Original Article

# Association of systemic therapy with survival among adults with advanced non-small cell lung cancer

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**Background:** Uptake of new systemic therapy treatments among patients with advanced non-small cell lung cancer (NSCLC) occurred rapidly after FDA approval. Few studies have characterized the association of these therapies on survival in community settings. We assessed survival by type of systemic therapy received among patients diagnosed with advanced NSCLC who were treated in community-based settings.

**Methods:** In this retrospective cohort, patients diagnosed with de novo stage IV NSCLC between March 2012 and December 2020 were followed through December 31, 2021. Survival was ascertained with restricted mean survival time from treatment receipt through 12 and 60 months and compared by RMST differences adjusting for demographic and tumor characteristics. Trends in one-year survival probabilities were assessed using joinpoint regression.

**Results:** Of 945 patients receiving systemic therapy, 46% received cytotoxic chemotherapy (Chemo-Only), 15% bevacizumab +/– Chemo, 22% immunotherapy +/– Chemo, and 16% targeted therapies. Median days from diagnosis to treatment ranged from 32 to 42. Compared to those receiving Chemo-Only, patients receiving immunotherapy +/– Chemo survived 1.4 months longer [95% confidence interval (CI): 0.5 to 2.3 months; P=0.002] and 3.2 months longer (95% CI: –1.4 to 7.9 months; P=0.18) through 12 and 60 months follow-up, respectively. Relative to those receiving Chemo-Only, patients receiving targeted therapies survived 1.6 months longer (95% CI: 0.7 to 2.5 months; P<0.001) and 5.5 months longer (95% CI: 0.7 to 10.4 months; P=0.02) through 12- and 60-months follow-up. One-year survival significantly increased from 30% to 59% between 2012 and 2020 (P=0.007).

**Conclusions:** We found patients receiving targeted therapies and immunotherapy +/– Chemo survived longer than those on Chemo-Only. One-year survival probabilities significantly increased between 2012 and 2020. Additional research is needed to better understand the potential benefits and harms, including patient adverse events and financial toxicity.

**Keywords:** Non-small cell lung cancer (NSCLC); first-course treatment; restricted mean survival time (RMST); immunotherapy; targeted therapies

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## Introduction

### *Background*

Lung cancer remains the leading cause of cancer death in the US despite implementation of lung cancer screening, advancements in radiotherapy, and rapid approval and uptake of new systemic therapies to treat those with advanced disease (1). Advances in understanding the biologic mechanisms of tumor growth allowed for evolution in cancer treatments through the identification of molecular targets (2). This resulted in systemic therapy treatment guidelines for patients diagnosed with advanced non-small cell lung cancer (NSCLC) quickly shifting from platinum-based chemotherapy to anti-angiogenesis inhibitors such as bevacizumab, and more recently, to new immunotherapies and targeted therapies (3-5). Bevacizumab is a recombinant humanized monoclonal antibody and, in 2006, became the first clinically used angiogenesis inhibitor for treatment of NSCLC (2). Since 2006, therapies targeting actionable mutations such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and c-ros oncogene1 (ROS1) have improved outcomes for NSCLC patients in clinical trials (6-9). Additionally, the introduction of immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) in the first-line setting with or without chemotherapy provided additional therapeutic options in 2016 (10-15). These new therapies have led to a decrease in the proportion of patients who receive platinum-based chemotherapy. In 2012, 65% of patients in an advanced NSCLC cohort received only cytotoxic chemotherapy, however, by 2020 that proportion dropped to 12% (3,16).

**Highlight box**

**Key findings**

- Relative to patients receiving cytotoxic chemotherapy, patients receiving targeted agents survived 21% longer through 12 months and 31% longer through 60 months of follow-up.
- Relative to patients receiving cytotoxic chemotherapy, patients receiving systemic therapy that includes immunotherapy survived 19% longer through 12 months of follow-up but had similar survival through 60 months of follow-up.
- Overall, 1-year survival increased significantly from 30% in 2012 to 59% in 2020.

**What is known and what is new?**

- Uptake of immunotherapy and targeted therapies occurred quickly after Food and Drug Administration approval among patients with advanced non-small cell lung cancer (NSCLC).
- Few studies have characterized the association of these therapies on overall survival in community settings.
- We describe survival by type of systemic therapy received among patients with advanced NSCLC.

**What is the implication, and what should change now?**

- Modest increased survival was observed among patients receiving newer systemic therapy treatments.
- Additional research is needed to better understand the potential benefits and harms, including patient adverse events and financial toxicity.

### *Rationale and knowledge gap*

Few studies have evaluated the association of this shift in therapy on survival among patients with advanced NSCLC in community settings outside of randomized clinical trials (RCTs). Assessing treatment related survival patterns outside of clinical trial populations is important because patients selected into clinical trials often do not reflect the characteristics of patients in real-world community settings who are not randomized into tightly controlled RCTs (17-21). Evaluating changes in survival by type of systemic therapy received is critical to generate additional evidence as to the magnitude of benefit of treatments outside of RCT findings (18).

Moreover, the methodology used in most current studies often assess survival using hazard ratios (I) that are difficult to translate into clinical practice, and (II) whose proportional hazard assumptions are often violated (5,22,23). Using other easy-to-interpret methods that do not rely on proportional hazards assumptions helps to quantify the absolute rather than the relative differences in survival associated with these novel treatments (24).

### *Objective*

In this study, we used restricted mean survival time (RMST) to address gaps in the literature on survival among patients diagnosed with advanced NSCLC who are treated in community-based settings with different types of systemic

therapy. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-749/rc).

## Methods

### *Study setting and data sources*

Data for this retrospective cohort study were obtained from 4 diverse healthcare systems that participate in the Population-based Research to Optimize the Screening Process (PROSPR)-Lung consortium: Henry Ford Health, the Kaiser Permanente regions of Colorado and Hawaii, and Marshfield Clinic Health System (25). The PROSPR-Lung Consortium developed a Common Data Model (CDM) which contains standardized EHR-derived patient demographics, procedures, diagnoses, infused therapies, and pharmacy dispenses (26-28). Socioeconomic status (SES) was assessed through census-based indices calculated by mapping the patient's residential address to census tract data using geocoding software. Cancer registry data were derived from abstracted tumor registry data consistent with the North American Association of Central Cancer Registries standards (29). Death data were derived from cancer registries, health plan membership data, and state level death datasets. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Interregional Institutional Review Board (IRB) of Kaiser Permanente (No. 00013581) and individual consent for this retrospective analysis was waived.

### *Study population*

Consistent with the identification of our cohort and associated methods described in Carroll *et al.* (3), patients meeting the following criteria were included in this study: patients between the ages of 35 and 89 years at the time of *de novo* stage IV NSCLC diagnosis between March 1, 2012 and December 31, 2020. In addition, patients had to be either an enrolled member in the healthcare system at the time of diagnosis or had a recorded primary care encounter in the year prior to their lung cancer diagnosis and survive a minimum of 30 days post diagnosis. Patients were followed from the start of systemic therapy treatment until the end of the study period (December 31, 2021), death, or the date of their last documented encounter within the health system, whichever occurred first.

Information on first-line systemic therapy, age at diagnosis, tumor characteristics, sex, and self-reported race and ethnicity were collected from cancer registry data, EHR, and claims data within the CDM. Those identifying in a racial group that comprised less than 1% of the study population and those with unknown race were categorized as "unknown/another race". This included individuals identifying as American Indian and multiple races. Cigarette smoking status was assessed at the closest recorded encounter prior to lung cancer diagnosis and was categorized as current, former, never, and unknown. The last body mass index (BMI) captured prior to a patient's lung cancer diagnosis was captured and categorized into the following categories: healthy (<25 kg/m$^2$), overweight (25–29 kg/m$^2$), obese (30 or more kg/m$^2$), and unknown. The Deyo adaptation of the Charlson comorbidity index (CCI) was used to assess the comorbidity burden of all patients (30,31). SES was assessed by the Yost index, an area-level composite measure of SES that is comprised of household income, poverty, rent, home value, employment, education, and working class (32,33).

Receipt of first-line systemic therapy was defined as the receipt of at least one cytotoxic chemotherapy, anti-angiogenesis, immunotherapy, or molecularly targeted therapy agent administered to the patient within 180 days of diagnosis (16,34-36). Bevacizumab is an anti-angiogenesis inhibitor which prevents the growth of new blood vessels that feed tumors by targeting vascular endothelial growth factor (VEGF) and is considered a different therapeutic treatment relative to an immune checkpoint inhibitor which targets the cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), or its ligand-1 (PD-L1). (37,38). The distinction between the two types of therapies have been highlighted in recent studies comparing the effectiveness of bevacizumab to immunotherapy treatments (39,40). Therefore, we made the decision to categorize any regimen containing bevacizumab as its own category and define checkpoint inhibitors as immunotherapy. A previously developed algorithm was used to identify all regimens for each patient's entire course of systemic therapy treatment (36,41). The first systemic therapy agent administered is identified and all additional systemic therapy agents received within 10 days of the first systemic therapy agent is considered part of the same regimen. The first regimen received was considered first-line systemic therapy.

First-line systemic therapy regimens were grouped as follows: "Chemo-Only" contained regimens that included cytotoxic chemotherapy agents with no anti-

 

angiogenesis, immunotherapy, or targeted therapy agents; "Beva +/– Chemo" contained regimens that included bevacizumab with or without a cytotoxic chemotherapy agent; "IMO +/– Chemo" contained regimens that included all immunotherapy agents with or without a cytotoxic chemotherapy agent; and "Targeted" contained regimens of targeted therapy agents (*Table 1*).

### *Statistical analysis*

Patient characteristics were stratified by type of first-line systemic therapy and differences in baseline characteristics between types of first-line systemic therapy were evaluated using the Chi-squared test.

The primary outcome was overall survival and was defined as the number of months from start of treatment to date of death from any cause. Patients who were alive at the date of their last documented encounter within the health system were censored on that date. Differences in overall survival by type of treatment was ascertained using unadjusted and multivariable adjusted RMST through 12 months and, separately, through 60 months follow-up (42). RMST represents the area under the survival curve between 0 and a patient specific observed interval of time (12 and 60 months) (24,43,44). The treatment effect was expressed as the difference in RMST between the types of systemic therapy with confidence intervals constructed through the standard error of the difference in RMST (45). The RMST difference represents the length of average gain or loss in life expectancy (43). RMST was chosen (I) for its model-free properties since the proportional hazards assumption was violated in our cohort, and (II) its ability to present survival as both an absolute and relative measure of survival (45). The multivariable RMST model was adjusted for histology, sex, race and ethnicity, health system, CCI, year of diagnosis, receipt of surgery as part of first course therapy, receipt of radiation as part of first-course therapy, age, smoking status, BMI, each person's total number of lines of therapy, and the Yost Index. Multivariable adjusted RMST for Beva +/– Chemo, IMO +/– Chemo, and targeted were compared separately to Chemo-Only. Differences in survival were assessed by adjusted RMST (aRMST) differences and 95% confidence intervals (CIs) and aRMST ratios and 95% CIs. Trends of one-year survival probabilities over time were assessed by joinpoint regression analysis and average annual percent change (AAPC) (46). AAPC uses segmented regression allowing for significant breakpoints in the time series and is computed as a weighted average of the annual percent changes estimated over each time segment. We estimated the AAPCs by fitting a log-linear segmented regression model with no breakpoints and assumed homoscedasticity and autocorrelation of the random errors. The 95% CIs of the AAPCs were calculated using a parametric approach based on the normal distribution (46). Kaplan Meier curves were created to graphically depict unadjusted survival and were compared with a log-rank test.

Analyses were performed using SAS® Software version 9.4M6 (SAS Institute Inc., Cary, NC, USA), Joinpoint Regression Program (47), and RStudio (Rstudio Team, 2023) using the "survRM2" package (48).

## Results

A total of 949 patients received any type of first-line systemic therapy between 2012 and 2020 (*Figure 1*). Four patients receiving systemic therapy regimens not indicated for NSCLC were excluded from further analyses, leaving 945 patients; 438 (46%) received Chemo-Only, 141 (15%) received Beva +/– Chemo, 211 (22%) received IMO +/– Chemo, and 155 (16%) received targeted therapies (*Table 2*). The percentage of patients receiving IMO +/– Chemo increased from 7.0% in 2016 to 66.1% in 2020 while patients receiving Chemo-Only decreased from 65.2% in 2012 to 11.9% in 2020 (*Figure 2*; P<0.001). The percentage of patients receiving targeted therapies varied over time starting at 20% in 2012 and ending at 22% in 2020 (P=0.053).

Compared with patients receiving Chemo-Only, Beva +/– Chemo, and IMO +/– Chemo, patients receiving targeted therapies were more likely to have adenocarcinomas (56% *vs.* 89% *vs.* 73% *vs.* 92%); were more likely to be female (46% *vs.* 49% *vs.* 46% *vs.* 69%); were less likely to be White (68% *vs.* 77% *vs.* 65% *vs.* 45%); were more likely to have never smoked cigarettes (11% *vs.* 16% *vs.* 14% *vs.* 56%); and were more likely to have the highest Yost index (i.e., most affluent; 14% *vs.* 11% *vs.* 22% *vs.* 28%; *Table 2*). Overall median follow-up time was 65 months (95% CI: 59–72 months), 82 months (95% CI: 67–92 months), 34 months (95% CI: 30–38 months), and 50 months (95% CI: 40–62 months) for those receiving Chemo-Only, Beva +/– Chemo, IMO +/– Chemo, and targeted therapies, respectively.

### *Unadjusted survival*

Patients receiving targeted therapies started treatment

**Table 1** First-line systemic therapy regimens observed among patients diagnosed with advanced non-small lung cancer, 2012–2020

| Regimen | N |
|---|---|
| Chemo-Only | |
| CARBOPLATIN/PEMETREXED | 143 |
| CARBOPLATIN/PACLITAXEL | 138 |
| CARBOPLATIN/GEMCITABINE | 42 |
| CISPLATIN/PEMETREXED | 32 |
| CISPLATIN/ETOPOSIDE | 21 |
| CISPLATIN/GEMCITABINE | 13 |
| CHEMOTHERAPY NOS | 12 |
| PEMETREXED | 10 |
| CARBOPLATIN/ETOPOSIDE | 8 |
| PACLITAXEL | 6 |
| DOCETAXEL | 3 |
| VINORELBINE | 3 |
| CARBOPLATIN | 2 |
| CISPLATIN/DOCETAXEL | 2 |
| CISPLATIN | 1 |
| CISPLATIN/ETOPOSIDE/PACLITAXEL | 1 |
| CISPLATIN/PACLITAXEL | 1 |
| Beva +/– Chemo | |
| BEVACIZUMAB/CARBOPLATIN/PEMETREXED | 58 |
| BEVACIZUMAB/CARBOPLATIN/PACLITAXEL | 50 |
| BEVACIZUMAB/CISPLATIN/PEMETREXED | 27 |
| BEVACIZUMAB | 4 |
| BEVACIZUMAB/CARBOPLATIN/ETOPOSIDE | 1 |
| BEVACIZUMAB/CISPLATIN/DOXORUBICIN | 1 |
| IMO +/– Chemo | |
| CARBOPLATIN/PEMBROLIZUMAB/PEMETREXED | 87 |
| PEMBROLIZUMAB | 84 |
| CARBOPLATIN/PACLITAXEL/PEMBROLIZUMAB | 26 |
| NIVOLUMAB | 6 |
| ATEZOLIZUMAB/CARBOPLATIN/ETOPOSIDE | 3 |
| CISPLATIN/PEMBROLIZUMAB/PEMETREXED | 2 |
| IPILUMUMAB/NIVOLUMAB | 2 |
| ATEZOLIZUMAB/CARBOPLATIN/PACLITAXEL | 1 |
| Targeted | |
| ERLOTINIB | 66 |
| OSIMERTINIB | 31 |
| CRIZOTINIB | 23 |
| GEFITINIB | 16 |
| ALECTINIB | 10 |
| AFATINIB | 5 |
| DABRAFENIB/TRAMETINIB | 2 |
| NINTEDANIB | 1 |
| SELPERCATINIB | 1 |

Beva, bevacizumab; Chemo, chemotherapy; IMO, immunotherapy.

sooner relative to patients receiving Chemo-Only, Beva +/– Chemo, and IMO +/– Chemo (34 *vs.* 45 *vs.* 45 *vs.* 46 mean days, respectively; P<0.001; *Table 3*). Patients receiving Chemo-Only had the shortest median time from treatment start to death: 8.2 months (95% CI: 6.9–9.5 months). The median survival for those receiving Beva +/– Chemo was 11.7 months (95% CI: 9.6–15.1 months), 13.7 months (95% CI: 9.9–16.3 months) for those receiving IMO +/– Chemo, and 24.5 months (95% CI: 16.7–29.5 months) for those receiving Targeted therapies (*Figure 3*, *Table 3*). Unadjusted RMST through 12 months was 7.6, 8.8, 8.6, and 9.7 months for those receiving Chemo-Only, Beva +/– Chemo, IMO +/– Chemo, and targeted therapies, respectively. Through 60 months, unadjusted RMST was 16.1, 20.1, 22.9, and 27.5 months for those receiving Chemo-Only, Beva +/– Chemo, IMO +/– Chemo, and targeted therapies, respectively.

### *Multivariable adjusted survival*

After multivariable adjustment through 12 months follow-up (*Table 4*), patients receiving Beva +/– Chemo had similar survival relative to those receiving Chemo-Only (aRMST difference =0.6 months; 95% CI: 0.1 to 1.4 months; P=0.10). Similar survival persisted at 60 months of follow-up with an aRMST difference of 1.5 (95% CI: –2.2 to 5.1) months (P=0.44). Patients receiving IMO +/– Chemo had longer survival relative to those who received Chemo-only (aRMST difference =1.4 months; 95% CI: 0.5 to

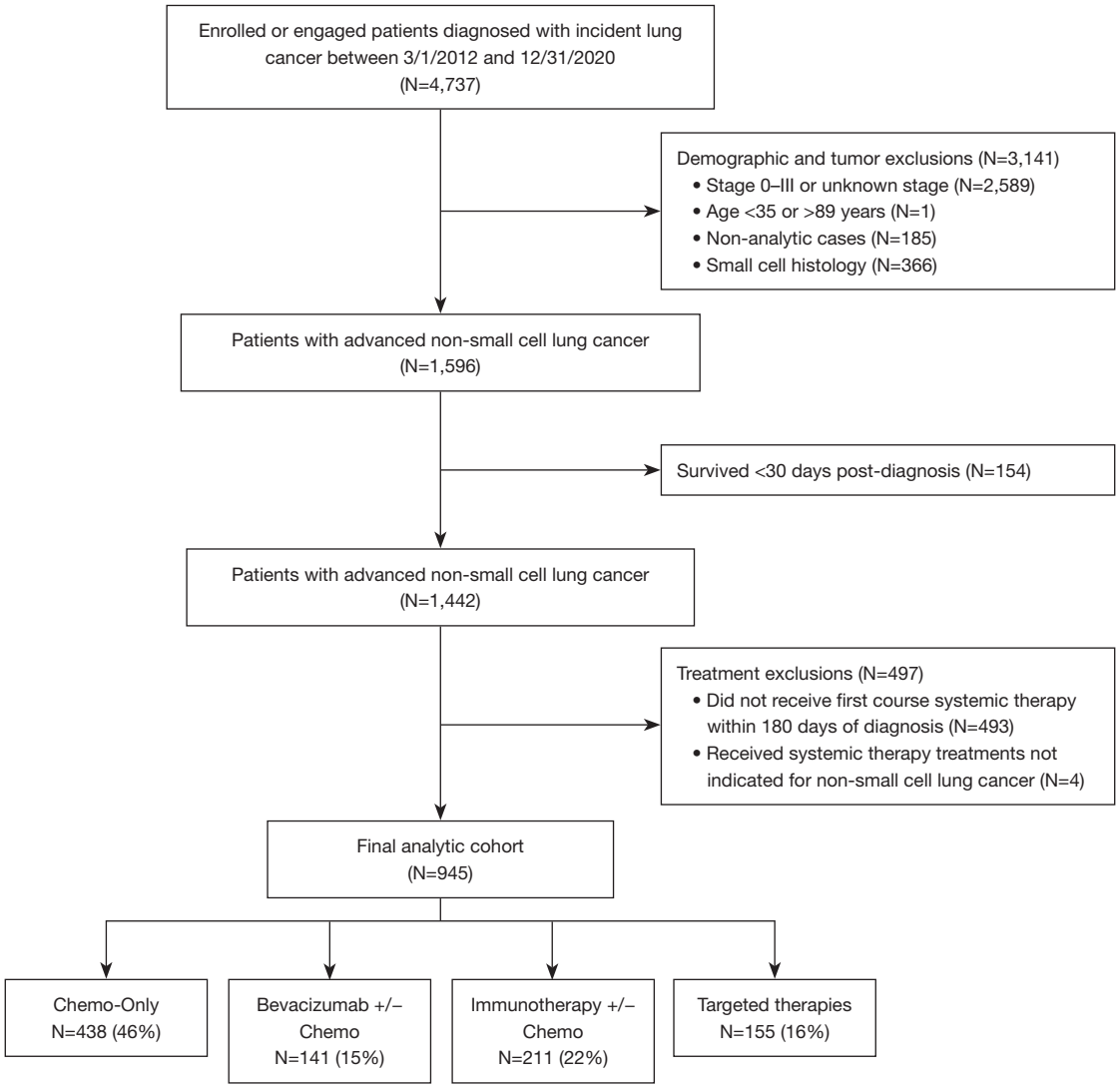


**Figure 1** Waterfall diagram of patients selected for this study. Chemo, chemotherapy.

2.3 months; P=0.002). Through 60 months of follow-up, this difference was abated with an aRMST difference of 3.2 (95% CI: −1.4 to 7.9) months (P=0.18). Compared to those who received Chemo-only, patients receiving targeted therapies had longer survival through 12 months of follow-up (aRMST difference =1.6; 95% CI: 0.7 to 2.5 months; P<0.001). Through 60 months of follow-up, the difference increased to 5.5 (95% CI: 0.7 to 10.4) months (P=0.02).

Factors that were independently associated with multivariable adjusted RMST were estimated (*Table 5*). The coefficient value listed for each characteristic represents the number of additional months of survival gained or lost if that characteristic was present, relative to the reference group for that covariate. After 60 months of follow-up, having an unknown or another race had the largest negative effect on RMST (−6.2 months; P=0.004) and Hispanic race and ethnicity had a 6.1 month decrease in survival (P=0.01) while receipt of surgery as part of first course therapy was associated with longer survival for patients receiving Beva +/− Chemo (10.8 months; P=0.04). Receipt of radiation as part of first course therapy had the largest positive effect for patients receiving IMO +/− Chemo (3.8 months; P=0.02) and unknown or another race was associated with inferior RMST (−6.4 months; P=0.03). For patients receiving targeted therapies, being female was associated with 4.3 months longer survival (P=0.009) and being between 64

 

**Table 2** Demographic and tumor characteristics among patients diagnosed with advanced NSCLC by type of first-line systemic therapy received, 2012–2020

| Characteristics | Patients receiving Chemo-Only | Patients receiving Beva +/– Chemo | Patients receiving IMO +/– Chemo | Patients receiving targeted therapies | All patients receiving first-line systemic therapy | P value[†] |
|---|---|---|---|---|---|---|
| Total number of patients | 438 [46] | 141 [15] | 211 [22] | 155 [16] | 945 [100] | |
| Follow-up time (months) | 65 (59 to 72) | 81 (67 to 92) | 34 (30 to 38) | 50 (40 to 62) | 54 (47 to 62) | N/A |
| Histology | | | | | | <0.001 |
| Adenocarcinoma | 245 [56] | 126 [89] | 154 [73] | 143 [92] | 668 [71] | |
| Squamous | 123 [28] | <5 | 35 [17] | <5 | 116 [12] | |
| All other NSCLC | 70 [16] | 14 [10] | 22 [10] | 10 [7] | 161 [17] | |
| Year of diagnosis | | | | | | <0.001 |
| 2012 | 45 [10] | 10 [7] | <5 | 14 [9] | 69 [7] | |
| 2013 | 70 [16] | 26 [18] | <5 | 7 [5] | 103 [11] | |
| 2014 | 66 [15] | 28 [20] | <5 | 19 [12] | 113 [12] | |
| 2015 | 74 [17] | 33 [23] | <5 | 18 [12] | 125 [13] | |
| 2016 | 70 [16] | 21 [15] | 9 [4] | 29 [19] | 129 [14] | |
| 2017 | 61 [14] | 11 [8] | 43 [20] | 26 [17] | 141 [15] | |
| 2018 | 31 [7] | 12 [9] | 59 [28] | 20 [13] | 122 [13] | |
| 2019 | 14 [3] | <5 | 61 [29] | 9 [6] | 84 [9] | |
| 2020 | 7 [2] | <5 | 39 [19] | 13 [8] | 59 [6] | |
| Sex | | | | | | <0.001 |
| Female | 201 [46] | 69 [49] | 96 [45] | 107 [69] | 473 [50] | |
| Male | 237 [54] | 72 [51] | 115 [55] | 48 [31] | 472 [50] | |
| Race and ethnicity | | | | | | <0.001 |
| Asian | 31 [7] | 6 [4] | 19 [9] | 43 [28] | 99 [10] | |
| Black | 54 [12] | 16 [11] | 22 [10] | 9 [6] | 101 [11] | |
| Hispanic | 16 [4] | <5 | 7 [3] | 7 [5] | 33 [3] | |
| Native Hawaiian/Pacific Islander | 18 [4] | 4 [3] | 14 [7] | 18 [12] | 54 [6] | |
| Unknown/another race[‡] | 23 [5] | <5 | 12 [6] | 9 [6] | 47 [5] | |
| White | 296 [68] | 109 [77] | 137 [65] | 69 [45] | 611 [65] | |
| Age at diagnosis (years) | | | | | | 0.12 |
| 35–64 | 169 [39] | 63 [45] | 85 [40] | 75 [48] | 392 [41] | |
| 65–74 | 162 [37] | 53 [38] | 82 [39] | 42 [27] | 339 [36] | |
| 75–89 | 107 [24] | 25 [18] | 44 [21] | 38 [25] | 214 [23] | |
| Smoking status at diagnosis | | | | | | <0.001 |
| Current | 146 [33] | 44 [31] | 64 [30] | 11 [7] | 265 [28] | |
| Never | 47 [11] | 22 [16] | 29 [14] | 86 [55] | 184 [20] | |
| Former | 217 [50] | 65 [46] | 114 [54] | 49 [32] | 445 [47] | |
| Unknown/missing | 28 [6] | 10 [7] | <5 | 9 [6] | 51 [5] | |

**Table 2** (*continued*)

**Table 2** (*continued*)

| Characteristics | Patients receiving Chemo-Only | Patients receiving Beva +/– Chemo | Patients receiving IMO +/– Chemo | Patients receiving targeted therapies | All patients receiving first-line systemic therapy | P value[†] |
|---|---|---|---|---|---|---|
| Charlson comorbidity index (1 year prior to diagnosis)[§] | | | | | | 0.12 |
| 0 | 85 [19] | 33 [23] | 31 [15] | 36 [23] | 185 [20] | |
| 1–2 | 103 [24] | 34 [24] | 59 [28] | 48 [31] | 244 [26] | |
| 3+ | 250 [57] | 74 [53] | 121 [57] | 71 [46] | 516 [55] | |
| BMI status at diagnosis (kg/m$^2$) | | | | | | 0.96 |
| <25 (healthy) | 179 [41] | 56 [40] | 87 [41] | 68 [44] | 390 [41] | |
| 25–29 (overweight) | 142 [32] | 46 [33] | 67 [32] | 48 [31] | 303 [32] | |
| 30+ (obese) | 103 [24] | 36 [26] | 54 [26] | 35 [23] | 228 [24] | |
| Unknown | 14 [3] | <5 | <5 | 5 [3] | 25 [3] | |
| Yost state quintile (census based) | | | | | | <0.001 |
| Quintile 1 (lowest) | 104 [24] | 31 [22] | 41 [19] | 22 [14] | 198 [21] | |
| Quintile 2 | 101 [23] | 22 [16] | 31 [15] | 21 [14] | 175 [19] | |
| Quintile 3 | 100 [23] | 40 [28] | 51 [24] | 32 [21] | 223 [24] | |
| Quintile 4 | 70 [16] | 32 [23] | 41 [19] | 36 [23] | 179 [19] | |
| Quintile 5 (highest) | 63 [14] | 16 [11] | 47 [22] | 44 [28] | 170 [18] | |
| Receipt of surgery as part of first course therapy (tumor registry based) | | | | | | 0.40 |
| No | 427 [97] | 135 [96] | 207 [98] | 153 [99] | 922 [98] | |
| Yes | 11 [3] | 6 [4] | <5 | <5 | 23 [2] | |
| Receipt of radiation as part of first course therapy (tumor registry based) | | | | | | 0.57 |
| No | 133 [30] | 49 [35] | 74 [35] | 53 [34] | 309 [33] | |
| Yes | 305 [70] | 92 [65] | 137 [65] | 102 [66] | 636 [67] | |
| Total lines of therapy[¶] | 1.7±0.8 | 1.7±0.9 | 1.3±0.6 | 1.4±0.8 | 1.6±0.8 | 0.14 |

Data are presented as n [%], median (25$^{th}$ to 75$^{th}$ percentile) or mean ± standard deviation. [†], groups compared with the Chi-squared test; [‡], another race includes patients self-identifying as American Indian (<1%) and multiple races (<1%); [§], modified Charlson comorbidity index excludes HIV/AIDS diagnoses; [¶], groups compared with ANOVA. NSCLC, non-small cell lung cancer; Chemo, chemotherapy; Beva, bevacizumab; IMO, immunotherapy; N/A, not applicable; BMI, body mass index; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ANOVA, analysis of variance.

and 74 was the factor associated with the largest reduction in RMST (–6.6 months; P<0.001).

### *Changes in survival over time*

Overall, 1-year survival probabilities significantly increased from 30.4% in 2012 to 58.5% in 2020 (AAPC =6.1; 95% CI: 2.2 to 10.1; P=0.007; *Figure 4*). Among patients receiving Chemo-Only, 1-year survival increased from 24.4% in 2012 to 71.4% in 2020 (AAPC =9.3; 95% CI: 0.3 to 19.0; P=0.04). Small sample sizes drove outliers of high 1-year survival in 2019 and 2020. Limiting the years of observation to 2012–2018 for those receiving Chemo-Only, the 1-year survival increased from 24.4% in 2012 to 35.5% in 2018 (AAPC =1.5; 95% CI: –8.9 to 13.1; P=0.74). Eliminating these outliers had little effect on 1-year survival overall with the survival increasing from 30.4% in 2012 to 56.7% in 2020 (AAPC =5.6; 95% CI: 1.7 to 9.7; P=0.01). Among patients receiving Beva +/– Chemo, 1-year survival increased from 40.0% in 2012 to 41.7% in 2018 (AAPC

 

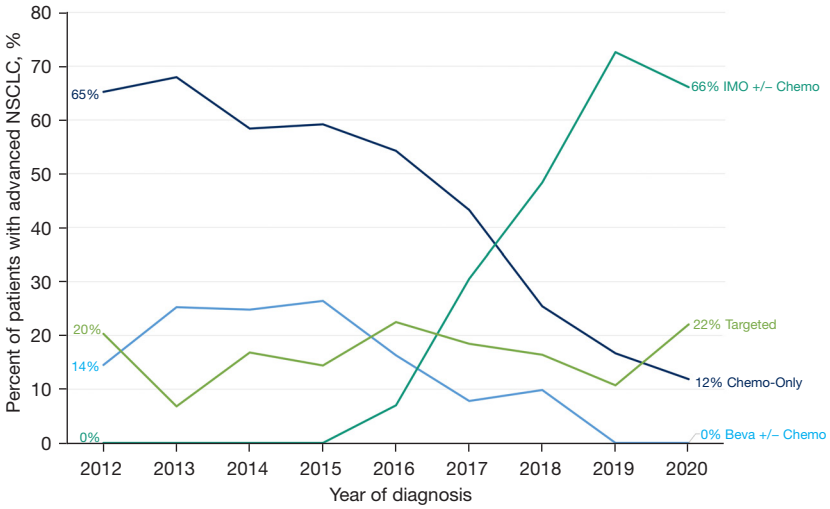


**Figure 2** Type of systemic therapy treatment received among patients with stage IV NSCLC, 2012–2020. NSCLC, non-small cell lung cancer; IMO, immunotherapy; Chemo, chemotherapy; Beva, bevacizumab.

**Table 3** Unadjusted estimates of survival by type of first-line systemic therapy, 2012–2020

| Measure | Chemo-Only | Beva +/– Chemo | IMO +/– Chemo | Targeted | P value |
|---|---|---|---|---|---|
| Days from diagnosis to treatment start, median (25th to 75th percentile) | 40 (28 to 57) | 40 (26 to 60) | 42 (30 to 56) | 32 (22 to 42) | <0.001† |
| RMST at 12 months (months) (95% CI) | 7.6 (7.2 to 8.0) | 8.8 (8.2 to 9.5) | 8.6 (8.0 to 9.1) | 9.7 (9.1 to 10.4) | <0.001‡ |
| RMST at 60 months (months) (95% CI) | 16.1 (14.3 to 17.8) | 20.1 (16.9 to 23.3) | 22.9 (19.7 to 26.2) | 27.5 (24.0 to 31.0) | <0.001‡ |
| Median survival (months) (95% CI) | 8.2 (6.9 to 9.5) | 11.7 (9.6 to 15.1) | 13.7 (9.9 to 16.3) | 24.5 (16.7 to 29.5) | <0.001§ |
| 1-year survival | 38.5% | 48.9% | 52.3% | 67.4% | NA |
| 2-year survival | 22.2% | 30.3% | 35.4% | 51.2% | NA |
| 3-year survival | 15.7% | 19.2% | 28.8% | 33.4% | NA |
| 4-year survival | 12.0% | 16.9% | 19.6% | 24.1% | NA |
| 5-year survival | 8.5% | 10.7% | 19.6% | 18.5% | NA |

†, comparison by the Kruskal-Wallis test; ‡, comparison by the test of equality; §, comparison by the log rank test. Chemo, chemotherapy; Beva, bevacizumab; IMO, immunotherapy, RMST, restricted mean survival time; CI, confidence interval; NA, not applicable.

=1.8; 95% CI: −9.6 to 14.6; P=0.72). Among patients receiving IMO +/− Chemo, 1-year survival changed from 44.4% in 2016 to 53.1% in 2020 (AAPC =3.7; 95% CI: −6.3 to 14.8; P=0.34). One-year survival for patients receiving targeted therapies increased from 42.9% in 2012 to 67.7% in 2020 (AAPC =4.6; 95% CI: −0.4 to 9.9; P=0.07).

## Discussion

### *Key findings*

Our study is among the earliest to validate randomized controlled trial (RCT) findings, showing that the use of first-line targeted therapies or immunotherapies enhances survival time in adult patients diagnosed with NSCLC who receive both primary care and oncology care services within our four diverse community-based healthcare systems. Specifically, patients receiving targeted therapies survived 1.6 months longer through 12 months of follow-up and survived 5.5 months longer through 60 months follow-up relative to patients receiving Chemo-Only. We found patients receiving IMO +/− Chemo survived 1.4 months longer through 12 months follow-up relative to

 

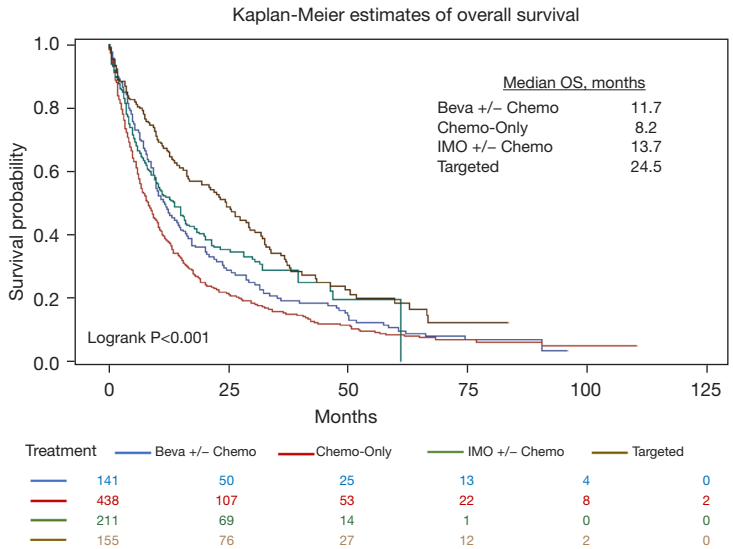


**Figure 3** Kaplan-Meier estimates of survival by type of first-course systemic therapy received, 2012–2020. OS, overall survival; Chemo, chemotherapy; IMO, immunotherapy; Beva, bevacizumab.

**Table 4** Multivariable adjusted RMST among patients diagnosed with advanced non-small cell lung cancer[†]

| Comparison | Adjusted RMST (95% CI) | Difference (95% CI) | P value | Ratio (95% CI) | P value |
|---|---|---|---|---|---|
| RMST through 12 months of follow-up | | | | | |
| Chemo-Only | 7.8 (7.4 to 8.2) | 0.6 (0.1 to 1.4) | 0.10 | 1.08 (1.00 to 1.16) | 0.11 |
| Beva +/– Chemo | 8.4 (7.8 to 9.1) | | | | |
| Chemo-Only | 7.5 (7.0 to 7.9) | 1.4 (0.5 to 2.3) | 0.002 | 1.19 (1.11 to 1.28) | 0.002 |
| IMO +/– Chemo | 8.9 (8.2 to 9.6) | | | | |
| Chemo-Only | 7.8 (7.4 to 8.2) | 1.6 (0.7 to 2.5) | <0.001 | 1.21 (1.12 to 1.30) | 0.001 |
| Targeted | 9.4 (8.6 to 10.1) | | | | |
| RMST through 60 months of follow-up | | | | | |
| Chemo-Only | 16.9 (15.2 to 18.6) | 1.5 (–2.2 to 5.1) | 0.44 | 1.09 (0.92 to 1.25) | 0.48 |
| Beva +/– Chemo | 18.4 (15.3 to 21.5) | | | | |
| Chemo-Only | 17.3 (15.2 to 19.4) | 3.2 (–1.4 to 7.9) | 0.18 | 1.19 (0.98 to 1.40) | 0.17 |
| IMO +/– Chemo | 20.5 (17.1 to 24.0) | | | | |
| Chemo-Only | 17.8 (15.8 to 19.8) | 5.5 (0.7 to 10.4) | 0.02 | 1.31 (1.11 to 1.51) | 0.07 |
| Targeted | 23.3 (19.4 to 27.2) | | | | |

[†], all results mutually adjusted for healthcare system in addition to all variables listed in *Table 1*. RMST, restricted mean survival time; Chemo, chemotherapy; Beva, bevacizumab; IMO, immunotherapy; CI, confidence interval.

patients receiving Chemo-Only. Patients receiving Beva +/– Chemo had similar survival relative to patients receiving Chemo-Only.

### *Strengths and limitations*

There are several strengths of this study. The majority of primary care and oncology care within our cohort is

**Table 5** Multivariable models of RMST through 12 and 60 months from start of systemic therapy for patients diagnosed with advanced non-small cell lung cancer

| Characteristics | Beva +/− Chemo | | IMO +/− Chemo | | Targeted therapies | |
|---|---|---|---|---|---|---|
| | Coefficient[†] (95% CI) | P value | Coefficient[†] (95% CI) | P value | Coefficient[†] (95% CI) | P value |
| 12 months follow−up | | | | | | |
| Intercept | 79.7 (−269.6 to 429.1) | 0.65 | 41.9 (−319.7 to 403.5) | 0.82 | −41.1 (−362.5 to 280.3) | 0.80 |
| Year of diagnosis | −0.04 (−0.2 to 0.1) | 0.67 | −0.02 (−0.2 to 0.2) | 0.84 | 0.02 (−0.1 to 0.2) | 0.79 |
| Sex (*vs*. male) | | | | | | |
| Female | 1.2 (0.6 to 1.9) | <0.001 | 0.7 (0.1 to 1.3) | 0.03 | 1.2 (0.5 to 1.8) | <0.001 |
| Race and ethnicity (*vs*. White) | | | | | | |
| Asian | 0.4 (−1.2 to 1.9) | 0.64 | 0.6 (−0.8 to 2.0) | 0.40 | 0.3 (−0.9 to 1.6) | 0.60 |
| Black | 0.2 (−1.0 to 1.5) | 0.73 | −0.1 (−1.2 to 1.1) | 0.92 | 0.2 (−1.1 to 1.4) | 0.79 |
| Hispanic | −0.3 (−1.7 to 1.1) | 0.68 | −0.3 (−1.6 to 1.1) | 0.70 | −0.04 (−1.5 to 1.4) | 0.96 |
| Native Hawaiian/Pacific Islander | 0.7 (−1.4 to 2.8) | 0.49 | 0.8 (−0.9 to 2.6) | 0.36 | 0.2 (−1.5 to 1.9) | 0.81 |
| Unknown/another race[‡] | −0.9 (−2.4 to 0.6) | 0.22 | −1.3 (−2.7 to 0.1) | 0.07 | −1.1 (−2.6 to 0.4) | 0.14 |
| Age at diagnosis (years) (*vs*. 35–64) | | | | | | |
| 65–74 | 0.1 (−0.7 to 0.8) | 0.90 | −0.3 (−1.1 to 0.4) | 0.37 | −0.3 (−1.0 to 0.5) | 0.47 |
| 75–89 | 0.8 (−0.1 to 1.7) | 0.08 | 0.1 (−0.8 to 1.0) | 0.85 | 0.4 (−0.5 to 1.3) | 0.38 |
| Smoking status at diagnosis (*vs*. current) | | | | | | |
| Never | 0.3 (−0.7 to 1.4) | 0.53 | 0.02 (−1.0 to 1.1) | 0.96 | 0.3 (−0.8 to 1.4) | 0.62 |
| Former | −0.3 (−1.1 to 0.5) | 0.45 | −0.4 (−1.2 to 0.3) | 0.28 | −0.2 (−1.0 to 0.7) | 0.67 |
| Unknown/missing | −1.0 (−2.7 to 0.6) | 0.21 | −0.5 (−2.6 to 1.6) | 0.63 | −1.1 (−3.1 to 0.8) | 0.26 |
| Charlson comorbidity index (1 year prior to diagnosis)[§] | −0.3 (−0.7 to 0.1) | 0.20 | −0.4 (−0.8 to 0.02) | 0.06 | −0.3 (−0.7 to 0.1) | 0.13 |
| BMI status at diagnosis (kg/m$^2$) [*vs*. <25 (healthy)] | | | | | | |
| 25–29 (overweight) | −0.1 (−0.9 to 0.6) | 0.74 | −0.1 (−0.8 to 0.6) | 0.78 | 0.3 (−0.4 to 1.0) | 0.40 |
| 30+ (obese) | −0.5 (−1.3 to 0.4) | 0.29 | 0.04 (−0.8 to 0.8) | 0.92 | −0.1 (−1.0 to 0.7) | 0.77 |
| Unknown | 0.8 (−1.5 to 3.2) | 0.49 | 1.1 (−1.5 to 3.7) | 0.42 | 1.3 (−1.1 to 3.6) | 0.29 |
| Yost state quintile (census based) | −0.04 (−0.3 to 0.2) | 0.75 | −0.1 (−0.3 to 0.2) | 0.55 | −0.01 (−0.3 to 0.2) | 0.96 |
| Histology (*vs*. all other NSCLC) | | | | | | |
| Squamous | 1.0 (−0.1 to 2.1) | 0.07 | 0.9 (−0.1 to 1.9) | 0.09 | 0.8 (−0.2 to 1.9) | 0.13 |
| Adenocarcinoma | 1.8 (0.8 to 2.7) | <0.001 | 1.6 (0.7 to 2.5) | <0.001 | 1.5 (0.5 to 2.5) | 0.003 |
| Receipt of surgery as part of first course therapy (tumor registry based) (*vs*. no) | | | | | | |
| Yes | 1.6 (−0.3 to 3.5) | 0.09 | −0.2 (−2.7 to 2.4) | 0.90 | −1.0 (−3.8 to 1.9) | 0.51 |
| Receipt of radiation as part of first course therapy (tumor registry based) (*vs*. no) | | | | | | |
| Yes | 0.9 (0.2 to 1.6) | 0.02 | 0.8 (0.1 to 1.5) | 0.02 | 0.7 (0.02 to 1.4) | 0.045 |
| Total lines of therapy[¶] | 1.5 (1.2 to 1.9) | <0.001 | 1.7 (1.3 to 2.1) | <0.001 | 1.6 (1.3 to 2.0) | <0.001 |

**Table 5** (*continued*)

**Table 5** (*continued*)

| Characteristics | Beva +/− Chemo | | IMO +/− Chemo | | Targeted therapies | |
|---|---|---|---|---|---|---|
| | Coefficient[†] (95% CI) | P value | Coefficient[†] (95% CI) | P value | Coefficient[†] (95% CI) | P value |
| 60 months follow−up | | | | | | |
| Intercept | −1,559.4 (−3,127.8 to 9.1) | 0.05 | −1,730.2 (−3,432.2 to −28.3) | 0.046 | −2,298.3 (−3,779.1 to −817.4) | 0.002 |
| Year of diagnosis | 0.8 (0 to 1.6) | 0.049 | 0.9 (0.02 to 1.7) | 0.04 | 1.2 (0.4 to 1.9) | 0.002 |
| Sex (*vs*. male) | | | | | | |
| Female | 5.4 (2.3 to 8.4) | <0.001 | 2.9 (−0.3 to 6.0) | 0.07 | 4.3 (1.1 to 7.6) | 0.009 |
| Race and ethnicity (*vs*. White) | | | | | | |
| Asian | −0.6 (−7.7 to 6.5) | 0.87 | 5.2 (−1.6 to 11.9) | 0.14 | 1.4 (−5.2 to 7.9) | 0.69 |
| Black | 0.01 (−5.9 to 5.9) | >0.99 | −0.1 (−6.1 to 5.9) | 0.97 | −0.9 (−6.9 to 5.1) | 0.77 |
| Hispanic | −6.1 (−11.0 to −1.3) | 0.01 | −5.1 (−10.7 to 0.5) | 0.08 | 0.1 (−7.9 to 8.1) | 0.98 |
| Native Hawaiian/Pacific Islander | 2.8 (−6.1 to 11.7) | 0.53 | 3.1 (−4.9 to 11.0) | 0.45 | −0.7 (−9.0 to 7.6) | 0.86 |
| Unknown/another race[‡] | −6.2 (−10.5 to − 2.0) | 0.004 | −6.4 (−12.1 to −0.8) | 0.03 | −4.5 (−10.5 to 1.6) | 0.15 |
| Age at diagnosis (years) (*vs*. 35–64) | | | | | | |
| 65–74 | −4.1 (−7.7 to −0.5) | 0.03 | −4.9 (−8.6 to −1.2) | 0.009 | −6.6 (−10.3 to −2.9) | <0.001 |
| 75–89 | −2.8 (−6.9 to 1.2) | 0.17 | −3.1 (−7.3 to 1.1) | 0.15 | −4.8 (−9.0 to −0.6) | 0.02 |
| Smoking status at diagnosis (*vs*. current) | | | | | | |
| Never | 5.1 (−0.5 to 10.8) | 0.07 | 1.9 (−3.7 to 7.5) | 0.51 | 2.1 (−3.5 to 7.5) | 0.45 |
| Former | −1.5 (−5.1 to 2.2) | 0.43 | −2.8 (−6.5 to 0.9) | 0.14 | −1.5 (−5.5 to 2.5) | 0.46 |
| Unknown/missing | −3.3 (−10.1 to 3.4) | 0.33 | −2.7 (−11.7 to 6.2) | 0.55 | −1.3 (−10.1 to 7.5) | 0.78 |
| Charlson comorbidity index (1 year prior to diagnosis)[§] | −0.6 (−2.6 to 1.4) | 0.54 | −2.0 (−4.2 to 0.1) | 0.06 | −1.5 (−3.5 to 0.5) | 0.15 |
| BMI status at diagnosis (kg/m$^2$) [*vs*. <25 (healthy)] | | | | | | |
| 25–29 (overweight) | −0.7 (−4.1 to 2.8) | 0.70 | −0.9 (−4.5 to 2.6) | 0.61 | 1.5 (−2.1 to 5.0) | 0.42 |
| 30+ (obese) | −1.6 (−5.6 to 2.5) | 0.45 | 0.9 (−3.2 to 5.0) | 0.68 | 1.2 (−3.0 to 5.4) | 0.58 |
| Unknown | 5.3 (−5.7 to 16.3) | 0.35 | −2.7 (−11.7 to 6.2) | 0.55 | 2.2 (−9.3 to 13.7) | 0.71 |
| Yost state quintile (census based) | −0.3 (−1.5 to 1.0) | 0.69 | 0.1 (−1.2 to 1.3) | 0.90 | 0.2 (−1.0 to 1.4) | 0.72 |
| Histology (*vs*. all other NSCLC) | | | | | | |
| Squamous | 2.5 (−2.3 to 7.2) | 0.31 | −0.02 (−4.9 to 4.9) | 0.99 | 1.2 (−4.0 to 6.4) | 0.65 |
| Adenocarcinoma | 5.6 (1.4 to 9.9) | 0.009 | 3.4 (−1.3 to 8.1) | 0.16 | 4.1 (−0.9 to 9.0) | 0.11 |
| Receipt of surgery as part of first course therapy (tumor registry based) (*vs*. no) | | | | | | |
| Yes | 10.8 (0.7 to 20.9) | 0.04 | 0.3 (−10.2 to 10.8) | 0.95 | −1.4 (−13.1 to 10.3) | 0.82 |
| Receipt of radiation as part of first course therapy (tumor registry based) (*vs*. no) | | | | | | |
| Yes | 3.2 (0.02 to 6.4) | 0.048 | 3.8 (0.60 to 7.0) | 0.02 | 3.1 (−0.2 to 6.4) | 0.07 |
| Total lines of therapy | 1.2 (−0.5 to 2.8) | 0.17 | 0.8 (−1.0 to 2.7) | 0.37 | 1.3 (−0.4 to 3.1) | 0.13 |

[†], the coefficient value represents the number of additional months of survival gained or lost if the corresponding characteristic were present, relative to the reference group for that covariate. For example, a female patient receiving Beva +/− Chemo has a 1.2 month longer mean survival compared to a male patient; [‡], another race includes patients self-identifying as American Indian (<1%) and multiple races (<1%); [§], modified Charlson comorbidity index excludes HIV/AIDS diagnoses. RMST, restricted mean survival time; Chemo, chemotherapy; Beva, bevacizumab; IMO, immunotherapy; CI, confidence interval; Ref, reference; BMI, body mass index; NSCLC, non-small cell lung cancer; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

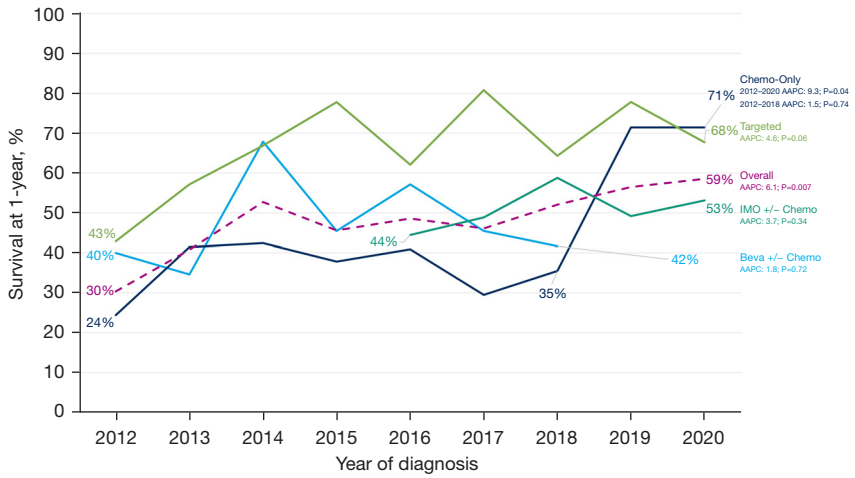


**Figure 4** One-year survival probabilities by type of first-course systemic therapy, 2012–2020. Chemo, chemotherapy; AAPC, average annual percent change; IMO, immunotherapy; Beva, bevacizumab.

delivered by salaried physicians in plan-owned facilities. This allowed us to capture and summarize detailed treatment data and adjust for patient characteristics that are not found in data from other recent studies that are limited to select oncology data without patient level characteristics (5,49). Our study looked at survival within a population who received any systemic treatment regardless of type of systemic therapy, thereby expanding our results/conclusion to what survival looks like in a population rather than survival within a cohort receiving specific regimens or a cohort with specific driver mutations (5,49-51). There were also limitations in our study. This is a retrospective observational study that addressed the association, not causal effects, of the receipt of alternative systemic therapies on survival after a diagnosis of advanced NSCLC. Other limitations include small samples sizes in the later years of our study that resulted in wide confidence intervals, the lack of access to data on tumor genomic and other molecular marker testing, and performance status. We also did not address other sources of observed and unobserved selection bias that may have been associated with provider and patient preferences related to use of IMO or targeted therapies (52). Lastly, our cohort is predominantly insured, so our results may not be generalizable to uninsured populations diagnosed with lung cancer or those with barriers to optimal access to care.

### *Comparison with similar research*

While the source of our underlying patient populations differed, our median survival findings are consistent with the findings of similar time frames noted in the 2018 The US Oncology Network-based study (53), a community-based study conducted in the Netherlands (54), a study among patients 75 years and older in Japan (55), and among older SEER-Medicare patients with synchronous brain metastases (56). Estimates for patients receiving Chemo-Only ranged between 6.2 and 12.8 months whereas our estimate was 8.2 months (53,54,56). Estimates for patients receiving IMO +/– Chemo ranged between 6.2 and 20.0 months while our estimate was 13.7 months (20,49-51,54-57). Published estimates for patients receiving targeted therapies were between 15.2 and 24.3 months where our estimate was slightly higher at 24.5 months (51,53,54).

Estimates of RMST from randomized clinical trials are not directly comparable to our estimates due to different follow-up times and the specific IMO drugs being compared. However, with follow-up times ranging between 27 and 35 months, RMST differences in IMO +/– Chemo relative to standard cytotoxic chemotherapy ranged between 0.32 and 2.85 months (58). Our estimate of differences in RMST of IMO +/– Chemo relative to Chemo-Only was 1.4 months through 12 months follow-up and 3.2 months through 60 months of follow-up. This suggests that the magnitude of increase that newer therapies offer patients diagnosed with advanced lung cancer may be small, but survival benefits in real-world community settings may not differ from estimates from randomized clinical trials.

Despite evidence of lower tumor burden among Black and Asian patients which could impact the efficacy of

 

immune checkpoint inhibitors (59), we did not find a difference in reduced survival among Blacks nor Asians in our Beva +/– Chemo group nor our IMO +/– Chemo group. This could be due to our insured cohort where patients were required to be engaged within their health system (60). We did find reduced survival among patients that were Hispanic and unknown/another race among patients receiving Beva +/– Chemo and reduced survival among patients with unknown/another race among patients receiving IMO +/– Chemo. Despite our small sample sizes, these results corroborate results from recent, similar studies that did not find differences in survival among these races in a cohort receiving immunotherapy (61-63).

We found an overall 1-year survival probability of 47.8% which falls within previously reported estimates in the literature that ranged between 45.1% and 50% (49,50,64). We found a significant increase in 1-year survival probabilities from 30.4% in 2012 to 58.5% in 2020 for an average annual percent change of 6.1% (P=0.007). This increase was comparable to a cohort of patients diagnosed with NSCLC in France whose 2-year survival increased from 26.4% between 2000 and 2009 to 43.4% between 2018 and 2020 (65). Consistent with our results, analyses of changes in lung cancer incidence and mortality in other studies in the United States suggest that new therapies are contributing to declines in overall lung cancer mortality through impacts on improved lung cancer patient survival (66,67,68).

Somewhat of a counterfactual relative to recent studies noting that genomic testing is associated with delays in treatment, and that time to treatment may be inversely related to outcomes, we found patients receiving targeted therapies started therapy 8–10 days sooner than patients receiving Beva +/– Chemo, targeted, or Chemo-Only. Given that relative to the other treatment cohorts, those receiving targeted therapies were more likely to be younger, female, living in higher SES neighborhoods, and have a lower comorbidity burden, it is plausible that unobservable patient and provider preferences for rapid testing and treatment initiation were associated with noted favorable survival outcomes (69-72). Additionally, time to treatment may be shorter for oral targeted therapies that are available through an outpatient pharmacy versus delays that may be encountered for intravenous therapies where patients may need to wait for open infusion chair appointments (73).

### *Implications and actions needed*

Additional research is needed to better understand the potential benefits and harms, including patient adverse events, and financial toxicities, of the use of these new therapies in community-based settings

## Conclusions

In this community-based, comparative effective analysis, we found patients diagnosed with advanced lung cancer receiving targeted therapies and IMO +/– Chemo survived longer relative to those on Chemo-Only. One-year survival probabilities have significantly increased between 2012 and 2020.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-749/rc

*Data Sharing Statement:* Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-749/dss

*Peer Review File:* Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-749/prf

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Interregional Institutional Review Board (IRB) of Kaiser Permanente (No. 00013581) and individual consent for this retrospective analysis was waived.



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