.17–33.58]             | 34.4 [10.61–NC]             | 8 [1.4]                    | 10.0 [1.87–25.49]             | 42.9 [17.08–42.94]            |
| RT                               | 52                       | 10 [3.5]                  | 9.2 [1.08–19.88]              | 41.2 [8.87–NC]              | 42 [7.1]                   | 10.8 [7.49–17.58]             | 21.3 [13.40–48.99]            |
| RT + Targeted therapy            | 25                       | 14 [4.9]                  | 21.7 [8.61–26.84]             | 42.6 [25.43–NC]             | 11 [1.9]                   | 42.9 [2.53–NC]                | 48.3 [2.73–NC]               |
| Targeted therapy                 | 78                       | 69 [24.0]                 | 10.9 [7.46–13.40]             | 25.4 [21.62–34.92]          | 9 [1.5]                    | 8.3 [0.03–32.30]              | 41.8 [2.14–NC]               |

Data are only shown, when the total number of patients is at least 10.
cCRT, concurrent chemoradiotherapy; CI, confidence interval; CT, chemotherapy; EGFRm, epidermal growth factor receptor mutation; EGFRwt, epidermal growth factor receptor wild-type; mOS, median overall survival; NC, non-calculable; NSCLC, non-small-cell lung carcinoma; RT, radiotherapy; rwPFS, real-world progression-free survival; sCRT, sequential chemoradiotherapy.
Figure 2. Kaplan–Meier plot of total PFS and OS after initial therapy by EGFR type before propensity score matching: (a) rwPFS in overall patients with stage III NSCLC.
Kaplan–Meier survival curves for progression-free survival for all stage III NSCLC patients with EGFRm and EGFRwt are shown in blue or red, respectively.
Median rwPFS for EGFRm, 14.0 months [95% CI: 12.4–15.7].
Median rwPFS for EGFRwt, 12.2 months [95% CI: 11.4–13.4].
(b) OS in overall patients with stage III NSCLC.
Kaplan–Meier survival curves for overall survival for all stage III NSCLC patients with EGFRm and EGFRwt are shown in blue or red, respectively.
mOS for EGFRm, 50.3 months [95% CI: 44.8–66.7].
mOS for EGFRwt, 40.0 months [95% CI: 33.2–47.9].
CI, confidence interval; EGFRm, epidermal growth factor receptor mutation; EGFRwt, EGFR wild-type; mOS, median overall survival; NSCLC, non-small-cell lung cancer; OS, overall survival; rwPFS, real-world median progression-free survival.
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Results using propensity score matching were similar (Supplemental Table 2 and Supplemental Figure S3A and S3B). The EGFRm patients were older (66 years versus 62 years); more likely to be female (70% versus 24%); to have adenocarcinoma (87% versus 67%) and to be never-smokers (78% versus 20%) (data not shown).

Outcomes in patients with EGFRm by initial therapy in unresectable stage III disease

In unresectable patients with EGFRm NSCLC, cCRT as initial therapy resulted in better OS compared with EGFR-TKI monotherapy without any local irradiation (48 months versus 24 months; \(p < 0.001\)); median rwPFS was found to be similar for initial therapy with cCRT and TKI monotherapy without any local irradiation (10.5 months versus 14.6 months; \(p = 0.825\)) [Figure 3(c) and (d)]. In a small number of patients with exon19del (\(n = 22\)), cCRT resulted in an OS of 50.79 (95% CI: 35.29–NC) months versus 47.21 (95% CI: 21.52–NC) months in patients with L858R (\(n = 13\)) mutation. The CIs between exon19del and L858R are overlapping. In another small subgroup, EGFR-TKI monotherapy without any local irradiation showed an OS of 30.52 (95% CI: 15.67–NC) months in patients with exon19del (\(n = 13\)) versus 14.62 (95% CI: 13.31–NC) months in patients with L858R mutation (\(n = 15\)). Gefitinib was used in 23, erlotinib in 10, afatinib in 5 and osimertinib in one patient(s); three patients had to change their TKI, one patient changed twice. Due to the small sample size (\(n = 72\) before matching) and high heterogeneity between the cCRT and EGFR-TKI group, the propensity score matching was not successful. The patients with unresectable EGFRm disease treated with cCRT were younger (66 years versus 74 years) and fitter (ECOG 0/1 73% versus 37%) than those treated with TKI monotherapy, without any local irradiation (data not shown).

Initial therapy and second-line therapy

Figure 4 depicts the initial and second-line post-progression therapies in EGFRm patients with unresectable tumours after initial treatment with EGFR-TKI monotherapy without any irradiation or cCRT.

In patients who progressed on initial cCRT (\(n = 30\)), 25 patients (83%) received treatment after first progression, 20 (80.0%) of them received a TKI-based therapy at first progression. Of the 13 patients progressing on the first subsequent treatment, 12 received treatment, among whom 5 (41.7%) received a TKI-based therapy as second subsequent therapy.

Among the patients progressing on EGFR-TKI as initial monotherapy (\(n = 23\)), 16 (70%) received first post-progression therapy. CT alone was the most preferred first post-progression therapy (\(n = 8/16, 50\%\)). For 4 of the 9 patients progressing on first subsequent therapy in this group, all modalities (EGFR-TKI-based, CRT-based, CT alone and others) were used for one patient each as second post-progression therapy.

Outcomes as per line of targeted therapy in all patients

In univariate analysis of rwPFS and OS (Table 4), targeted therapy only in initial line as monotherapy, without local irradiation, was significantly associated with higher risk for worse rwPFS (HR: 1.487, 95% CI: 1.187–1.863; \(p = 0.0006\)) compared with those not having targeted monotherapy, without local irradiation in initial line only. However, better OS was significantly associated with targeted therapy in any line (HR: 0.795, 95% CI: 0.679–0.931, \(p = 0.0043\)). A significant association for better OS was also noted in patients with stage IIIB disease receiving a targeted therapy in any line of treatment, whereas there was a trend for such an association in patients with stage IIIA disease.

Local recurrence was the most common type of cancer progression in both groups of patients with EGFRm and EGFRwt and the type of progression was similar for overall, resectable and unresectable category with EGFRm and EGFRwt (\(p > 0.05\)). In patients with EGFRm, central nervous system was the most common site for distant extra thoracic metastasis (overall: 17%, resectable: 20% and unresectable: 15%); for unresectable EGFRm category, non-visceral lymph nodes were the most common site for distant extra thoracic metastasis in 20.7% patients. In patients with EGFRwt, non-visceral lymph nodes were the most common site for distant extra thoracic metastasis (overall: 21.8%, resectable: 22% and unresectable: 21.8%) (Supplemental Table 3).

Predictors of overall survival

A multi-variate analysis of OS in this patient population tested for EGFRm (Table 5) revealed a significantly better OS in patients with EGFRm compared with EGFRwt (HR: 0.765, 95% CI: 0.590–0.995).
0.604–0.969, \( p = 0.0264 \)), stage IIIA compared with stage IIIB (HR: 0.669, 95% CI: 0.554–0.807, \( p < 0.001 \)) and adenocarcinoma compared with other types of NSCLC (HR: 0.757, 95% CI: 0.602–0.952, \( p = 0.0172 \)). Male patients (HR: 1.396, 95% CI: 1.072–1.820; \( p = 0.0135 \)) and patients aged >65 years were more likely to have shorter OS (HR: 1.425, 95% CI: 1.173–1.731, \( p = 0.0004 \)) compared with females and those aged \( \leq 65 \) years. The OS was not influenced by ECOG performance status, region or ethnicity.

A multivariate analysis of rwPFS based on initial treatment in EGFRm patients (Table 6) revealed that surgery was associated with significantly longer rwPFS (HR: 0.546, 95% CI: 0.394–0.756, \( p = 0.0003 \)) and only targeted therapy, without local irradiation, was associated with significantly higher odds for worse rwPFS (HR: 1.528, 95% CI: 0.05–0.999).
A multi-variate analysis of OS based on initial treatment in EGFRm patients (Table 6) revealed that patients with initial treatment using targeted therapy alone, without any local irradiation, were twice more likely to have shorter OS (HR: 1.983, 95% CI: 1.079–3.643; \( p = 0.0273 \)).

### Discussion

This secondary analysis from the retrospective KINDLE study conducted in Asia, MENA and LA, focused on the rate of EGFRm testing, the prevalence of EGFR mutations, the use of TKI-based and other therapies, as well as survival.
These results are from the era when durvalumab consolidation post-cCRT in stage III NSCLC and adjuvant osimertinib post-resection in EGFRm NSCLC were not approved and recommended. In our study, the overall testing rate for EGFRm was 35% and was highest in the Asian patient subset (46%). The overall EGFRm testing rate was comparable to that reported previously in the Asia-Pacific region (31.8%) in patients with advanced NSCLC\textsuperscript{19} and was reported in a recent study from China (42.54%) in patients with recurrent stage IIIB/IV NSCLC.\textsuperscript{20} Despite the College of American Pathology, the

| Table 5. Multi-variate analysis of overall survival in stage III NSCLC tested for EGFR mutations. |
|---------------------------------------------------------------|
| **Patient characteristics** | **HR (95% CI)** | **p Value** |
| EGFRm versus EGFRwt (327 versus 653) | 0.765 (0.604–0.969) | 0.0264 |
| Stage IIIA versus IIIB (554 versus 426) | 0.669 (0.554–0.807) | <0.0001 |
| Age > 65 versus ≤65 (405 versus 575) | 1.425 (1.173–1.731) | 0.0004 |
| ECOG 0/1 versus 2/3/4 (903 versus 77) | 0.912 (0.655–1.268) | 0.5820 |
| Male versus Female (646 versus 334) | 1.396 (1.072–1.820) | 0.0135 |
| Smoking history yes versus no (600 versus 380) | 1.000 (0.766–1.306) | 0.9986 |
| Adenocarcinoma versus Others (782 versus 198) | 0.757 (0.602–0.952) | 0.0172 |
| Asian versus Africa and Middle (752 versus 177) | 0.845 (0.660–1.082) | 0.1810 |
| Latin America versus Africa and Middle (51 versus 177) | 0.939 (0.587–1.504) | 0.7948 |

Patients with an EGFRm have a higher percentage of women, non-smokers, resectable tumours and adenocarcinoma (Table 2). Values in bold represent statistically significant (p < 0.05).

ECOG, Eastern Cooperative Oncology Group; EGFRm, epidermal growth factor receptor mutation; EGFRwt, epidermal growth factor receptor wild-type; HR, hazard ratio.

| Table 6. A multi-variate analysis for rwPFS and OS of various regimens as initial treatment of stage III NSCLC with EGFR mutation. |
|---------------------------------------------------------------|
| **Characteristics** | **PFS** | **OS** |
| | **Number** | **HR (95% CI)** | **p Value** | **Number** | **HR (95% CI)** | **p Value** |
| Surgery (yes versus no) | 115 versus 214 | 0.546 [0.394–0.756] | **0.0003** | 115 versus 213 | 0.631 [0.373–1.068] | 0.0865 |
| cCRT (yes versus no) | 73 versus 256 | 1.058 [0.732–1.527] | 0.7652 | 73 versus 255 | 0.598 [0.322–1.110] | 0.1035 |
| sCRT (yes versus no) | 53 versus 276 | 1.087 [0.742–1.592] | 0.6692 | 53 versus 275 | 0.827 [0.448–1.528] | 0.5448 |
| CT alone (yes versus no) | 28 versus 301 | 1.306 [0.792–2.153] | 0.2951 | 28 versus 300 | 0.720 [0.323–1.605] | 0.4215 |
| RT alone (yes versus no) | 10 versus 319 | 1.498 [0.749–2.999] | 0.2533 | 10 versus 318 | 0.842 [0.245–2.893] | 0.7849 |
| EGFR-TKI alone (yes versus no) | 69 versus 260 | 1.528 [1.023–2.283] | **0.0384** | 69 versus 259 | 1.983 [1.079–3.643] | **0.0273** |
| IO (yes versus no) | 7 versus 322 | 1.092 [0.442–2.702] | 0.8481 | 7 versus 321 | 1.129 [0.270–4.731] | 0.8680 |

Values in bold represent statistically significant (p < 0.05).

cCRT, concurrent chemoradiotherapy; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; IO, immunotherapy; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; rwPFS, real-world PFS; sCRT, sequential chemoradiotherapy; TKI, tyrosine kinase inhibitor.
International Association for the Study of Lung Cancer and the Association for Molecular Pathology guideline (2018) recommendations for testing for molecular biomarkers in newly diagnosed NSCLC, the overall testing rate was found to be low in our study.

EGFR mutations are found in up to 50% of Asian patients and 10%–15% of white patients with lung adenocarcinoma. In our study, the Asia subset had the highest rate of EGFRm (34.3%) and MENA had the lowest prevalence of 20%. A recent systematic review and meta-analysis (SRMA) from MENA reported a similar prevalence of 21.2% in NSCLC; however, there was heterogeneity regarding the stage of patients in the studies included in this SRMA. The prevalence of EGFRm observed in our study was lower than that observed in patients with stage IB to IIA screened for the ADAURA trial (44%) and in studies of advanced NSCLC from China (46.4%) and South East-Asia (51.4%). In a retrospective study of patients with NSCLC in MENA, a slightly lower frequency of EGFR mutations was observed in patients with stage I-II disease (17.6%; 12 of 68 patients), while a higher frequency was observed in patients with stage IV disease (31.3%; 30 of 96 patients). Differences in the patient population such as squamous cell subtype and stage of disease might explain the variation.

Consistent with previous reports, the prevalence of EGFRm compared with EGFRwt was higher in females (51%), non-smokers (58%) and patients with adenocarcinoma (92%); these patient populations also underwent a higher rate of testing for EGFRm (females: 34%; non-smokers: 34%; adenocarcinoma: 79%).

Our results also show that a higher percentage of patients with resectable tumours were tested for EGFRm (tested 39% versus untested 24%) and had EGFRm in higher proportions (EGFRm 48% versus EGFRwt 35%) when compared with unresectable tumours. This finding suggests that in real-world practice, oncologists sometimes request EGFRm testing on resected samples of NSCLC, which complies with the current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines In Oncology (NCCN guidelines®), recommending molecular testing for EGFR mutation on diagnostic biopsy or surgically resected sample for ensuring availability of EGFR mutation results to decide adjuvant treatment for patients with stage IIB to IIIA NSCLC or high-risk patients with stage IB to IIA NSCLC.

Although the guidelines at the time of conduct of our study suggested first-line use of EGFR-TKIs in patients with advanced or metastatic NSCLC and common sensitizing EGFRm with no role for targeted agents in stage III NSCLC outside clinical trials, the most common initial therapy used in patients with EGFRm in our study was EGFR-TKI monotherapy (24%). This underscores the importance of understanding the outcomes of EGFRm stage III NSCLC treated with EGFR-TKIs alone.

In patients tested for EGFRm, the median rwPFS was similar irrespective of EGFRm status (EGFRm, 14 months versus EGFRwt, 12.2 months; \(p = 0.95\)). However, median OS was significantly better in patients with EGFRm compared with those patients with EGFRwt (50.3 months versus 40.0 months; \(p = 0.00063\)) and was found to be markedly higher than the findings of Aguiar et al. (20.0 months versus 11.0 months; \(p = 0.007\)).

In resectable stage III NSCLC patients, the median rwPFS and OS were similar despite the EGFR status (\(p = 0.31\)). Interestingly, Izar et al. reported significantly higher OS in patients with EGFRm compared with EGFRwt (HR: 0.30; 95% CI: 0.14–0.67; \(p = 0.003\)); however, their study was focusing on stage I NSCLC patients only. In patients with unresectable NSCLC, we found the median rwPFS was similar irrespective of EGFR mutation status, but median OS was significantly better in patients with EGFRm than EGFRwt (47.5 months versus 32.4 months; \(p = 0.01\)). The OS benefit may possibly be due to the use of subsequent targeted treatment in EGFRm patients.

In patients with EGFRm NSCLC (resectable and unresectable), we observed that EGFR-TKI monotherapy as initial therapy, without any irradiation, was associated with lower median rwPFS (HR: 1.528; 95% CI: 1.023–2.283, \(p = 0.0384\)) and lower median OS (HR: 1.983; 95% CI: 1.079–3.643, \(p = 0.0273\)) compared with other therapies. In stage III NSCLC, locally directed RT together with CT are given with curative intent. Chemotherapy or EGFR-TKI monotherapy alone does not deliver the same clinical benefit as curative intent treatment containing both systemic and local therapy. Tumour reduction and the use of systemic therapy to potentiate the effect
of irradiation are important in the treatment of unresectable tumours and our data appear to support this. Adjuvant treatments post-surgery and post-CRT have the ability to treat micrometastatic disease with the potential to deliver additional benefits as part of a curative intent treatment regimen. It may also be the case in our study that patients with poor ECOG performance may have been selected for TKI monotherapy, potentially resulting in decreased OS in this patient group.

In unresectable patients, initial treatment with cCRT was equally effective in both EGFRm and EGFRwt patients with a trend of a better OS seen in patients with EGFRm. This might be due to the use of subsequent targeted treatment. Furthermore, initial therapy with cCRT was found to significantly improve OS (48 months versus 24 months; \( p < 0.001 \)) when compared with TKI monotherapy, without any irradiation whereas rwPFS was found to be similar irrespective of EGFRm status (10.5 months versus 14.6 months; \( p = 0.825 \)). These results contradict a recent study in stage IIIB EGFRm patients with adenocarcinoma, where no significant differences were found in survival when TKIs were compared with cCRT.\(^1\) Our results suggest that treatment with curative intent cCRT provides better survival benefit in unresectable EGFRm stage III NSCLC patients than EGFR-TKI monotherapy without any irradiation, highlighting the importance of local and systemic treatments as part of curative intent regimens. These data may be confounded by the fact that patients in the TKI monotherapy group were slightly older, less fit, received fewer post-progression therapies and were treated with palliative intention.

Several recent studies have examined the role of adjuvant and neoadjuvant EGFR-TKIs in early-stage (II/III) EGFR-mutated resectable NSCLC. Osimertinib as adjuvant therapy was found to significantly improve PFS compared with placebo in the ADAURA trial in patients with stage IB to IIIA completely resected EGFRm NSCLC. Among the patients with stage IIIA disease, a higher percentage of patients in the osimertinib group (88%, 95% CI: 79–94) were alive and disease-free at 24 months compared with those in the placebo group (32%, 95% CI: 23–41, HR: 0.12; 95% CI: 0.07–0.20).\(^1\)\(^4\)

The ongoing clinical trial LAURA (NCT03521154) is evaluating osimertinib maintenance in unresectable EGFRm stage III NSCLC (cCRT followed by osimertinib \textit{versus} cCRT). This trial will finally answer the question whether cCRT followed by osimertinib maintenance improves the outcome \textit{versus} cCRT in this patient population.\(^1\)\(^5\)

In our study, having EGFRm, stage IIIA disease and adenocarcinomas independently predicted better OS in a multi-variate analysis, whereas male gender, older patients (aged > 65 years) were the negative predictors. A large-scale real-world study in patients with stage IIIB and IV disease also observed the same predictors for OS.\(^3\)\(^1\) This observation again highlights the prognostic value of EGFRm in localized or locally advanced NSCLC.

Our study had several important limitations. It was a secondary analysis of the main KINDLE study and the study was not aimed at exploring predictors of survival outcomes in EGFR-mutated patients. Some of our analyses might also suffer from immortal time bias and or survival bias. Being a real-world study, the data collection was limited by the availability of existing medical records, resulting in missing data because some patients might have been lost to routine clinical follow-up, some patients with EGFRwt NSCLC or unknown mutation status may have received TKIs leading to confounding results and some patients might not have availed EGFRm testing as prescribed.

**Conclusions**

The KINDLE study provided important insights into real-world testing practices, rates of EGFRm, treatment patterns, outcomes and positioning of EGFR-TKIs in the treatment trajectory of stage III EGFR-mutated NSCLC patients, in particular unresectable EGFRm stage III NSCLC. Our study highlights the importance of EGFRm testing and treating every patient with curative intent, if possible. cCRT followed by an EGFR-TKI is potentially the most promising strategy for unresectable EGFRm NSCLC. The ongoing LAURA study (NCT03521154) will ultimately define the role of EGFR-TKIs in EGFRm stage III NSCLC treated with cCRT.

**Declarations**

\textit{Ethics approval and consent to participate}

The study protocol (NCT03725475) was approved by the independent ethics committees/
institutional review boards of all participating 153 centres.

Consent for publication
None.

Author contribution[s]
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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon request.

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