ORIGINAL ARTICLE

Real-World Treatment Patterns and Clinical Outcomes in Patients With Stage III NSCLC: Results of KINDLE, a Multicountry Observational Study

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ABSTRACT

Introduction: Stage III NSCLC is a heterogeneous disease requiring a multimodal management approach. We conducted a real-world, global study to characterize patients, treatment patterns, and their associated clinical outcomes for stage III NSCLC.

Methods: KINDLE was a retrospective study in patients with stage III NSCLC (American Joint Committee on Cancer, seventh edition) diagnosed between January 2013 and December 2017, with at least 9 months of documented follow-up since index diagnosis. In addition to descriptive statistics, Kaplan-Meier methodology evaluated survival estimates; two-sided 95% confidence interval was

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computed. Cox proportional hazards model was used for univariate and multivariate analyses.

Results: A total of 3151 patients from more than 100 centers across 19 countries from Asia, Middle East, Africa, and Latin America were enrolled. Median age was 63.0 years (range: 21.0–92.0); 76.5% were males, 69.2% had a smoking history, 53.7% had adenocarcinoma, and 21.4% underwent curative resection. Of greater than 25 treatment regimens, concurrent chemoradiotherapy was the most common (29.4%). The overall median progression-free survival (95% confidence interval) and median overall survival (mOS) were 12.5 months (12.06–13.14) and 34.9 months (32.00–38.01), respectively. Significant associations ($p < 0.05$) were observed for median progression-free survival and mOS with respect to sex, region, smoking status, stage, histology, and Eastern Cooperative Oncology Group status. In univariate and multivariate analyses, younger age, stage IIIA, better Eastern Cooperative Oncology Group status, concurrent chemoradiotherapy, and surgery as initial therapy predicted better mOS.

Conclusions: KINDLE reveals the diversity in treatment practices and outcomes in stage III NSCLC in a real-world setting in the preimmuno-oncology era. There is a high unmet medical need, necessitating novel approaches to optimize outcomes.

Keywords: Lung cancer; Stage III NSCLC; Combined modality; Immunotherapy; Concurrent chemoradiotherapy

Introduction

Lung cancer is the most common cancer globally, with 2.1 million new cases. It is responsible for the greatest cancer-related mortality with 1.8 million deaths in 2018.[1] NSCLC accounts for almost 85% of all new lung cancer cases.[2] Approximately 25% to 30% of patients are diagnosed with locally advanced (stage III) NSCLC.[3-5] Stage III NSCLC represents a heterogeneous disease group that includes a wide spectrum of clinical presentations, often with a considerable variation in tumor size (T1–T4) and extent of lymph node involvement (N0–N3).[6] Stages IIIA and IIIB are the two main subsets within this classification as per the American Joint Committee on Cancer (AJCC), seventh edition, and a third, IIIC, was added in AJCC, eighth edition for T3 or T4, N3M0 tumors.[3] The prognosis, treatment options, and long-term clinical outcomes differ considerably on the basis of the stage at initial presentation. There is a wide diversity in the incidence and mortality of NSCLC in low- and middle-income countries (LMICs). LMICs have considerable burden of disease owing to several lifestyle factors, such as tobacco smoking.[7]

Surgical management of stage III NSCLC is generally considered in a subset of patients with stage IIIA disease.[5,6] Successful curative resection is usually followed by adjuvant chemotherapy (CT). In addition, for patients with completely resected stage IIIA EGFR mutation-positive NSCLC who received previous adjuvant CT or are ineligible to receive platinum-based CT, osimertinib is recommended.[5] If resection margins are positive, sequential chemoradiation (sCRT) for R1 (microscopic residual disease) or concurrent chemoradiation (cCRT) for R1 or R2 (macroscopic residual disease) is usually prescribed. Nevertheless, many patients in stage III are not ideal candidates for surgical resection at diagnosis, especially those with T4 tumors and N2 or N3 disease.[5] Several randomized clinical studies have revealed improved survival with cCRT compared with either radiotherapy (RT) alone or sCRT in unresectable stage III NSCLC; median overall survival (mOS) in patients receiving cCRT ranged from 15 to 29 months compared with approximately 14 months and 9 to 12 months in patients receiving sCRT and RT alone, respectively.[8-13] The recommendations for treatment of NSCLC in LMICs are dictated by the international guidelines, but their application in routine clinical practice has not been studied widely.

Long-term outcomes for stage III disease are still poor, with 5-year survival rate of 36% for stage IIIA, 26% for stage IIIB, and 13% for stage IIIC.[3] To improve survival outcomes, appropriate combinations, optimum timing, sequencing of individual treatment components, alternative RT fractionation (particularly hypofractionation), intensity-modulated radiation therapy, and proton RT to provide higher radiation doses with less toxicity are being actively researched for all stage III disease subsets.[14,15] Other therapeutic modalities being researched include neoadjuvant immunotherapy and neoadjuvant EGFR tyrosine kinase inhibitors as monotherapy or in combination with CT. Considering the high disease burden and the evolving lung cancer treatment landscape with dynamic algorithms and new approaches of sequencing, it is important to identify patient management patterns and survival outcomes arising from the current standard of care (SoC). Understanding of treatment practices in the real-world setting has been limited for patients with stage III NSCLC, particularly in the LMICs, wherein it is not clear as to what extent the prescribed treatments align with the international guideline recommendations. To explore the diversity, "KINDLE," a real-world, multinational study, was conducted in non-United States (U.S.), non-European countries to determine the treatment patterns and their associated clinical outcomes in patients with stage III

NSCLC, as defined by the AJCC criteria (seventh edition), in the pre-PACIFIC study era.

Materials and Methods

Study Design

KINDLE was an international, multicenter, retrospective, noninterventional study conducted at more than 100 centers from 19 countries (Supplementary Table 0) across Asia, Africa, Middle East, and Latin America. The study protocol (NCT03725475) was approved by the independent ethics committees/institutional review boards of all participating centers. The study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation, good clinical practices, good pharmacoepidemiology practices, and the applicable legislation on noninterventional studies and observational studies. The reporting has been done in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology checklist.[16] Adult patients (≥18 y of age) diagnosed with de novo locally advanced stage III NSCLC (AJCC seventh edition) between January 2013 and December 2017, and with medical records available for at least nine months from the date of diagnosis (index date), were included in the study. Staging was performed according to local practices. Patients with a concomitant cancer at the time of diagnosis of stage III NSCLC or within 5 years before NSCLC diagnosis, except for nonmetastatic, nonmelanoma skin cancers or in situ or benign neoplasms, were excluded as were patients with an initial diagnosis of stages I to II NSCLC and diagnosed with stage III disease at the time of relapse. Patients who participated in clinical trials were not specifically excluded from this study.

Data Collection and Study Outcomes

After obtaining written informed consent from the patients or their next of kin/legal representatives (in the case wherein patients were deceased), retrospective data were collected from patients' medical records and transcribed on to the electronic case report forms. Data collection included sociodemographics (age, gender, body mass index, and smoking status), clinical characteristics (Eastern Cooperative Oncology Group [ECOG] performance status, histology, EGFR status, programmed cell death ligand status, and stage as per seventh edition AJCC), and treatment patterns (treatment modality and line of treatment). EGFR testing practice, mutation status, and related analyses will be presented in a subsequent publication. The data were extracted from the index date (date of initial diagnosis) to the end of the follow-up, defined as the earliest of death, last available medical record, or end of the data collection. The occurrence and date of disease progression were determined from documentation within the patients' records, such as pathology reports, imaging reports, and oncologists' notes and statements, on disease progression. Progression-free survival (PFS) was defined as the time from the start of the treatment to documented disease progression or death owing to any cause, whichever occurred first. The first progression interval was defined as the period between the index date and the first disease progression; the subsequent progression intervals were defined as the period between sequential progressions. For patients who received treatment, sequential treatment regimens were documented within each progression interval. Disease progression was defined as a record of diagnosis of progressive disease, after treatment initiation. If disease progression or death was not recorded, patients were censored at the earliest of last available data in medical records or the end of the observation period. The PFS data reported represent real-world PFS measurements derived from medical records. OS was calculated as the time from the stage III NSCLC diagnosis or start of the treatment to death owing to any cause.

Statistical Analyses

Descriptive statistics were used to summarize patient demographics, disease characteristics, and treatment modalities. The treatment patterns and their associated clinical outcomes were analyzed for the overall cohort followed by further analyses in patients with stage IIIA and IIIB diseases and as per resectability. Median survival estimates (OS and PFS), including rates of the affected patients, were evaluated descriptively using the Kaplan-Meier survival curves. The median survival estimates are reported along with the two-sided 95% confidence interval (CI). Inferential statistics as correlation analyses were used to determine association between survival outcomes (PFS and OS) and clinical and treatment variables. A p value of less than 0.05 was considered statistically significant. A multivariate Cox proportional hazards regression model was used to evaluate the impact of stage-based grouping and histology-based grouping on PFS and OS while controlling for demographic and clinical covariates. More details on statistical analyses can be found in the Supplementary Data.

Results

Sociodemographic and Clinical Characteristics

Of the total 3151 enrolled patients from more than 100 centers across 19 countries from Asia, Middle East, Africa, and Latin America, most (59.5%) were recruited from Asian countries. The median age (range) of patients was 63.0 (21.0–92.0) years; most (76.5%) were men, and 69.2% had a history of smoking. In addition, most

Table 1. Baseline Sociodemographic and Clinical Characteristics of Patients With Stage III NSCLC

Parameters	Total (N = 3151)	Africa and Middle East (n = 1046)	Asia (n = 1874)	Latin America (n = 231)
Age (y), median (range)	63.0 (21-92)	61.0 (24-89)	63.0 (24-92)	65.0 (21-89)
Gender, male, n (%)	2411 (76.5)	870 (83.2)	1401 (74.8)	140 (60.6)
BMI (kg/m^2), median (range)	23.5 (12-65)	25.9 (12-48)	22.5 (13-65)	24.8 (17-37)
Vital status, n (%)				
Alive	1789 (56.8)	505 (48.3)	1142 (60.9)	142 (61.5)
Dead	1362 (43.2)	541 (51.7)	732 (39.1)	89 (38.5)
Smoking status,[a] n (%)				
Current smoker	976 (31.2)	385 (37.7)	508 (27.1)	83 (35.9)
Exsmoker	1187 (38.0)	440 (43.1)	653 (34.9)	94 (40.7)
Never smoker	712 (22.8)	151 (14.8)	524 (28.0)	37 (16.0)
AJCC stage (seventh edition), n (%)				
Stage IIIA	1568 (55.9)	489 (58.9)	976 (54.7)	103 (53.4)
Stage IIIB	1239 (44.1)	341 (41.1)	808 (45.3)	90 (46.6)
Histology type, n (%)				
Adenocarcinoma	1665 (53.7)	480 (47.8)	1039 (55.7)	146 (64.0)
Squamous cell/epidermoid carcinoma	1134 (36.6)	432 (43.0)	648 (34.7)	54 (23.7)
Other	96 (3.1)	9 (0.9)	76 (4.1)	11 (4.8)
Large cell carcinoma	61 (2.0)	27 (2.7)	24 (1.3)	10 (4.4)
Mixed	34 (1.1)	13 (1.3)	19 (1.0)	2 (0.9)
Bronchiole-alveolar	14 (0.5)	11 (1.1)	3 (0.2)	0
ECOG performance status, n (%)				
0	663 (30.3)	303 (33.9)	295 (25.5)	65 (48.5)
1	1278 (58.4)	489 (54.7)	735 (63.4)	54 (40.3)
≥2	246 (11.3)	102 (11.4)	129 (11.1)	15 (11.2)
T stage, n (%)				
T1	37 (1.2)	37 (3.7)	0	0
T1a	75 (2.4)	5 (0.5)	61 (3.3)	9 (3.9)
T1b	111 (3.6)	6 (0.6)	100 (5.4)	5 (2.2)
T1c	26 (0.8)	12 (1.2)	11 (0.6)	3 (1.3)
T2	130 (4.2)	130 (12.9)	0	0
T2a	460 (14.8)	44 (4.4)	382 (20.5)	34 (14.9)
T2b	241 (7.8)	52 (5.2)	167 (8.9)	22 (9.6)
T3	1007 (32.5)	376 (37.3)	557 (29.8)	74 (32.5)
T4	951 (30.6)	324 (32.1)	562 (30.1)	65 (28.5)
TX	41 (1.3)	20 (2.0)	14 (0.8)	7 (3.1)
N/A	24 (0.8)	3 (0.3)	12 (0.6)	9 (3.9)
N stage, n (%)				
N0	242 (7.8)	93 (9.2)	134 (7.2)	15 (6.6)
N1	338 (10.9)	136 (13.5)	171 (9.2)	31 (13.6)
N2	1745 (56.2)	601 (59.5)	1009 (54.1)	135 (59.2)
N3	715 (23.0)	150 (14.9)	529 (28.3)	36 (15.8)
NX	64 (2.1)	30 (3.0)	23 (1.2)	11 (4.8)

Note: Unknown and missing data are not included.
[a]Current smoker: patients who smoke one or more tobacco products. Never smoker: patients who have never smoked more than 20 grams of tobacco (1 pack of 20 cigarettes) in their lifetime. Exsmoker: Patients who stopped smoking more than or equal to 365 days ago.
AJCC, American Joint Committee on Cancer; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

patients (88.7%) had an ECOG performance status of less than or equal to 1. At diagnosis, more than half of the patients (55.9%) had stage IIIA disease as per AJCC, seventh edition. Adenocarcinoma was the most common histologic type (53.7%), followed by squamous cell/epidermoid carcinoma (36.6%). Most tumors were classified as T3 (32.3%), T4 (30.6%), with nodal involvement N2 (56.0%) and N3 (23.8%). Table 1 describes the sociodemographic and clinical characteristics for the entire study population and region-specific cohorts.

Treatment Patterns

Initial therapy included more than 25 treatment regimens, including surgery, CT alone, RT alone, cCRT,

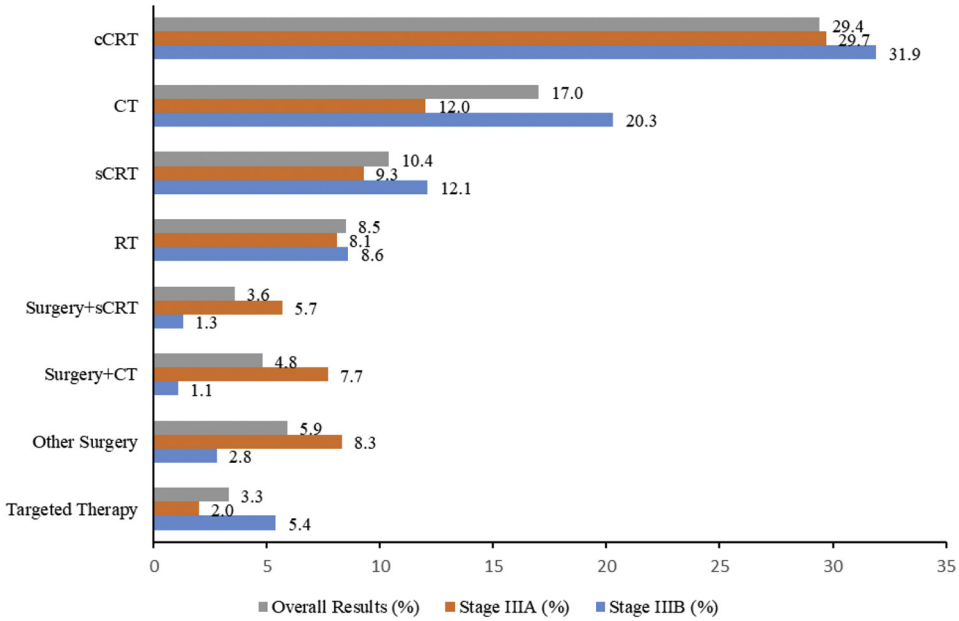

Figure 1. Frequent treatment modalities for stage III NSCLC. "Other Surgery" includes any kind of therapy used in combination with surgery (except for the following: surgery alone, surgery + cCRT, surgery + sCRT, surgery + CT, surgery + RT, neoadjuvant CRT + surgery, neoadjuvant chemotherapy + surgery), with each pattern has less than 10 patients. "Targeted Therapy" included agents such as erlotinib, afatinib, gefitinib, crizotonib, osimertinib, and bevacizumab. The most frequent treatment modalities for all-stage III NSCLC are found in gray. The treatments used for stage IIIA and stage IIIB are found in orange or blue, respectively. cCRT, concurrent chemoradiation; CRT, chemoradiation; CT, chemotherapy; RT, radiotherapy; sCRT, sequential chemoradiation.

sCRT, targeted therapy alone, and immunotherapy alone or in combination with other therapies. Figure 1 illustrates the most common treatment modalities administered as initial therapy (overall and by substage). All treatment modalities used are summarized in Supplementary Tables 1, 2, and 3. Approximately one-fifth of the patients (21.4%, 614 of 2873) who received initial therapy underwent surgical resection, and approximately half of these patients (48%, 296 of 614) received either cCRT, sCRT, CT alone, or RT alone as adjuvant treatment postsurgery (Supplementary Table 1). Overall, 2873 (91%) patients (stage IIIA: 1478 [47%] and stage IIIB: 1158 [37%]) received initial therapy; 1121 patients (36%) and 339 patients (11%) received second-line and third-line therapies, respectively. The remaining patients (8.8%, 278 of 3151) did not receive any cancer therapy. cCRT was the most common treatment modality overall, administered in 845 patients (29.4%) (stage IIIA: 439, 29.7% and stage IIIB: 369, 31.9%), followed by CT alone in 488 (17.0%) (stage IIIA: 179, 12.0% and stage IIIB: 235, 20.3%) as initial therapy. The next most frequently used modalities in stage IIIA and IIIB diseases as initial therapy were sCRT (137, 9.3% and 140, 12.1%) and RT alone (119, 8.1% and 100, 8.6%) (Supplementary Table 2). Pooling the patients who received surgery with/without any kind of additional treatment, 556 patients (21.0%) underwent surgery (stage IIIA: 472, 32.0% and stage IIIB: 84, 7.0%) (Supplementary Table 2).

In the study period, 62% (396 of 639) of patients with resectable NSCLC who received an initial therapy relapsed (i.e., progressed, 350 or died, 46). In unresectable disease, in patients who received an initial therapy, the relapse rate was higher (79%, 1122 of 1419); 900 patients progressed and 222 died. Of the 350 patients with resectable stage III NSCLC who progressed, 240 (69%) received a second-line therapy, whereas 579 of the 900 patients (64%) who progressed with unresectable NSCLC received a second-line therapy. As expected, most patients (79%; 506 of 639) with tumors deemed resectable underwent a surgical intervention as initial therapy (Supplementary Table 3).

Survival Outcomes

The median PFS (mPFS) for the entire population was 12.5 months (95% CI: 12.06–13.14) (Fig. 2*A*): stage IIIA, 14.3 months (95% CI: 13.37–15.34) and stage IIIB, 10.2 months (95% CI: 9.43–11.01). The mOS for the entire population was 34.9 months (95% CI: 32.00–38.01) (Fig. 2*B*): stage IIIA, 43.8 months (95% CI: 38.83–48.56) and stage IIIB, 27.7 months (95% CI: 24.87–29.73). The survival outcomes according to the initial therapy received are described in Supplementary Table 4. The

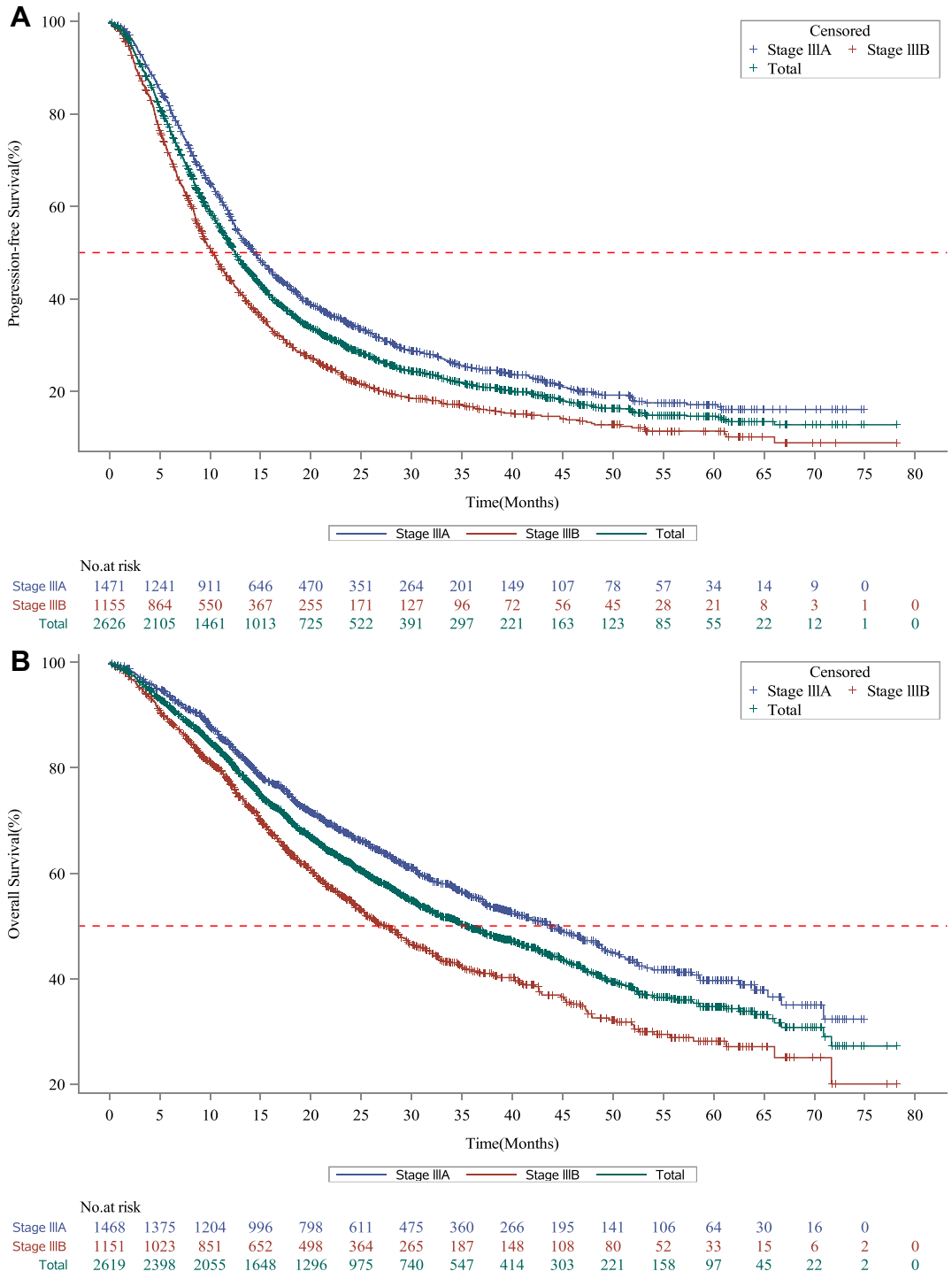

Figure 2. (*A*) Kaplan-Meier survival curves for progression-free survival by disease stage. Kaplan-Meier survival curves for progression-free survival for all patients with stage III NSCLC are found in green, whereas patients in stages IIIA and IIIB are found in blue or red, respectively. mPFS for the entire cohort was 12.5 months (95% CI: 12.06–13.14). mPFS for stage IIIA was 14.3 months (95% CI: 13.37–15.34). mPFS for stage IIIB was 10.2 months (95% CI: 9.43–11.01). (*B*) Kaplan-Meier survival curves for overall survival by disease stage. Kaplan-Meier survival curves for overall survival for all patients with stage III NSCLC are found in green, whereas patients in stages IIIA and IIIB are found in blue or red, respectively. mOS for the entire cohort was 34.9 months (95% CI: 32.00–38.01). mOS for stage IIIA was 43.8 months (95% CI: 38.83–48.56). mOS for stage IIIB was 27.7 months (95% CI: 24.87–29.73). CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival.

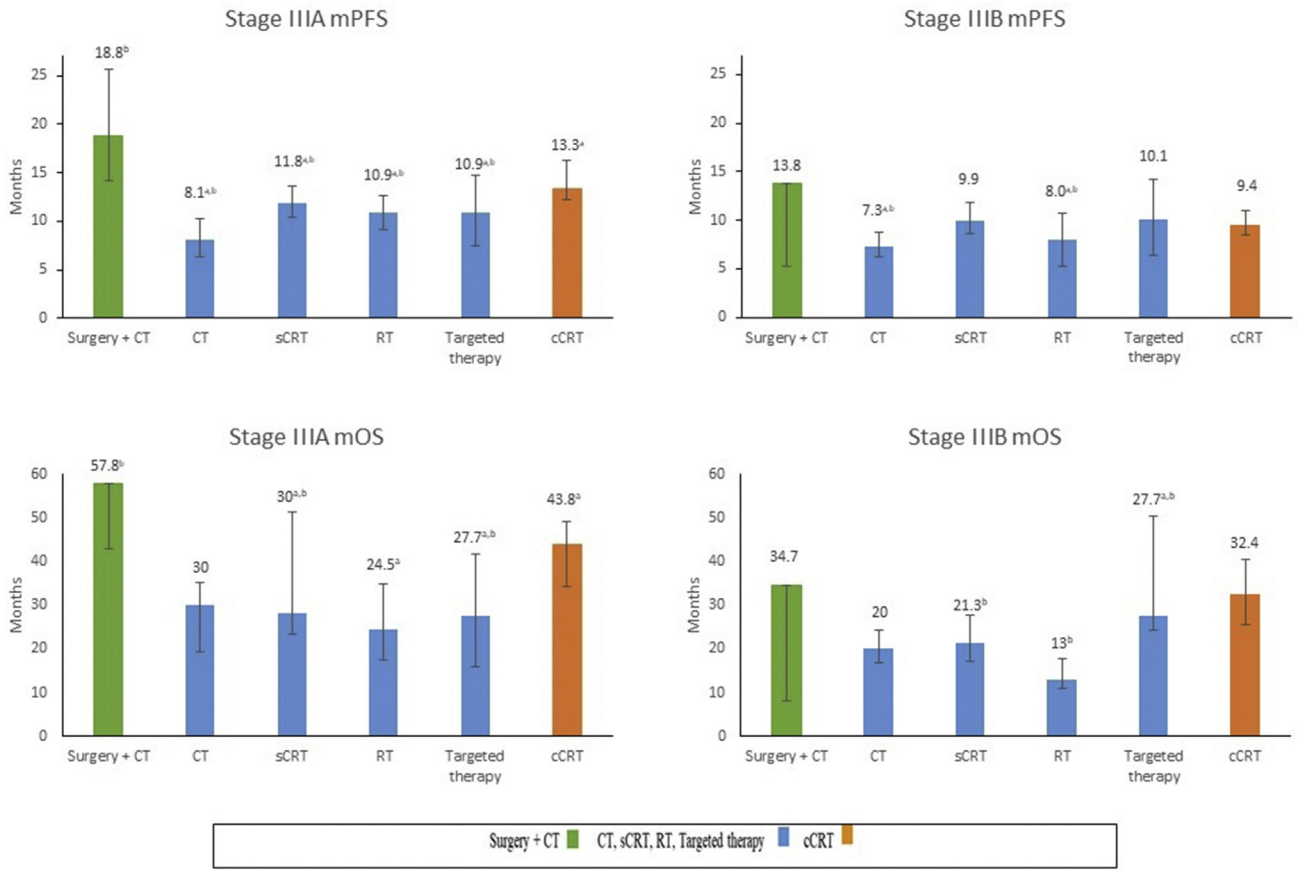

Figure 3. Association of survival outcomes with initial treatment patterns. CT (CT was the only initial treatment received); surgery + CT (surgery was followed by CT); cCRT (cCRT was the only initial treatment received); RT (RT was the only initial treatment received); sCRT (sCRT was the only initial treatment received); targeted therapy (targeted therapy was the only initial treatment received). [a]Significant difference when compared with surgery + CT ($p < 0.05$). [b]Significant difference with cCRT ($p < 0.05$). Patients on surgery + CT are found in green, patients on CT, sCRT, RT, and targeted therapy are found in blue, and patients on cCRT are found in orange. Errors bars indicate 95% CIs. cCRT, concurrent chemoradiation; CI, confidence interval; CT, chemotherapy; mOS, median overall survival; mPFS, median progression-free survival; RT, radiotherapy; sCRT, sequential chemotherapy.

mPFS and mOS were 19.9 months (95% CI: 18.50–22.67) and 65.4 months (95% CI: 57.86 to noncalculable [NC]) in 639 (available PFS data) and 637 patients (available OS data) with resectable NSCLC and 10.6 months (95% CI: 9.89–11.40) and 25.0 months (95% CI: 22.80–27.10) in 1410 (available PFS data) and 1407 (available OS data) patients with unresectable disease (Supplementary Figs. 1 and 2). In patients with resectable tumors, the results suggested that the mPFS of neoadjuvant CT plus surgery and of surgery plus adjuvant CT were both significantly longer (all $p < 0.05$) than that of either cCRT or CT alone. Nevertheless, there was no significant difference in mOS of neoadjuvant CT plus surgery and surgery plus adjuvant CT and other treatment modalities. In unresectable disease (stage IIIA and stage IIIB), the mPFS and mOS for cCRT were significantly longer (all $p < 0.05$) than for sCRT, CT alone, or RT alone (Supplementary Table 5).

Figure 3 presents the mPFS and mOS observed for the most frequently administered treatment modalities. In stage IIIA, 58 patients who were eligible for, and underwent, only surgical resection had the longest mOS (62.6 mo, 95% CI: 27.89–66.73). A similar outcome was found in 114 patients with stage IIIA who underwent surgery and received adjuvant CT (57.9 mo, 95% CI: 42.94–NC) and 16 patients who underwent surgery plus RT (58.6 mo, 95% CI: 17.68–NC). In patients with stage IIIB, the use of cCRT alone (n = 369) was associated with an mOS of 32.4 months (95% CI: 25.59–40.61). In patients with stage IIIA whom surgery was not performed, cCRT was associated with an mOS of 43.8 months (95% CI: 34.33–49.31); it was also associated with longer mPFS (13.3 mo; 95% CI: 12.25–16.26) than that observed for CT alone, sCRT, RT alone, or targeted therapy (all $p < 0.05$). Among the five most frequent treatment modalities used in stage IIIB disease, mOS was the

Table 2. Survival Outcomes (PFS and OS) as Per Clinical Characteristics

	N	mPFS (95% CI), no	*p* Value	mOS (95% CI), mo	*p* Value
Age (y)					
≤65	1719	12.8 (12.25-13.70)	0.0628	39.9 (34.86-43.43)	**0.0001**
>65	1144	12.1 (11.33-12.94)		30.2 (27.96-33.77)	
Gender					
Female	685	14.6 (13.24-16.07)	**0.0057**	50.8 (45.73-62.55)	**<0.0001**
Male	2178	12.1 (11.43-12.68)		30.0 (27.73-32.46)	
Region					
Asia	1772	12.8 (12.19-13.70)	**0.0025**	42.3 (38.08-46.75)	**<0.0001**
Africa and Middle East	888	11.8 (10.64-12.42)		22.9 (21.16-26.25)	
Latin America	203	14.8 (12.06-18.56)		48.6 (34.73-NC)	
Smoking status					
Current smoker	889	12.0 (10.87-13.14)	**0.0138**	27.7 (24.44-31.77)	**<0.0001**
Exsmoker	1087	11.9 (11.07-12.71)		30.8 (27.73-34.50)	
Never smoker	663	14.8 (13.47-16.07)		50.8 (42.64-62.55)	
Unknown/missing	218	12.4 (9.72-14.29)		45.0 (32.89-NC)	
Stage (AJCC seventh edition)					
Stage IIIA	1471	14.3 (13.37-15.34)	**<0.0001**	43.8 (38.83-48.56)	**<0.0001**
Stage IIIB	1155	10.2 (9.43-11.01)		27.7 (24.87-29.73)	
Surgical resection of primary tumor					
Resectable	639	19.9 (18.50-22.67)	**<0.0001**	65.4 (57.86-NC)	**<0.0001**
Unresectable	1410	10.6 (9.89-11.40)		25.0 (22.80-27.10)	
Histology type					
Adenocarcinoma	1514	13.4 (12.62-14.36)	**0.0005**	46.3 (41.76-51.45)	**<0.0001**
Squamous Cell/epidermoid Carcinoma	1065	11.9 (10.74-12.48)		25.1 (23.20-27.10)	
Others[a]	92	9.3 (6.31-12.52)		28.9 (18.43-37.09)	
Large cell carcinoma	55	22.0 (9.30-51.61)		42.3 (19.48-NC)	
Mixed	33	11.2 (7.06-20.30)		47.9 (10.18-61.24)	
Bronchiole-alveolar	13	10.1 (2.33-11.56)		16.1 (2.33-20.57)	
ECOG performance status					
0	627	14.3 (12.52-15.97)	**<0.0001**	40.2 (34.04-50.79)	**<0.0001**
1	1192	11.8 (10.91-12.48)		29.6 (27.04-32.36)	
2	182	9.9 (8.90-12.45)		22.6 (19.38-27.99)	
3	38	10.2 (6.14-14.65)		16.3 (8.41-21.42)	
4	3	1.4 (1.12-NC)		8.1 (1.45-NC)	

Note: Unknown and missing data are not included. Values in bold indicate significant difference ($p < 0.05$). Analysis for EGFR mutation status will be presented in a separate report.

[a]"Others" include (not exhaustive): adenosquamous carcinoma; lymphoepithelioid; squamous metaplasia with atypia, not otherwise specified; lymphoepithelioma-like carcinoma; carcinosarcoma; anaplastic carcinoma; sarcomatoid carcinoma; squamous cell carcinoma with sarcomatoid element; pleomorphic carcinoma; "carcinoma"; undifferentiated carcinoma; pleomorphic carcinoma; small cell carcinoma; epithelial epithelioid; (large cell) neuroendocrine carcinoma; adenoid cystic carcinoma; dual squamous and glandular differentiation.

AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; mOS, median overall survival; mPFS, median progression-free survival; NC, noncalculable; OS, overall survival; PFS, progression-free survival.

longest with cCRT (n = 367; 32.4 mo; 95% CI: 25.59–40.61), followed by targeted therapies alone (n = 63; 27.7 mo; 95% CI: 24.18–50.33), sCRT (n = 140; 21.3 mo; 95% CI: 17.08–27.79), CT alone (n = 235; 20.0 mo; 95% CI: 16.82–24.25), and RT alone (n = 100; 13.0 mo; 95% CI: 10.91–17.84).

Significantly longer mOS were observed with younger age (<65 y), female gender, never smokers, stage IIIA disease, surgical resection of the tumor, adenocarcinoma histology, and ECOG status less than 2 ($p \leq 0.0001$) (Table 2). In addition, patients from Latin American and Asian countries had higher mOS compared with those from Middle East and African countries ($p < 0.001$).

Logistic Regression

Univariate and multivariate analyses for the overall cohort are presented in Supplementary Tables 6 and 7. Univariate and multivariate analyses for mPFS and mOS by stage for clinicodemographic characteristics and treatment modalities are found in Supplementary Table 8 (stage IIIA) and Supplementary Table 9 (stage IIIB). In the univariate analyses for stage IIIA, significantly longer mPFS and mOS were observed in patients aged less than 65 years, with ECOG less than 2, of Asian origin, who were nonsmokers, with resected disease, and with adenocarcinoma histology ($p < 0.05$). The primary treatments associated with longer survival in both stages IIIA and IIIB were surgery, cCRT, and triple therapy (the

combination of surgery and CRT). In the univariate analyses for stage IIIB, female gender and resected disease predicted better mPFS; female gender, ECOG less than 2, Asian origin, nonsmokers, resected disease, and adenocarcinoma histology predicted better mOS (all $p < 0.05$).

In multivariate analyses, only a few parameters were found to have a significant independent association with survival. Initial treatments associated with longer OS in stage IIIA were surgery, cCRT, and triple therapy (surgery and CRT) and surgery and cCRT in stage IIIB disease. Clinicodemographic characteristics independently associated with longer survival in both stage IIIA and IIIB diseases were ECOG less than 2, Asian origin, and adenocarcinoma histology. For the overall population, stage IIIA disease, female gender, age less than 65 years, ECOG less than 2, Asian descent, adenocarcinoma histology, and surgery or cCRT or triple therapy (surgery and CRT) as initial therapy were significantly associated with longer mOS ($p < 0.05$).

Discussion

To our knowledge, this retrospective, observational, real-world study of stage III NSCLC is the largest study of its type, conducted in 19 countries, across diverse regions and involving 3151 patients. Our data provide insights into the treatment approaches and the survival outcomes for patients with stage III NSCLC, including many LMICs from the non-US, non-European regions. It should be noted that this study gives an overview of treatment patterns between 2013 and 2017, that is, before the approval of durvalumab, the first and only immunotherapy agent approved for the treatment of unresectable/inoperable stage III NSCLC.[17] We found a substantial diversity in the treatment patterns with more than 25 treatment approaches being used as initial therapy, which is far beyond what would be expected from guideline-conforming patient management.[5] Approximately one-fifth of patients (21%) underwent potentially curative surgical resection. Almost one-third of patients (~30%) in both stage IIIA and IIIB diseases received cCRT. The lack of SoC treatment could be caused by the following several factors: lack of multidisciplinary teams in defining the treatment approach, proximity to RT facilities in some countries, educational gaps, or the general lack of adherence to clinical guidelines in stage III NSCLC. There were no differences in the stage distribution (IIIA and IIIB) between the various regions (stage IIIA: Asia [54.7%], Latin America [53.4%], Africa and Middle East [58.9%]; stage IIIB: Asia [45.3%], Latin America [46.6%], Africa and Middle East [41.1%]). In the study period, the relapse rates were high in patients with resected and unresectable diseases (approximately 62% and 79%, respectively). Of the patients receiving an initial therapy, approximately 50% relapsed and approximately 75% of these received a second-line therapy. Of those having received a second-line therapy, 30% went on to receive a third-line therapy. On relapse, CT alone was the most preferred of the second-line and third-line therapies, followed by RT alone in greater than 20% of the patients. Although there exist guidelines for the treatment of stage III NSCLC, the real-world data especially for LMICs are limited. Our results reveal that a limited number of patients were treated as per international guidelines in force at the time.[18,19]

Our study reports significant differences between stage IIIA and IIIB diseases in terms of mPFS (14.3 versus 10.2 mo, hazard ratio [HR] = 0.86 [95% CI: 0.77–0.96], $p < 0.01$) and mOS (43.8 versus 27.7 mo, HR = 0.78 [95% CI: 0.68–0.90], $p = 0.0005$). Patients with stage IIIA who were eligible for and who underwent surgery only had the longest mOS (62.6 mo), but this was a limited number of patients (n = 58). Patients who received adjuvant CT (n = 114) or adjuvant RT (n = 17) after surgery also had an mOS of greater than 57 months in stage IIIA. For definitive CRT as initial therapy, patients who received cCRT compared with those who received sCRT had longer mPFS (13.3 versus 11.8 mo, $p = 0.0078$) and mOS; there was a nonsignificant trend for longer mOS in patients with stage IIIA (43.8 versus 28.2 mo, $p = 0.26$), whereas the difference reached statistical significance for patients with stage IIIB (32.4 versus 21.3 mo, $p = 0.02$). Similarly, there was a significant difference in mOS between patients who received cCRT compared with those who only received CT (43.8 versus 30.0 mo [$p = 0.005$] in IIIA and 32.4 versus 20.0 mo [$p = 0.002$] in stage IIIB). The mOS in patients with unresectable disease was higher in our study compared with other studies in a similar population.[8,11-13,20] A recently published retrospective study in Korean patients with data extraction between 2007 and 2017 (before the use of durvalumab) reported similar OS.[21] Several randomized clinical studies have also revealed improved survival outcomes with cCRT compared with sCRT or RT alone in unresectable patients.[8-10] The mOS in patients with stage III NSCLC receiving cCRT ranges from 15 to 29 months in controlled and in real-world studies.[11-13,20,22] Meta-analyses of individual patient data from randomized controlled studies have revealed significant improvement in mOS with cCRT compared with sCRT (HR = 0.84, $p = 0.004$) and compared with RT alone (HR = 0.89, $p = 0.02$).[8,22] Earlier studies have revealed that the use of triple therapy (surgery + definitive CRT) did not lead to significantly better outcomes than other therapies.[23-25] Preliminary results of an ongoing multicenter, international PERTAIN study suggest significantly improved PFS (17.0 versus 11.0 mo) and OS (23.0

versus 14.0 mo [$p = 0.012$ for both]) with fluorodeoxyglucose positron emission tomography/CT-guided cCRT compared with routine diagnosis followed by sequential or cCRT.[26] In our study, although the number of patients receiving triple therapy (surgery + CRT) was small (<2%), they had significantly longer survival. This is in line with some recent studies wherein triple therapy regimens have revealed significant survival benefits compared with CRT alone as initial therapy.[27-29]

For both stages IIIA and IIIB, the significant predictors for longer OS were female gender (HR = 1.74 and 1.59 and $p < 0.0001$), nonsmoking status (HR = 1.94 and 1.43, $p < 0.008$), surgical resection (HR = 0.50 and 0.38, $p < 0.0001$) and triple therapy (surgery + CRT) as initial treatment (HR = 0.52 and 0.34, $p < 0.002$). Multivariate analyses revealed that female gender (HR = 1.43, $p < 0.05$), ECOG performance status (HR = 0.71 and 0.72, $p < 0.05$), and surgical resection as initial treatment (HR = 0.63 and 0.43, $p < 0.05$) were significantly associated with improved OS. In a recent real-world study, good ECOG performance status, stage IIIA disease, and RT as initial therapy were associated with a lower risk of death.[30] Female gender, younger age, good ECOG performance status, early stage disease, and triple therapy (surgery + CRT) were associated with a lower risk of death in univariate analyses of another real-world study.[27]

It is important to note that the National Comprehensive Cancer Network (NCCN) Clinical Practice In Oncology Guidelines® recommend (category 1) consolidation immunotherapy with durvalumab after cCRT as definitive therapy in unresectable stage III NSCLC.[5] In addition, the clinical guidelines now recommend consolidation immunotherapy with durvalumab in the same setting for patients with unresectable stage II NSCLC, although with a category 2A recommendation.[5] The advent of immune checkpoint inhibitors has led to a paradigm shift in the treatment of NSCLC in the past few years. The PACIFIC trial revealed a significant improvement in PFS (HR = 0.52) and OS (HR = 0.68) with consolidation durvalumab after cCRT.[31,32] Several other studies evaluating neoadjuvant and adjuvant uses of immune checkpoint inhibitors have revealed beneficial effects in resectable stage III NSCLC. NADIM, a single-arm, phase 2 trial evaluating neoadjuvant and adjuvant nivolumab combined with platinum-based CT in patients with resectable stage IIIA(N2) NSCLC (n = 41) has revealed 85% major pathologic response at resection.[33] SAKK16/14, an open-label single-arm phase 2 study of neoadjuvant durvalumab with CT followed by adjuvant durvalumab in 68 patients with resectable NSCLC stage IIIA(N2), has revealed a radiographic response rate of 44.8% (95% CI: 32.60–57.40) post-neoadjuvant immunotherapy and 1-year event-free survival of 73.3% (90% CI: 62.5–81.4).[34] Similarly, the SoC and the guidelines changed recommending adjuvant osimertinib for patients with completely resected stage IIIA EGFR mutation-positive NSCLC who received previous adjuvant CT or are ineligible to receive platinum-based CT.[5,35] It is expected that the survival of patients with stage III NSCLC will improve in the future as newer agents, such as targeted and immune-oncology therapies, get approved and are adopted into routine clinical practice.

Nevertheless, the findings also highlight the need for newer treatment options in patients with stage III NSCLC given the high relapse rates in patients with resected and unresectable diseases (62% and 79%, respectively) in the study period. Overall, almost 50% of patients relapsed on initial therapy whereas 43.2% were dead at the time of data collection; this reiterates the need for development of novel therapeutic agents for increasing the OS of patients with NSCLC along with improving PFS in the first-line setting. The current study provides a benchmark for understanding the existing treatment landscape from the preimmunotherapy period, which will be important for evaluating the effectiveness of newer therapies in this population. The evidence presented here should help the implementation of new advances into the management of NSCLC including in LMICs. With use of novel therapies for management of stage III NSCLC and better adherence to treatment guidelines, significant improvements in both PFS and OS can be expected.

The limitations of this study include the known challenges of a retrospective study design in real-world settings. In addition, data collection was limited to the availability of existing health records, resulting in missing data as many patients could have been lost to routine clinical follow-up. The study period covers the era before approval of immunotherapy in the first-line setting. Thus, the data on effectiveness of newer therapies have not been captured in the study.

In conclusion, KINDLE, a large multicountry, observational study, reveals the diversity of treatment practices in this heterogeneous stage III NSCLC population and provides insights on the clinical outcomes from real-world settings. The study reports limited adherence to treatment guidelines applicable in the pre–immuno-oncology era, with the minority of patients with unresectable disease receiving cCRT as initial therapy (<40%). There is a definite gap in optimal selection and sequencing of various treatment approaches. The survival outcomes with both surgery and cCRT were comparatively higher than other therapies. In addition, approaches to optimize patient outcomes, including implementation of guidelines, physician education, and improved access to innovative medicines and quality

care, should be undertaken to improve the quality of life of patients. It becomes clear that a disease requiring multidisciplinary care for optimal management is difficult to treat in certain health care systems with limited resources. The data collected from this study will also contribute to a centralized platform to help identify the newer treatment needs, besides providing baseline data for evaluating the impact of novel therapies for treating stage III NSCLC in future. Additional analyses from our study will focus on testing practices, in-depth regional differences, and country-level specifics.

CRediT Authorship Contribution Statement

Abdul Rahman Jazieh, Reto Huggenberger: Conceptualization, Writing, Methodology, Visualization, Investigation, Editing, Validation.

Huseyin Cem Onal, Daniel Shao Weng Tan, Ross A. Soo, Kumar Prabhash: Conceptualization, Investigation, Methodology, Editing.

Amit Kumar, Stephen Robb, Cho Byoung-Chul: Conceptualization, Methodology, Editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.05.003.

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