Real-world treatment patterns among advanced non-small cell lung cancer patients in the US

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Abstract

Objectives: The rapid evolution of the treatment landscape for non-small cell lung cancer (NSCLC) indicates a need to assess real-world treatment patterns in clinical practice in the US. This study aims to describe treatment patterns and patient characteristics, taking into account new drug entities and newly emerging biomarkers for NSCLC.

Methods: A descriptive cohort study was conducted using a specialized electronic health record data for NSCLC. Patients who initiated NSCLC treatment following diagnosis of advanced NSCLC (stage IIIB/IIIC/IV) from 01/01/2015–12/31/2021 were identified. Baseline characteristics and treatment patterns were described; continuous variables were described as mean and standard deviation (SD) and categorical variables as proportions.

Results: Of 8,811 patients identified with advanced NSCLC, 67.9% had non-squamous cell carcinoma, 22.5% had squamous cell carcinoma, and 9.6% had an unknown histology. The majority of patients (78.7%) were treated at community hospitals, while 13.4% were treated at academic centers, and 7.9% had an unknown treatment setting. Most patients (59.0%) were aged 65 years or older, and 47.3% were female. There were 22 patients (0.2%) with documentation of NSCLC but no identified guideline-recommended line of therapy (LoT). Among all patients, 51.6% received a second line of therapy (LoT2), and 26.4% received third-line therapy (LoT3). For stage IIIB/IIIC patients, the five most common first-line therapies (LoT1), accounting for 83.2% of all LoT1, included traditional platinum-based chemotherapy or pembrolizumab. In stage IV patients, the five most common LoT1, comprising 64.4% of all LoT1, were pembrolizumab either as monotherapy or combined with other platinum-based chemotherapeutic agents.

Conclusions: Traditional platinum-based chemotherapy was the most common LoT1 for stage IIIB/IIIC patients, while the extensive use of immunotherapy (IO) was found in stage IV patients and in later lines of treatment in stage IIIB/IIIC patients. Results indicate that new evidence regarding treatment patterns is rapidly adopted into practice and medication therapy management.

Keywords: non-small cell lung cancer, platinum-based chemotherapy, immunotherapy, targeted therapy, real-world evidence

Introduction

Lung cancer is the second most common cancer in the US and the leading cause of cancer deaths. In 2024, the National Cancer Institute estimated approximately 234,580 new cases and 125,070 deaths in the US.[1]

There are two main types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for 80% to 85% of all lung cancer cases, with three main histological types: adenocarcinoma (40%), squamous cell carcinoma (25%–30%), and large cell (5%–10%).[2] Patients with NSCLC are usually diagnosed at an advanced stage, because early symptoms are often misinterpreted, ignored, or not present.[3] Based on Surveillance, Epidemiology, and End Results (SEER) data, about 50% of NSCLC patients are diagnosed at an advanced stage.[4] While the overall 5-year relative survival rate of lung cancer was 26.7% in the US,[1] it was only 9% for advanced NSCLC.[5] This late detection and low survival rate highlights the need for effective management strategies to improve patient outcomes.

Cytotoxic therapies have been applied to lung cancer since the 1940s, but recent decades have provided advances in NSCLC therapies that offer patients more treatment options. The identification of oncogenic driver mutations, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements, has led to treatments specifically targeting molecular mutations that improve quality of life and survival. More recently, immunotherapies (IO) have been introduced; these act against checkpoint proteins including CTLA-4, PD-1, and PD-L1, heralding a new chapter in NSCLC treatment.

Advances in treatment options have posed challenges in the real-world adoption of new clinical evidence, translation of evidence into up-to-date treatment guidelines, and subsequent adoption into patient care. Nonadherence to treatment guidelines is common in real-world clinical settings.[6,7] To ensure that clinical practice keeps pace with rapid scientific advancements, adherence to cancer guidelines, such as those provided by the National Comprehensive Cancer Network (NCCN), is essential. Understanding how treatments perform outside of controlled clinical trials can provide insights into the gap between new clinical evidence and real-world clinical practice, ultimately leading to enhanced treatment protocols and better care for NSCLC patients.

Real-world data about treatment patterns is crucial for bridging the gap between clinical evidence and practice. Given the rapid advancements in NSCLC therapies, there is a critical need for more current evidence to accurately reflect contemporary practices. Our study aims to assess patient characteristics and current NSCLC treatment patterns in clinical practice in the US.

Methods

Study Design and Data Sources

A retrospective, observational cohort study was conducted using ConcertAI Patient 360™ data (ConcertAI, LLC, Cambridge, MA, USA), an electronic health records (EHR) database. Clinical data is collected from a wide range of US healthcare providers, including community and academic oncology practices. The database contains structured (e.g., lab tests, medications), unstructured (e.g., histology, biomarkers, radiology reports), and derived (e.g., line of therapy) information. This study was determined exempt from University of Minnesota Institutional Review Board approval as it was a secondary database analysis.

Patient Cohort

Eligible patients met the following criteria: 1) at least one documented diagnosis of advanced NSCLC (SNOMEDCT code of 254637007 with stage of IIIB, IIIC, or IV) between January 1, 2015, and December 31, 2021; 2) known age and gender; 3) age≥18 years at first line therapy (LoT1) initiation; and 4) at least one lung cancer treatment (Appendix Table 1) following advanced NSCLC diagnosis. Patients enrolled in a clinical trial or with a diagnosis of other primary malignant neoplasm were excluded. The study index date was defined as the start date of LoT1 following a diagnosis of advanced NSCLC. Patients were followed until the end of EHR documented activity, death, or end of data availability (28 Feb 2023), whichever occurred first.

Study Variables

Demographics included age at index date, sex, race, ethnicity, regional location of healthcare facility, and healthcare organization type (i.e., academic, community). Clinical characteristics included cancer stage, histological types, biomarkers, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), and smoking status.

LoT1 was defined as all systemic therapy received within 28 days from the earliest treatment date until tumor progression or use of a new agent after a 90-day gap (Figure 1). Only NCCN guideline-recommended drugs were included (Appendix Table 1). A regimen was considered a combination if two or more drugs were initiated within 28 days of the first agent. Line of therapy (LoT) advanced if the regimen changed after 28 days of the start of the previous regimen, unless it was maintenance therapy, or if there was a treatment gap of more than 90 days. Maintenance therapy, prescribed to maintain cancer remission induced by prior therapy, included switch and continuation maintenance per NCCN guidelines.[8]

Two sensitivity analyses were performed in this study to account for variations in the therapy gap window. Applying the most commonly used windows in the literature,[9,10] we used 60-day and 120-day therapy gap windows.

Statistical Analysis

Descriptive methods were used to summarize baseline characteristics and treatment patterns. Regimens were categorized into chemotherapy (CT), immunotherapy (IO) monotherapy, IO combination therapy (e.g., IO plus CT), and other targeted therapies. Distribution of treatment classes and sequences was assessed for overall population and subgroups. The top ten most frequent regimens for the first three LoTs were reported by cancer stage. Treatment patterns were illustrated using a Sankey diagram depicted using R Studio version 4.3.2 (R Studio, Boston, MA, USA).[11] Statistical analysis was performed using SAS software 9.4 (SAS Institute, Cary, NC).

Results

Patient Characteristics

In total, 8,811 patients met the inclusion criteria, including 1,370 stage IIIB/IIIC and 7,441 stage IV patients (Figure 2).

Baseline demographics and clinical characteristics are presented in Table 1. The majority (59%) of patients were aged ≥65 years, with a mean age of 66.6 years (SD=10.0); 47.3% were female; and 76.7% were white. Most (78.7%) received care from community hospitals, and 84.7% reported a smoking history. Histology distribution varied by stage. In stage IIIB/IIIC, 45.7% had squamous cell carcinoma, 44.3% had non-squamous cell carcinoma, and 10.0% had other or unknown histology types. In stage IV, 72.2% had non-squamous cell carcinoma, while only 18.3% had squamous cell carcinoma. Additionally, ECOG PS ≥2 was observed in 22.1% of stage IV and 14.4% of stage IIIB/IIIC patients.

Biomarker testing rates were low: EGFR, 51.5%; ALK, 50.6%; ROS1, 46.8%; PD-L1, 52.1%; KRAS, 34.2%; BRAF, 39.4%; NTRK, 20.3%; MET, 28.5%; and RET, 28.0%). Biomarker testing rates were higher in stage IV than stage IIIB/IIIC. Positivity rates among those tested were: EGFR, 16.9%; ALK, 3.6%; ROS1, 1.5%; PD-L1 ≥1%, 61.9%; KRAS, 29.8%; BRAF, 6.3%; NTRK, 1.1%; MET, 11.3%; RET, 1.2%) and HER2, 7.0%.

Baseline characteristics by LoT1 are presented in Table 2. CT was the most common treatment across all ages in stage IIIB/IIIC. In both stages, patients receiving IO monotherapy were slightly older (stage IIIB/IIIC: median age 69 [61, 77]; stage IV: 71 [63, 78]), with a higher proportion having an ECOG PS ≥2. Most patients receiving targeted therapies had non-

squamous cell carcinoma (stage IIIB/IIIC: 65.7%; stage IV: 89.9%).

Treatment Patterns

Of 8,811 patients studied, 8,789 (99.8%) received NCCN guideline-recommended NSCLC treatment, regardless of the appropriateness of biomarker status. The remaining 22 patients had a documentation of NSCLC but without any guideline-recommended treatment, and were excluded from further analysis. Approximately 33% died after LoT1, and 4,552 (51.7%) patients received LoT2. Of those, one-third died, and 2,318 (26.3%) patients received LoT3.

Treatment modalities varied by cancer stage (Figure 3). In stage IIIB/IIIC, treatment was similar between squamous and non-squamous cell carcinoma, although more targeted therapies were used slightly more often with the latter. Traditional platinum-based CT was the predominant treatment modality in LoT1 (85.5%). IO monotherapy and combination therapy were most common in LoT2 (75.5%) and LoT3 (55.5%). Targeted therapies were used infrequently, comprising less than 5% in LoT1 and LoT2, and less than 15% in LoT3.

In stage IV, the use of CT alone was substantially lower, while the use of IO and targeted therapy was more prevalent. IO therapies dominated all LoTs, accounting for 48.9%, 49.0%, and 40.1% of treatments, respectively. Targeted therapies increased in later LoTs, comprising 21.3%, 23.6%, and 27.2% of treatments in LoT1, LoT2, and LoT3, respectively. Additionally, treatment modalities varied among histology types. Patients with non-squamous carcinoma received more targeted therapy across all LoTs. (See Appendix Table 2)

The top ten most frequently used treatment regimens were similar by histology types, while they varied by cancer stage (Table 3). For stage IIIB/IIIC patients, the five most common LoT1, accounting for 83.2% of all LoT1, were carboplatin + paclitaxel, cisplatin, carboplatin + pemetrexed, cisplatin + pemetrexed, and pembrolizumab. The five most common LoT2, representing 74.7% of all LoT2, were durvalumab, nivolumab, carboplatin + paclitaxel, pembrolizumab, and carboplatin + pemetrexed. The five most common LoT3, making up 49.2% of all LoT3, included durvalumab, nivolumab, pembrolizumab, docetaxel, and carboplatin + paclitaxel.

For stage IV patients, the five most common LoT1, comprising 64.4% of all LoT1, were pembrolizumab + pemetrexed, pembrolizumab, carboplatin + paclitaxel, carboplatin + pemetrexed, and carboplatin + paclitaxel + pembrolizumab. Nivolumab was the most common LoT2 and LoT3 regimen. The use of other regimens in LoT2 and LoT3 was more evenly distributed, with no single regimen predominating significantly.

During the study period, IO use in LoT1 has increased over time, especially in stage IV (Figure 4). In 2022, about 70.5% of stage IV and 20.8% of stage IIIB/IIIC patients used IO as LoT1. Slight decreases were found in 2020 and 2021; the reasons for the declines cannot be ascertained from the data, but may possibly reflect the impact of the COVID-19 pandemic.[12] Use of IO stabilized thereafter.

The progression of LoTs is visualized in Sankey diagrams (Figure 5). For stage IIIB/IIIC patients, 19.8% died after LoT1 and 24.0% after LoT2. The main pathways from LoT1 to LoT3 were from platinum-based CT to IO therapies. In stage IV patients, the mortality rates were higher, with 34.8% dying after LoT1, and 32.8% after LoT2. The main pathways started with either platinum-based CT or IO combination therapies in LoT1, and transitioned to IO therapies or targeted therapies in subsequent lines.

Two sensitivity analyses were performed to assess the robustness of our LoT definition by employing 60-day and 120-day therapy gap windows. In both analyses, platinum-based CT was the most common LoT1 for stage IIIB/IIIC patients, while IO monotherapy was most common in LoT2 and LoT3. For stage IV patients, IO combination therapy predominated LoT1 and LoT2, with LoT3 treatments being more evenly distributed. The most common regimens remained consistent, although their order varied slightly. For example, docetaxel + ramucirumab was the second most common LoT2 (6.6%) in the primary analysis, while it was the third most common (6.1%) using the 60-day therapy gap. The consistency between primary and sensitivity analyses confirms the reliability of our definition.

Discussion

This retrospective observational study utilized a large NSCLC-specific EHR database, capturing data from 2015 to 2023. Given the rapid evolution of treatment options, our study provides a current reflection of treatment patterns among advanced NSCLC patients.

Among the 8,811 patients, the median age was 67 years, and most were diagnosed at stage IV, consistent with trends reported in the literature.[4] Most patients received treatment included in NCCN guidelines. The progression of LoTs was accompanied by a substantial mortality rate. About one-third of patients died after initiation of LoT1, and another one-third died after LoT2, highlighting the aggressive nature of NSCLC and the critical need for effective first-line treatments.

The distribution of treatment modalities varied by cancer stage. Stage IIIB/IIIC patients primarily received CT in LoT1 (85.5%). In contrast, for stage IV patients, the distribution of treatment modalities was more balanced, indicating a more diverse treatment approach for advanced stages. Treatment modality was generally consistent between histology types,

although non-squamous patients used more targeted therapies. This variation is aligned with the molecular profiles of cancer histology types and current NCCN guidelines, where non-squamous cell carcinoma presents more actionable mutations compared to squamous cell carcinoma.[8]

While platinum-based CT has historically been the standard treatment for advanced NSCLC, the use of novel IO and targeted agents has largely increased. Since 2015, nivolumab and several other IO agents have been approved, showing greater efficacy and tolerability.[13] Additionally, new molecular alterations and corresponding targeted treatments have been developed and increasingly used as LoT1. In our study, CT remained the most common LoT1 for stage IIIB/IIIC patients, while IO therapies and targeted therapies predominated LoT1 for stage IV patients. The extensive use of IO and targeted therapies in stage IV and later lines of stage IIIB/IIIC treatments reflects the shift towards personalized medicine tailored to genetic profiles and tumor biomarkers.[14]

The predominant treatment regimen for stage IIIB/IIIC patients in our study was carboplatin + paclitaxel, accounting for 59.5% of all treatments in LoT1, while durvalumab was the most common treatment in LoT2 and LoT3, accounting for 49.6% and 14.9% of treatments, respectively. These findings are consistent with NCCN guidelines, which recommend CT as the initial treatment for stage IIIB/IIIC patients, followed by durvalumab as subsequent therapy.[8] For stage IV patients, the most frequently used LoT1 were carboplatin + pembrolizumab + pemetrexed and pembrolizumab monotherapy, with nivolumab being the most common in LoT2 and LoT3. According to NCCN guidelines (version 3, 2023), treatment for stage IV NSCLC with IO and targeted therapies such as these is expected, especially when biomarker testing results are available.[8]

Instances of non-adherence were observed. First, a small proportion of patients did not receive any guideline-recommended treatment, indicating potential gaps in healthcare delivery or documentation. Second, some stage IV patients with positive PD-L1 and other actionable biomarker mutations received platinum-based CT as LoT1. Notably, this analysis does not account for biomarker test results; inclusion of these results could reveal higher rates of non-adherence to guidelines.

Two sensitivity analyses were conducted to validate our algorithm of LoT, using 60-day and 120-day therapy gap windows. Both analyses confirmed the same distribution of treatment modalities and maintained the same top ten most common treatments across LoTs, which reinforced the robustness of our observations.

Our findings align with recent treatment patterns observed in real-world clinical settings, showing a shift from CT to increased use of IO, especially in later stages of NSCLC.[15–20] Ge et al. (2022), using the Flatiron database, found that use of IO among stage IV patients increased over time, accounting for more than 60% of LoT1 since 2019.[20] Our study showed the same pattern, and found that about 70% of LoT1 in stage IV patients were IO since 2019. While most of the published studies used data collected before 2020, our study includes newer agents approved in recent years. Unlike studies focused on patients with specific biomarker mutations, our broader cohort allows for comparison of treatment modalities between locally advanced and metastatic NSCLC, and examination of patient characteristics across different treatment groups.

As treatment landscapes continue to evolve, ongoing education and training for healthcare providers on the latest advances in NSCLC therapies are crucial. Additionally, the observation that a small percentage of patients did not receive guideline-recommended treatments calls for a review of clinical practices and patient management strategies. Clinical pharmacists play a critical role in providing individual optimized treatment. More research is needed to understand the gap between clinical evidence and real-world practice.

Our study has several strengths. First, it examines treatment patterns over an extended period, from 2015 to 2023. This timeframe covers advancements in IO and targeted therapies, ensuring our findings reflect the latest NSCLC treatment advances. Second, it leverages comprehensive EHR data with detailed information on medications, patient demographics, and clinical characteristics, enabling a thorough analysis of treatment practices.

This study has several limitations. First, as a retrospective observational study, data collection was restricted to information available within the EHR database. EHR data may be incomplete if patients received care outside the network. Moreover, certain variables, such as biomarker tests and socioeconomic status, may not be fully captured. Second, it is challenging to distinguish between medications actually administered and those merely ordered, particularly oral medications. Third, the EHR database utilized in this study focuses specifically on NSCLC patients and primarily sources data from oncology clinics. As a result, non-NSCLC-related information, such as comorbidities, is not thoroughly documented, leading to lower observed rates of comorbidities than expected given the patient population's age and disease severity. This reflects a common limitation of diseases specific EHR databases. Fourth, this study focused only on pharmacologic treatments and did not evaluate the use of radiotherapy, which could be an important component of treatment for patients with stage III NSCLC. As a result, certain therapies such as cisplatin may have been classified as a single agent and not as combination therapy with radiation therapy. Likewise, consolidation durvalumab following chemoradiation

may have been classified as subsequent lines of therapy rather than consolidation therapy.

Conclusions

In conclusion, this study illustrates the complex interplay of treatment modalities in NSCLC management in real-world clinical settings. Traditional platinum-based CT remains the most common LoT1 for stage IIIB/IIIC patients, reflecting its continued importance in foundational management of NSCLC. However, IO therapies have become the most common LoT1 for stage IV patients, and their use has increased with cancer progression. Results indicate that new evidence regarding treatment patterns is rapidly adopted into practice and medication therapy management.

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Disclaimer: The statements, opinions, and data contained in all publications are those of the authors.

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Table 1. Demographic and clinical characteristics of patients with advanced non-small cell lung cancer

Patient Characteristics	Overall (n=8,811)	Stage IIIB and IIIC (n=1,370)	Stage IV (n=7,441)
Age			
Mean (SD)	66.6 (10.0)	66.8 (9.4)	66.6 (10.1)
Median [IQR]	67 [60, 74]	67 [60, 74]	67 [60, 74]
Age categories			
18-44	171 (1.9%)	14 (1.0%)	157 (2.1%)
45-64	3,446 (39.1%)	531 (38.8%)	2,915 (39.2%)
65-74	3,125 (35.5%)	517 (37.7%)	2,608 (35.0%)
75+	2,069 (23.5%)	308 (22.5%)	1,761 (23.7%)
Sex			
Female	4,167 (47.3%)	616 (45.0%)	3,551 (47.7%)
Male	4644 (52.7%)	754 (55.0%)	3890 (52.3%)
Race			
Asian	286 (3.2%)	35 (2.6%)	251 (3.4%)
Black or African American	1,077 (12.2%)	181 (13.2%)	896 (12.0%)
White	6,761 (76.7%)	1,062 (77.5%)	5,699 (76.6%)
Other or unknown	687 (8.9%)	92 (6.7%)	595 (8.0%)
Region			
Midwest	2,654 (30.1%)	415 (30.3%)	2,239 (30.1%)
Northeast	1,255 (14.2%)	217 (15.8%)	1,038 (13.9%)
South	3,886 (44.1%)	581 (42.4%)	3,305 (44.4%)
West	973 (11.0%)	149 (10.9%)	824 (11.1%)
Unknown	43 (0.5%)	8 (0.6%)	35 (0.5%)
Organization type			
Academic	1,177 (13.4%)	175 (12.8%)	1,002 (13.5%)
Community	6,935 (78.7%)	1,075 (78.5%)	5,860 (78.8%)
Unknown	699 (7.9%)	120 (8.8%)	579 (7.8%)
Histology type			
Non-squamous cell carcinoma	5,982 (67.9%)	607 (44.3%)	5,375 (72.2%)
Squamous cell carcinoma	1,984 (22.5%)	626 (45.7%)	1,358 (18.3%)
Other or unknown	845 (9.6%)	137 (10.0%)	708 (9.5%)
Smoking status			
Ever smoked	7,463 (84.7%)	1,263 (92.2%)	6,200 (83.3%)
Never smoked	1,224 (13.9%)	89 (6.5%)	1,135 (15.3%)
Unknown	124 (1.4%)	18 (1.3%)	106 (1.4%)
ECOG PS			
0-1	5,957 (67.6%)	1,050 (76.6%)	4,907 (65.9%)
≥2	1,845 (20.9%)	197 (14.4%)	1,648 (22.1%)
Unknown	1,009 (11.5%)	123 (9.0%)	886 (11.9%)
EGFR mutation positive[1]	766 (16.9%)	39 (8.7%)	727 (17.7%)
ALK rearrangement positive[1]	159 (3.6%)	8 (1.9%)	151 (3.7%)
ROS1 rearrangement positive[1]	63 (1.5%)	5 (1.3%)	58 (1.6%)
KRAS mutation positive[1]	896 (29.8%)	80 (28.3%)	816 (29.9%)

Patient Characteristics	Overall (n=8,811)	Stage IIIB and IIIC (n=1,370)	Stage IV (n=7,441)
BRAF mutation positive[1]	218 (6.3%)	17 (4.9%)	201 (6.4%)
NTRK 1/2/3 fusion positive[1]	19 (1.1%)	5 (3.3%)	14 (0.9%)
MET mutation positive[1]	283 (11.3%)	36 (15.6%)	247 (10.8%)
RET rearrangement positive[1]	29 (1.2%)	6 (2.7%)	23 (1.0%)
HER2 mutation positive[1]	169 (7.0%)	14 (6.4%)	155 (7.1%)
PD-L1≥1%[1]	2,841 (61.9%)	305 (58.1%)	2,536 (62.4%)

1. Among patients with biomarker test results

Table 2. Demographic and clinical characteristics of patients with advanced non-small cell lung cancer by first line treatment

Patient Characteristics	Stage IIIB and IIIC (n=1,366)[1]				Stage IV (n=7,423)				
	CT + IO (n=61)	CT (n=1,186)	IO (n=83)	Targeted therapy/CT + Targeted therapy (n=35)	CT + IO (n=2,411)	CT (n=2,538)	IO (n=1,250)	Targeted therapy/CT + Targeted therapy (n=1,148)	Other (n=76)
Age									
Mean (SD)	67.3 (8.2)	66.6 (9.2)	68.8 (10.4)	68.2 (11.3)	66.3 (9.1)	65.5 (9.8)	70.3 (9.8)	66.1 (12.2)	65.6 (11.9)
Median [IQR]	68 [62, 71]	67 [60, 73]	69 [61, 77]	69 [60, 78]	66 [60, 73]	66 [59, 73]	71 [63, 78]	67 [59, 75]	66 [57, 75]
Age categories*									
18-44	1	12	1		36	53	9	56	3
	1.6%	1.0%	1.2%	0	1.5%	2.1%	0.7%	4.9%	4.0%
	7.1%	85.7%	7.1%		22.9%	33.8%	5.7%	35.7%	1.9%
45-64	21	462	32	14	982	1,136	352	413	28
	34.4%	39.0%	38.6%	40.0%	40.7%	44.8%	28.2%	36.0%	36.8%
	4.0%	87.3%	6.1%	2.7%	33.7%	39.0%	12.1%	14.2%	1.0%
65-74	29	455	23	9	934	868	420	356	25
	47.5%	38.4%	27.7%	25.7%	38.7%	34.2%	33.6%	31.0%	32.9%
	5.6%	88.2%	4.5%	1.7%	35.9%	33.4%	16.1%	13.7%	1.0%
75+	10	257	27	12	459	481	469	323	20
	16.4%	21.7%	32.5%	34.3%	19.0%	19.0%	37.5%	28.1%	26.3%
	3.3%	84.0%	8.8%	3.9%	26.2%	27.5%	26.8%	18.4%	1.1%
Sex*									
Female	28	527	42	18	1,013	1,094	631	757	46
	45.9%	44.4%	50.6%	51.4%	42.0%	43.1%	50.5%	65.9%	60.5%
	4.6%	85.7%	6.8%	2.9%	28.6%	30.9%	17.8%	21.4%	1.3%
Male	33	659	41	17	1,398	1,444	619	391	30
	54.1%	55.6%	49.4%	48.6%	58.0%	56.9%	49.5%	34.1%	39.5%
	4.4%	87.8%	5.5%	2.3%	36.0%	37.2%	16.0%	10.1%	0.8%
Race*									
Asian	2	29		4	42	44	22	135	8
	3.2%	2.5%	0	11.4%	1.7%	1.7%	1.8%	11.8%	10.5%
	5.7%	82.9%		11.4%	16.7%	17.5%	8.8%	53.8%	3.2%
Black or African American	5	158	11	5	288	349	155	94	8
	8.2%	13.3%	13.3%	14.3%	11.9%	13.8%	12.4%	8.2%	10.5%
	2.8%	88.3%	6.2%	2.8%	32.2%	39.0%	17.3%	10.5%	0.9%

Patient Characteristics	Stage IIIB and IIIC (n=1,366)[1]				Stage IV (n=7,423)				
	CT + IO (n=61)	CT (n=1,186)	IO (n=83)	Targeted therapy/CT + Targeted therapy (n=35)	CT + IO (n=2,411)	CT (n=2,538)	IO (n=1,250)	Targeted therapy/CT + Targeted therapy (n=1,148)	Other (n=76)
White	48	925	65	21	1,890	1,991	988	758	57
	78.7%	78.0%	78.3%	60.0%	78.4%	78.5%	79.0%	66.0%	75.0%
	4.5%	87.3%	6.1%	2.0%	33.3%	35.0%	17.4%	13.3%	1.0%
Other or unknown	6	74	7	5	191	154	85	161	3
	9.8%	6.2%	8.4%	14.3%	7.9%	6.1%	6.8%	14.0%	12.6%
	6.5%	80.4%	7.6%	5.4%	32.2%	25.9%	14.3%	27.1%	0.5%
Region*									
Midwest	22	358	27	7	796	719	375	319	24
	36.1%	30.2%	32.5%	20.0%	33.0%	28.3%	30.0%	27.8%	31.6%
	5.3%	86.5%	6.5%	1.7%	35.7%	32.2%	16.8%	14.3%	1.1%
Northeast	17	182	12	4	388	294	185	152	17
	27.9%	15.3%	14.5%	11.4%	16.1%	11.6%	14.8%	13.2%	22.4%
	7.9%	84.7%	5.6%	1.9%	37.5%	28.4%	17.9%	14.7%	1.6%
South	14	517	34	14	1,000	1,248	561	461	27
	23.0%	43.6%	41.0%	40.0%	41.5%	49.2%	44.9%	40.2%	35.5%
	2.4%	89.1%	5.9%	2.4%	30.3%	37.9%	17.0%	14.0%	0.8%
West	8	123	9	9	223	252	127	212	8
	13.1%	10.4%	10.8%	25.7%	9.2%	9.9%	10.2%	18.5%	10.5%
	5.4%	82.6%	6.0%	6.0%	27.1%	30.7%	15.5%	25.8%	1.0%
Unknown		6	1	1	4	25	2	4	
	0	0.5%	1.2%	2.9%	0.2%	1.0%	0.2%	0.4%	0
		75.0%	12.5%	12.5%	11.4%	71.4%	5.7%	11.4%	
Organization type*									
Academic	7	150	12	5	283	370	181	157	10
	11.5%	12.6%	14.5%	14.3%	11.7%	14.6%	14.5%	13.7%	13.2%
	4.0%	85.7%	6.9%	2.9%	28.3%	37.0%	18.1%	15.7%	1.0%
Community	52	924	68	27	1,935	2,013	942	891	62
	85.2%	77.9%	81.9%	77.1%	80.3%	79.3%	75.4%	77.6%	81.6%
	4.9%	86.3%	6.4%	2.5%	33.1%	34.5%	16.1%	15.3%	1.1%
Unknown	2	112	3	3	193	155	127	100	4
	3.3%	9.4%	3.6%	8.6%	8.0%	6.1%	10.2%	8.7%	5.3%
	1.7%	93.3%	2.5%	2.5%	33.3%	26.8%	21.9%	17.3%	0.7%
Histology type*									

Patient Characteristics	Stage IIIB and IIIC (n=1,366)[1]				Stage IV (n=7,423)				
	CT + IO (n=61)	CT (n=1,186)	IO (n=83)	Targeted therapy/CT + Targeted therapy (n=35)	CT + IO (n=2,411)	CT (n=2,538)	IO (n=1,250)	Targeted therapy/CT + Targeted therapy (n=1,148)	Other (n=76)
Non-squamous cell carcinoma	30	522	30	23	1,744	1,694	823	1,032	69
	49.2%	44.1%	33.7%	65.7%	72.3%	66.8%	65.8%	89.9%	90.8%
	5.0%	86.1%	4.8%	3.9%	32.5%	31.6%	15.4%	19.3%	1.3%
Squamous cell carcinoma	23	550	45	5	425	587	299	42	2
	37.7%	46.4%	54.2%	14.3%	17.6%	23.1%	23.9%	3.7%	2.6%
	3.7%	88.3%	7.2%	0.8%	31.4%	43.3%	22.1%	3.1%	0.2%
Other or unknown	8	114	8	7	242	257	128	74	5
	13.1%	9.6%	9.6%	20.0%	10.0%	10.1%	10.2%	6.5%	6.6%
	5.8%	83.2%	5.8%	5.1%	34.3%	36.4%	18.1%	10.5%	0.7%
Smoking status*									
Never smoked	6	64	4	15	192	43	108	24	1
	9.8%	5.4%	4.8%	42.9%	8.0%	1.7%	8.6%	2.1%	1.3%
	6.7%	71.9%	4.5%	16.9%	16.9%	41.0%	9.5%	22.9%	1.0%
Ever smoked	55	1,109	76	18	2,203	205	1,121	591	38
	90.2%	93.5%	91.6%	51.4%	91.4%	8.1%	89.7%	51.5%	50.0%
	4.4%	88.1%	6.0%	1.4%	35.6%	18.1%	18.1%	52.1%	3.4%
Unknown		13	3	2	16	2,290	21	533	37
	0	1.1%	3.6%	3.6%	0.7%	90.2%	1.7%	46.4%	48.7%
		72.2%	16.7%	16.7%	15.2%	37.0%	20.0%	8.6%	0.6%
ECOG PS*									
0-1	50	928	54	16	1,715	1,694	725	715	54
	82.0%	78.2%	65.1%	45.7%	71.1%	66.7%	58.0%	62.3%	71.1%
	4.8%	88.6%	5.2%	1.5%	35.0%	34.6%	14.8%	14.6%	1.1%
≥2	7	163	18	7	509	539	371	199	19
	11.5%	13.7%	21.7%	20.0%	21.1%	21.2%	29.7%	17.3%	25.0%
	3.6%	83.2%	9.2%	3.6%	31.1%	32.9%	22.7%	12.2%	1.2%
Unknown	4	95	11	12	187	305	154	234	3
	6.6%	8.0%	13.3%	34.3%	7.8%	12.0%	12.3%	20.4%	4.0%
	3.3%	77.9%	9.0%	9.8%	21.2%	34.5%	17.4%	26.5%	0.3%
Biomarker status[3,*]									
EGFR mutation	2	26	2	9	95	62	45	504	21
	6.1%	7.3%	6.1%	47.4%	7.1%	5.3%	5.5%	67.8%	58.3%
	5.1%	66.7%	5.1%	23.1%	13.1%	8.5%	6.2%	69.3%	2.9%

Patient Characteristics	Stage IIIB and IIIC (n=1,366)[1]				Stage IV (n=7,423)				
	CT + IO (n=61)	CT (n=1,186)	IO (n=83)	Targeted therapy/CT + Targeted therapy (n=35)	CT + IO (n=2,411)	CT (n=2,538)	IO (n=1,250)	Targeted therapy/CT + Targeted therapy (n=1,148)	Other (n=76)
ALK rearrangement	0	7 2.0% 87.5%	0	1 5.3% 12.5%	16 1.2% 10.6%	12 1.1% 7.9%	10 1.2% 6.6%	108 15.3% 71.5%	5 13.5% 3.3%
ROS1 rearrangement	0	4 1.3% 80.0%	0	1 5.3% 20.0%	7 0.5% 12.1%	5 0.5% 8.6%	5 0.5% 8.6%	39 6.0% 67.2%	2 5.6% 3.4%
KRAS mutation	10 41.7% 12.5%	65 28.6% 81.3%	4 23.5% 5.0%	1 7.1% 1.3%	342 34.2% 41.9%	213 30.9% 26.1%	236 43.1% 28.9%	22 4.7% 2.7%	3 13.6% 0.4%
BRAF mutation	0	15 5.4% 88.2%	1 4.0% 5.9%	1 6.7% 5.9%	78 6.5% 38.8%	31 4.4% 15.4%	42 6.4% 20.9%	48 8.7% 23.9%	2 7.1% 1.0%
NTRK 1/2/3 fusion	1 9.1% 20.0%	4 3.4% 80.0%	0	0	5 0.8% 35.7%	3 0.9% 21.4%	2 0.6% 14.3%	4 1.3% 28.6%	0
MET mutation	2 11.1% 5.7%	26 14.1% 74.3%	3 18.8% 8.6%	4 33.3% 11.4%	78 8.8% 31.6%	51 10.7% 20.6%	60 12.7% 24.3%	55 12.9% 22.3%	3 16.7% 1.2%
RET rearrangement	1 5.6% 16.7%	4 2.3% 66.7%	0	1 7.1% 16.7%	8 0.9% 34.8%	4 0.8% 17.4%	4 0.9% 17.4%	7 1.7% 30.4%	0
PD-L1≥1%	25 59.5% 8.2%	229 55.7% 75.3%	39 73.6% 12.8%	10 58.8% 3.3%	865 56.8% 34.1%	396 44.0% 15.6%	869 88.3% 34.3%	376 61.8% 14.8%	29 61.7% 1.1%

1. One patient in the stage IIIB/IIIC NSCLC group received other treatment modality: a white male, 84 years old, with non-squamous cell carcinoma, ECOG PS of 2, and a history of smoking, received care from an academic hospital in the South area.
2. CT: chemotherapy; IO: immunotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status.
3. Column percentage is among patients with biomarker test results.

* For categorical variables, each row within a cell represents number of patients, column percent within stage, and row percent within stage.

Table 3. Top ten most common first-line regimens of the first three treatment lines by cancer stage

Stage IIIB/IIIC (n=1,366)		Stage IV (n=7,423)	
LoT1			
Patients with LoT1 (n=1,366)		Patients with LoT1 (n=7,423)	
1. Carboplatin + paclitaxel	813 (59.5%)	1. Carboplatin + pembrolizumab + pemetrexed	1,680 (22.6%)
2. Cisplatin	120 (8.8%)	2. Pembrolizumab	1,010 (13.6%)
3. Carboplatin + pemetrexed	104 (7.6%)	3. Carboplatin + paclitaxel	873 (11.8%)
4. Cisplatin + pemetrexed	60 (4.4%)	4. Carboplatin + pemetrexed	713 (9.6%)
5. Pembrolizumab	39 (2.9%)	5. Carboplatin + paclitaxel + pembrolizumab	507 (6.8%)
6. Carboplatin + pembrolizumab + pemetrexed	31 (2.3%)	6. Osimertinib	394 (5.3%)
7. Durvalumab	30 (2.2%)	7. Carboplatin + bevacizumab + pemetrexed	274 (3.7%)
8. Carboplatin + paclitaxel + pembrolizumab	24 (1.8%)	8. Erlotinib	233 (3.1%)
9. Carboplatin	12 (0.9%)	9. Nivolumab	131 (1.8%)
10. Carboplatin + bevacizumab + pemetrexed	10 (0.7%)	10. Carboplatin + bevacizumab + paclitaxel	118 (1.6%)
10. Cisplatin + docetaxel	10 (0.7%)		
10. Nivolumab	10 (0.7%)		
LoT2			
Patients with LoT2 (n=922)		Patients with LoT2 (n=3,630)	
1. Durvalumab	457 (49.6%)	1. Nivolumab	691 (19.0%)
2. Nivolumab	101 (11.0%)	2. Docetaxel + ramucirumab	239 (6.6%)
3. Carboplatin + paclitaxel	50 (5.4%)	3. Pembrolizumab	239 (6.6%)
4. Pembrolizumab	49 (5.3%)	4. Carboplatin + paclitaxel	178 (4.9%)
5. Carboplatin + pemetrexed	31 (3.4%)	5. Carboplatin + pemetrexed	166 (4.6%)
6. Paclitaxel	26 (2.8%)	6. Carboplatin + pembrolizumab + pemetrexed	156 (4.3%)
7. Carboplatin + pembrolizumab + pemetrexed	24 (2.6%)	7. Docetaxel	149 (4.1%)
8. Carboplatin	21 (2.3%)	8. Paclitaxel	130 (3.6%)
9. Carboplatin + gemcitabine	14 (1.5%)	9. Osimertinib	126 (3.5%)
10. Carboplatin + pembrolizumab + paclitaxel	14 (1.5%)	10. Carboplatin + pembrolizumab + paclitaxel	76 (2.1%)
LoT3			
Patients with LoT3 (n=423)		Patients with LoT3 (n=1,895)	
1. Durvalumab	63 (14.9%)	1. Nivolumab	247 (13.0%)
2. Nivolumab	59 (13.9%)	2. Docetaxel	147 (7.8%)
3. Pembrolizumab	32 (7.6%)	3. Docetaxel + ramucirumab	143 (7.5%)
4. Docetaxel	29 (6.9%)	4. Osimertinib	114 (6.0%)
5. Carboplatin + paclitaxel	25 (5.9%)	5. Pembrolizumab	88 (4.6%)
6. Carboplatin + pembrolizumab + paclitaxel	21 (5.0%)	6. Gemcitabine	85 (4.5%)
7. Carboplatin + pembrolizumab + pemetrexed	19 (4.5%)	7. Carboplatin + paclitaxel	79 (4.2%)
8. Gemcitabine	18 (4.3%)	8. Carboplatin + pemetrexed	63 (3.3%)
9. Carboplatin + pemetrexed	16 (3.8%)	9. Ipilimumab + nivolumab	63 (3.3%)
10. Docetaxel + ramucirumab	14 (3.3%)	10. Paclitaxel	49 (2.6%)

Figure 1. Definition of progression-based line of therapy (LoT)

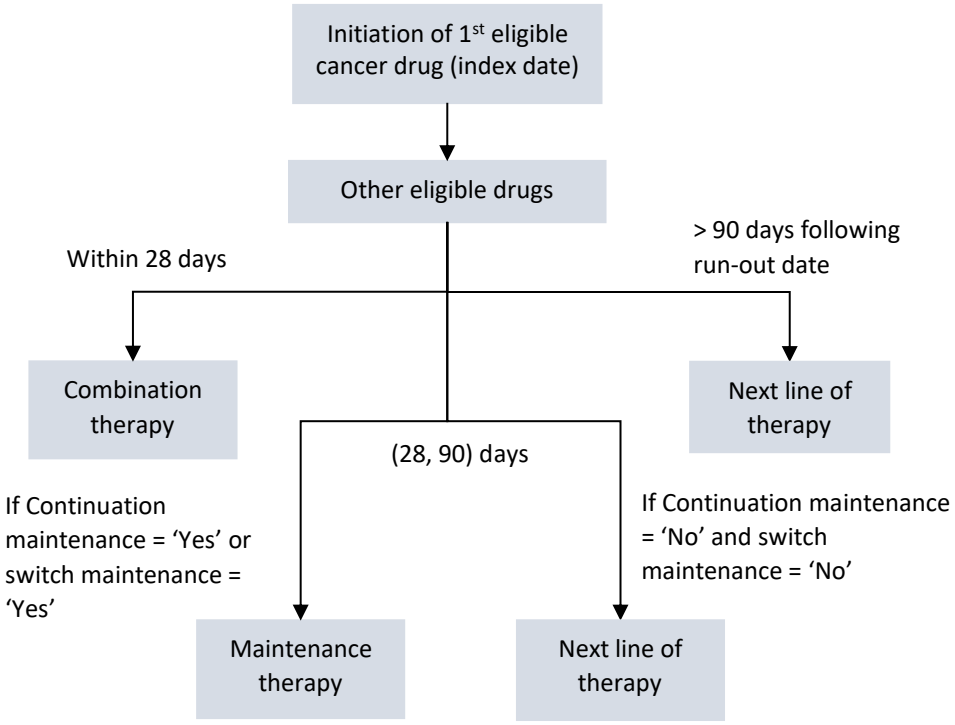


Figure 2. CONSORT flow diagram

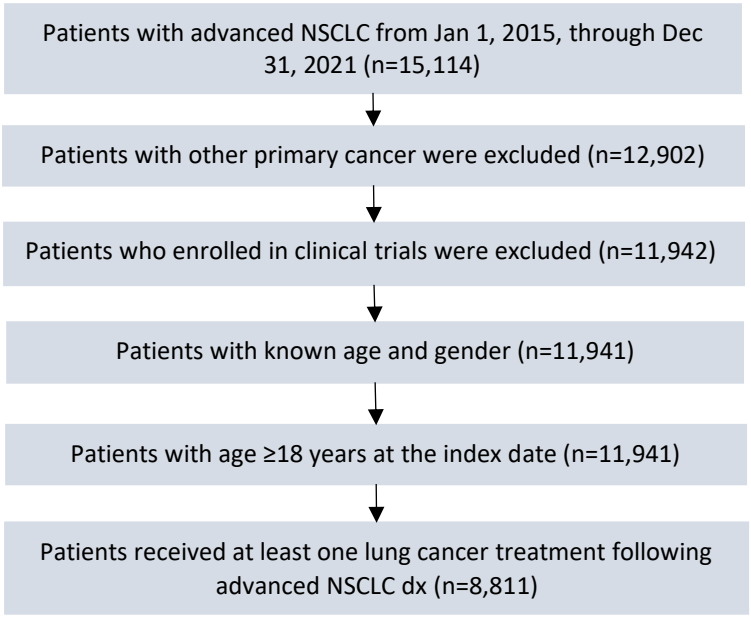
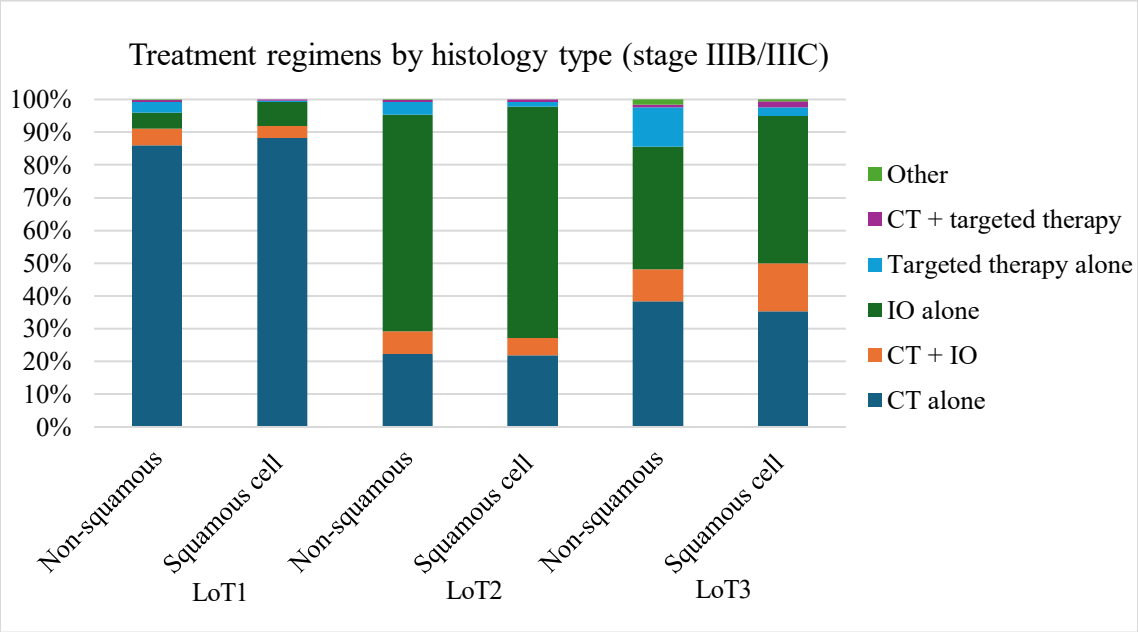


Figure 3. Treatment classes of the first three treatment lines by stage group and histology type



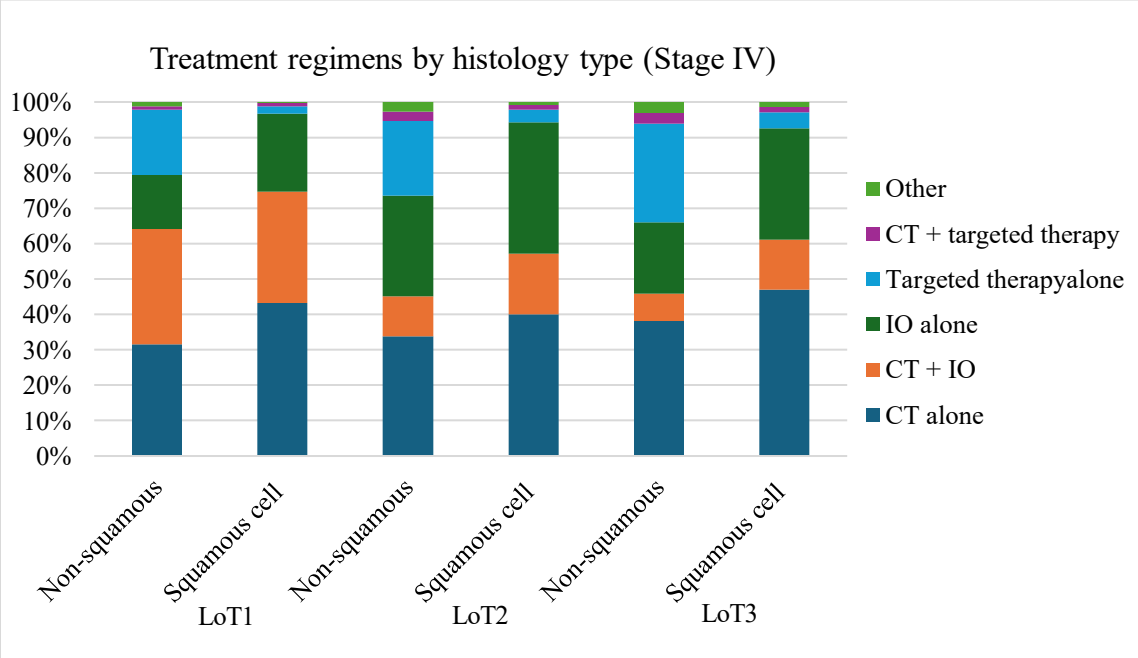


Figure 4. Use of immunotherapy in the first line setting among advanced non-small cell lung cancer patients by cohort entry year

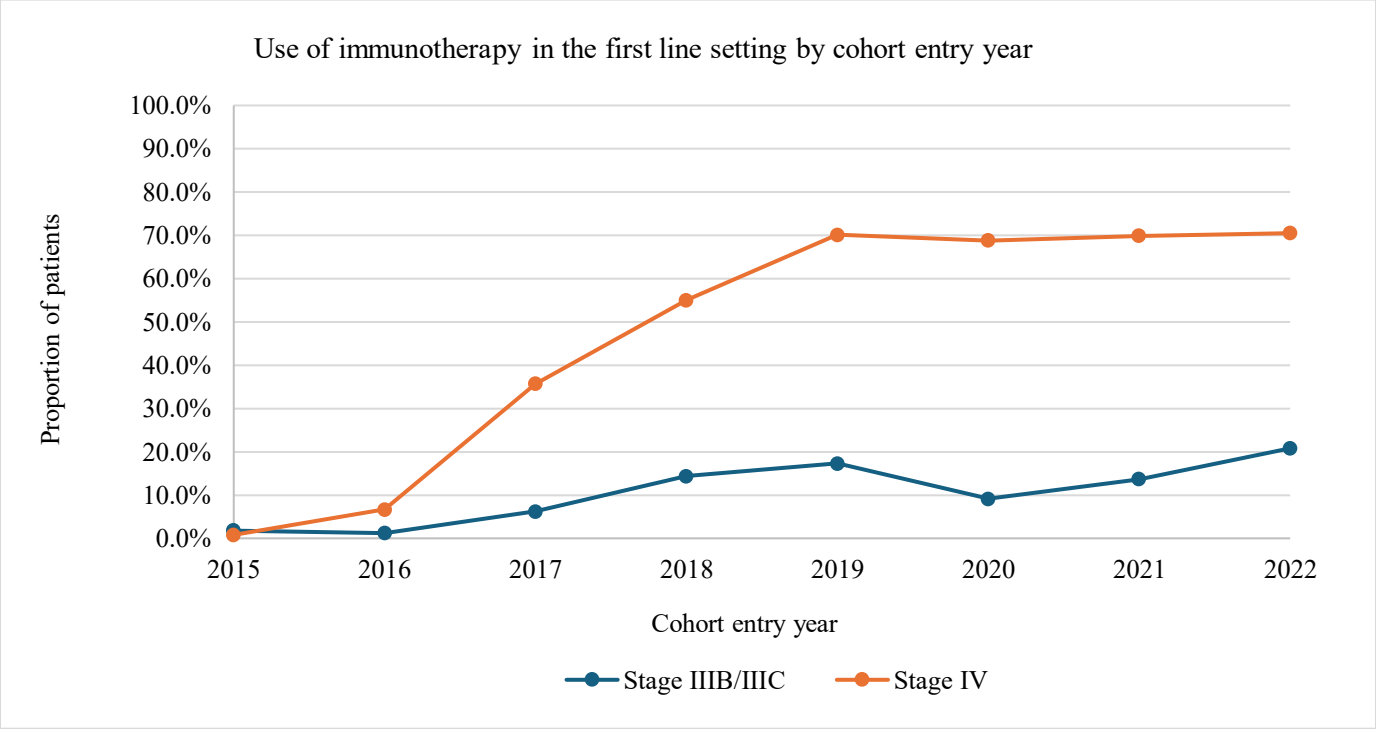
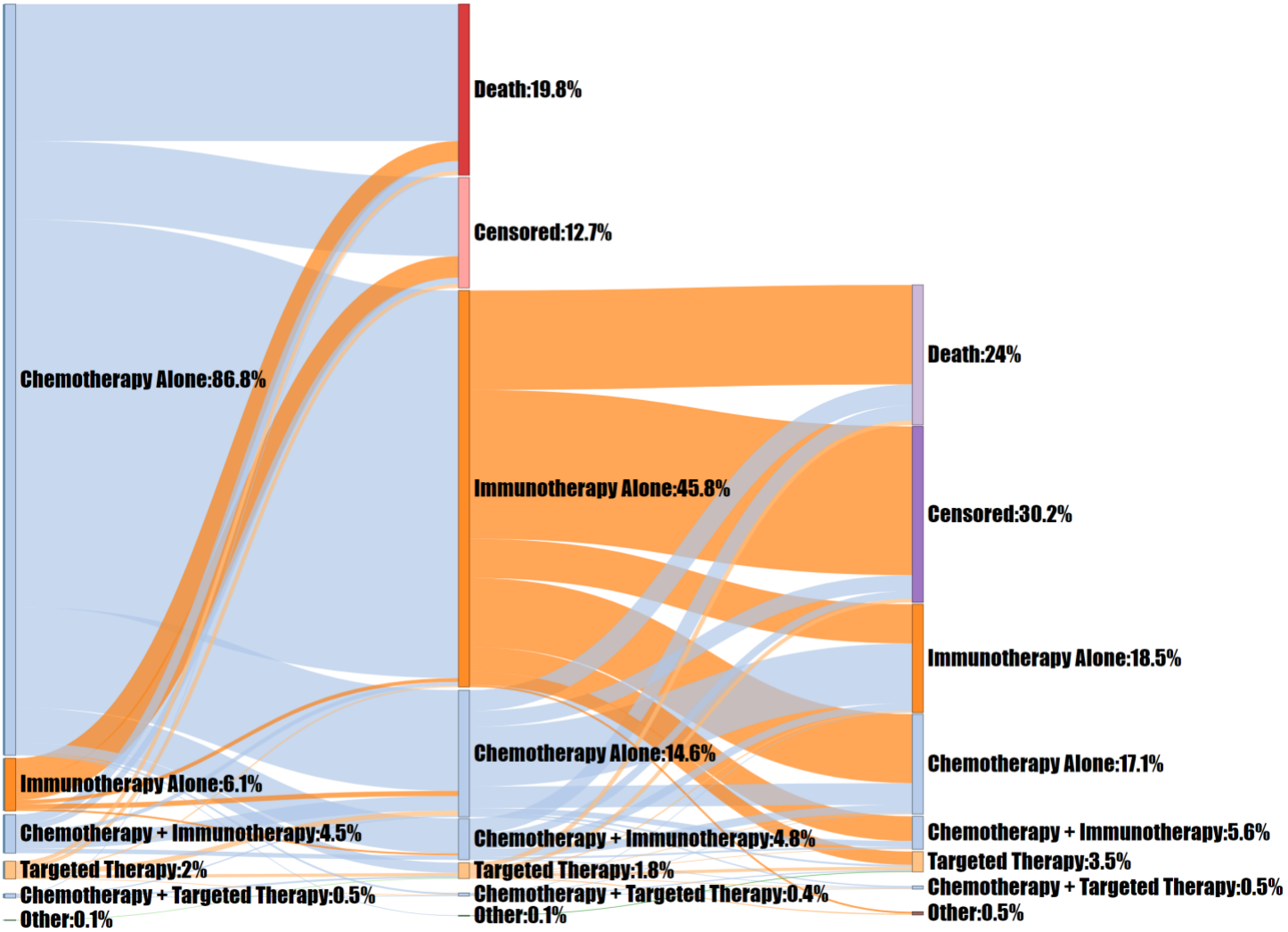
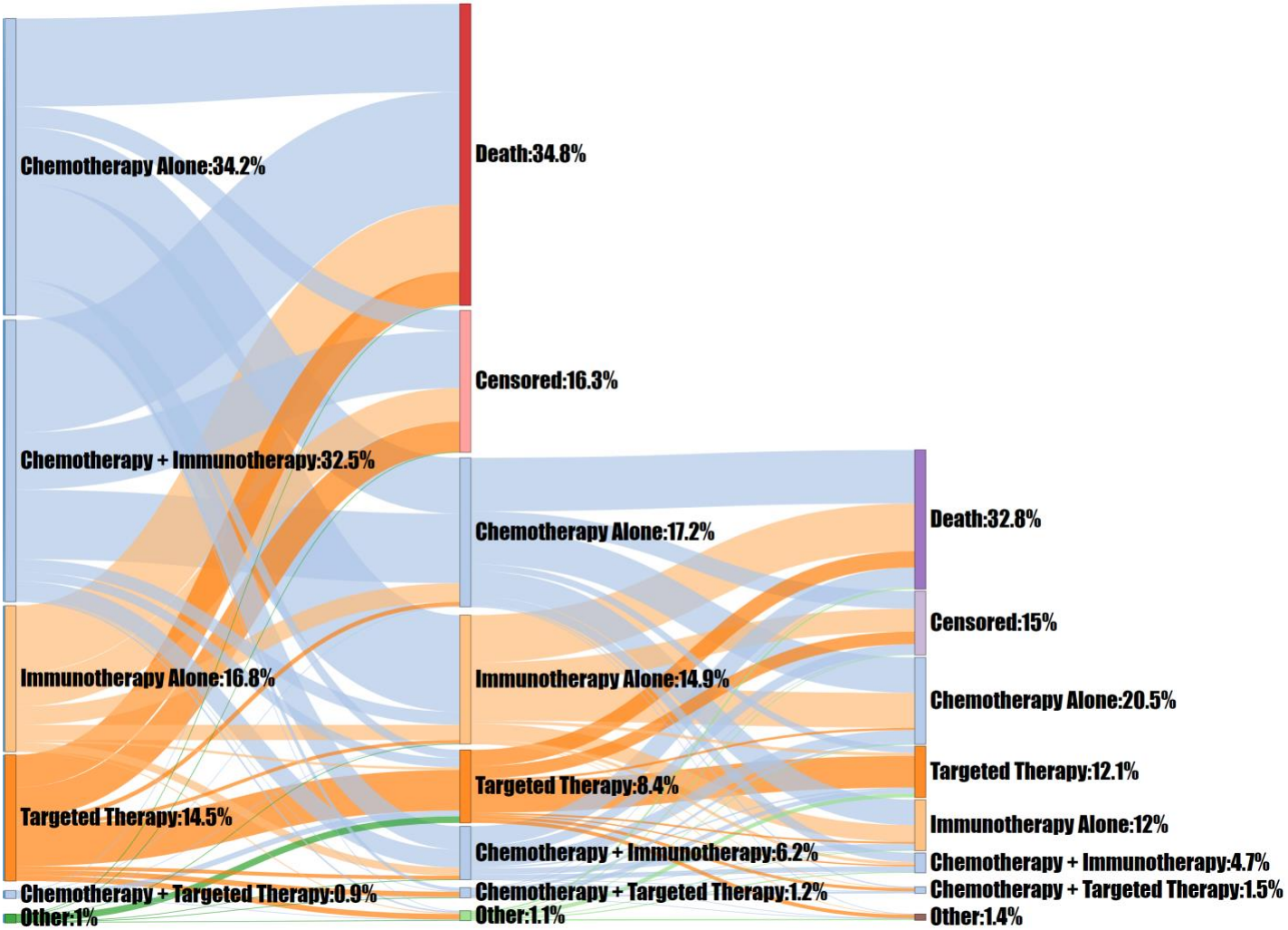


Figure 5. Sankey diagram of advanced non-small cell lung cancer treatments by cancer stage



(a). Stage IIIB/IIIC patients



(b). Stage IV patients

Appendix

Table 1. Lung cancer drugs

Generic names	Brand names (US)	Included in NCCN non-small cell lung cancer guidelines (Yes/No)[1]
Non-small cell lung cancer		
Adagrasib	Krazati	Yes
Ado-trastuzumab emtansine	Kadcyla	Yes
Afatinib	Gilotrif	Yes
Alectinib	Alecensa	Yes
Amivantamab	Rybrevant	Yes
Atezolizumab	Tecentriq	Yes
Bevacizumab	Alymsys, Avastin, Mvasi, Zirabev	Yes
Brigatinib	Alunbrig	Yes
Cabozantinib	Cabometyx	Yes
Capmatinib	Tabrecta	Yes
Carboplatin	Paraplatin	Yes
Cemiplimab-rwlc	Libtayo	Yes
Ceritinib	Zykadia	Yes
Cisplatin	Platinol	Yes
Crizotinib	Xalkori	Yes
Dabrafenib	Tafinlar	Yes
Dacomitinib	Vizimpro	Yes
Docetaxel	Taxotere	Yes
Durvalumab	Imfinzi	Yes
Entrectinib	Rozlytrek	Yes
Erlotinib	Tarceva	Yes
Fam-trastuzumab deruxtecan-nxki	Enhertu	Yes
Gefitinib	Iressa	Yes
Gemcitabine	Gemzar	Yes
Ipilimumab	Yervoy	Yes
Larotrectinib	Vitrakvil	Yes
Lorlatinib	Lorbrena	Yes
Mobocertinib	Exkivity	Yes
Necitumumab	Portrazza	Yes[2]
Nivolumab	Opdivo	Yes
Osimertinib	Tagrisso	Yes
Paclitaxel	Taxol	Yes
Paclitaxel, protein-bound	Abraxane	Yes
Pembrolizumab	Keytruda	Yes
Pemetrexed	Alimta	Yes
Pralsetinib	Gavreto	Yes
Ramucirumab	Cyramza	Yes
Selpercatinib	Retevmo	Yes
Sotorasib	Lumakras	Yes
Tepotinib	Tepmetko	Yes

Trametinib	Mekinist	Yes
Tremelimumab	Imjudo	Yes
Vemurafenib	Zelboraf	Yes
Vinblastine	Velban	Yes[3]
Vinorelbine	Navelbine	Yes
Small cell lung cancer		
Anlotinib	Focus V	-
Atezolizumab	Tecentriq	-
Bendamustine	Bendeka, Treanda, Belrapzo	-
Cyclophosphamide	Cytoxan, Neosar	-
Doxorubicin	Adriamycin, Rubex	-
Durvalumab	Imfinzi	-
Epirubicin	Pharmorubicin	-
Etoposide	Toposar, Etopophos	-
Everolimus	Afinitor	-
Irinotecan	Camptosar	-
Lurbinectedin	Zepzelca	-
Methotrexate	Rheumatrex, Trexall, Otrexup, Rasuvo	-
Nivolumab	Opdivo	-
Rovalpituzumab	Rova-T	-
Temozolomide	Temodar	-
Topotecan	Hycamtin	-
ABT-888	Veliparib	-
Vincristine	Oncovin, Vincasar, Vincrex	-

1. National Comprehensive Cancer Network (NCCN).
2. Necitumumab was previously included in NCCN guidelines and has been deleted since 2018. We still included necitumumab in line of therapy definition since we had data back to 2015.
3. Vinblastine was previously included in NCCN guidelines and has been deleted since 2021. We still included vinblastine in line of therapy definition since we had data back to 2015.

Table 2. Treatment modalities by cancer stage and histology types

Treatment classes	Stage IV (n=7,423)			
	Overall	**Non-squamous cell carcinoma**	**Squamous cell carcinoma**	**Other or unknown**
First-line treatment				
CT	2538 (34.2%)	1694 (31.6%)	587 (43.3%)	257 (36.4%)
CT + IO	2411 (32.5%)	1744 (32.5%)	425 (31.4%)	242 (34.3%)
IO	1250 (16.8%)	823 (15.3%)	299 (22.1%)	128 (18.1%)
Targeted therapy	1080 (14.5%)	984 (18.4%)	29 (2.1%)	67 (9.5%)
CT + targeted therapy	68 (0.9%)	48 (0.9%)	13 (1%)	7 (1%)
Other	76 (1.0%)	69 (1.3%)	2 (0.2%)	5 (0.7%)
Second-line treatment				
CT	1274 (35.1%)	885 (33.8%)	271 (40%)	118 (35.1%)
IO	1103 (30.4%)	744 (28.4%)	250 (36.9%)	109 (32.4%)
Targeted therapy	624 (17.2%)	551 (21.1%)	25 (3.7%)	48 (14.3%)
CT + IO	457 (12.6%)	297 (11.3%)	116 (17.1%)	44 (13.1%)
CT + targeted therapy	87 (2.4%)	68 (2.6%)	9 (1.3%)	10 (3%)
Other	85 (2.3%)	72 (2.8%)	6 (0.8%)	7 (2.1%)
Third-line treatment				
CT	743 (39.2%)	534 (38.1%)	161 (47.1%)	48 (31.8%)
Targeted therapy	438 (23.1%)	391 (27.9%)	15 (4.4%)	32 (21.2%)
IO	436 (23%)	282 (20.1%)	108 (31.6%)	46 (30.5%)
CT + IO	170 (9%)	110 (7.8%)	48 (14%)	12 (7.9%)
CT + targeted therapy	56 (3%)	42 (3%)	5 (1.5%)	9 (6%)
Other	52 (2.8%)	33 (2.1%)	5 (1.5%)	4 (2.7%)
Treatment classes	**Stage IIIB/IIIC (n=1,366)**			
	Overall	**Non-squamous cell carcinoma**	**Squamous cell carcinoma**	**Other or unknown**
First-line treatment				
CT	1186 (86.8%)	522 (86.1%)	550 (88.3%)	114 (83.2%)
IO	83 (6.1%)	30 (5%)	45 (7.2%)	8 (5.8%)
CT + IO	61 (4.5%)	30 (5%)	23 (3.7%)	8 (5.8%)
Targeted therapy	28 (2%)	20 (3.3%)	3 (0.5%)	5 (3.6%)
CT + targeted therapy	7 (0.5%)	3 (0.5%)	2 (0.3%)	2 (1.5%)
Other	1 (0.1%)	1 (0.2%)	0	0
Second-line treatment				
IO	626 (67.9%)	285 (66.1%)	283 (70.9%)	58 (63%)
CT	200 (21.7%)	96 (22.3%)	87 (21.8%)	17 (18.5%)
CT + IO	65 (7%)	30 (7%)	21 (5.3%)	14 (15.2%)
Targeted therapy	25 (2.7%)	17 (3.9%)	5 (1.3%)	3 (3.3%)
CT + targeted therapy	5 (0.5%)	2 (0.5%)	3 (0.8%)	0
Other	1 (0.1%)	1 (0.2%)	0	0
Third-line treatment				
IO	171 (40.4%)	78 (37.5%)	80 (44.9%)	13 (35.1%)
CT	158 (37.4%)	80 (38.5%)	63 (35.4%)	15 (40.5%)
CT + IO	52 (12.3%)	20 (9.6%)	26 (14.6%)	6 (16.2%)
Targeted therapy	32 (7.6%)	25 (12%)	5 (2.8%)	2 (5.4%)
CT + targeted therapy	5 (1.2%)	2 (1%)	3 (1.7%)	0
Other	5 (1.1%)	3 (1.5%)	1 (0.6%)	1 (2.7%)

CT: chemotherapy; IO: immunotherapy