Treatment Pattern and Overall Survival of Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer: A Multicentric Real-World Study in China (CTONG1506)

Qing Zhou
Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences
Yong Song
Nanjing General Hospital of Nanjing Military Command
Xin Zhang
Zhongshan Hospital, Fudan University
Gongyan Chen
Harbin Medical University Cancer Hospital
Yiping Zhang
Zhejiang Cancer Hospital
Ping Yu
Sichuan Cancer Hospital
Jianhua Chen
Hunan Cancer Hospital
Zhuang Yu
The Affiliated Hospital of Qingdao University
Yi Hu
Chinese People's Liberation Army General Hospital
Xia Song
Shanxi Cancer Hospital
Diansheng Zhong
Tianjin Medical University General Hospital
Guosheng Feng
People's Hospital of Guangxi Zhuang Autonomous Region
Lulu Yang
Lilly Suzhou Pharmaceutical Co.,Ltd
Lu jing Zhan
Lilly Suzhou Pharmaceutical Co., Ltd
Xiao Ma
Lilly Suzhou Pharmaceutical Co.,Ltd

Xingwei Lu
Shanghai Centennial Scientific Co.,Ltd
Yi-Long Wu (syylwu@live.cn)
Guangdong Lung Cancer Institute

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Abstract

Background:

CTONG1506, an observational study assessed the real-world treatment patterns and overall survival (OS) of Chinese advanced non-squamous non-small cell lung cancer (NSCLC) patients in current treatment practices.

Methods:

Patients initiated with 1st line therapy were identified from 12 tertiary hospitals across China. Survival data were collected 1- and 2-years after study initiation. OS was estimated using the Kaplan-Meier method.

Results:

Among 540 patients with survival data, median OS was 21.4 months (95% CI: 18.1–25.5), and 2-year OS rate was 46.3% (95% CI: 42.0%-51.0%). Median OS for patients with epidermal growth factor receptor *(EGFR*+) mutation (n = 203), anaplastic lymphoma kinase (*ALK*+) rearrangement (n = 24), *EGFR-/ALK-* were 27.9 months (95% CI: 23.4-NA), 24.5 months (95% CI: 18.1-NA), and 15.7 (95% CI: 13.1–21.1) months, respectively. Median OS was not reached in *EGFR* exon 19 deletion patients compared to *EGFR* exon 21 L858R mutation patients (21.4 months, 95% CI: 16.7–35.6, P = 0.038). 93 *EGFR +* patients received tyrosine kinase inhibitor (TKI) alone, 21 received chemotherapy alone and 66 received TKI and chemotherapy [median OS 25.5 months, 18.1 months, and 35.6 months, respectively]. For *EGFR +* patients, TKI alone was the preferred therapy in 1st (58.2%) and 2nd (56.8%) line when compared to chemotherapy (35.1% and 31.1% respectively). In 3rd line, chemotherapy was preferred (46.0%) over TKI only (38.0%) in these patients.

Conclusions

OS for patients with advanced non-squamous NSCLC patients aligned with previous trials. *EGFR +* patients who received both TKI and chemotherapy had longer median OS, which is consistent with results from other trials.

Background

Lung cancer is the leading cause of mortality with incidence of 2.1 million new cases and 1.8 million deaths in 2018 world-wide (1). In China, lung cancer remains the most common issue, accounting for 18.1% of new cases and is also the leading cause of cancer death (2). It has been reported that the 5-year survival of patients diagnosed with lung cancer is around 17.8% and patients die within one year of diagnosis (3). The 5- year survival rate for lung cancer in China remains low in men with frequency of 16.8% and 25.1% in women from 2012–2015 (4). Additionally, an increase in the incidence and mortality with age in both the genders is observed (5).

The international treatment guidelines recommend chemotherapy, programmed death ligand 1 (PDL-1), or combination of PDL1 and chemotherapy, as first line treatment for NSCLC without oncogenic driver mutations (6). In patients with epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements, tyrosine kinase inhibitors (TKIs) are the recommended first-line treatment.

Approximately, 19.2% of Western and 47.9% of Asian population with NSCLC- adenocarcinoma subtype harbour *EGFR* mutation (7). Thus, TKIs directed against *EGFR*, such as Erlotinib, and Gefitinib, have demonstrated promising outcomes for this subgroup of patients (8); thereby representing as a standard first-line treatment for *EGFR* mutated NSCLC (9).

Additionally, superiority of *EGFR* TKIs over platinum-doublet chemotherapy in providing better progression free survival (PFS) in *EGFR*+ NSCLC has also been demonstrated by various randomized, phase III studies (10–16). Similar findings have also been reported in other studies wherein prolonged PFS relative to chemotherapy was observed with Afatinib but overall survival (OS) was similar in both groups (17). Evidence suggests that treatment with *EGFR* TKI in first line setting improves PFS but did not show much benefit in OS compared to chemotherapy (10–12).

Despite growing evidence in proving the efficacy of various therapeutic strategies, limited information concerning the use of appropriate treatment modality for advanced NSCLC in a real-world setting raises a serious concern to the clinicians. Therefore, data from real-world will help generate evidence on the effectiveness and use of medical products in daily practice (18), will provide insights on patient response, disease patterns, along with clinical outcomes in patients of all ages (19). This study was thus conducted to assess the treatment patterns and OS of advanced non-squamous NSCLC patients in a Chinese population in current treatment practices (CTONG 1506).

Methods

Study design

This retrospective, series of cross-sectional study extracted data from medical charts of patients discharged from 12 tertiary hospitals across China between August 2015 and March 2016. The protocol was approved by the Research Ethics Committee of the Guangdong General Hospital, Guangzhou, Guangdong, China.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and was supported by the Chinese Thoracic Oncology Group (CTONG study number 1506).

Study population

The medical charts of patients meeting the following criteria were included for review: aged ≥ 18 years; diagnosis of unresectable Stage IIIB or IV (according to the American Joint Committee on Cancer staging system, 7th edition), non-squamous NSCLC; no previous systemic anticancer treatment for Stage IIIB or IV

disease; and most recent hospitalization was for anticancer treatment. Patients aged < 18 and > 80 or diagnosed with squamous cell carcinoma or stage I/II or not imitated on treatment and non-hospitalised patients were excluded from the study. A total of 540 patients with 2-year survival data were identified in this survey and included in analysis.

Data collection

Data from patients' medical charts were extracted and entered into the Medical Record Abstraction Form (MERAF) by designated hospital staff after patient discharge. Extracted data included demographics, NSCLC histological type, Eastern Cooperative Oncology Group (ECOG) performance status (PS), gene aberration status and first-line anticancer treatment regimen. Data entry was reviewed on-site by an independent data management organization (Shanghai Centennial Scientific Ltd., Shanghai, China), who assessed accuracy of data entry by checking 20% of all MERAFs collected at one hospital selected at random. Completed MERAFs were collected for analysis. Data from all collected MERAFs were entered into a database for analysis, with data entered and verified twice to ensure accurate data entry. MERAFs were excluded from analysis if data were missing for gene aberration test status or first-line anticancer treatment regimen and if more than 10% of other data were missing.

Study outcome

Survival information OS was collected one and two years after patients received initial treatment. Follow-up data was obtained from medical chart abstraction or telephonic interview.

Statistical analysis

Age (< 65, ≥ 65), sex (male, female), hospital location (hospital location, developed area), smoking status (never smoker, former smoker, current smoker), histological subtype (adenocarcinoma, other), ECOG PS (0, 1, ≥ 2) at baseline were described. The categorical data were presented as frequencies and percentages. OS were evaluated by Kaplan-Meier (KM) method with 95% confidence intervals (CIs). Patients who lost the follow-up or could not be confirmed about survival status at any follow-up were not included in the survival analysis. Two-tailed P-values, less than 0.05 will be considered statistically significant. All analysis was performed using R software (Version 3.5.1).

Results

Baseline and demographic details

The demographic and baseline clinical characteristics of the overall study population was categorized based on mutational status as presented in Table 1. Among the 12 tertiary hospitals that were included in the study, majority of hospitals belonged to developed area in China. A total of 540 patients who had a 2-year follow-up survival data were included in the study. There were 183 patients with *EGFR-/ALK-* wild type and most of them were < 65 years of age (72.1%). It was seen that 74.6% of the included patients

were < 65 years. A total of 87 (42.8%) patients had exon 19 deletion and 82 (40.3%) patients had *EGFR* exon 21 L858R mutation in *EGFR*+ group.

Table 1
Demographic and baseline characteristics of patients

Characteristic, n (%)	Total n = 540	*EGFR*+ n = 203	*ALK*+ n = 24	*EGFR*-&*ALK*- n = 183
Age				
< 65 years	403 (74.6)	142 (70.0)	20 (83.3)	132 (72.1)
≥ 65 years	137 (25.4)	61 (30.0)	4 (16.7)	51 (27.9)
Sex				
Male	310 (57.4)	86 (42.4)	14 (58.3)	132 (72.1)
Female	230 (42.6)	117 (57.6)	10 (41.7)	51 (27.9)
Hospital location				
Developing area	197 (36.5)	68 (33.5)	7 (29.2)	53 (29.0)
Developed area	343 (63.5)	135 (66.5)	17 (70.8)	130 (71.0)
Smoking status				
Never smoker	306 (56.9)	142 (70.3)	16 (66.7)	78 (42.6)
Former smoker	129 (24.0)	34 (16.8)	3 (12.5)	56 (30.6)
Current smoker	103 (19.1)	26 (12.9)	5 (20.8)	49 (26.8)
Histologic subtype				
Adenocarcinoma	516 (95.9)	201 (99.5)	24 (100.0)	170 (92.9)
Other	22 (4.1)	1 (0.5)	0 (0.0)	13 (7.1)
ECOG PS				
0	173 (32.2)	63 (31.2)	5 (20.8)	53 (29.0)
1	316 (58.7)	122 (60.4)	18 (75.0)	110 (60.1)
≥ 2	49 (9.1)	17 (8.4)	1 (4.2)	20 (10.9)

ALK: Anaplastic Lymphoma Kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: Epidermal Growth Factor Receptor

Treatment pattern in various lines of therapy

It was seen that in *EGFR*+ patients, TKI only was the preferred mode of therapy in 1st (58.2%) and 2nd (56.8%) line when compared to chemotherapy (35.1% and 31.1% respectively). In 3rd line, chemotherapy was preferred (46.0%) over TKI only (38.0%) in these patients.

On the other hand, chemotherapy only was the most common mode of treatment in *ALK*+ patients in 1st (58.5%) and 2nd (59.1%) line. However, chemotherapy and TKI was prescribed as 1st line to 2.0% *EGFR*+ and 4.6% *ALK*+ patients in 2nd line. None of the patients received this pattern at 3rd line (Table 2).

Table 2
Treatment patterns across the lines of therapy

Line of therapy	*EGFR*+	Wild-type	*ALK*+	Wild-type
Ist line				
TKI only (n = 146, %)	58.2%	8.4%	39.0%	32.0%
Chemotherapy only (n = 88, %)	35.1%	83.1%	58.5%	59.6%
Chemotherapy plus TKI (n = 5, %)	2.0%	1.2%	0.0%	1.3%
2nd line				
TKI only (n = 75, %)	56.8%	15.0%	31.8%	36.5%
Chemotherapy only (n = 41, %)	31.1%	64.0%	59.1%	47.6%
Chemotherapy plus TKI (n = 1, %)	0.8%	2.0%	4.6%	1.6%
3rd line				
TKI only (n = 19, %)	38.0%	21.1%	62.5%	28.1%
Chemotherapy only (n = 23, %)	46.0%	44.7%	12.5%	42.1%
Chemotherapy plus TKI (n = 0, %)	0.0%	0.0%	0.0%	0.0%

ALK: Anaplastic Lymphoma Kinase; EGFR: Epidermal Growth Factor Receptor; TKI: Tyrosine Kinase Inhibitor

OS in patients with different mutations

The median OS for 540 patients was 21.4 months (95% CI: 18.1–25.5), 1-year and the 2-year OS rate was 69.5% (95% CI: 66.0–74.0) and 46.3% (95% CI: 42.0–51.0), respectively (Fig. 1A). It was seen that the median OS for patients with *EGFR* mutation (n = 203), *ALK* rearrangement (n = 24), and wild-type *EGFR* with negative *ALK* rearrangement (n = 183) were 27.9 months (95% CI: 23.4-NA), 24.5 months (95% CI: 18.1-NA), and 15.7 months (95% CI: 13.1–21.1), respectively (Fig. 1B).

Median OS was not reached in patients with *EGFR* exon 19 deletion and it was 21.4 months (95% CI: 16.7–35.6) in *EGFR* exon 21 L858R mutation patients. Statistically significant difference (P = 0.038) was seen in OS between the groups (Fig. 2).

OS in patients with various 1st line treatments

In *EGFR*+ patients, the median OS was 27.9 months (95% CI: 19.3–35.6) in patients receiving TKI in the first-line setting; whereas in *EGFR*+ patients who received chemotherapy, the median OS was 27.7 months (95%CI: 19.5-NA) with log rank P = 0.36 (Fig. 3A). Even in *ALK*+ patients, TKI was the most common first-line treatment regimen (62.5%, 15/24), while the median OS was not reached.

In patients with *EGFR-/ALK-*, 84.2% (154/183) received first-line chemotherapy, with a median OS of 14.5 months (95% CI: 12.6–19.4). It was seen that median OS in patients treated with pemetrexed-based and non-pemetrexed-based chemotherapy were 15.6 months (95%CI: 13.1–21.1) and 12.6 (95%CI: 10.6–33.9) months, respectively with log rank P = 0.65 (Fig. 3B).

OS in EGFR + patients in all treatment course

TKI was administered to 93 *EGFR*+ patients, whereas 21 received chemotherapy alone, and 66 received both TKI and chemotherapy sequentially. The median OS of these three group of patients was 25.5 months (95% CI: 19.3-NA), 18.1 months (95% CI: 12.1-NA), and 35.6 months (95% CI: 24.4-NA), respectively with log rank test: P = 0.25 (Fig. 4).

Discussion

This study evaluated the real-world treatment patterns and the survival benefits provided by *EGFR* TKIs and other current, systemic anti-cancer therapies in advanced NSCLC with different mutated and non-mutated profiles in China. The treatment pattern observed in current study is in agreement with the Chinese Expert Consensus on the diagnosis and treatment of advanced NSCLC (2016 version) (20) with TKI being the preferred 1st line option. However, platinum-based regimen remains the standard treatment for patients without mutations in China with gemcitabine, docetaxel, paclitaxel and pemetrexed being the most common choices for 1st line chemotherapy (21). A retrospective chart review study examining real-world treatment pattern in Japan revealed *EGFR* TKIs to be the most commonly prescribed drug for *EGFR* mutated NSCLC across all treatment lines (22).

Pemetrexed is the preferred regimen in patients with NSCLC adenocarcinoma based on the results of previous randomized studies due to its superior outcomes in terms of PFS (23, 24). Likewise, even in current study, Pemetrexed (30.3%, 22.7%) and Cisplatinum (23.9%, 13.6%) were the most frequently used chemotherapeutic drugs as 1st and 2nd line, respectively whereas, among TKIs, Gefitinib (31.5%, 17.4%) and Icotinib (20.3%, 15.9%) were the frequently used treatment in 1st and 2nd line, respectively. This treatment pattern is not in line with other patterns reported elsewhere wherein docetaxel was used in 14.0–16.0% of patients in 2nd line (25, 26).

Our study revealed that although non-significant, *EGFR*+ patients who received sequential TKI and chemotherapy had longer median OS. This corroborates findings from a study by Chung et.al who demonstrated that the 1st line chemotherapy followed by *EGFR*-TKIs in *EGFR*+ advanced lung

adenocarcinoma had better OS than that of 1st line TKIs followed by 2nd-line chemotherapy (median: 662 versus 390 days, P < 0.0001. Similar findings were reported by another phase III study, OPTIMAL which showed improved OS in patients receiving sequential combination of TKI and chemotherapy than those who received either TKI or chemotherapy (29.7 versus 20.7 or 11.2 months respectively, P < 0.0001) (27). Overall, these findings strongly support the fact that TKI in combination with chemotherapy is efficient when compared to either TKI or chemotherapy alone for treating *EGFR*+ mutation patients.

In our study, targeted therapy either using TKI alone or sequential chemotherapy was found to have better OS in *EGFR*+ patients compared to *EGFR*- patients highlighting the importance of TKI in first line setting for *EGFR*+ patients. This is in line with findings from a recent trial which reported the OS of Icotinib plus pemetrexed and carboplatin to be 36 months (28). Similarly, another study comparing the efficacy of combination therapy of *EGFR*-TKI with chemotherapy with *EGFR*-TKI alone and chemotherapy alone revealed significant improved PFS in combination therapy compared to *EGFR*-TKI alone (29). Additionally, combination therapy was better compared to chemotherapy alone both in PFS and OS in *EGFR*+ NSCLC patients. In our study the median OS in *EGFR*+ patients receiving TKI alone was 27.9 months compared to 14.5 months in *EGFR*- patients who received chemotherapy. Results from our real-world study support the efficacy of *EGFR* TKIs as established in clinical trials.

Going forward, remarkable progress made in treatment of NSCLC is due to the discovery of several, clinically relevant activating pathways including *EGFR*-activating mutations and *ALK* rearrangements (30) and treatment guidelines recommend the use of first line *EGFR*-TKI for patients with exon 19 deletions and the exon 21 L858R mutation (6). Data also reflect that patients harbouring exon 19 deletions or exon 21 L858R point mutations in *EGFR* show substantially increased benefit from treatment with *EGFR* TKIs compared to those who do not harbour these mutations (31). This has been attributed to TKI's inhibitory action and its role in downstream signalling of *EGFR*. The mechanism of action of TKI is to inhibit the kinase activation and signal transduction downstream by binding to the ATP binding site of the kinase domain of *EGFR* (32). Treatment with TKI has shown around 74.0% response rate with a median PFS of 10.0–14.0 months (12, 15). However, recent studies have shown mixed outcomes due to exon 19 and 21 mutations in such patients in response to both EGFR-TKIs and chemotherapy (33–35). These difference in response between *EGFR* exon 19 deletions and exon 21 L858R mutation might be related to intrinsic structural basis and differential drug sensitivity (36–38). In our study, median OS was not reached in patients with exon 19 deletion and it was 21.4 months (95%CI: 16.7–35.6) in those with exon 21 L858R mutation ($P = 0.038$). This was in agreement with study findings reported elsewhere. Jiang et.al reported significantly improved overall response rate (ORR) and PFS in patients with deletions in exon 19 compared with those with exon 21 mutation following *EGFR*-TKI treatment for NSCLC (31). The same was re-confirmed by Banno et.al wherein NSCLC patients with *EGFR* exon 19 deletions had a significant advantage following the treatment of Afatinib compared with the patients with *EGFR* exon 21 mutations (39). These findings re-substantiate the importance of appropriate treatment selection especially for *EGFR*+ NSCLC patients. With the approval of first immuno-oncology agent, Opdivo (Nivolumab injection) by China National Drug Administration based on results of pivotal phase III, Checkmate-078 trial that demonstrated significantly better OS with nivolumab compared to docetaxel in

previously treated non-mutated *EGFR/ALK* NSCLC, better management is foreseen in this subset of patients (40). *ALK*-rearrangement has been identified in many cancers including NSCLC. *ALK*-rearrangement leads to oncogenic *ALK* tyrosine kinase that drives cell proliferation by activating downstream signalling pathways (41). *ALK*-TKIs are preferred option in advanced NSCLC with *ALK* rearrangements (42, 43).

The strengths of the study are that this multicentric survey demonstrated the real-world treatment patterns and the survival benefits of *EGFR* TKIs, and other systemic therapies in *EGFR* mutated advanced NSCLC in first line, second- and third-line setting. Additionally, this study reports the 2-year follow-up data for treatment and survival parameters. Limitations of this analysis are reflective of the data source and collection. Few of the treatment information in our study was unavailable due to loss to follow up, thereby plausibly causing non-significant findings for the first line treatment parameters. It is also important to note that a longer and continuous follow up may yield completer data especially for OS.

Conclusions

OS for patients with advanced non-squamous NSCLC patients aligned with previous trials. *EGFR*-mutated patients who received both TKI and chemotherapy had a longer median OS, and patients with *EGFR* wild-type and *ALK*-negative NSCLC showed a longer median OS with pemetrexed-based first line chemotherapy compared to those with non-pemetrexed-based chemotherapy.

Abbreviations

OS
Overall survival
PFS
Progression free survival
NSCLC
Non-small cell lung cancer
EGFR
Epidermal growth factor receptor
ALK
Anaplastic lymphoma kinase
TKI
Tyrosine kinase inhibitor
PDL-1
Programmed death ligand 1
CTONG
Chinese Thoracic Oncology Group
MERAF
Medical Record Abstraction Form

ECOG
Eastern Cooperative Oncology Group
PS
Performance Status
KM
Kalpan-Meier method
CI
Confidence intervals

Declarations

Ethics approval and consent to participate:

The protocol was approved by the Research Ethics Committee of the Guangdong General Hospital, Guangzhou, Guangdong, China. Each site obtained its own institutional review board (IRB) or ethics committee approval before the start of the study. The study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived by IRB for this retrospective analysis, except the IRB of Harbin Medical University Cancer Hospital.

Consent for publication:

Not Applicable

Availability of data and material:

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

LLY, LJZ and XM are employees of Lilly Suzhou Pharmaceutical Co., China. XWL is an employee from Shanghai Centennial Scientific Co., Ltd. Y-LW has received speaker fees from AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly, Pfizer, BMS, and MSD. QZ has received speaker fees from AstraZeneca, Roche.

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Authors Contributions:

QZ, YS, XZ, GC and YZ proposed the conception and designed the study. PY, JC, ZY, YH and XS acquired the study data DZ, GF, LY, LZ, XM, XL, YW analyzed, and interpreted the study data. All the authors critically reviewed the manuscript and approved the final version for submission. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Figures

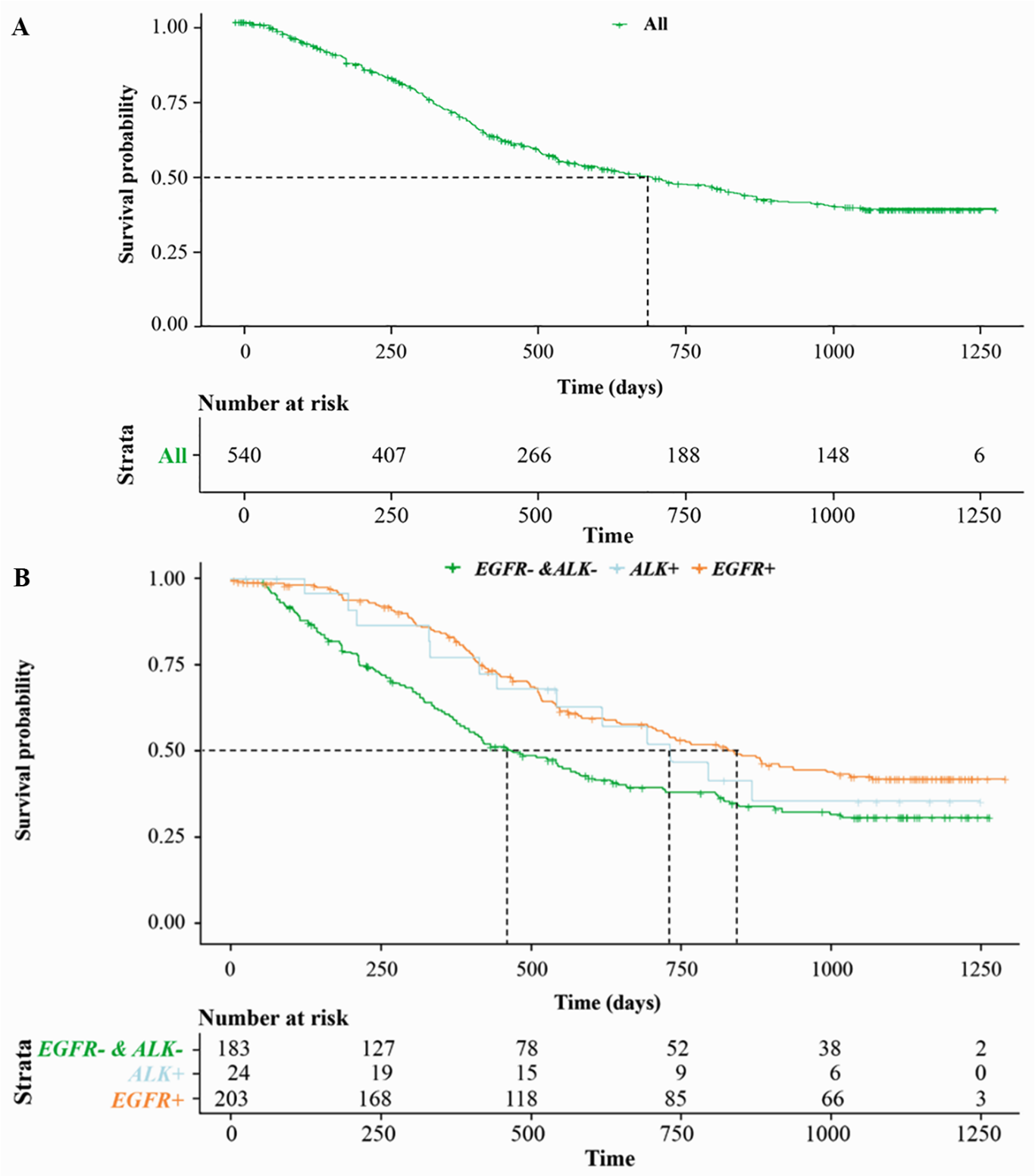

Figure 1

KM curve for OS in patients with different mutations. (A) Median OS for all 540 patients was 21.4 months (95% CI: 18.1-25.5). (B) Median OS for patients with EGFR+, ALK+, EGFR-/ALK- were 27.9 months (95% CI: 23.4-NA), 24.5 months (95% CI: 18.1-NA) and 15.7 months (95% CI: 13.1-21.1), respectively.

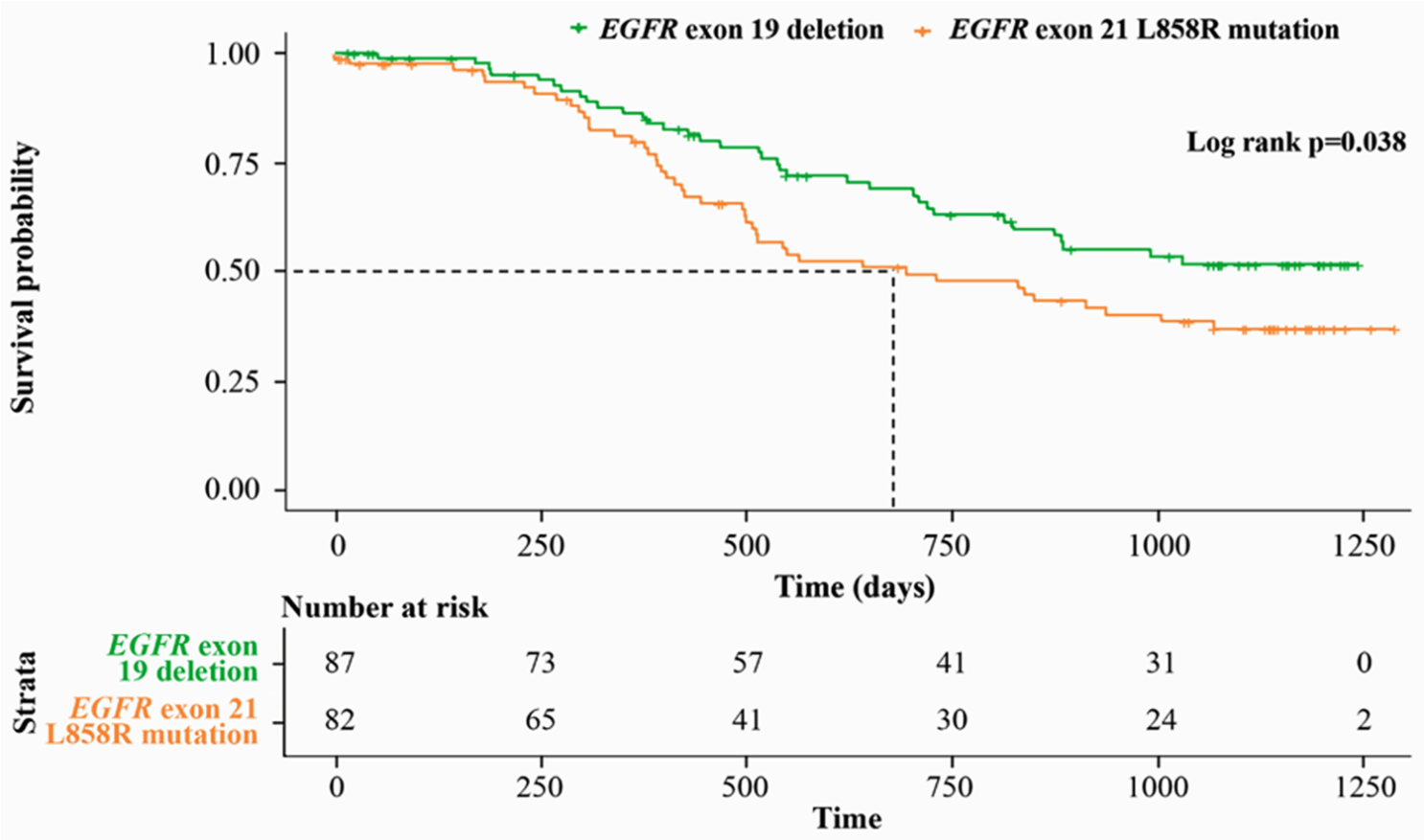

Figure 2

OS in patients with EGFR exon 19 deletion/exon 21 L858R mutation Median OS for EGFR exon 19 deletion had not reached and in patients with EGFR exon 21 L858R mutation it was 21.4 months (95% CI: 16.7-35.6).

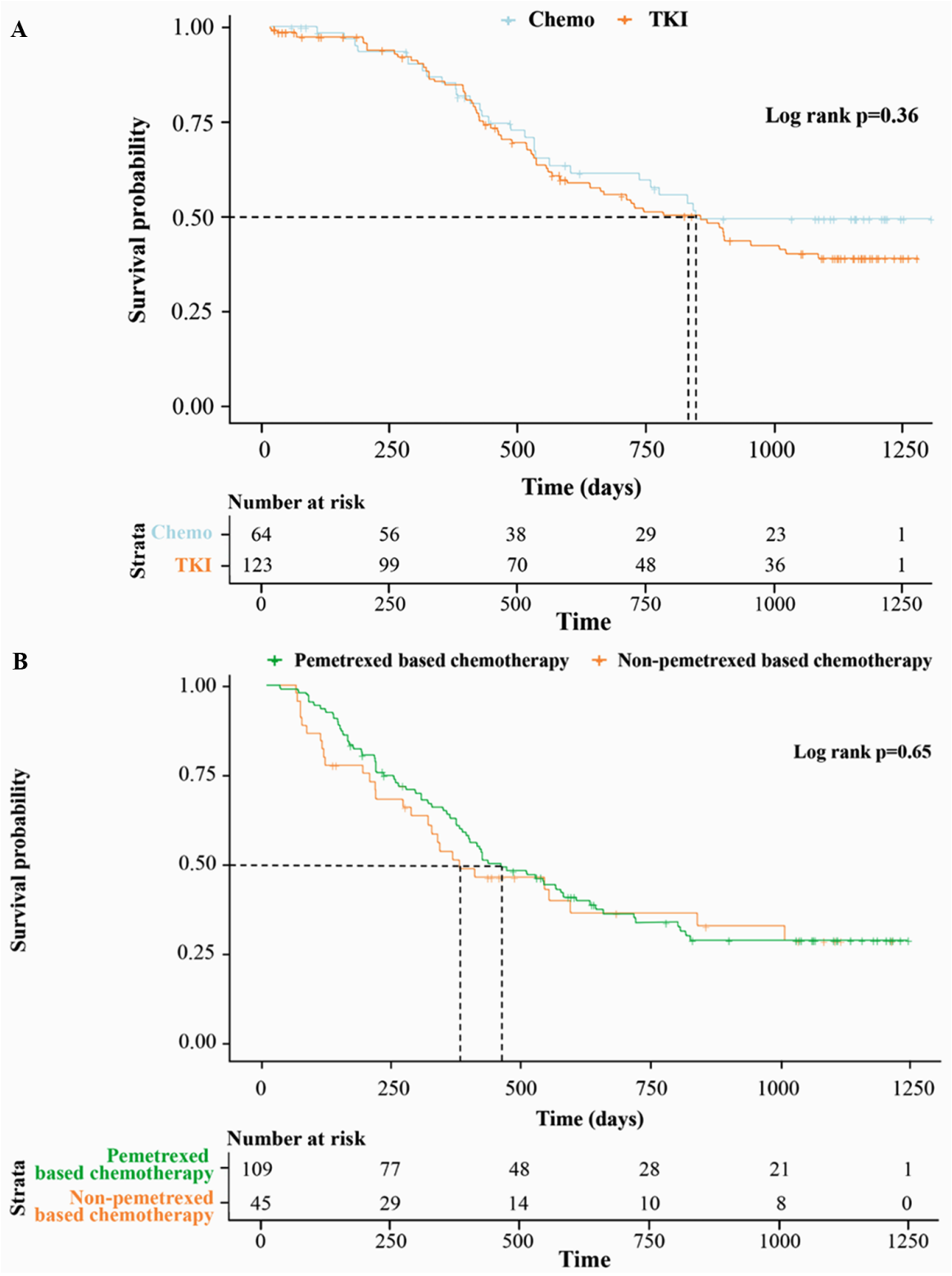

Figure 3

OS in patients received various 1st line treatments (A) Median OS was 27.7 months (95%CI: 19.5-NA) in EGFR+ patients who received chemotherapy and 27.9 months (95% CI: 19.3-35.6) in those who received TKI as 1st line. (B) Median OS of patients treated with pemetrexed-based and non-pemetrexed-based chemotherapy were 15.6 months (95%CI: 13.1-21.1) and 12.6 (95%CI: 10.6-33.9) months, respectively.

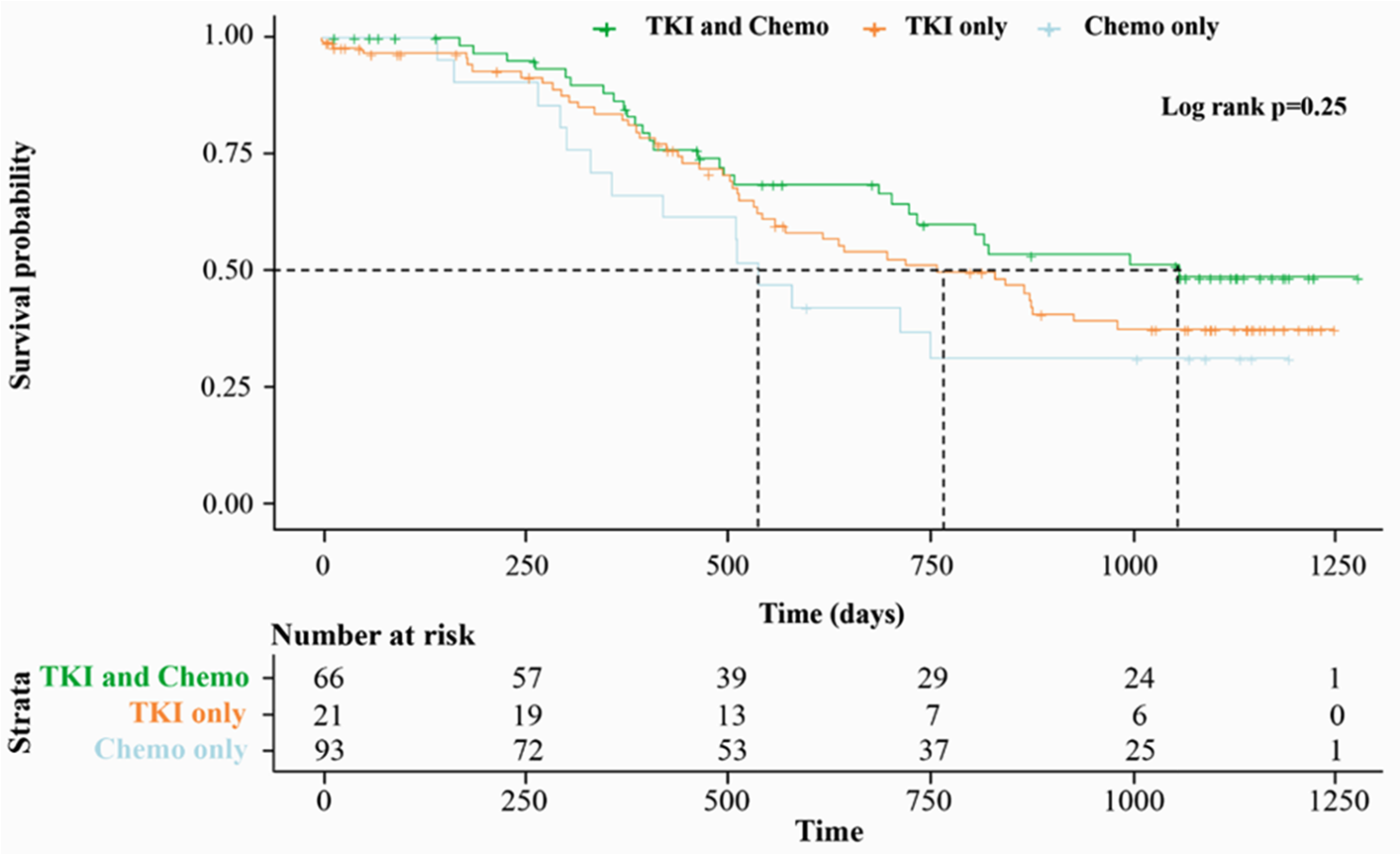

Figure 4

OS in EGFR+ patients who received all treatment course Median OS for patients who received TKI and chemotherapy: 35.6 months (95% CI: 24.4-NA); TKI only: 25.5 months (95% CI: 19.3-NA) and chemotherapy only: 18.1 months (95% CI: 12.1-NA).