THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

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

Ther Adv Med Oncol

2022, Vol. 14: 1–17

DOI: 10.1177/17588359221122720

Abdul Rahman Jazieh, Huseyin Cem Onal, Daniel Shao-Weng Tan, Ross A. Soo, Kumar Prabhash, Amit Kumar, Reto Huggenberger and Byoung Chul Cho

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.

Trial Registration: NCT03725475.

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

Received: 2 February 2022; revised manuscript accepted: 11 August 2022.

Correspondence to:
Ross A. Soo
National University Cancer Institute, Level 7 NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228, Singapore.
ross_soo@nuhs.edu.sg

Abdul Rahman Jazieh
Cincinnati Cancer Advisors, Cincinnati, OH, USA

Huseyin Cem Onal
Department of Radiation Oncology, Adana Dr. Turgut Noyan Research and Treatment Centre, Baskent University, Adana, Turkey

Daniel Shao-Weng Tan
Division of Medical Oncology, National Cancer Centre, Singapore

Kumar Prabhash
Department of Medical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

Amit Kumar
AstraZeneca Pharma India Ltd, Bangalore, Karnataka, India

Reto Huggenberger
AstraZeneca, Switzerland

Byoung Chul Cho
Yonsei University College of Medicine, Seoul, Republic of Korea

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 diagnosis[3] [sub-classified

into stage IIIA and IIIB according to the seventh edition of American Joint Committee on Cancer (AJCC) staging classification; stage IIIC was added according to the eighth edition of AJCC staging classification].[4]

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 stage IB-IIIA NSCLC was recently shown in the ADAURA trial (NCT02511106) where adjuvant osimertinib significantly improved disease-free survival *versus* placebo in completely resected EGFRm stage IB-IIIA 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.[17] The details of the study design, eligibility criteria and data collection methods have been reported by Jazieh *et al.*[18]

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.*[18] 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.*[18]

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* $\geqslant 1\%$) (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

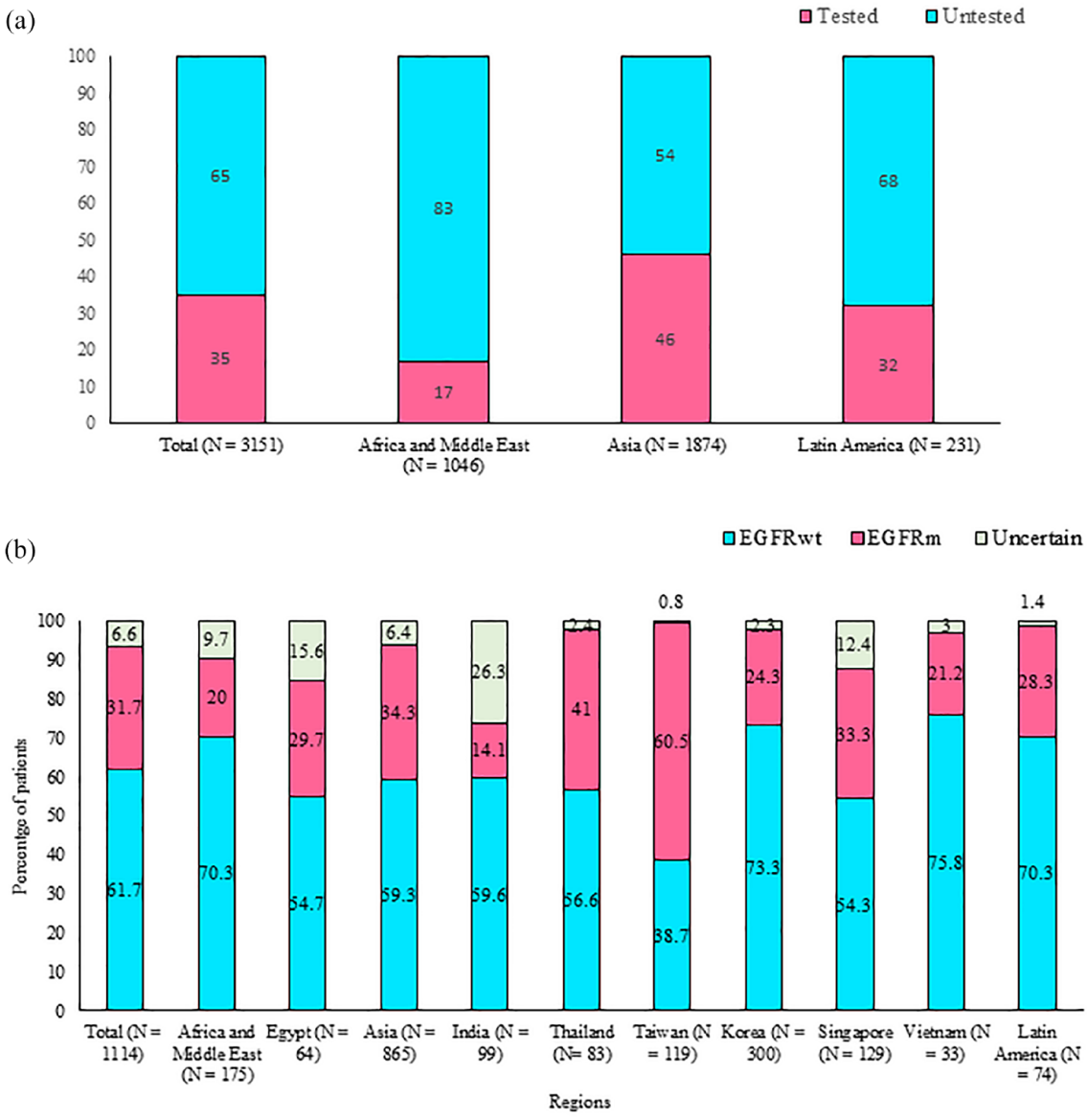

Figure 1. Region-wise prevalence of (a) EGFR testing and (b) EGFR mutations.
EGFR, epidermal growth factor receptor; EGFRwt, EGFR wild-type.

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).

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

($n=28$, 9.7%), whereas cCRT ($n=181$, 30.6%), CT alone ($n=124$, 20.9%) and sCRT ($n=49$, 8.3%) were the main treatment modalities in patients with EGFRwt tumours (Table 3).

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).

Table 1. Frequency and type of EGFR mutations in patients with stage III NSCLC.

Type of mutations	Patients with mutation *n* (%) (*N* = 353)
Number of mutations present	
1	316 (89.5)
2[a]	29 (8.2)
3[b]	1 (0.3)
4[c]	7 (2.0)
Type of EGFRm, (*N* = 405)	
Exon 18	
G719X (G719C/G719S/G719A	23 (5.6)
Others	9 (2.2)
Exon 19	
Deletion	179 (44.2)
Others	10 (2.5)
Exon 20	
Insertion	9 (2.2)
S768I	8 (2.0)
T790M	13 (3.2)
Others	7 (1.7)
Exon 21	
L858R	129 (31.9)
L861Q	7 (1.7)
Others	11 (2.7)

There was one exon 18 E709V, one exon 19 E746-T751 plus one exon 19 deletion-insertion, and one exon 20 L782R mutation indicated by the investigators. The rest was not further specified.
[a]Ex19del+T790M (2x); Ex19del+L858R; T790M+L858R (3x); G719X+T790M; S768I+L858R (2x); G719X+S768I.
[b]Ex19del+S768I+L858R.
[c]G719X+Ex19del+Ex20ins+L858R (2x); G719X+Ex19del+T790M+L858R; G719X+Ex19del+S768I+L858R.
EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer.

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[a], *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 (46)	58 (55)	0.16	35 (60)	77 (40)	0.008
Positive	188 (51)	141 (54)	47 (45)		23 (40)	113 (60)	

[a]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.

Table 3. Initial treatment and survival outcomes in patients with stage III NSCLC with or without EGFR mutations.

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.

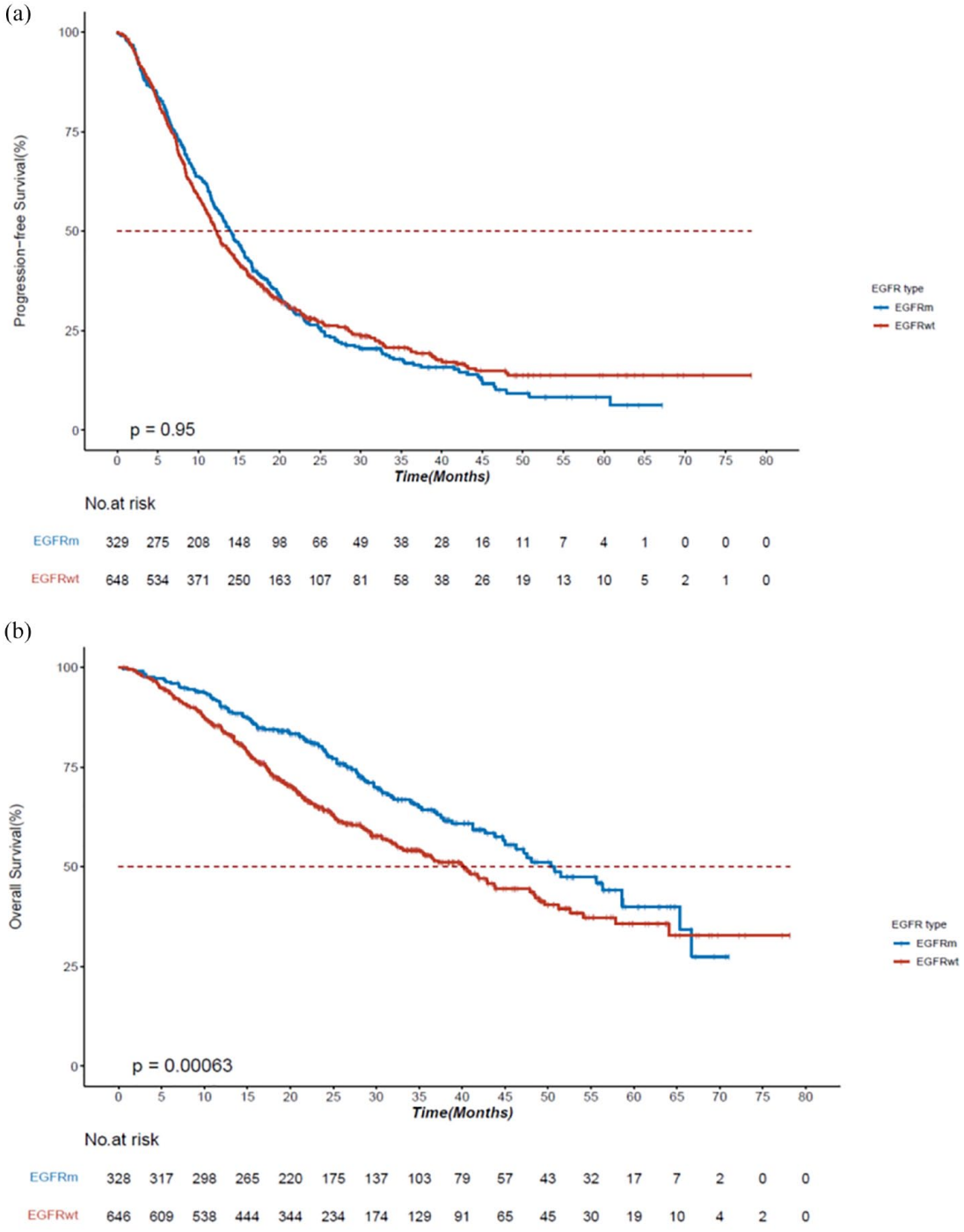

Figure 2. Kaplan–Meier plot of total PFS and OS after initial therapy by EGFR type before propensity score matching: (a) rwPFS in overall patients with stage III NSCLC.
Kaplan–Meier survival curves for progression-free survival for all stage III NSCLC patients with EGFRm and EGFRwt are shown in blue 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.

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:

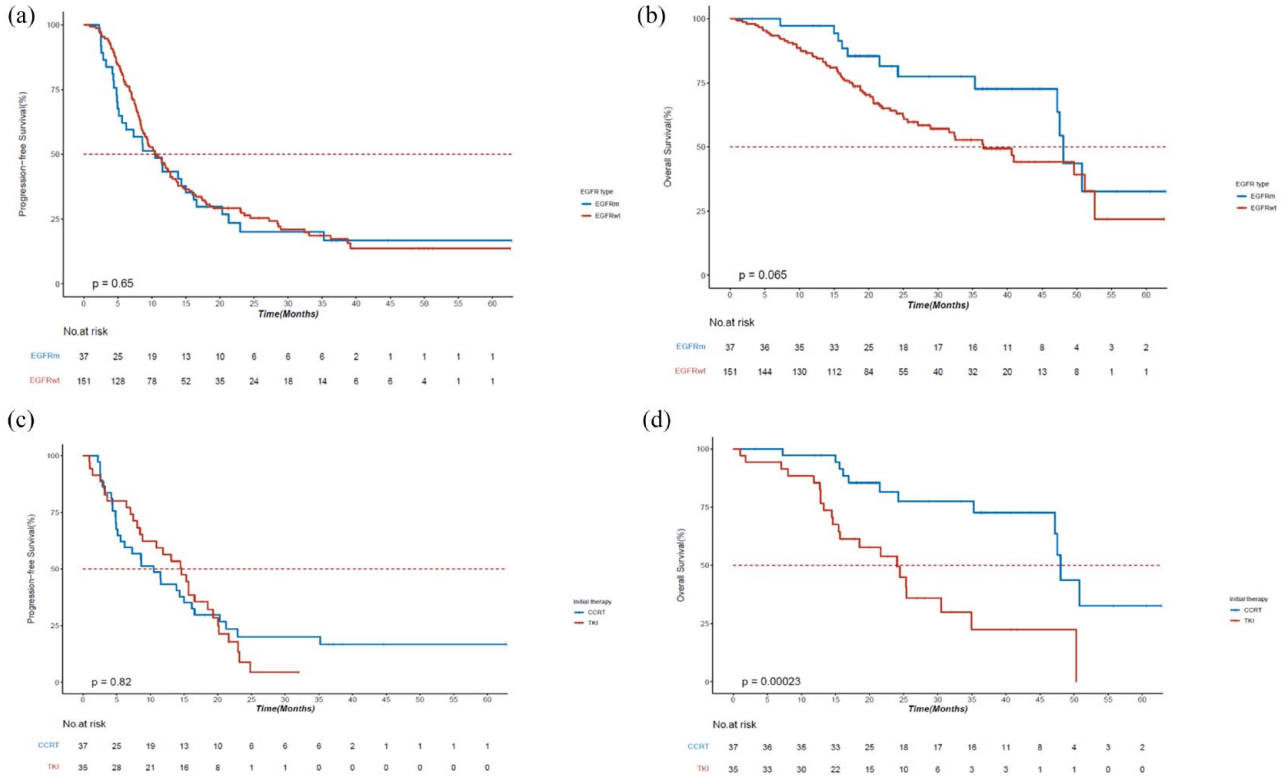

Figure 3. Kaplan–Meier plot of PFS and OS in unresectable stage III patients with and without EGFRm following cCRT and cCRT or EGFR-TKI as initial therapy: (a) rwPFS following cCRT Kaplan–Meier survival curves for PFS following cCRT for stage III NSCLC patients with EGFRm and EGFRwt are shown in blue or red, respectively.
Median rwPFS for EGFRm, 10.5 months (95% CI: 5.6–16.6).
Median rwPFS for EGFRwt, 10.8 months (95% CI: 9.0–12.7).
(b) OS following cCRT
Kaplan–Meier survival curves for OS following cCRT for stage III NSCLC patients with EGFRm and EGFRwt are shown in blue or red, respectively.
mOS for EGFRm, 48.0 months (95% CI: 47.2–NC).
mOS for EGFRwt, 36.5 months (95% CI: 28.9–NC).
(c) rwPFS following cCRT or TKI monotherapy
Kaplan–Meier survival curves for PFS for stage III NSCLC patients with EGFRm following cCRT and TKI monotherapy without irradiation are shown in blue or red, respectively.
Median rwPFS for cCRT, 10.5 months (95% CI: 5.6–16.6).
Median rwPFS for TKI monotherapy without irradiation, 14.6 months (95% CI: 8.9–19.3).
(d) OS following cCRT or TKI monotherapy.
Kaplan–Meier survival curves for OS following cCRT for stage III NSCLC patients with EGFRm and EGFRwt are shown in blue or red, respectively.
mOS for EGFRm, 48.0 months (95% CI: 47.2–NC).
mOS for TKI monotherapy without irradiation, 24.0 months (95% CI: 15.7–NC).
cCRT, concurrent chemoradiotherapy; CI, confidence interval; 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 cancer; OS, overall survival; PFS, progression-free survival; rwPFS, real-world PFS; TKI, tyrosine kinase inhibitor.

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 ⩽65years. 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:

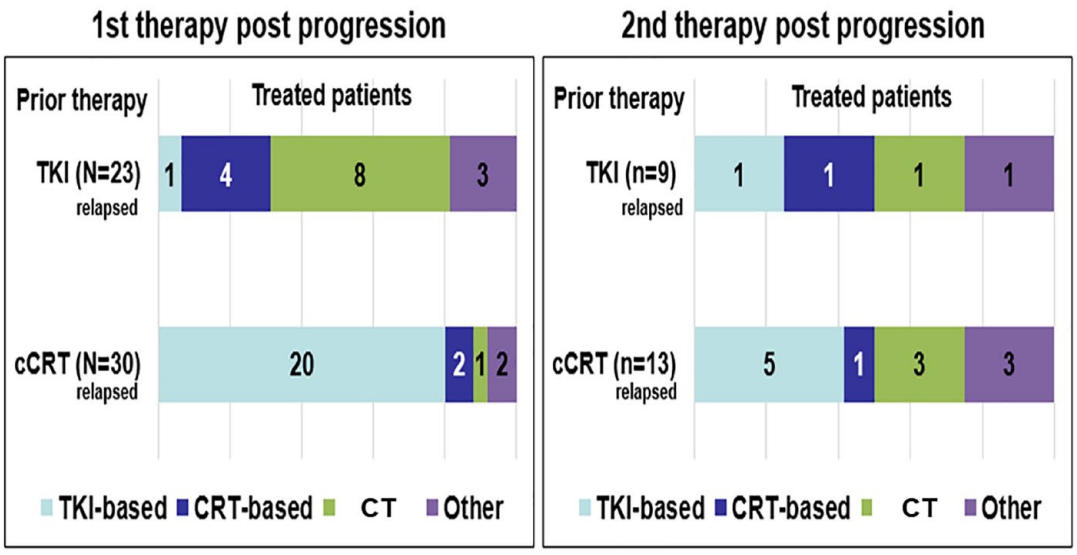

Figure 4. Initial therapy and second-line therapy post-progression.
cCRT, concurrent chemoradiotherapy; Chemo, chemotherapy; CRT, chemoradiotherapy; TKI, tyrosine kinase inhibitor.

Table 4. Univariate analyses of targeted therapy for median rwPFS and mOS (full analysis set, according to stage at seventh edition).

Outcome	NSCLC stage	Stage III			Stage IIIA			Stage IIIB		
		Numbers	HR (95% CI)	*p* Value	Numbers	HR (95% CI)	*p* Value	Numbers	HR (95% CI)	*p* Value
Median rwPFS	Targeted therapy without local treatment in initial line only: yes *versus* no	92 *versus* 2534	1.487 (1.187–1.863)	**0.0006**	29 *versus* 1442	1.780(1.205–2.629)	0.0038	63 *versus* 1092	1.202(0.910–1.587)	0.1947
mOS	Targeted therapy without local treatment in initial line only: yes *versus* no	92 *versus* 2527	1.195 (0.881–1.621)	0.2526	29 *versus* 1439	1.520(0.876–2.637)	0.1364	63 *versus* 1088	0.928(0.642–1.340)	0.6891
	Targeted therapy in any line: yes *versus* no	436 *versus* 3570	0.795 (0.679–0.931)	**0.0043**	226 *versus* 1992	0.812 (0.644–1.023)	0.0776	210 *versus* 1578	0.742 (0.598–0.920)	**0.0067**

Values in bold represent statistically significant ($p < 0.05$).
CI, confidence interval; HR, hazard ratio; mOS, median overall survival; NSCLC, non-small-cell lung cancer; rwPFS, real-world progression-free survival.

1.023–2.283, $p = 0.0384$). 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

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.

outcomes in patients with stage III NSCLC. 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[19] and was reported in a recent study from China (42.54%) in patients with recurrent stage IIIB/IV NSCLC.[20] Despite the College of American Pathology, the

International Association for the Study of Lung Cancer and the Association for Molecular Pathology guideline (2018) recommendations for testing for molecular biomarkers[21] 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.[8] 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.[22] The prevalence of EGFRm observed in our study was lower than that observed in patients with stage IB to IIIA screened for the ADAURA trial (44%)[23] and in studies of advanced NSCLC from China (46.4%) and South East-Asia (51.4%).[24] In a retrospective study of patients with NSCLC in MENA, a slightly lower frequency of EGFR mutations was observed in patients with stage I-III 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).[25] Differences in the patient population such as squamous cell subtype and stage of disease might explain the variation.

Consistent with previous reports,[26,27] 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®),[7] 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,[28] 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.*[29] (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.*[30] 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.[31] 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 (I/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).[14]

The ongoing clinical trial LAURA (NCT03521154) is evaluating osimertinib maintenance in unresectable EGFRm stage III NSCLC (cCRT followed by osimertinib *versus* cCRT). This trial will finally answer the question whether cCRT followed by osimertinib maintenance improves the outcome *versus* cCRT in this patient population.[15]

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.[31] 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

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)
Abdul Rahman Jazieh: Formal analysis; Investigation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Huseyin Cem Onal: Investigation; Methodology; Resources; Writing – review & editing.

Daniel Shao – Weng Tan: Investigation; Methodology; Resources; Writing – review & editing.

Ross A. Soo: Formal analysis; Investigation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Kumar Prabhash: Investigation; Methodology; Resources; Writing – review & editing.

Amit Kumar: Formal analysis; Validation; Writing – original draft; Writing – review & editing.

Reto Huggenberger: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing.

Byoung Chul Cho: Investigation; Methodology; Resources; Writing – review & editing.

Acknowledgements
The authors thank Ms. Neelam Joglekar, M.Sc. from Labcorp Scientific Services & Solutions Pvt. Ltd., India for medical writing support in accordance with GPP3 guidelines (http://www.ismpp.org/gpp3).

Funding
The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: The study was funded by AstraZeneca.

Competing interests
Disclosure: ARJ reports receiving research support from AstraZeneca, Merck Sharp & Dohme, and Pfizer and travel support from Bristol-Myers Squibb and AstraZeneca. DSWT reports having advisory role and serving as consultant for Novartis, Bayer, Boehringer Ingelheim, Celgene, AstraZeneca, Eli Lilly, and Loxo Oncology; receiving travel support and honorarium from Merck, Pfizer, Novartis, Boehringer Ingelheim, Roche, and Takeda Pharmaceuticals; and receiving research funding from Novartis, AstraZeneca, GlaxoSmithKline, Bayer, and Pfizer. RAS reports being on advisory board for Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Taiho, Takeda Pharmaceuticals, and Yuhan; and receiving research grant support from AstraZeneca and Boehringer Ingelheim. KP reports receiving research funding from Alkem Laboratories, BDR Pharmaceutics, Biocon, Dr. Reddy's Laboratories, Fresenius Kabi, Natco Pharma, and Roche. AK reports having employment (full time) in AstraZeneca Pharma India Ltd. RH reports having employment (full time) in AstraZeneca Plc.; and stock ownership for Allogene Therapeutics, AstraZeneca, CStone Pharmaceuticals, GlaxoSmith Kline Plc, Imugene Limited, Innate Pharma, Swedish Orphan Biovitrium AB, Chinook Therapeutics, and Adaptimmune Therapeutics. BCC reports receiving research funding from Novartis, Bayer, AstraZeneca, Mogam Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono Pharmaceuticals, Dizal Pharma, Merck Sharp & Dohme, AbbVie, Medpacto, GI Innovation, Eli Lilly, Blueprint Medicines, and Interpark Bio Convergence Corp.; having consulting role for Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Bristol-Myers Squibb, Ono Pharmaceuticals, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, Merck Sharp & Dohme, Janssen, Medpacto, and Blueprint Medicines; having stock ownership for TheraCanVac Inc., Gencurix Inc., Bridgebio Therapeutics, Kanaph Therapeutic Inc., Cyrus Therapeutics, and Interpark Bio Convergence Corp.; being on scientific advisory board for Kanaph Therapeutic Inc., Brigebio Therapeutics, Cyrus Therapeutics, and Guardant Health; serving as board of director for Gencurix Inc. and Interpark Bio Convergence Corp.; having royalty for Champions Oncology; and serving as founder for DAAN Biotherapeutics. HCO declares no conflict of interest.

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

ORCID iD
Byoung Chul Cho https://orcid.org/0000-0002-5562-270X

Supplemental material

Supplemental material for this article is available online.

References

1. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2. Barta JA, Powell CA and Wisnivesky JP. Global epidemiology of lung cancer. *Ann Glob Health* 2019; 85: 8.
3. Tan WL, Chua KLM, Lin CC, *et al.* Asian Thoracic Oncology Research Group expert consensus statement on optimal management of stage III NSCLC. *J Thorac Oncol* 2020; 15: 324–343.
4. Detterbeck FC, Boffa DJ, Kim AW, *et al.* The eighth edition lung cancer stage classification. *Chest* 2017; 151: 193–203.
5. Yoon SM, Shaikh T and Hallman M. Therapeutic management options for stage III non-small cell lung cancer. *World J Clin Oncol* 2017; 8: 1–20.
6. Huber RM, Ruysscher DD, Hoffmann H, *et al.* Interdisciplinary multimodality management of stage III nonsmall cell lung cancer. *Eur Respir Rev* 2019; 28: 190024.
7. Ettinger DS, Wood DE, Aisner DL, *et al.* Referenced with permission from the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.7.2021. © National Comprehensive Cancer Network, Inc. All rights reserved. Accessed [November 09, 2021]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
8. Harrison PT, Vyse S and Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. *Semin Cancer Biol* 2020; 61: 167–179.
9. Yang JC, Schuler M, Popat S, *et al.* Afatinib for the treatment of NSCLC harboring uncommon EGFR mutations: a database of 693 cases. *J Thorac Oncol* 2020; 15: 803–815.
10. Sehgal K, Rangachari D, VanderLaan PA, *et al.* Clinical benefit of tyrosine kinase inhibitors in advanced lung cancer with EGFR-G719A and other uncommon EGFR mutations. *Oncologist* 2021; 26: 281–287.
11. Gristina V, La Mantia M, Galvano A, *et al.* Non-small cell lung cancer harboring concurrent EGFR genomic alterations: a systematic review and critical appraisal of the double dilemma. *J Mol Pathol* 2021; 2: 173–196.
12. Vickers AD, Winfree KB, Cuyun Carter G, *et al.* Relative efficacy of interventions in the treatment of second-line non-small cell lung cancer: a systematic review and network meta-analysis. *BMC Cancer* 2019; 19: 353.
13. Ramalingam SS, Vansteenkiste J, Planchard D, *et al.* Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med* 2020; 382: 41–50.
14. Wu YL, Tsuboi M, He J, *et al.* Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 2020; 383: 1711–1723.
15. Lu S, Casarini I, Kato T, *et al.* Osimertinib maintenance after definitive chemoradiation in patients with unresectable EGFR mutation positive stage III non-small-cell lung cancer: LAURA trial in progress. *Clin Lung Cancer* 2021; 22: 371–375.
16. Robinson C, Hu C, Machtay M, *et al.* P1.18-12 PACIFIC-4/RTOG 3515: phase III study of durvalumab following SBRT for unresected stage I/II, lymph-node negative NSCLC. *J Thorac Oncol* 2019; 14: S630–S631.
17. Vandenbroucke JP, von Elm E, Altman DG, *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med* 2007; 4: e297.
18. Jazieh AR, Onal HC, Tan DSW, *et al.* Real-world treatment patterns and clinical outcomes in patients with stage III NSCLC: results of KINDLE, a multicountry observational study. *J Thorac Oncol* 2021; 16: 1733–1744.
19. Yatabe Y, Kerr KM, Utomo A, *et al.* EGFR mutation testing practices within the Asia Pacific region: results of a multicenter diagnostic survey. *J Thorac Oncol* 2015; 10: 438–445.
20. Cheng Y, Wang Y, Zhao J, *et al.* Real-world EGFR testing in patients with stage IIIB/IV non-small-cell lung cancer in North China: a multicenter, non-interventional study. *Thorac Cancer* 2018; 9: 1461–1469.
21. Lindeman NI, Cagle PT, Aisner DL, *et al.* Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of

Lung Cancer, and the Association for Molecular Pathology. *Arch Pathol Lab Med* 2018; 142: 321–346.

22. Benbrahim Z, Antonia T and Mellas N. EGFR mutation frequency in Middle East and African non-small cell lung cancer patients: a systematic review and meta-analysis. *BMC Cancer* 2018; 18: 891.
23. Tsuboi M, Herbst RS, John T, *et al.* Frequency of epidermal growth factor receptor (EGFR) mutations in stage IB–IIIA EGFR mutation positive non-small cell lung cancer (NSCLC) after complete tumour resection. *Ann Oncol* 2019; 30: v589.
24. Lindeman NI, Cagle PT, Beasley MB, *et al.* Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013; 8: 823–859. Erratum in: *J Thorac Oncol* 2013; 8: 1343.
25. Jazieh AR, Bounedjar A, Al Dayel F, *et al.*; In collaboration with the Arab Collaborative Hematology Oncology Group (ACHOG). The study of druggable targets in nonsquamous non-small-cell lung cancer in the Middle East and North Africa. *J Immunother Precis Oncol* 2020; 2: 4–7.
26. Midha A, Dearden S and McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). *Am J Cancer Res* 2015; 5: 2892–2911.
27. Zhang YL, Yuan JQ, Wang KF, *et al.* The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget* 2016; 7: 78985–78993.
28. Eberhardt WEE, De Ruysscher D, Weder W, *et al.* 2nd ESMO consensus conference in lung cancer: locally advanced stage III non-small-cell lung cancer. *Ann Oncol* 2015; 26: 1573–1588.
29. Aguiar F, Fernandes G, Queiroga H, *et al.* Overall survival analysis and characterization of an EGFR mutated non-small cell lung cancer (NSCLC) population. *Arch Bronconeumol* 2018; 54: 10–17.
30. Izar B, Sequist L, Lee M, *et al.* The impact of EGFR mutation status on outcomes in patients with resected stage I non-small cell lung cancers. *Ann Thorac Surg* 2013; 96: 962–968.
31. Okamoto I, Morita S, Tashiro N, *et al.* Real world treatment and outcomes in EGFR mutation-positive non-small cell lung cancer: long-term follow-up of a large patient cohort. *Lung Cancer* 2018; 117: 14–19.