Real World Treatment Patterns and Outcomes Among Patients with Early Non-Small Cell Lung Cancer

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Abstract

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Background: Worldwide, about two million people are diagnosed with lung cancer each year, 85% of whom have non-small cell lung cancer (NSCLC). Over the last fifteen years, noteworthy progress has been made in treating advanced metastatic NSCLC with targeted systemic therapies. As early and comprehensive care can potentially improve and extend the lives of patients, attention is now turning towards Stages I – IIIA, or early NSCLC (eNSCLC), with new and recent approval of neoadjuvant and adjuvant systemic therapies. With this rapidly changing treatment landscape, it is critical to understand how care is implemented and to whom, to appreciate the real-world adoption of innovative treatments in eNSCLC as they enter the market. **Methods:** This retrospective observational study used Flatiron Health, a US nationwide electronic health record derived and de-identified database spanning from January 2019 - March 2024 to (1) describe eNSCLC patient demographic and clinical characteristics, (2) the real-world neoadjuvant and adjuvant treatment patterns, and (3) how these treatment patterns relate to long-term patient outcomes. **Results:** We studied 7,410 patients, mostly female (52.9%), with a mean age of 71.0 ± 8.5 years. Most were diagnosed at Stage I (n = 4,098), with the rest at Stages II and IIIA. About 65% received curative-intent treatment: surgery (50%), radiation (4.6%), or chemoradiation (10.7%). The rest did not receive definitive treatment. Neoadjuvant use was rare, and adjuvant use was limited. Surgical patients, primarily at Stage I, did not receive adjuvant or neoadjuvant systemic therapy (62.1%). In contrast, smaller fractions of definitive radiation or chemoradiation treatment groups went without neoadjuvant / adjuvant systemic therapies, 24.6% and 50% respectively. Immunotherapy monotherapy

was the most common adjuvant therapy for patients undergoing definitive radiation or chemoradiation, while surgical patients received platinum chemotherapy. Survival outcomes were higher for patients treated with adjuvant systemic therapy following definitive radiation or chemoradiation. Patients undergoing definitive radiation without neoadjuvant / adjuvant systemic therapy had lower survival rates, but adjuvant therapy improved these rates. A similar trend was observed in patients who received chemoradiation. **Conclusions:** The landscape of treatment possibilities for patients diagnosed with eNSCLC is expanding rapidly. However, our comprehension of how these advancements is integrated into clinical practice and their impact on patient outcomes is just starting to unfold. A crucial initial step in improving patient outcomes is to confront and address the underutilization of neoadjuvant / adjuvant systemic therapy for eNSCLC patients.

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1. INTRODUCTION:

As the third most common cancer diagnosis and the most common cause of cancer deaths for men and women in the United States, lung cancer is a significant health concern[1]. Of those diagnosed, approximately 85% are diagnosed with non-small cell lung cancer (NSCLC)[2], a group of histologically unrelated lung cancers which have been historically treated similarly. Over the last 15 years, targeted systemic treatments including immunotherapy (IO), tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (ICIs), have improved survival from months to years in advanced NSCLC[2-4]. Owing to their success in later stages of NSCLC, attention is finally turning to earlier stages of the disease, where the prognosis is much better, and the patient may achieve remission. However, recurrence remains high and several ongoing and recently completed clinical trials are focused on the neoadjuvant and adjuvant space with the hope of extending remission or achieving a cure.

Only 23% of NSCLC is caught “early”, at Stages I – IIIA, or prior to the development of metastatic disease, (www.lung.org) when the course of treatment includes promising curative intent or definitive options[3]. The most common and effective definitive option is surgical resection, which results in conditional survival at five years of ~85% for patients with fully resectable Stage I tumors[5]. However, factors such as patient age (on average 65 years or older), poor health, and the technical challenges of surgical resection due to anatomical location may classify some early tumors as unresectable[3]. Additionally, patients may forgo surgical resection despite clinical referral[6]. If surgery is not an option, definitive radiation or definitive chemoradiation, wherein a course of chemotherapy is provided either sequentially or concurrently with a definitive radiation course[7], remain important options.

On either side of these definitive options, the patient may be treated with systemic neoadjuvant and/or adjuvant therapies. However, up until 2020, the only approved systemic treatment for eNSCLC patients in the neoadjuvant / adjuvant systemic therapy setting was chemotherapy. Since then, the introduction of novel targeted systemic therapies has rapidly transformed the landscape of eNSCLC care[5] (Fig 1). Owing to the recent changes to care, improvements in real-world outcomes are not fully understood.

Given the rapidly changing landscape of neoadjuvant / adjuvant systemic therapy care options in the setting of eNSCLC, it is important to understand how and where care is implemented. Recently published real world treatment pattern studies in eNSCLC have been restricted to a limited geographical area or

country outside the US (e.g., Canada[8], Denmark[9], or Norway[10]), an associated genetic biomarker[11], or a specific clinical outcome (e.g., local recurrence[11] or post-resection use of adjuvant[12]), or are based on data prior to 2019 and lack the many changes in eNSCLC care that have occurred since 2020[3,13]. In addition, the narrow inclusion criteria, and common use of chemotherapy as the control arm in most clinical trials have led to inconsistencies in interpretation and application of new therapeutics, particularly timing and duration, at the clinician level[1,14,15]. Further, the cancer's genetic signature (EGFR mutant, PDL1+, and/or ALK rearrangement) defines candidacy for treatment, underscoring the role and importance of biomarker testing.

Using real world data from electronic health records, the objectives of this study are to describe (1) the demographic and clinical characteristics of a real-world eNSCLC population (2) the treatment patterns of their care and (3) the impact of care on survival outcomes of patients diagnosed with eNSCLC. The results from this work can help inform clinical care and identify misalignment between promising clinical trial evidence and real-world adoption of innovative treatments in eNSCLC.

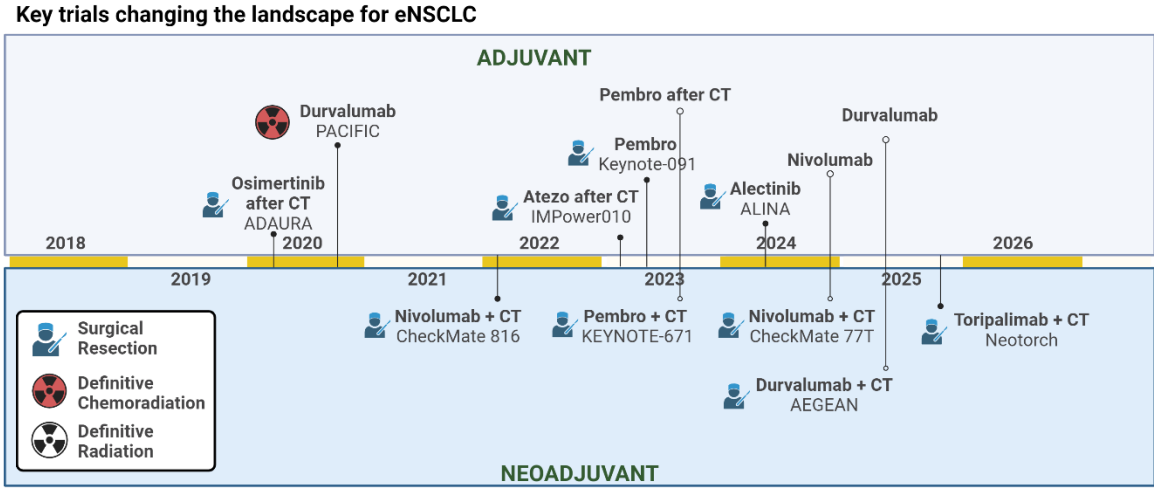

Figure 1: Rapidly Changing Therapeutic Options for eNSCLC
Although radiation and chemotherapy have long been approved for the neoadjuvant / adjuvant systemic therapy space, targeted therapeutics available for advanced NSCLC care are now attaining approval for use in early NSCLC.

2. METHODS:

2.1. Study Design and Data Source

This retrospective observational study used de-identified electronic health record (EHR) data, extracted and maintained by Flatiron Health, a US-based oncology health technology group that draws data from a mix of community and academic oncology settings[16]. Flatiron Health employs "technology-enabled" chart abstraction, and every data point sourced from unstructured documents is manually reviewed by trained clinical chart abstractors. The database includes demographic and diagnostic information (e.g., stage, pathology, molecular information, and radiology), extent of disease, lab values, treatments (e.g., line of therapy, dosing, and regimens), and patient outcomes. Dates of death are obtained from a composite mortality variable comprising the EHR structured data linked to commercial mortality data, publicly available obituaries, and the Social Security Death Index and are resolved to the month of death[17]. The Flatiron Health early NSCLC dataset used for this study spans January 1, 2019, through March 31, 2024.

2.2. Inclusion/Exclusion Criteria

All patients in the study were at least 18 years old and diagnosed with lung cancer based on the following patient record criteria: (1) included ICD-9 162.x or ICD-10 C34x or C39.9 coding, (2) pathology record confirmed a diagnosis of early-stage (Stages I – IIIA), non-metastatic disease, in line with the American Joint Committee on Cancer's lung cancer staging system[18], (3) had a minimum of two clinical visits on separate days and (4) overall electronic health data included a minimum of six months of baseline data and six months of follow-up data, indexed from their date of diagnosis.

2.3. Population (Figure 1)

Of the 8,756 patients included in the eNSCLC dataset, a total of 7,410 patients met inclusion criteria. Patients were grouped according to curative-intent or definitive treatment. Definitive treatment cohorts were as follows: patients who underwent primary surgical resection were classified as Primary Surgery, while the remaining non-surgical patients were divided into groups based on receipt of a definitive course of radiation. Considering the practicalities of treatment, we broadened the NCCN definition for definitive radiation (6 – 7 weeks)[7] to include patients who completed a radiation course lasting more than five but no more than nine weeks. Patients who received definitive radiation were segregated further according to receipt of a concurrent or sequential course of chemotherapy, with sequential chemo and radiation occurring no more

than seven weeks apart. Those who received both radiation and chemotherapy were classified as the Definitive Chemoradiation group. Those who did not receive chemotherapy were classified as the Definitive Radiation group. The remaining patients, who did not receive definitive treatment, were assigned to the No Definitive Treatment group.

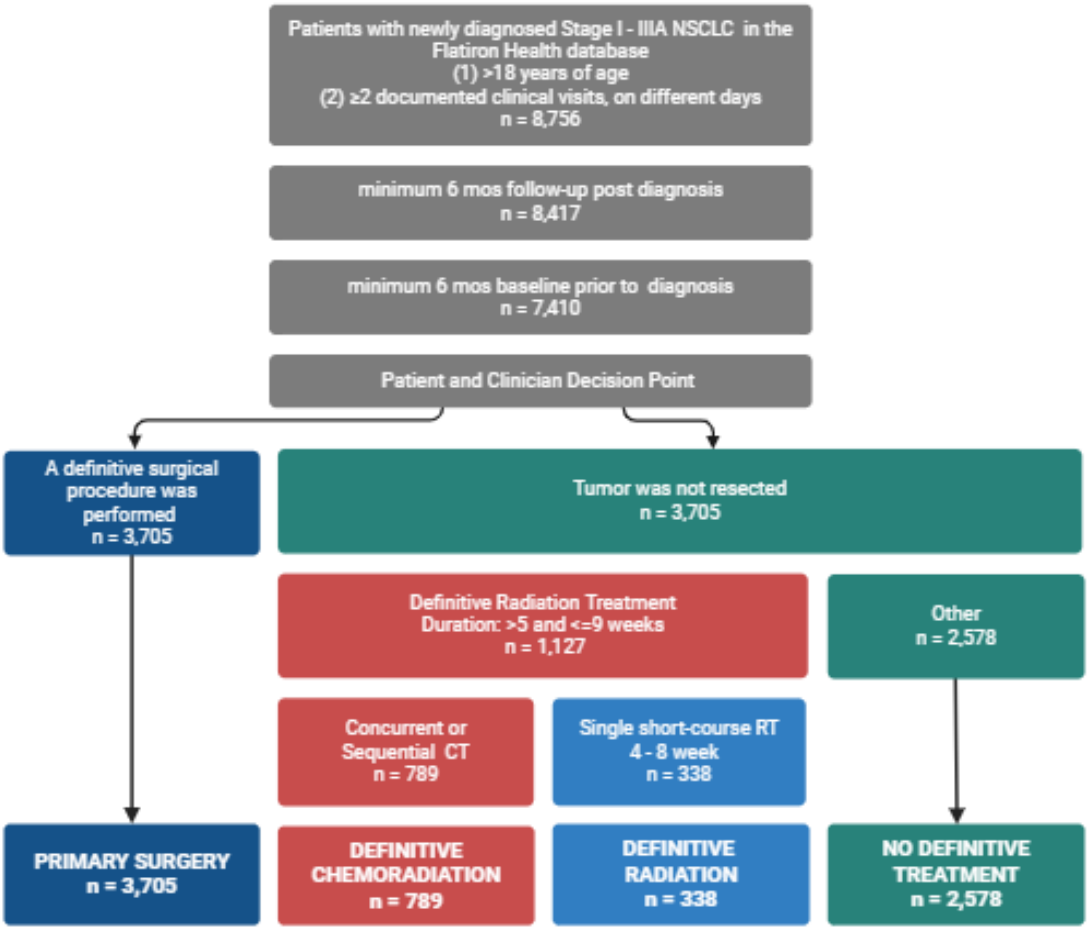

Figure 2: Attrition Table: Delineation of Definitive Treatment Groups

2.4. Statistical Analysis

Statistical analyses were performed using R Language (version 4.4.0, R Project for Statistical Computing, RRID:SCR_001905). Categorical variables were summarized by count and percent and continuous variables as mean and standard deviation. Survival outcomes were analyzed using Kaplan-Meier analysis and median time to event and 95% CIs were reported if achieved.

2.5. Objective-Specific Analyses

2.5.1. Baseline Demographic and Clinical Characteristics by Stage at Diagnosis and Definitive Treatment Group

We gathered baseline demographic and clinical characteristics using the date of diagnosis as the index date and the baseline period as the six months prior. If multiple instances of a characteristic were available during the baseline period, the instance closest to and preceding the date of diagnosis was used. Owing to the time required to process patient samples, we allowed one exception: PDL1, EGFR and ALK biomarker results associated with a specimen collected during this baseline period or up to six months post diagnosis was allowed, in line with recently published literature[19]. Characteristics were stratified by the stage at diagnosis and the presence or absence of a definitive treatment in the patient's course of care. Demographic characteristics included sex, categorical and mean age, US geographic region, and race/ethnicity. Clinical characteristics included baseline ECOG, smoking history, histological subtype (squamous or non-squamous), and three key biomarkers (ALK, EGFR, and PDL1).

2.5.2. Use of Neoadjuvant/Adjuvant Systemic Therapies by Definitive Treatment Group and Stage at Diagnosis

Adjuvant treatment was defined as occurring after the end of definitive treatment, but prior to recurrence. Neoadjuvant treatments were defined as occurring after diagnosis but prior to definitive treatment. Patterns of treatment were grouped by stage at diagnosis and the presence or absence of a definitive treatment. Sankey plots were generated to describe treatment patterns with neoadjuvant, definitive treatment, and adjuvant, either generally or by specific line name, as the three nodes across which patients progressed.

2.5.3. Event-Driven Outcomes by Treatment Group and Neoadjuvant/Adjuvant Use

We defined our index as the initiation of definitive treatment: primary surgery, definitive radiation, or definitive chemoradiation, allowing that, for some patients, the index date could be preceded by neoadjuvant treatment. Outcomes were estimated from the first day of definitive treatment, i.e., date of resection, first day of definitive radiation, or first day of chemotherapy.

Outcomes were organized by definitive treatment group and adjuvant and/or neoadjuvant treatments. Real-world overall survival was estimated from initiation of definitive treatment to death from any cause, loss to follow-up, or study end. Real-world event-free survival was estimated from initiation of definitive

treatment until death from any cause, local or distant recurrence, loss to follow-up, or study end. For all survival analyses, individuals were censored at the date of last visit or end of study, March 31, 2024, whichever occurred first. To account for the changes in approved targeted therapeutic options occurring over the period of our study, definitive treatment cohorts were also segregated by year of diagnosis (rolling admissions) and subgroup analyses were performed accordingly.

3. RESULTS

3.1. Baseline Demographic and Clinical Characteristics by Stage at Diagnosis and Definitive Treatment Group (Tables 1 and 2)

To characterize the eNSCLC study population, data were organized by stage of disease at diagnosis, definitive treatment, and patient demographic and clinical characteristics when available (**Table 1**). A total of 7,410 patients with an average age of 71.0 ± 8.5 years were included in the study. More than half of the patients were diagnosed with Stage I NSCLC (n = 4,098), with the remainder split between Stages II (n = 1340) and IIIA (n = 1972). The overall population was predominantly female (52.9 vs. 47.1%), a trend driven by the large proportion of women diagnosed at stage I (55.9 vs. 44.1%). However, when stratified by stage at diagnosis, this difference reverses by Stage IIIA, with 52.3% of male patients diagnosed at this later stage vs. 47.7% female. Nearly 75% of the study population fell between ages 65 and 84, and ~90% had a history of smoking, although this trended from below to above 90% from stages I to IIIA.

Patients were stratified into distinct cohorts based on the type of definitive treatment received: primary surgery, definitive radiation, and definitive chemoradiation (**Figs 2,3**), in accordance with NCCN guidelines[7]. Patients who were subjected to a primary surgical resection were classified under the 'Primary Surgery' cohort (50%), n = 3705. Those who underwent a definitive course of radiation therapy were categorized into the 'Definitive Radiation' cohort (10.6%), n = 789. Furthermore, a separate cohort, termed 'Definitive Chemoradiation', was established for patients who, in addition to undergoing a definitive course of radiation therapy, were also administered chemotherapy either concurrently or in a sequential manner (4.6%), n =

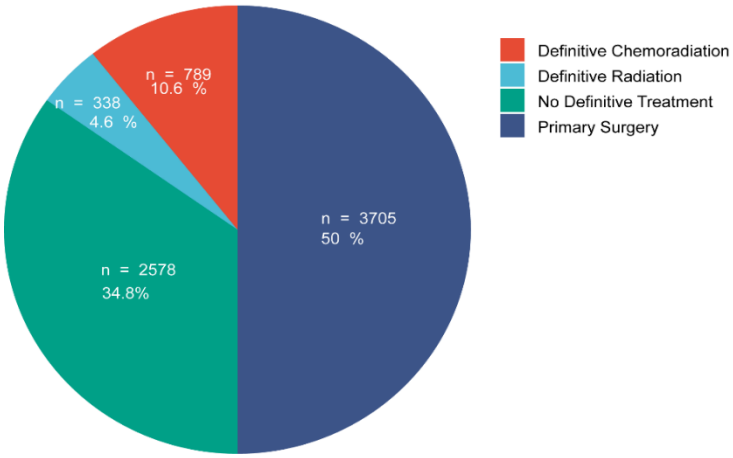

Figure 3: Representation of Definitive Treatment Groups

338. Patients who did not undergo treatment meeting a definitive definition were defined as the 'No Definitive Treatment' cohort (34.8%), n = 2,578.

In line with patient health requirements for surgical resection and recovery, patients in the primary surgery group were less likely to smoke (85.7%) compared to those receiving definitive radiation (95.0%), definitive chemoradiation (95.9%), or no definitive treatment (94.2%). Most patients who underwent primary tumor resection were diagnosed at Stage I (65.4%), while most patients receiving definitive radiation and definitive chemoradiation were diagnosed at Stage III (76.3% and 77.7%, respectively). Overall, patients were primarily diagnosed with non-squamous histology (65.1% vs. squamous, 32.8%), and a higher fraction of non-squamous patients underwent primary surgery (75.6%) compared to those receiving definitive radiation (51.8%), definitive chemoradiation (46.6%), or no definitive treatment (57.5%).

Nearly one-half of patients overall were not tested within six months of diagnosis for the common biomarkers, ALK, PDL1, or EGFR, a rate which was lower than advanced NSCLC testing rates[20]. However, as the stage at diagnosis increased, testing rates increased from (~40 - 70%). Testing rates were similar between the two definitive radiation groups (56.8 – 62.7%), while the no definitive treatment group and primary surgery group had slightly lower rates of testing (45.9 - 46.9% and 53.6 - 58.9%, respectively). Biomarker positivity, out of those tested, for PDL1, EGFR, and ALK, was 52.4%, 11%, and 1.5%, respectively. Of note, a larger fraction of primary surgery patients had EGFR positive status (15.4%) when compared to definitive radiation (3.4%), definitive chemoradiation (3.1%), and no definitive treatment patients (7.5%).

Table 1: Baseline Patient Demographics and Clinical Characteristics By Stage At Diagnosis					
Stage at diagnosis:		Any Stage	Stage I	Stage II	Stage IIIA
Total		7410	4098	1340	1972
Patient Demographics					
Definitive Treatment (n, %)	Surgery	3705 (50.0)	2422 (59.1)	775 (57.8)	508 (25.8)
	Definitive Radiation	338 (4.6)	30 (0.7)	50 (3.7)	258 (13.1)
	Definitive Chemoradiation	789 (10.6)	19 (0.5)	157 (11.7)	613 (31.1)
	No Definitive Treatment	2578 (34.8)	1627 (39.7)	358 (26.7)	593 (30.1)
Gender (n, %)	Male	3488 (47.1)	1806 (44.1)	650 (48.5)	1032 (52.3)
	Female	3922 (52.9)	2292 (55.9)	690 (51.5)	940 (47.7)
Age at diagnosis (n, %)	19-34	3 (0.04)	2 (0.1)	1 (0.1)	0 (0)
	35-49	87 (1.2)	40 (1.0)	15 (1.1)	32 (1.6)
	50-64	1542 (20.8)	798 (19.5)	286 (21.3)	458 (23.2)
	65-74	2682 (36.2)	1508 (36.8)	466 (34.8)	708 (35.9)
	74-84	2968 (40.0)	1691 (41.3)	542 (40.4)	735 (37.3)
	85+	128 (1.7)	59 (1.4)	30 (2.2)	39 (2.0)
	Mean (SD)	71.0 (8.5)	71.2 (8.2)	71.1 (8.7)	70.4 (8.8)
Race/Ethnicity (n, %)	White/Caucasian	5093 (68.7)	2853 (69.6)	923 (68.9)	1316 (66.7)
	Black/African American	578 (7.8)	297 (7.2)	109 (8.1)	172 (8.7)
	Asian	161 (2.2)	98 (2.4)	28 (2.1)	35 (1.8)
	Other Race	428 (5.8)	211 (5.1)	78 (5.8)	139 (7.0)
	Not documented	1150 (15.5)	639 (15.6)	202 (15.1)	309 (15.7)
Geographic region (n, %)	Midwest	694 (9.4)	326 (8.0)	145 (10.8)	223 (11.3)
	South	3035 (41.0)	1580 (38.6)	560 (41.8)	895 (45.4)
	Northeast	871 (11.8)	529 (12.9)	154 (11.5)	188 (9.5)
	West	897 (12.1)	478 (11.7)	185 (13.8)	234 (11.9)
	Other Territories	33 (0.4)	18 (0.4)	6 (0.4)	9 (0.5)
	Not documented	1880 (25.4)	1167 (28.5)	290 (21.6)	423 (21.5)
Clinical Characteristics					
ECOG (n, %)	0	2417 (32.6)	1356 (33.0)	433 (32.3)	628 (33.2)
	1	2195 (29.6)	1031 (25.2)	473 (35.3)	691 (36.5)
	2	591 (8.0)	281 (6.9)	115 (8.6)	195 (10.3)
	3+	140 (1.9)	52 (1.3)	35 (2.6)	53 (2.8)
	Not documented	2067 (27.9)	1378 (33.6)	284 (21.2)	405 (17.2)
Smoking History (n, %)	History of smoking	6680 (90.1)	3613 (88.2)	1231 (91.9)	1836 (93.1)
	No history of smoking	727 (9.8)	484 (11.8)	108 (8.1)	135 (6.8)
	Not documented	3 (0.04)	1 (0.02)	1 (0.07)	1 (0.1)
Tumor Characteristics					
Histological Subtype (n, %)	Non-Squamous	4827 (65.1)	2940 (71.7)	798 (59.6)	1089 (55.2)
	Squamous	2425 (32.8)	1103 (26.9)	513 (38.3)	809 (41.0)
	Unknown/Not specified	158 (2.1)	55 (1.3)	29 (2.2)	74 (3.8)
PDL1 Staining (n, % of tested)	Patients Tested (n, % total)	3,936 (53.1)	1,789 (43.7)	837 (62.5)	1,310 (66.4)
	<1% staining	912 (23.2)	450 (25.2)	174 (20.8)	288 (22.0)
	1-49% staining	1319 (33.5)	593 (33.1)	305 (36.4)	421 (32.1)
	>=50% staining	744 (18.9)	258 (14.4)	185 (22.1)	301 (23.0)
	Inconclusive	961 (24.4)	488 (27.3)	173 (20.7)	300 (22.9)
EGFR Status (n, % of tested)	Patients Tested (n, % total)	4,067 (54.9)	1,705 (41.6)	927 (69.2)	1,435 (72.8)
	Positive	448 (11.0)	253 (14.8)	83 (9.0)	112 (7.8)
	Negative	3311 (81.4)	1304 (76.5)	774 (83.5)	1233 (85.9)
	Inconclusive/Unknown	308 (7.6)	148 (8.7)	70 (7.6)	90 (6.3)
ALK Status (n, % of tested)	Patients Tested (n, % total)	3,867 (52.2)	1,570 (38.3)	864 (64.5)	1,433 (72.7)
	Positive	57 (1.5)	17 (1.1)	20 (2.3)	20 (1.4)
	Negative	3479 (90.0)	1384 (88.2)	781 (90.4)	1314 (91.7)
	Inconclusive/Unknown	331 (8.6)	169 (10.8)	63 (7.3)	99 (6.9)

Table 2: Baseline Patient Demographics and Clinical Characteristics By Definitive Treatment Group					
Definitive Treatment Group		Primary Surgery (n = 3705)	Definitive Radiation (n = 338)	Definitive Chemoradiation (n = 789)	No Definitive Treatment (n = 2578)
Patient Demographics					
Gender (n, %)	Male	1629 (44.0)	177 (52.4)	400 (50.7)	1282 (49.7)
	Female	2076 (56.0)	161 (47.6)	389 (49.3)	1296 (50.3)
Age at diagnosis (n, %)	19-34	3 (0.1)	0 (0)	0 (0)	0 (0)
	35-49	60 (1.6)	3 (0.9)	6 (0.8)	18 (0.7)
	50-64	963 (26.0)	78 (23.1)	165 (20.9)	336 (13.0)
	65-74	1512 (40.8)	114 (33.7)	280 (35.5)	776 (30.1)
	74-84	1153 (31.1)	138 (40.8)	335 (42.5)	1342 (52.1)
	85+	14 (0.4)	5 (1.5)	3 (0.4)	106 (4.1)
	Mean (SD)	69.0 (8.2)	70.8 (8.3)	71.0 (8.2)	73.8 (8.2)
Race/Ethnicity (n, %)	White	2609 (70.4)	215 (63.6)	541 (68.6)	1726 (67.0)
	Black/African American	266 (7.2)	42 (12.4)	70 (8.9)	200 (7.8)
	Asian	112 (3.0)	7 (2.1)	8 (1.0)	34 (1.3)
	Other	189 (5.1)	14 (4.1)	56 (7.1)	169 (6.6)
	Not documented	528 (14.3)	59 (17.5)	114 (14.4)	449 (17.4)
Geographic region (n, %)	Midwest	331 (8.9)	32 (9.5)	101 (12.8)	230 (8.9)
	South	1340 (36.2)	163 (48.2)	417 (52.9)	1115 (43.3)
	Northeast	430 (11.6)	42 (12.4)	67 (8.5)	332 (12.9)
	West	409 (11.0)	34 (10.1)	85 (10.8)	369 (14.3)
	Other Territories	17 (0.5)	0 (0)	4 (0.5)	12 (0.5)
	Not documented	1178 (31.8)	67 (19.8)	115 (14.6)	520 (20.1)
Clinical Characteristics					
Stage at Diagnosis (n, %)	Stage I	2422 (65.4)	30 (8.9)	19 (2.4)	1627 (63.1)
	Stage II	775 (20.9)	50 (14.8)	157 (19.9)	358 (13.9)
	Stage III	508 (13.7)	258 (76.3)	613 (77.7)	593 (23.0)
ECOG (n, %)	0	1344 (36.3)	90 (26.6)	290 (36.8)	693 (26.9)
	1	906 (24.5)	115 (34.0)	328 (41.6)	846 (32.8)
	2	138 (3.7)	26 (7.7)	90 (11.4)	337 (13.1)
	3+	21 (0.6)	9 (2.7)	17 (2.2)	93 (3.6)
	Not documented	1296 (35.0)	98 (29.0)	64 (8.1)	609 (23.6)
Smoking History (n, %)	History of smoking	3174 (85.7)	321 (95.0)	757 (95.9)	2428 (94.2)
	No history of smoking	530 (14.3)	17 (5.0)	32 (4.1)	148 (5.7)
	Not documented	1 (0.03)	0 (0.0)	0 (0.0)	2 (0.1)
Tumor Characteristics					
Histological Subtype (n, %)	Non-Squamous	2801 (75.6)	175 (51.8)	368 (46.6)	1483 (57.5)
	Squamous	875 (23.6)	147 (43.5)	382 (48.4)	1021 (39.6)
	Unknown/Not specified	29 (0.8)	16 (4.7)	39 (4.9)	74 (2.9)
PDL1 Staining (n, %)	Patients Tested (n, % total)	2,063 (55.7)	192 (56.8)	472 (59.8)	1,209 (46.9)
	<1% staining	490 (23.8)	42 (21.9)	100 (21.2)	280 (23.2)
	1-49% staining	727 (35.2)	61 (31.8)	139 (29.4)	392 (32.4)
	>=50% staining	369 (17.9)	39 (20.3)	122 (25.8)	214 (17.7)
	Inconclusive	477 (23.1)	50 (26.0)	111 (23.5)	323 (26.7)
EGFR Status (n, %)	Patients Tested (n, % total)	2,183 (58.9)	207 (61.2)	487 (61.7)	1,190 (46.2)
	Positive	337 (15.4)	7 (3.4)	15 (3.1)	89 (7.5)
	Negative	1717 (78.7)	178 (86.0)	442 (90.8)	974 (81.8)
	Inconclusive/Unknown	129 (5.9)	22 (10.6)	30 (6.2)	127 (10.7)
ALK Status (n, %)	Patients Tested (n, % total)	1,986 (53.6)	202 (59.8)	495 (62.7)	1,184 (45.9)
	Positive	37 (1.9)	3 (1.5)	6 (1.2)	11 (0.9)
	Negative	1806 (90.9)	182 (90.1)	453 (91.5)	1038 (87.7)
	Inconclusive/Unknown	143 (7.2)	17 (8.4)	36 (7.3)	135 (11.4)

3.2. Use of Neoadjuvant/Adjuvant Systemic Therapies by Definitive Treatment Group and Stage at Diagnosis

We found an increase of systemic adjuvant or neoadjuvant therapeutics (**Table 3 and Fig 4**) in patients Stages II and III. Our data reveals that lack of adjuvant and/or neoadjuvant therapy was more prevalent among surgical patients (62.1%), who were primarily at Stage I (65%). This stands in contrast to the two cohorts who underwent definitive radiation, where 24.6% of the patients receiving definitive chemoradiation and 50.0% of those receiving definitive radiation did not receive neoadjuvant / adjuvant systemic therapy. Among patients who underwent definitive chemoradiation, only 2.4% were at Stage I, and 24.6% did not receive any neoadjuvant / adjuvant systemic therapy. While the use of adjuvant therapy remained relatively steady for patients undergoing primary surgery between 2019 and 2023, we observed an increase over time in its use among both definitive radiation groups (**Fig 5**). Conversely, the use of neoadjuvant therapy remained limited across all groups, regardless of disease stage, definitive treatment, or when given in combination with adjuvant therapy.

Table 3: Neoadjuvant / Adjuvant Systemic Therapy Use by Definitive Treatment Group and Stage at Diagnosis

Stage at diagnosis:	Overall	Stage I	Stage II	Stage IIIA
	7410	4098	1340	1972
SURGERY, n = 3705				
Surgery alone	2301 (62.1)	1946 (80.3)	241 (31.1)	114 (22.4)
Neoadjuvant	125 (3.4)	78 (3.2)	24 (3.1)	23 (4.5)
Adjuvant	1153 (31.1)	333 (13.7)	482 (62.2)	338 (66.5)
Neoadjuvant + Adjuvant	126 (3.4)	65 (2.7)	28 (3.6)	33 (6.5)
DEFINITIVE CHEMORADIATION, n = 789				
Definitive Chemoradiation alone	194 (24.6)	8 (42.1)	59 (37.6)	127 (20.7)
Neoadjuvant	14 (1.8)	1 (5.3)	4 (2.5)	9 (1.5)
Adjuvant	546 (69.2)	9 (47.4)	93 (59.2)	444 (72.4)
Neoadjuvant + Adjuvant	35 (4.4)	1 (5.3)	1 (0.6)	33 (5.4)
DEFINITIVE RADIATION, n = 338				
Definitive Radiation alone	169 (50.0)	27 (90.0)	59 (37.6)	111 (43.0)
Neoadjuvant	15 (4.4)	1 (3.3)	4 (2.5)	12 (4.7)
Adjuvant	131 (38.8)	1 (3.3)	93 (59.2)	115 (44.6)
Neoadjuvant + Adjuvant	23 (6.8)	1 (3.3)	1 (0.6)	20 (7.8)
NO DEFINITIVE TREATMENT, n = 2578				
No treatment (none + adj)	2435 (94.4)	1553 (95.5)	331 (92.5)	552 (93.1)
Neoadjuvant (both + neo)	143 (5.6)	74 (4.5)	27 (7.5)	41 (6.9)

Upon examining the subset of patients who received neoadjuvant / adjuvant systemic therapy (**Fig 6 and Table 4, Supplemental Table 1, 2**), we observed a greater diversity in treatment modalities in the neoadjuvant context compared to the adjuvant setting. This was consistent across all cohorts, including those who received neoadjuvant systemic therapy but did not proceed to definitive treatment. The most frequently administered neoadjuvants across all cohorts were either platinum combined with chemotherapy or other monotherapies (primary surgery, 19.9%; definitive radiation, 50.0%; definitive chemoradiation, 59.2%, no definitive treatment, 31.5%), or IO in conjunction with platinum and chemotherapy or other monotherapies (primary surgery, 39.0%; definitive radiation, 36.8%; definitive chemoradiation, 16.3%, no definitive treatment, 10.5%). It is noteworthy that a substantial proportion (15.5%) of surgical patients who received a neoadjuvant were administered a clinical study drug in this setting.

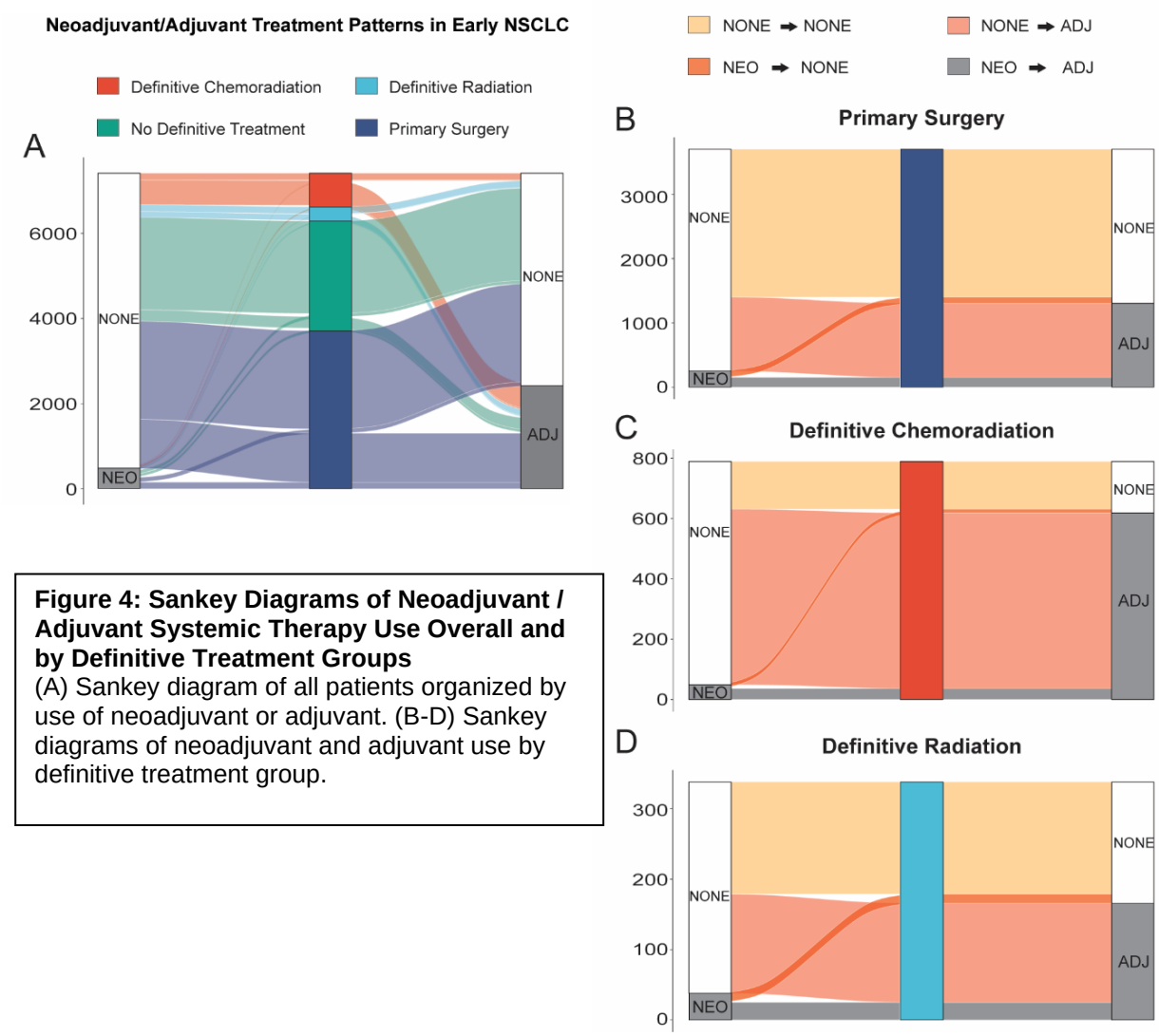

Figure 4: Sankey Diagrams of Neoadjuvant / Adjuvant Systemic Therapy Use Overall and by Definitive Treatment Groups
(A) Sankey diagram of all patients organized by use of neoadjuvant or adjuvant. (B-D) Sankey diagrams of neoadjuvant and adjuvant use by definitive treatment group.

In the adjuvant setting, IO monotherapy emerged as the predominant therapeutic approach for patients undergoing definitive radiation or chemoradiation, with 86.4% and 96.4% respectively receiving this therapy. Conversely, only 5.8% of surgical patients were administered IO monotherapy in this context. Surgical patients were more commonly administered adjuvant platinum chemotherapy, often in combination with other systemic therapies. The administration of TKIs, either as a monotherapy or in combination with chemotherapy or another monotherapy, was confined to the adjuvant context for surgical patients (8.0%) and the neoadjuvant context for patients who did not receive definitive treatment (11.2%).

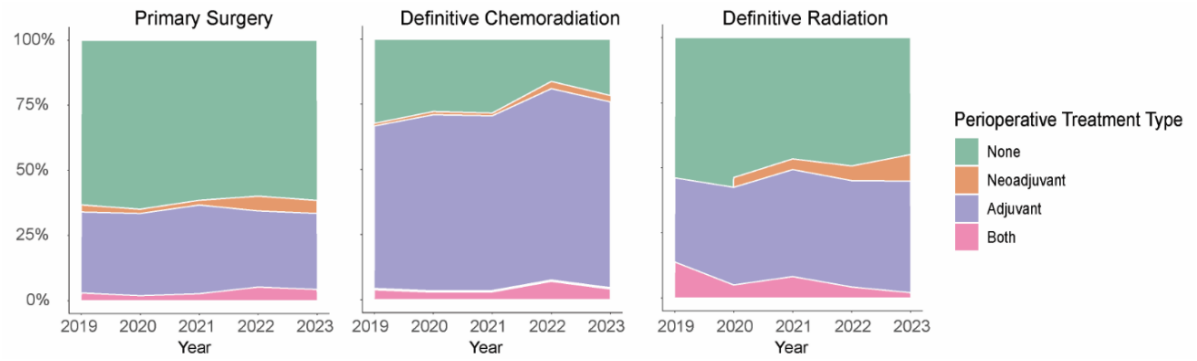

Figure 5: Changes in Neoadjuvant and Adjuvant Treatment Use Over Time by Definitive Treatment Groups

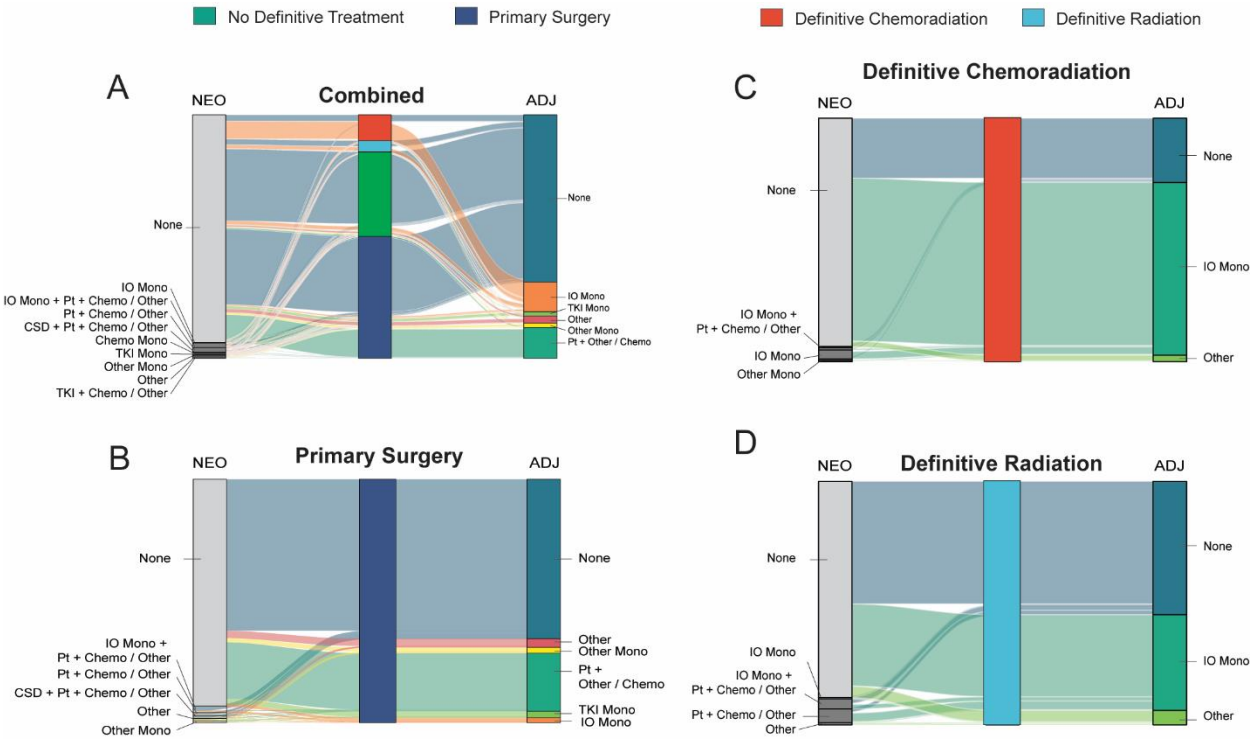

Figure 6: Neoadjuvant / Adjuvant Systemic Therapy Use by Definitive Treatment Groups
(A) Overall patient treatment patterns (including No Definitive Treatment group) and neoadjuvant / adjuvant systemic therapy patterns in (B) Primary Surgery, (C) Definitive Chemoradiation, and (D) Definitive Radiation populations.

Table 4: Neoadjuvant / Adjuvant Line Names by Treatment Group				
Primary Surgery				
Stage at Diagnosis	**Any Stage**	**Stage I**	**Stage II**	**Stage III**
Neoadjuvant, n = 251				
Clinical Study Drug + Platinum + Chemo/Other (n, %)	39 (15.5)	24 (16.8)	4 (7.7)	11 (19.6)
IO Monotherapy + Platinum + Chemo/Other (n, %)	98 (39.0)	49 (34.3)	33 (63.5)	16 (28.6)
Other Monotherapy (n, %)	24 (9.6)	18 (12.6)	1 (1.9)	5 (8.9)
Platinum + Chemo/Other (n, %)	50 (19.9)	24 (16.8)	8 (15.4)	18 (32.1)
Other (n, %)	40 (15.9)	28 (19.6)	6 (11.5)	6 (10.7)
Adjuvant n = 1278				
IO Monotherapy (n, %)	74 (5.8)	33 (8.3)	26 (5.1)	15 (4.0)
Other Monotherapy (n, %)	89 (7.0)	80 (20.1)	5 (1.0)	4 (1.1)
Platinum + Chemo/Other (n, %)	883 (69.0)	143 (35.9)	433 (84.9)	307 (82.7)
TKI Monotherapy (n, %)	100 (7.8)	59 (14.8)	18 (3.5)	23 (6.2)
Other (n, %)	133 (10.4)	3 (20.9)	28 (5.5)	22 (5.9)
Definitive Chemoradiation				
Neoadjuvant, n = 49				
IO Monotherapy (n, %)	3 (6.1)	0 (0.0)	1 (20.0)	2 (4.8)
IO Monotherapy + Platinum + Chemo/Other (n, %)	8 (16.3)	0 (0.0)	1 (20.0)	8 (19.0)
Other Monotherapy (n, %)	4 (8.2)	0 (0.0)	2 (40.0)	3 (7.1)
Platinum + Chemo/Other (n, %)	29 (59.2)	2 (100.0)	0 (0.0)	25 (59.5)
Other (n, %)	5 (10.0)	0 (0.0)	1 (20.0)	4 (9.5)
Adjuvant, n = 581				
IO Monotherapy (n, %)	560 (96.4)	10 (100.0)	90 (95.7)	460 (91.1)
Other (n, %)	21 (3.6)	0 (0.0)	4 (4.3)	12 (8.9)
Definitive Radiation				
Neoadjuvant, n = 38				
IO Monotherapy (n, %)	2 (5.3)	1 (50.0)	0 (0.0)	1 (3.1)
IO Monotherapy + Platinum + Chemo/Other (n, %)	14 (36.8)	0 (0.0)	3 (75.0)	11 (34.4)
Platinum + Chemo/Other (n, %)	19 (50.0)	0 (0.0)	0 (0.0)	19 (59.4)
Other (n, %)	3 (7.8)	1 (50.0)	1 (25.0)	1 (3.1)
Adjuvant, n = 153				
IO Monotherapy (n, %)	133 (86.4)	0 (0.0)	10 (58.8)	123 (91.1)
Other (n, %)	21 (13.6)	1 (100.0)	7 (41.2)	12 (8.9)
No Definitive Treatment				
Neoadjuvant, n = 143				
Chemotherapy Monotherapy (n, %)	11 (7.7)	8 (10.8)	2 (7.1)	1 (2.4)
IO Monotherapy (n, %)	9 (6.3)	6 (8.1)	1 (3.6)	2 (4.9)
IO Monotherapy + Platinum + Chemo/Other (n, %)	15 (10.5)	3 (4.1)	4 (14.3)	8 (19.5)
Other Monotherapy (n, %)	27 (18.9)	23 (31.1)	3 (10.7)	1 (2.4)
Platinum + Chemo/Other (n, %)	45 (31.5)	9 (12.2)	9 (32.1)	27 (65.9)
TKI + Chemo/Other (n, %)	8 (5.6)	8 (10.8)	0 (0.0)	0 (0.0)
TKI Monotherapy (n, %)	8 (5.6)	4 (5.4)	4 (14.3)	0 (0.0)
Other (n, %)	20 (14.0)	13 (17.6)	5 (17.9)	2 (4.9)

3.3. Event-Driven Outcomes by Treatment Group and Neoadjuvant/Adjuvant Use

In patients with resectable eNSCLC, neoadjuvant and/or adjuvant in conjunction with primary surgery generally saw a lower overall survival rate over time, compared to those who did not receive such treatment (**Fig 7**). In the context of patients treated with definitive radiation or chemoradiation, adjuvant systemic therapy survival outcomes were higher relative to those who did not receive neoadjuvant and/or adjuvant systemic therapy (**Fig 7**). These patterns were mirrored in the event-free survival (EFS) rates (**Fig 7**), where patients who underwent tumor resection without neoadjuvant and/or adjuvant systemic therapy saw a lower EFS over time, while patients who received adjuvant therapy after definitive radiation or chemoradiation higher overall EFS over time.

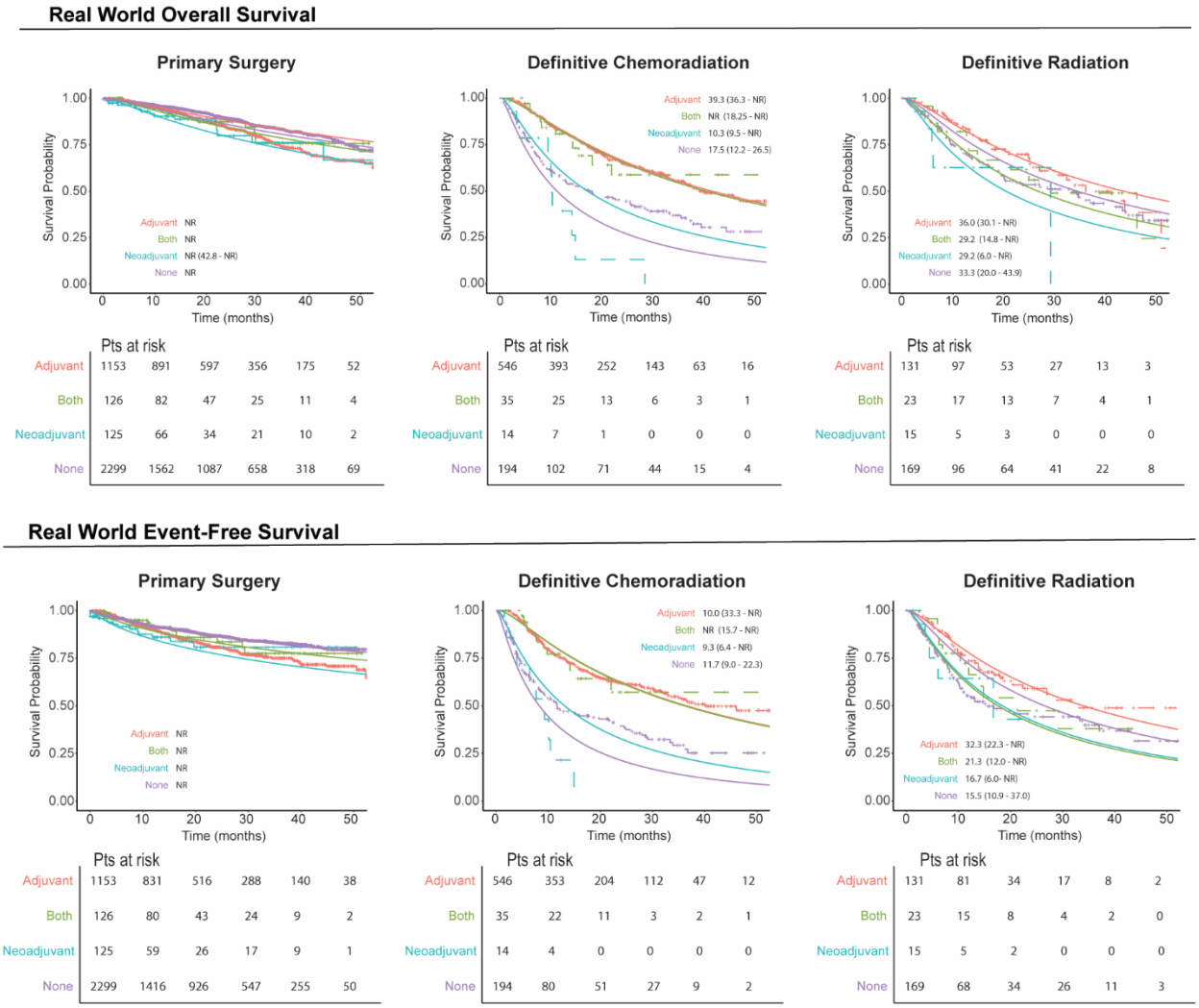

Figure 7: Real World Overall and Event-Free Survival by Definitive Treatment Groups Stratified by Neoadjuvant / Adjuvant Systemic Therapy

The 1-year survival for patients who underwent surgical resection without neoadjuvant and/or adjuvant systemic therapy regardless of stage at diagnosis, held steady and ranged from 94.7 - 97.9% (**Fig 8 and Supplemental Tables 3 and 4**). For patients undergoing definitive chemoradiation without neoadjuvant and/or adjuvant systemic therapy, 1-year survival rates were generally lower, ranging from 37.9 - 71.7%, but patients in this group that received adjuvant saw higher 1-year survival rates, 80.0 - 100%, although the sample size was small (n = 21 – 30 for each year). Similar values were seen in 2-year survival rates. A trend similar to that seen with definitive radiation alone was observed in patients who received definitive radiation alone, although the survival rates of these patients were slightly higher overall ranging from 66.3 - 96.8%.

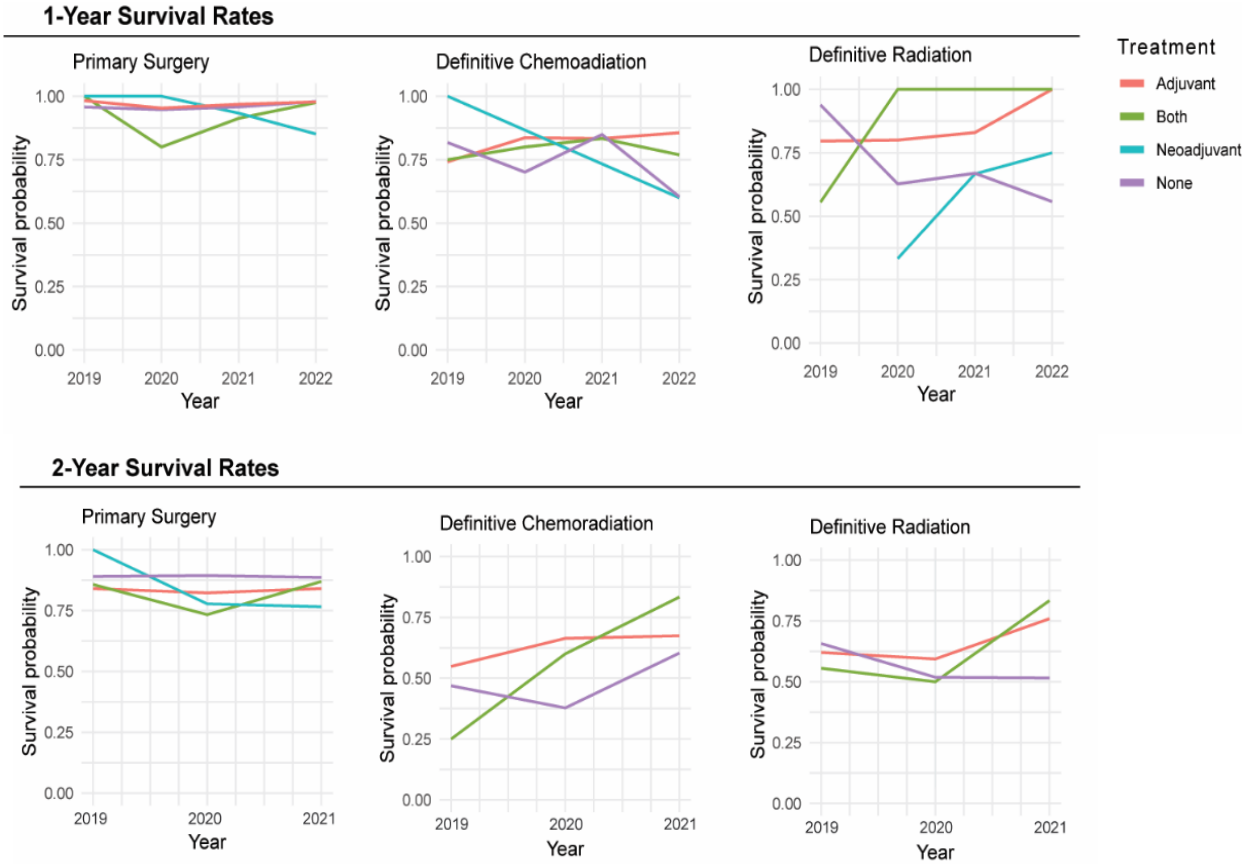

Figure 8: Real World 1 and 2-Year Survival by Definitive Treatment Groups Stratified by Neoadjuvant / Adjuvant Systemic Therapy (See Supplemental Tables 3 and 4)

Table 5: 1-year Survival by Definitive Treatment Group and Neoadjuvant / Adjuvant Systemic Therapy Use				
	2019	**2020**	**2021**	**2022**
Surgery alone	95.7% (93.4 - 98.1%), n = 303	94.7% (92.7 - 96.8%), n = 520	95.8% (94.0 - 97.6%), n = 538	97.9% (96.5 - 99.3%), n = 508
+ Neoadjuvant	100.0% (100.0 - 100.0%), n = 13	100.0% (100.0 - 100.0%), n = 13	93.3% (81.5 - 100.0%), n = 16	84.7% (74.1 - 96.9%), n = 48
+ Adjuvant	94.4% (90.6 - 98.2%), n = 149	91.8% (88.4 - 95.3%), n = 253	94.0% (91.2 - 96.8%), n = 298	94.9% (92.2 - 97.8%), n = 248
+ Neoadjuvant and Adjuvant	100.0% (100.0 - 100.0%), n = 14	80.0% (62.1 - 100.0%), n = 15	90.5% (78.8 - 100.0%), n = 23	97.4% (92.6 - 100.0%), n = 44
Definitive Chemoradiation alone	62.5% (47.8%, 81.7%), n = 32	53.3% (40.6%, 70.1%), n = 45	71.7% (60.5%, 84.9%), n = 53	37.9% (23.8%, 60.4%), n = 29
+ Neoadjuvant	100.0% (100.0%, 100.0%), n = 1	--	--	60.0% (29.3%, 100.0%), n = 5
+ Adjuvant	74.2% (64.1%, 85.9%), n = 62	83.6% (77.0%, 90.8%), n = 110	83.3% (77.1%, 90.1%), n = 126	85.6% (79.8%, 91.8%), n = 132
+ Neoadjuvant and Adjuvant	75.0% (42.6%, 100.0%), n = 4	80.0% (51.6%, 100.0%), n = 5	83.3% (58.3%, 100.0%), n = 6	76.9% (57.1%, 100.0%), n = 13
Definitive Radiation alone	96.8% (90.8 – 100.0%, n = 35	70.0% (57.1 – 85.7%), n = 43	80.0% (66.8 – 95.7%), n = 34	66.3% (51.2 – 85.8%), n = 35
+ Neoadjuvant	--	33.3% (6.7-100.0%), n = 3	66.7% (30.0 – 100.0%), n = 3	75% (42.6 – 100.0%), n = 4
+ Adjuvant	95.2% (86.6 – 100.0%), n = 21	80.0% (66.9 – 95.7%), n = 30	89.3% (78.5 – 100.0%), n = 30	100.0% (100.0 – 100.0%), n = 29
+ Neoadjuvant and Adjuvant	55.6% (31.0 – 99.7%), n = 9	100.0% (100.0 – 100.0%), n = 4	100.0% (100.0 – 100.0%), n = 6	100.0% (100.0 – 100.0%), n = 3

Table 6: 2-year Survival by Definitive Treatment Group and Neoadjuvant / Adjuvant Systemic Therapy Use			
	2019	**2020**	**2021**
Surgery alone	89.0% (85.2 - 92.9%), n = 303	89.4% (86.6 - 92.2%), n = 520	88.6% (85.6 - 91.7%), n = 538
+ Neoadjuvant	100.0% (100.0 - 100.0%), n = 13	77.8% (54.9 - 100.0%), n = 13	75.4% (54.0 - 100.0%), n = 16
+ Adjuvant	83.8% (77.8 - 90.2%), n = 149	82.3% (77.6 - 87.3%), n = 253	83.9% (79.6 - 88.5%), n = 298
+ Neoadjuvant and Adjuvant	85.7% (69.2 - 100.0%), n = 14	73.3% (54.0 - 99.5%), n = 15	85.7% (72.0 - 100.0%), n = 23
Definitive Chemoradiation alone	46.9% (32.4%, 67.8%), n = 32	37.8% (26.0%, 55.0%), n = 45	60.3% (48.5%, 75.1%), n = 53
+ Neoadjuvant	100.0% (100.0%, 100.0%), n = 1	--	--
+ Adjuvant	54.8% (43.8%, 68.7%), n = 62	66.4% (58.1%, 75.8%), n = 110	67.4% (59.7%, 76.1%), n = 126
+ Neoadjuvant and Adjuvant	25.0% (4.6%, 100.0%), n = 4	60.0% (29.3%, 100.0%), n = 5	83.3% (58.3%, 100.0%), n = 6
Definitive Radiation alone	64.5% (49.7 - 83.8%), n = 35	59.7% (46.2 - 77.1%), n = 43	50.0% (34.4 - 72.8%), n = 34
+ Neoadjuvant	--	33.3% (6.7 - 100.0%), n = 3	--
+ Adjuvant	78.7% (62.1 - 99.7%), n = 21	62.9% (47.6 - 83.0%), n = 30	74.6% (60.0 - 92.8%), n = 30
+ Neoadjuvant and Adjuvant	55.6% (31.0 - 99.7%), n = 9	33.3% (6.7 - 100.0%), n = 4	83.3% (58.3 - 100.0%), n = 6

4. DISCUSSION:

The landscape for approved targeted therapeutics in eNSCLC is undergoing rapid evolution[3,14]. This has catalyzed a growing demand for the wider application of neoadjuvant and adjuvant. In 2020, only one targeted therapeutic had been approved for this purpose and, currently in 2024, fewer than seven targeted therapeutics have been approved for the neoadjuvant / adjuvant systemic therapy setting, with the majority approved exclusively for the treatment of biomarker-positive resectable eNSCLC[1,14]. However, despite the potential for and severity of disease recurrence even after successful resection or radiation[21,22], the patient and clinical decision-making path to integrate effective neoadjuvant / adjuvant systemic therapy remains ambiguous. It is therefore crucial to observe how real-world treatment patterns over this period are evolving to provide guidance for clinical practice and pinpoint any discrepancies between the encouraging results of clinical trials and the actual uptake of these innovative treatments in real-world eNSCLC care.

Using real world de-identified data from US electronic health records, we selected a cohort of mostly female (52.9%) eNSCLC patients who met inclusion criteria, n = 7,410. We grouped patients according to curative-intent or definitive treatment (primary surgery, definitive radiation, and definitive chemoradiation) and evaluated the use of systemic neoadjuvant and adjuvant therapies administered before and after these definitive treatments by stage at diagnosis. A considerable fraction of each group did not receive neoadjuvant / adjuvant systemic therapies, most noticeably, 62.1% of surgery patients and to a lesser extent definitive radiation (50%) and chemoradiation (24.6%) cohorts. Targeted treatments were frequently used in patients undergoing definitive radiation or chemoradiation, with adjuvant IO monotherapy being the primary systemic treatment for 86.4% and 96.4% of these patients, respectively. In contrast, only a minor percentage of surgical patients (5.8%) were administered IO monotherapy as an adjuvant. Despite surgical patients generally being in better health, it remains uncertain why they receive chemotherapy more often than IO. This discrepancy could be attributed to a combination of addressable factors such as less biomarker testing for Stage I, the physician’s personal preference, patient access to care, or a perception, either physician or patient, of immunotherapies as new and unproven. Further work to understand the factors driving these findings will need to be explored as part of future studies.

Our analysis of real-world survival rates, overall and event-free, revealed that patients with resectable eNSCLC who underwent surgery without neoadjuvant / adjuvant systemic therapy generally had better

survival outcomes, while the use of adjuvant therapy improved outcomes for those treated with definitive radiation or chemoradiation. However, neoadjuvant / adjuvant systemic therapies, chemotherapy or targeted, are indicated for patients diagnosed at Stages IB-IIIA, to the exclusion of Stage IA. As our results grouped IA and IB, our interpretation of outcomes and use of neoadjuvant / adjuvant systemic therapies, particularly in the primary surgery group, are limited. Future post-hoc analyses separating out Stage IA are necessary. Across our study, 1- and 2-year survival rates were steady for surgery patients, regardless of neoadjuvant / adjuvant systemic therapy. Definitive chemoradiation and radiation, in contrast, saw a trend towards improved survival for those patients receiving either adjuvant on its own or in combination with neoadjuvant. The factors leading to this improvement, including the recent approval for durvalumab in these settings, are of particular interest.

Historically, clinical trials for eNSCLC have been primarily concentrated on patients who are candidates for surgery. In the neoadjuvant setting, all resectable patients who are suitable for immune-checkpoint inhibitors are considered for nivolumab and pembrolizumab, which were approved in 2022 and 2023 respectively, and are given in combination with platinum-based chemotherapy. The FDA's approval of pembrolizumab also encompasses a follow-up with pembrolizumab monotherapy as an adjuvant for up to one year. Durvalumab has also been approved for this indication. A similar application of nivolumab is scheduled for review in October 2024. In 2023, both atezolizumab and pembrolizumab received approval for adjuvant use after a four-cycle chemotherapy regimen. For post-surgery patients with EGFR mutations (a biomarker found in about 15% of NSCLC tumors[23]), the daily oral adjuvant osimertinib, an EGFR-targeting tyrosine-kinase inhibitor (TKI), was approved in 2020 for use up to three years[14]. Additionally, the combined treatment option of osimertinib following adjuvant chemotherapy was approved in 2024. With the recent evidence that tumor resection dominates over radiation-based care for overall survival, multiple clinical trials are currently underway combining definitive radiation with immunotherapy as a neoadjuvant prior to surgical resection. It is imperative to continuously monitor the progression of this data and observe the evolution of neoadjuvant and adjuvant therapeutics and their impact on patient outcomes.

These treatments can potentially enhance surgical outcomes, improve patient survival rates, and contribute to a more personalized approach to cancer care. However, the use of these therapies requires a thorough understanding of the patient's condition, the specific genetic and anatomical characteristics of

the tumor, and the potential benefits and risks associated with the treatment[3,14,24]. Critically, information on targetable biomarkers can only improve the care options and outcomes for patients. However, despite the increased use of biomarker testing with staging, we found rates of biomarker testing remain below those seen in advanced disease[20]. It is essential, then, to address access to testing including cost and healthcare infrastructure.

While primarily descriptive, our results underscore the unaddressed needs of patients diagnosed with eNSCLC. Guidelines for the standard of care for eNSCLC are widely accessible, offering a structured approach to treatment. Nevertheless, the actual trajectory of a patient's care is contingent upon a confluence of factors: the severity of the disease, the training and preferences of the physician and care team, patient decision-making[6], overall health status, and access to care and therapy[14]. The influence of disease severity, specifically tumor resectability, on the type of definitive care administered to the patient is readily observable, but comprehensive care options have, until recently, been limited[3,14]. It was unsurprising then that we found a severe underutilization of adjuvant and neoadjuvant therapies regardless of year across our study, underscoring the importance of efforts in this area.

5. LIMITATIONS:

Given the continuous emergence of newly approved targeted therapies over the span of our dataset, it is crucial to highlight the nascent stage of our analyses. A more insightful interpretation might be achieved by examining the data in the context of subgroups delineated by the year of diagnosis. Further, our classification of the three definitive treatment groups is based on the principle of curative intent and the inherent indications for the three definitive treatments impose limitations on between-group comparisons. However, we do not assert that this perfectly aligns with the therapeutic goals of the medical team. Our definitional framework is further restricted by the inclusion criteria, which only include patients who have completed their prescribed course of radiation or chemotherapy. As a result, patients who may have discontinued their treatment prematurely, and therefore do not meet our definitional criteria, were included in the study under the 'No Definitive Treatment' group. A more detailed investigation of the fragmented options offered to patients undergoing treatment without curative intent would provide valuable insights.

The racial and ethnic composition of the eNSCLC Flatiron Health database aligns closely with the national averages for the White/Caucasian population (68.7%). However, it underrepresents the Black (7.8% vs. a national average of 12.5%) and Asian (2.2% vs. 5.8%) populations in the US (www.neilsberg.com). Notably, over 40% of the patients were from the southern US, despite the south and the west having comparable total populations (72.6 million vs. 78.6 million, according to the US Census 2020). This could potentially indicate a limitation in the dataset due to an overrepresentation of oncology clinics in the southern US. However, previous research has suggested that the Flatiron Health datasets are generally representative of the overall US population distribution[25].

While our objective was to describe differences in the use of neoadjuvant and adjuvant systemic therapeutics within definitive treatment groups, the alignment of patient care from the initiation of any treatment, definitive or systemic, presented a challenge in assessing event-driven outcomes (1-year, 2-year, overall survival, and event-free survival). If we aligned patients at the initiation of any treatment, the index date would be the administration of neoadjuvant therapy for two of the four groups, neoadjuvant only and both (neoadjuvant + adjuvant), while the other two groups, definitive treatment alone and adjuvant only, would be indexed on the definitive treatment. We defined our index as the initiation of definitive treatment: primary surgery, definitive radiation, or definitive chemoradiation, allowing that, for some patients, the index date could be preceded by neoadjuvant treatment.

Our study continuously enrolled eNSCLC patients who typically have a lifespan exceeding our study duration, resulting in preliminary results that will become more robust over time. The potential for direct comparison or interpretation of our survival outcomes is therefore constrained by a considerable degree of non-random censoring due to differential follow-up times across the study duration. Future periodic re-analyses and collaborative studies which pool data from multiple sources will strengthen our ability to accurately interpret and statistically analyze the data to improve the reliability of our results.

6. CONCLUSIONS:

In this retrospective observational study of NSCLC diagnosed at stages I-IIIA, 50% of the patients underwent surgical resection, while 15% completed a course of definitive radiation with or without chemotherapy. The remaining patients underwent piecemeal courses of radiation or systemic treatment.

On either side of these definitive options, the use of systemic neoadjuvant was rare, and adjuvant use was limited despite growing evidence of its effectiveness for eNSCLC patients.

7. REFERENCES:

1 The Lancet Regional, H.-E. NSCLC: bridging the gap between clinical progress and real-world application. *Lancet Reg Health Eur* **38**, 100878, doi:10.1016/j.lanepe.2024.100878 (2024).

2 Eisenstein, M. New lung-cancer drugs extend survival times. *Nature* (2020).

3 Chaft, J. E. *et al.* Evolution of systemic therapy for stages I-III non-metastatic non-small-cell lung cancer. *Nat Rev Clin Oncol* **18**, 547-557, doi:10.1038/s41571-021-00501-4 (2021).

4 Simeone, J. C., Nordstrom, B. L., Patel, K. & Klein, A. B. Treatment patterns and overall survival in metastatic non-small-cell lung cancer in a real-world. *Future of Oncology* (2019).

5 Blandin Knight, S. *et al.* Progress and prospects of early detection in lung cancer. *Open Biol* **7**, doi:10.1098/rsob.170070 (2017).

6 Udelsman, B. V. *et al.* Overall survival in low-comorbidity patients with stage I non-small cell lung cancer who chose stereotactic body radiotherapy compared to surgery. *J Thorac Cardiovasc Surg* **167**, 822-833 e827, doi:10.1016/j.jtcvs.2023.07.021 (2024).

7 Riely, G. J. *et al.* Non–Small Cell Lung Cancer, Version 4.2024, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network* **22**, 249-274, doi:10.6004/jnccn.2204.0023 (2024).

8 O'Sullivan, D. E. *et al.* Real-World Treatment Patterns, Clinical Outcomes, and Healthcare Resource Utilization in Early-Stage Non-Small-Cell Lung Cancer. *Curr Oncol* **31**, 447-461, doi:10.3390/curroncol31010030 (2024).

9 Uldbjerg, E. M. *et al.* Diagnostic Workup, Treatment Patterns, and Clinical Outcomes in Early-Stage IB-IIIA Non-Small-Cell Lung Cancer Patients in Denmark. *Cancers (Basel)* **15**, doi:10.3390/cancers15215130 (2023).

10 Helland, A. *et al.* EGFR-mutation testing, treatment patterns and clinical outcomes in patients with stage IB-IIIA non-small cell lung cancer in Norway-a nationwide cohort study. *Cancer Treat Res Commun* **38**, 100785, doi:10.1016/j.ctarc.2023.100785 (2024).

11 Schmid, S. *et al.* Treatment patterns and outcomes in early-stage ALK-rearranged non-small cell lung cancer. *Lung Cancer* **166**, 58-62, doi:10.1016/j.lungcan.2022.01.020 (2022).

12 West, H. *et al.* Treatment Patterns and Outcomes in Resected Early-stage Non-small Cell Lung Cancer: An Analysis of the SEER-Medicare Data. *Clin Lung Cancer* **24**, 260-268, doi:10.1016/j.cllc.2022.12.005 (2023).

13 Banna, G. L. *et al.* Neoadjuvant Chemo-Immunotherapy for Early-Stage Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. *JAMA Netw Open* **7**, e246837, doi:10.1001/jamanetworkopen.2024.6837 (2024).

14 Houda, I. *et al.* Challenges and controversies in resectable non-small cell lung cancer: a clinician's perspective. *Lancet Reg Health Eur* **38**, 100841, doi:10.1016/j.lanepe.2024.100841 (2024).

15 NSCLC NCCN Guidelines. *Version 4.2024* (2024).

16 Singal, G. *et al.* Association of Patient Characteristics and Tumor Genomics With Clinical Outcomes Among Patients With Non–Small Cell Lung Cancer Using a Clinicogenomic Database. *JAMA* **321**, 1391-1399, doi:10.1001/jama.2019.3241 (2019).

17 Zhang, Q., Gossai, A., Monroe, S., Nussbaum, N. C. & Parrinello, C. M. Validation analysis of a composite real-world mortality endpoint for patients with cancer in the United States. *Health Services Research* **56**, 1281-1287, doi:https://doi.org/10.1111/1475-6773.13669 (2021).

18 Detterbeck, F. C. The eighth edition TNM stage classification for lung cancer: What does it mean on main street?

19 Yan, J. T. *et al.* Real-World Biomarker Test Utilization and Subsequent Treatment in Patients with Early-Stage Non-small Cell Lung Cancer in the United States, 2011-2021. *Oncol Ther* **11**, 343-360, doi:10.1007/s40487-023-00234-7 (2023).

20 John, A. A.-O., Yang, B. & Shah, R. Clinical Impact of Adherence to NCCN Guidelines for Biomarker Testing and First-Line Treatment in Advanced Non-Small Cell Lung Cancer (aNSCLC) Using Real-World Electronic Health Record Data.

21 Lou, F. *et al.* Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. *J Thorac Cardiovasc Surg* **145**, 75-81; discussion 81-72, doi:10.1016/j.jtcvs.2012.09.030 (2013).

22 Cai, B., Fulcher, N., Boyd, M. & Spira, A. Clinical outcomes and resource utilization after surgical resection with curative intent among patients with non-small cell lung cancer treated with adjuvant therapies in a community oncology setting: A real-world retrospective observational study. *Thorac Cancer* **12**, 2055-2064, doi:10.1111/1759-7714.14007 (2021).

23 Melosky, B. *et al.* Worldwide Prevalence of Epidermal Growth Factor Receptor Mutations in Non-Small Cell Lung Cancer: A Meta-Analysis. *Mol Diagn Ther* **26**, 7-18, doi:10.1007/s40291-021-00563-1 (2022).

24 Kalvapudi, S., Vedire, Y., Yendamuri, S. & Barbi, J. Neoadjuvant therapy in non-small cell lung cancer: basis, promise, and challenges. *Front Oncol* **13**, 1286104, doi:10.3389/fonc.2023.1286104 (2023).

25 Snow, T. *et al.* Comparison of Population Characteristics in Real-World Clinical Oncology Databases in the US: Flatiron Health-Foundation Medicine Clinico-Genomic Databases, Flatiron Health Research Databases, and the National Cancer Institute SEER Population-Based Cancer Registry. doi:10.1101/2023.01.03.22283682 (2023).

8. **APPENDIX:**

Supplemental Table 1: Line Names in Other (under 5% threshold)			
Definitive Treatment Group	**Adjuvant / Neoadjuvant**	**Line Name**	**N (%)**
Primary Surgery	Neoadjuvant	Chemotherapy + Platinum + Other / Chemo	4 (1.6)
		Chemotherapy Monotherapy	5 (2.0)
		IO Double	2 (0.8)
		IO Double + Platinum + Chemo / Other	2 (0.8)
		IO Monotherapy	5 (2.0)
		IO Monotherapy + Chemo / Other	1 (0.4)
		IO Monotherapy + TKI	1 (0.4)
		Other +	2 (0.8)
		Platinum Monotherapy	3 (1.2)
		TKI + Other / Chemo	3 (1.2)
		TKI + Platinum + Other / Chemo	1 (0.4)
		TKI Monotherapy	11 (4.4)
	Adjuvant	Chemotherapy + Platinum + Other / Chemo	9 (0.7)
		Chemotherapy Monotherapy	37 (2.9)
		Clinical Study Drug + Platinum + Other / Chemo	25 (2.0)
		IO Double	5 (0.4)
		IO Double + Platinum + Chemo / Other	2 (0.2)
		IO Monotherapy + Chemo / Other	3 (0.2)
		IO Monotherapy + Platinum + Chemo / Other	37 (2.9)
		IO Monotherapy + TKI + Other / Chemo	1 (0.1)
		Other +	6 (0.5)
		Platinum Monotherapy	3 (0.2)
		TKI + Other / Chemo	3 (0.2)
		TKI Double	1 (0.1)
Definitive Chemoradiation	Neoadjuvant	Chemotherapy Monotherapy	1 (2.0)
		Clinical Study Drug + Platinum + Other / Chemo	1 (2.0)
		Other +	1 (2.0)
		Platinum Monotherapy	1 (2.0)
		TKI + Other / Chemo	1 (2.0)
	Adjuvant	Clinical Study Drug + Platinum + Other / Chemo	3 (0.5)
		IO Double + Platinum + Chemo / Other	1 (0.2)
		IO Monotherapy + Chemo / Other	4 (0.7)
		IO Monotherapy + Platinum	1 (0.2)
		IO Monotherapy + Platinum + Chemo / Other	4 (0.7)
		Other Monotherapy	1 (0.2)
		Platinum + Other / Chemo	2 (0.3)
		TKI Monotherapy	5 (0.9)
Definitive Radiation	Neoadjuvant	Chemotherapy Monotherapy	1 (2.6)
		Other Monotherapy	1 (2.6)
		TKI + Platinum + Other / Chemo	1 (2.6)
	Adjuvant	ADC Monotherapy	1 (0.6)
		Chemotherapy + Platinum + Other / Chemo	1 (0.6)
		Chemotherapy Monotherapy	1 (0.6)
		IO Monotherapy + Chemo / Other	1 (0.6)
		IO Monotherapy + Platinum	1 (0.6)
		IO Monotherapy + Platinum + Chemo / Other	4 (2.6)
		IO Monotherapy + TKI + Other / Chemo	1 (0.6)
		Other +	1 (0.6)

		Other Monotherapy	2 (1.3)
		Platinum + Other / Chemo	6 (3.9)
		TKI Monotherapy	2 (1.3)
No Definitive Treatment	Neoadjuvant	ADC + Other / Chemo	2 (1.4)
		Chemotherapy + Platinum + Other / Chemo	3 (2.1)
		Clinical Study Drug + IO	1 (0.7)
		Clinical Study Drug + Platinum + Other / Chemo	4 (2.8)
		IO Double	1 (0.7)
		IO Double + Chemo / Other	1 (0.7)
		IO Monotherapy + Chemo / Other	2 (1.4)
		IO Monotherapy + TKI + Other / Chemo	1 (0.7)
		Platinum Monotherapy	4 (2.8)
		TKI Double	1 (0.7)

Supplemental Table 2: Systemic Line Name Composition			
Clinical Study Drug		**+ Pt-Chemo + Chemo /Other**	• Cisplatin, Clinical Study Drug, Pemetrexed • Carboplatin, Clinical Study Drug, Paclitaxel • Carboplatin, Clinical Study Drug, Pemetrexed • Clinical Study Drug, Pemetrexed • Bicalutamide, Clinical Study Drug, Leuprolide • Clinical Study Drug, Mesna • Carboplatin, Clinical Study Drug
		+ IO + Chemo/Other	• Clinical Study Drug, Pembrolizumab • Clinical Study Drug, Docetaxel, Pembrolizumab
Immunotherapy	**Monotherapy**	**+ None**	• Durvalumab • Pembrolizumab • Atezolizumab • Rituximab-Pvvr • Nivolumab • Rituximab • Cemiplimab • Rituximab/Hyaluronidase • Rituximab-Abbs-- Cetuximab • Rituximab-Arrx • Trastuzumab-Anns • Daratumumab/Hyaluronidase-Fihj • Bevacizumab • Teclistamab-Cqyv • Bevacizumab-Awwb • Avelumab • Daratumumab • Amivantamab-Vmjw • Ipilimumab
		+ Pt-Chemo	• Cisplatin, Pembrolizumab • Cisplatin, Durvalumab • Carboplatin, Pembrolizumab
		+ Chemo /Other	• Cyclophosphamide, Doxorubicin, Rituximab-Pvvr, Vincristine • Cyclophosphamide, Doxorubicin, Rituximab-Arrx, Vincristine • Leucovorin, Methotrexate, Rituximab-Pvvr • Durvalumab, Leuprolide • Durvalumab, Tamoxifen • Apalutamide, Durvalumab, Leuprolide • Durvalumab, Letrozole, Tamoxifen • Atezolizumab, Tamoxifen • Leuprolide, Pembrolizumab • Obinutuzumab, Venetoclax • Atezolizumab, Leuprolide • Abiraterone, Durvalumab, Leuprolide

			• Daratumumab, Pomalidomide • Daratumumab/Hyaluronidase-Fihj, Pomalidomide • Capecitabine, Durvalumab • Cetuximab, Fluorouracil • Paclitaxel, Trastuzumab-Anns • Bevacizumab-Awwb, Temozolomide • Daratumumab, Lenalidomide • Elotuzumab, Lenalidomide • Durvalumab, Letrozole • Durvalumab, Hydroxyurea • Durvalumab, Paclitaxel • Atezolizumab, Letrozole • Cyclophosphamide, Doxorubicin, Methotrexate, Rituximab-Pvvr, Vincristine • Bevacizumab-Awwb, Fluorouracil, Leucovorin • Cyclophosphamide, Doxorubicin, Leucovorin, Rituximab-Arrx • Anastrozole, Durvalumab, Gemcitabine, Paclitaxel Protein-Bound • Docetaxel, Ramucirumab • Anastrozole, Paclitaxel, Trastuzumab-Anns • Cyclophosphamide, Doxorubicin, Pembrolizumab • Bevacizumab-Awwb, Capecitabine • Gemcitabine, Paclitaxel, Pembrolizumab • Bendamustine, Rituximab-Arrx • Bendamustine, Rituximab • Fluorouracil, Irinotecan, Leucovorin, Pembrolizumab • Bendamustine, Rituximab-Pvvr • Anastrozole, Durvalumab • Bendamustine, Rituximab/Hyaluronidase • Paclitaxel Protein-Bound, Pembrolizumab" • Paclitaxel, Pembrolizumab • Bicalutamide, Nivolumab • Bevacizumab, Pemetrexed • "Nivolumab, Pemetrexed" • "Bevacizumab, Docetaxel, Gemcitabine" • Leuprolide, Nivolumab" • Bevacizumab-Awwb, Pemetrexed" • Cemiplimab, Pemetrexed" • Pembrolizumab, Vinorelbine" • Docetaxel, Gemcitabine, Necitumumab" • Pembrolizumab, Pemetrexed" • Bicalutamide, Leuprolide, Nivolumab • Docetaxel, Nivolumab • Letrozole, Pembrolizumab • Decitabine, Nivolumab • Paclitaxel Protein-Bound, Ramucirumab

			• Lenalidomide, Nivolumab • Paclitaxel, Ramucirumab • Nivolumab, Paclitaxel • Cyclophosphamide, Doxorubicin, Rituximab-Abbs, Vincristine • Everolimus, Paclitaxel, Ramucirumab • Anastrozole, Paclitaxel Protein-Bound, Pembrolizumab • Gemcitabine, Pembrolizumab • Durvalumab, Pemetrexed • Docetaxel, Pembrolizumab • Bevacizumab, Gemcitabine • Capecitabine, Trastuzumab-Qyyp
		+ Pt-Chemo + Chemo /Other	• Fluorouracil, Leucovorin, Oxaliplatin, Trastuzumab-Dttb • Atezolizumab, Carboplatin, Paclitaxel Protein-Bound • Carboplatin, Docetaxel, Pembrolizumab • Bevacizumab-Bvzr, Carboplatin, Paclitaxel, Pemetrexed • Carboplatin, Etoposide, Ifosfamide, Mesna, Rituximab-Arrx • Carboplatin, Gemcitabine, Nivolumab • Carboplatin, Pembrolizumab, Pemetrexed • Cisplatin, Nivolumab, Pemetrexed • Carboplatin, Nivolumab, Pemetrexed • Carboplatin, Docetaxel, Nivolumab • Carboplatin, Nivolumab, Paclitaxel • Carboplatin, Paclitaxel, Pembrolizumab • Carboplatin, Nivolumab, Paclitaxel Protein-Bound • Atezolizumab, Carboplatin, Etoposide • Atezolizumab, Cisplatin, Pemetrexed • Atezolizumab, Carboplatin, Pemetrexed • Cisplatin, Gemcitabine, Nivolumab • Carboplatin, Durvalumab, Paclitaxel • Carboplatin, Paclitaxel, Rituximab-Pvvr • Cisplatin, Fluorouracil, Pembrolizumab • Atezolizumab, Cisplatin, Etoposide • Cemiplimab, Cisplatin, Pemetrexed • Carboplatin, Docetaxel, Durvalumab • Cisplatin, Pembrolizumab, Pemetrexed • Bevacizumab-Awwb, Fluorouracil, Leucovorin, Oxaliplatin • Carboplatin, Durvalumab, Etoposide • Cisplatin, Nivolumab, Paclitaxel • Bevacizumab-Bvzr, Capecitabine, Oxaliplatin • Carboplatin, Docetaxel, Pertuzumab, Trastuzumab-Anns • Bevacizumab, Carboplatin, Paclitaxel • Anastrozole, Bevacizumab, Carboplatin, Paclitaxel

			• Carboplatin, Cetuximab, Paclitaxel • Carboplatin, Paclitaxel, Pembrolizumab, Pemetrexed • Carboplatin, Cemiplimab, Pemetrexed • Carboplatin, Durvalumab, Pemetrexed • Bevacizumab, Carboplatin, Pemetrexed • Carboplatin, Nivolumab, Paclitaxel, Pemetrexed • Bevacizumab-Bvzr, Fluorouracil, Leucovorin, Oxaliplatin • Carboplatin, Paclitaxel Protein-Bound, Pembrolizumab • Fluorouracil, Leucovorin, Oxaliplatin, Pembrolizumab • Durvalumab, Gemcitabine, Paclitaxel Protein-Bound • Cisplatin, Docetaxel, Pembrolizumab • Cisplatin, Docetaxel, Nivolumab, Paclitaxel • Carboplatin, Gemcitabine, Pembrolizumab • Bevacizumab-Maly, Carboplatin, Paclitaxel • Bevacizumab-Bvzr, Carboplatin, Paclitaxel • Atezolizumab, Carboplatin, Paclitaxel Protein-Bound • Atezolizumab, Carboplatin, Paclitaxel • Cisplatin, Paclitaxel, Pembrolizumab • Carboplatin, Cemiplimab, Paclitaxel • "Bevacizumab-Awwb, Carboplatin, Pemetrexed • Atezolizumab, Bevacizumab-Awwb, • Carboplatin, Paclitaxel • Carboplatin, Docetaxel, Paclitaxel, Pembrolizumab • Carboplatin, Leucovorin, Pembrolizumab, Pemetrexed • Bevacizumab-Awwb, Carboplatin, Paclitaxel • Nivolumab, Oxaliplatin, Paclitaxel • Carboplatin, Pemetrexed, Rituximab-Pvvr • Capecitabine, Carboplatin, Paclitaxel, Pembrolizumab • Bevacizumab-Bvzr, Carboplatin, Pemetrexed • Carboplatin, Etoposide, Pembrolizumab • Cemiplimab, Cisplatin, Paclitaxel
		+ TKI	• Bortezomib, Daratumumab/Hyaluronidase-Fihj • Axitinib, Pembrolizumab • Atezolizumab, Crizotinib • Bevacizumab, Niraparib • Bevacizumab, Niraparib, Olaparib

			• Carfilzomib, Daratumumab • Atezolizumab, Carfilzomib • Bortezomib, Daratumumab • Acalabrutinib, Pembrolizumab • Olaparib, Pembrolizumab • Osimertinib, Pembrolizumab • Pembrolizumab, Ribociclib • Ibrutinib, Nivolumab • Lenvatinib, Pembrolizumab • Bevacizumab-Awwb, Sotorasib
		+ TKI + Chemo /Other	• Carfilzomib, Daratumumab/Hyaluronidase-Fihj, Pomalidomide • Capecitabine, Durvalumab, Lapatinib • Anastrozole, Bevacizumab, Niraparib • Bortezomib, Daratumumab, Lenalidomide • Bortezomib, Daratumumab/Hyaluronidase-Fihj, Lenalidomide • Carfilzomib, Cyclophosphamide, Daratumumab/Hyaluronidase-Fihj • Cemiplimab, Nilotinib, Pemetrexed
		+ TKI Double	• Neratinib, Niraparib, Pembrolizumab
	Double	**+ None**	• Ipilimumab, Nivolumab • Pertuzumab, Trastuzumab-Anns • Pertuzumab, Trastuzumab • Pertuzumab, Trastuzumab-Dkst • Atezolizumab, Bevacizumab-Awwb • Durvalumab, Tremelimumab-Actl • Bevacizumab-Awwb, Pembrolizumab • Atezolizumab, Bevacizumab-Bvzr • Pembrolizumab, Rituximab • Pembrolizumab, Ramucirumab • Atezolizumab, Bevacizumab
		+ Chemo /Other	• Letrozole, Pertuzumab, Trastuzumab-Anns • Anastrozole, Pembrolizumab, Trastuzumab-Qyyp • Anastrozole, Pertuzumab, Trastuzumab • Exemestane, Pertuzumab, Trastuzumab-Anns • Daratumumab/Hyaluronidase-Fihj, Lenalidomide • Lenalidomide, Rituximab-Pvvr, Tafasitamab-Cxix • Bendamustine, Pembrolizumab, Rituximab-Abbs • Durvalumab, Paclitaxel Protein-Bound, Tremelimumab-Actl
		+ Pt-Chemo + Chemo /Other	• Atezolizumab, Cisplatin, Durvalumab, Pemetrexed • Carboplatin, Durvalumab, Paclitaxel, Tremelimumab-Actl

			• Carboplatin, Ipilimumab, Nivolumab, Paclitaxel • Anastrozole, Letrozole, Pertuzumab, Trastuzumab-Qyyp • Atezolizumab, Bevacizumab, Carboplatin, Pembrolizumab, Pemetrexed • Carboplatin, Gemcitabine, Ipilimumab, Nivolumab • Carboplatin, Durvalumab, Paclitaxel, Pembrolizumab • Atezolizumab, Bevacizumab, Carboplatin, Paclitaxel • Bevacizumab-Bvzr, Fluorouracil, Leucovorin, Oxaliplatin, Trastuzumab-Qyyp • Atezolizumab, Bevacizumab-Awwb, Carboplatin, Paclitaxel Protein-Bound • Carboplatin, Nivolumab, Pembrolizumab, Pemetrexed • Carboplatin, Docetaxel, Ipilimumab, Nivolumab • Carboplatin, Ipilimumab, Nivolumab, Pemetrexed • Atezolizumab, Bevacizumab-Bvzr, Carboplatin, Pemetrexed • Atezolizumab, Bevacizumab-Bvzr, Carboplatin, Paclitaxel • Carboplatin, Durvalumab, Pembrolizumab, Pemetrexed • Atezolizumab, Bevacizumab-Adcd, Carboplatin, Paclitaxel Protein-Bound • Carboplatin, Cemiplimab, Paclitaxel, Pembrolizumab
		+ TKI + Pt-Chemo + Chemo / Other	• Bortezomib, Carboplatin, Daratumumab/Hyaluronidase-Fihj, Pembrolizumab, Pemetrexed
	Triple	**+ None**	• Ipilimumab, Nivolumab, Rituximab-Pvvr
Pt-Chemotherapy	**Monotherapy**	**+ None**	• Carboplatin • Cisplatin
		+ Chemo /Other	• Apalutamide, Carboplatin, Paclitaxel • Capecitabine, Carboplatin, Paclitaxel • Cisplatin, Etoposide • Carboplatin, Docetaxel • Cisplatin, Pemetrexed • Cisplatin, Docetaxel • Carboplatin, Paclitaxel • Cisplatin, Gemcitabine • Carboplatin, Pemetrexed • Cisplatin, Paclitaxel • Carboplatin, Docetaxel, Paclitaxel Protein-Bound • Fluorouracil, Leucovorin, Oxaliplatin • Carboplatin, Paclitaxel Protein-Bound

			• Carboplatin, Gemcitabine • Carboplatin, Docetaxel, Paclitaxel • Carboplatin, Gemcitabine, Paclitaxel • Carboplatin, Etoposide, Paclitaxel • Carboplatin, Vinorelbine • Cisplatin, Vinorelbine • Anastrozole, Cisplatin, Pemetrexed • Anastrozole, Carboplatin, Paclitaxel • Carboplatin, Paclitaxel, Pemetrexed • Cisplatin, Docetaxel, Gemcitabine • Carboplatin, Leuprolide, Paclitaxel • Carboplatin, Letrozole, Paclitaxel • Fluorouracil, Irinotecan, Leucovorin, Oxaliplatin • Carboplatin, Fluorouracil • Carboplatin, Etoposide • Carboplatin, Gemcitabine, Pemetrexed • Cisplatin, Gemcitabine, Pemetrexed • Cisplatin, Gemcitabine, Methotrexate • Cisplatin, Fluorouracil • Oxaliplatin, Pemetrexed • Cisplatin, Etoposide, Paclitaxel • Carboplatin, Leucovorin, Pemetrexed • Bicalutamide, Cisplatin, Leuprolide, Pemetrexed • Capecitabine, Oxaliplatin • Enzalutamide, Fluorouracil, Oxaliplatin • Cisplatin, Leuprolide, Pemetrexed • Cisplatin, Hydroxyurea, Pemetrexed • Carboplatin, Docetaxel, Gemcitabine • Abiraterone, Cisplatin, Leuprolide, Pemetrexed • Abiraterone, Carboplatin, Paclitaxel • Cisplatin, Pemetrexed, Tamoxifen • Carboplatin, Exemestane, Paclitaxel Protein-Bound • Carboplatin, Enzalutamide, Pemetrexed • Cisplatin, Paclitaxel Protein-Bound • Carboplatin, Letrozole, Paclitaxel, Tamoxifen • Carboplatin, Letrozole, Paclitaxel Protein-Bound • Carboplatin, Docetaxel, Fluorouracil • Carboplatin, Gemcitabine,Tamoxifen
	Double	**+ Chemo/Other**	• Carboplatin, Oxaliplatin, Paclitaxel
Chemotherapy	**Monotherapy**	**+ None**	• Hydroxyurea • Methotrexate • Topotecan • Fluorouracil • Gemcitabine • Paclitaxel • Capecitabine

			• Eribulin • Docetaxel • Carmustine • Lurbinectedin • Paclitaxel Protein-Bound • Pemetrexed • Irinotecan • Cyclophosphamide • Romidepsin • Azacitidine • Melphalan • Temozolomide • Vinorelbine • Doxorubicin
		+ Chemo /Other	• Azacitidine, Venetoclax • Cladribine, Cytarabine • Docetaxel, Leuprolide • Leucovorin, Methotrexate • Capecitabine, Gemcitabine • Fluorouracil, Mitomycin • Gemcitabine, Paclitaxel Protein-Bound • Cyclophosphamide, Docetaxel • Docetaxel, Gemcitabine • Gemcitabine, Paclitaxel • Cyclophosphamide, Doxorubicin • Capecitabine, Temozolomide • Exemestane, Lenalidomide • Lenalidomide, Melphalan • Bicalutamide, Capecitabine, Leuprolide • Anastrozole, Gemcitabine, Paclitaxel Protein-Bound • Cyclophosphamide, Docetaxel, Letrozole • Busulfan, Cyclophosphamide, Fludarabine, Mesna • Bleomycin, Dacarbazine, Doxorubicin, Vinblastine • Capecitabine, Mitomycin • Gemcitabine, Vinorelbine • Gemcitabine, Hydroxyurea • Cyclophosphamide, Pomalidomide
TKI	**Monotherapy**	**+ None**	• Osimertinib • Ruxolitinib • Dasatinib • Asciminib • Olaparib • Acalabrutinib • Palbociclib • Ibrutinib • Vismodegib • Axitinib • Regorafenib • Erdafitinib • Neratinib

			• Sotorasib • Zanubrutinib • Lenvatinib • Alpelisib • Afatinib • Adagrasib • Nintedanib • Carfilzomib • Pazopanib • Abemaciclib • Umbralisib • Alectinib • Imatinib • Entrectinib • Fedratinib • Bortezomib • Nilotinib • Capmatinib • Lorlatinib • Tepotinib • Sunitinib • Pralsetinib • Erlotinib • Crizotinib • Selpercatinib • Brigatinib • Larotrectinib • Dabrafenib
		+ Pt-Chemo + Chemo /Other	• Carboplatin, Osimertinib, Pemetrexed • Bortezomib, Carboplatin, Lenalidomide, Paclitaxel • Capecitabine, Carboplatin, Lapatinib, Pemetrexed • Cemiplimab, Cisplatin, Nilotinib, Pemetrexed • Carboplatin, Nintedanib, Pemetrexed • Carboplatin, Osimertinib, Paclitaxel • Carboplatin, Gemcitabine, Ibrutinib
		+ Chemo /Other	• Bortezomib, Cyclophosphamide, Doxorubicin Pegylated Liposomal • Letrozole, Palbociclib • Carfilzomib, Cyclophosphamide, Pomalidomide • Anastrozole, Ibrutinib • Letrozole, Osimertinib • Anastrozole, Osimertinib • Anastrozole, Palbociclib • Fulvestrant, Olaparib • Fluorouracil, Vismodegib • Fulvestrant, Palbociclib • Bortezomib, Enzalutamide, Leuprolide, Paclitaxel • Abemaciclib, Fulvestrant

			• Doxorubicin Pegylated Liposomal, Olaparib • Carfilzomib, Cyclophosphamide • Bortezomib, Methotrexate • Exemestane, Osimertinib • Bortezomib, Cyclophosphamide • Bortezomib, Lenalidomide • Osimertinib, Tamoxifen • Carfilzomib, Pomalidomide • Ixazomib, Pomalidomide • Abemaciclib, Anastrozole • Acalabrutinib, Gemcitabine • Leuprolide, Selpercatinib • Gemcitabine, Olaparib • Sotorasib, Tamoxifen • Osimertinib, Paclitaxel Protein-Bound
	Double	**+ None**	• Ibrutinib, Osimertinib • Dabrafenib, Trametinib • Erlotinib, Osimertinib • Binimetinib, Encorafenib • Osimertinib, Ruxolitinib
Other	**Monotherapy**	**+ None**	• Tamoxifen • Enzalutamide • Apalutamide • Tretinoin • Bcg Vaccine • Leuprolide • Exemestane • Venetoclax • Bicalutamide • Triptorelin • Eflornithine • Porfimer • Leucovorin • Anastrozole • Letrozole • Degarelix • Everolimus • Lenalidomide • Abiraterone • Fulvestrant • Darolutamide
		+ Chemo/Other	• Bicalutamide, Leuprolide • Apalutamide, Leuprolide • Darolutamide, Leuprolide • Enzalutamide, Leuprolide • Anastrozole, Exemestane • Abiraterone, Leuprolide • Degarelix, Relugolix • Enzalutamide, Triptorelin • Anastrozole, Letrozole • Abiraterone, Degarelix, Enzalutamide • Abiraterone, Bicalutamide, Leuprolide

			• Exemestane, Letrozole • Enzalutamide, Relugolix • Bicalutamide, Lenvatinib, Leuprolide
ADC	**Monotherapy**	**+ None**	• Sacituzumab Govitecan-Hziy • Brentuximab Vedotin • Enfortumab Vedotin-Ejfv • Fam-Trastuzumab Deruxtecan-Nxki • Fam-Trastuzumab Deruxtecan-Nxki, Letrozole
		+ IO + Chemo /Other	• Brentuximab Vedotin,Dacarbazine, Doxorubicin,Vinblastine • Cyclophosphamide, Doxorubicin, Polatuzumab Vedotin-Piiq, Rituximab-Pvvr • Enfortumab Vedotin-Ejfv, Pembrolizumab