Original Article

Immune checkpoint inhibitors as subsequent treatment in older adults with non-small cell lung cancer and synchronous brain metastases

Ruchira V. Mahashabde[1], Sajjad A. Bhatti[2], Bradley C. Martin[1], Jacob T. Painter[1], Analiz Rodriguez[3], Jun Ying[4], Chenghui Li[1]

[1]Division of Pharmaceutical Evaluation and Policy, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [2]Division of Hematology and Medical Oncology, Department of Internal Medicine, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [3]Department of Neurosurgery, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [4]Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: RV Mahashabde, C Li; (IV) Collection and assembly of data: RV Mahashabde, C Li; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Chenghui Li, PhD. Division of Pharmaceutical Evaluation and Policy, College of Pharmacy, University of Arkansas for Medical Sciences, 4301 West Markham Street Slot 522, Little Rock, AR 72205, USA. Email: CLi@uams.edu.

Background: Immune checkpoint inhibitors (ICIs) have become the mainstay treatment for non-small cell lung cancer (NSCLC). However, there is a lack of studies assessing ICIs as subsequent treatment in older adults with NSCLC and brain metastasis (BM). This retrospective cohort study compared the real-world survival of older patients with NSCLC and BM at diagnosis [synchronous BM (SBM)] previously treated with chemotherapy receiving ICI versus chemotherapy as subsequent treatment.

Methods: Patients with NSCLC and SBM ≥65 years previously treated with chemotherapy were identified using the SEER-Medicare database (2010–2019). Patients receiving new chemotherapy and/or Food and Drug Administration (FDA)-approved ICIs as second/third-line treatment were included, excluding those ever-receiving targeted therapies. Each ICI patient was matched to one chemotherapy patient by time to subsequent treatment (within ±30 days) from diagnosis. Overall survival (OS) time was measured from the start of subsequent treatment to death, censored at disenrollment from Medicare Part A/B, enrollment in Part C, or end of study (December 31, 2019), whichever came first. OS curves were estimated and compared using the Kaplan-Meier (KM) method and log-rank test. Hazard ratio (HR) was estimated using a multivariable-adjusted Cox proportional hazards model.

Results: Matched cohorts included 546 patients [273 in each group; median age 71 (range, 65–87) years]. ICI patients were older, more likely non-Hispanic, with squamous cell carcinoma, and liver metastasis compared to chemotherapy. KM estimated better survival in ICI than chemotherapy {median survival: 209 days [95% confidence interval (CI): 160–275] *vs.* 155 days (95% CI: 135–187); log-rank P<0.001}. ICI was associated with a lower adjusted hazard of death [HR =0.63; 95% CI: 0.52–0.75; P<0.001] compared to subsequent chemotherapy treatment.

Conclusions: In this population-based study of older patients with NSCLC and SBM previously treated with chemotherapy, subsequent treatment with ICI was associated with improved survival compared to chemotherapy.

Keywords: Immune checkpoint inhibitors (ICIs); older adults; non-small cell lung cancer (NSCLC); subsequent treatment; brain metastasis (BM)

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Introduction

Immune checkpoint inhibitors (ICIs) have now become the mainstay treatment for non-small cell lung cancer (NSCLC). ICIs unleash the suppressed immune response by attaching to proteins (immune checkpoints) on T-cells of the immune system [cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death-1 (PD-1)], or its ligand on cancer cell [programmed cell death ligand 1 (PD-L1)], resulting in immune-mediated destruction of cancer cells (1). For patients who progressed after platinum-doublet chemotherapy, pivotal phase 3 trials [CheckMate 017 (2), CheckMate 057 (3), KEYNOTE 010 (4), OAK (5)] comparing subsequent ICI use with docetaxel have reported prolonged OS of ICI in both squamous and non-squamous NSCLC. Based on these trials, the Food and Drug Administration (FDA) approved nivolumab and pembrolizumab in 2015 and atezolizumab in 2016 as a second- or later-line treatment for NSCLC (6). Current clinical guidelines recommend ICIs as subsequent treatment after the progression of NSCLC for patients without any mutations, if not treated with immunotherapy in first-line (7,8).

Brain metastases (BMs) are a common complication of cancer, accounting for 10–26% of cancer deaths (9). The most common cancer that metastasizes to the brain is lung cancer; 7–10% of patients with NSCLC are diagnosed with BM ["synchronous BM" (SBM)] and 20–30% develop BM subsequently (metachronous BM) (9). Patients with BM have poor morbidity and mortality with a median overall survival (OS) ranging from 3–15 months (10). Treatment for BM, however, remains an unmet need. Recent studies of central nervous system (CNS) lymphatics that demonstrated the ability of immune cells and related systemic therapies to cross the blood-brain barrier have provoked the discussion about intracranial effectiveness of ICIs (11,12). Despite the frequent occurrence of BM and associated deleterious morbidity and mortality, many patients with BM were excluded from ICI clinical trials, resulting in only a small number of patients with stable and asymptomatic BM remaining in each trial (2-5). Two recent phase 2 trials in patients with untreated or recurrent, or progressing BM have reported promising intracranial benefit, further highlighting the potential of pembrolizumab in the treatment of BMs (13,14). Meta-analyses pooling data on patients with BM across trials have reported superior effectiveness of ICIs over chemotherapy in NSCLC (15,16) when used in the first-line setting. However, no trials have examined the effectiveness of ICIs as subsequent treatment in patients with BM. Only one post hoc exploratory study of the OAK trial separately reported analysis of patients with a history of asymptomatic treated BM (n=115) and found no statistically significant difference for death for subsequent atezolizumab compared to docetaxel [hazard ratio (HR) =0.74; 95% confidence interval (CI): 0.49–1.13], likely due to small sample size (17).

However, patients in the aforementioned studies are younger (median age 61–63 years), with better performance status (PS) (ECOG 0–1) and fewer comorbidities than patients in the "real world" clinical practice (2-5). Although there are a few single-center (18,19) and multi-center (20-22) analyses of ICI in previously treated NSCLC patients, they are all conducted outside of the United States (US). One US study of previously treated patients with NSCLC found atezolizumab to have significantly longer OS compared to docetaxel (HR =0.79; 95% CI: 0.64–0.97) (23). Also, these real-world studies did not provide information related to BM or older adults separately. A recent meta-analysis of 550 patients with NSCLC and BM from 12 studies (including two trials) demonstrated the intracranial effectiveness of PD-1 inhibitors (nivolumab or pembrolizumab) used mostly as second-line therapy; however, OS was not reported (24).

Addressing these gaps, the objective of our study was to retrospectively analyze a population-based data to assess survival outcomes of subsequent treatment with ICI compared to chemotherapy in older patients with NSCLC and SBM who were previously treated with chemotherapy in the US. We hypothesize that older patients with NSCLC and SBM treated with subsequent ICI therapy exhibit improved OS compared to those treated with subsequent chemotherapy. Patients 65 years or older account for approximately 71% of patients with lung cancer (25), but are underrepresented in clinical studies due to advanced age, poor PS, lack of social support, or multiple comorbid conditions (26,27). Thus, there exists an urgent need to understand the treatment outcomes of ICIs in this patient population. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-205/rc).

Methods

Data source

This retrospective cohort study used the Surveillance, Epidemiology, and End Results (SEER) cancer registry

data linked to Medicare enrollment and fee-for-service (FFS) claims data (SEER-Medicare). The methodology, data collection strategy, and structure of SEER-Medicare have been described previously (28,29). Briefly, SEER, a population-based US cancer registry, collects data on patient demographics and tumor characteristics as well as the first course of treatment (29). Currently, SEER registries cover approximately 48% of the US population. SEER has been linked by the National Cancer Institute to Medicare enrollment and claims which provides information on inpatient/outpatient care and prescription utilization. Linking of these data sources occurs biannually and nearly 96% of individuals aged 65 or older documented in SEER are matched to their Medicare claims records (29). This study included SEER data from January 2010–December 2017 and Medicare enrollment and claims from January 2009–December 2019.

Study population

Patients diagnosed with NSCLC and SBM between 2010–2017 who received platinum-based doublets/taxane/pemetrexed/gemcitabine, or their combinations as a first-line treatment followed by ICI or a new chemotherapy regimen as subsequent treatment were included for analysis. Details regarding treatment exposure groups are defined below. Since the SEER only has information on diagnosis month and year, we imputed the date of cancer diagnosis using the date of the first Medicare claim with lung cancer diagnosis code (ICD-9/10-CM code: 162.x/C34.x) if the month and year matched to those reported in SEER. Additional information regarding the imputation process has been provided in the Appendix 1. We used International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes to identify patients with primary malignant neoplasm of bronchus and lung with NSCLC histology (30). Diagnosis of SBM was determined using an indicator in SEER for the presence of BM at diagnosis available from 2010 onwards. Prescription of FDA-approved ICIs (pembrolizumab, nivolumab, ipilimumab, atezolizumab, durvalumab, cemiplimab) and chemotherapy (platinum-based doublets with taxane/pemetrexed/gemcitabine) for lung cancer were identified from Medicare claims using Healthcare Common Procedural Coding System (HCPCS) codes (30).

Since patients who lived longer had a higher chance of receiving subsequent treatment, we matched each ICI patient with a unique chemotherapy patient to ensure patients in both groups initiated subsequent treatment around the same time and thus likely had similar disease progression risk at the time when the subsequent treatment started. Specifically, a second-line chemotherapy patient was matched to a second-line ICI patient if the time from diagnosis to initiation of the second-line chemotherapy treatment was within ±30 days of the time from diagnosis to second-line ICI treatment initiation of the matched ICI patient. If more than one chemotherapy patients were found within that time window, one patient was randomly chosen as the match. Third-line chemotherapy patients were matched to third-line ICI patients using the same criteria. No matches were found for fourth-line ICI or chemotherapy treatment in our data. The index treatment date was defined as the start of second-line treatment for matched second-line ICI or chemotherapy patients or the start of third-line treatment for matched third-line ICI or chemotherapy patients.

Key inclusion criteria were: (I) age ≥65 years at the time of diagnosis; (II) with continuous coverage of both Medicare Part A and B but no Part C (Medicare advantage) coverage for at least 6 months before diagnosis (to assess baseline comorbidities and PS) till index treatment date (for observation of subsequent treatment). Exclusion criteria were: (I) diagnosed with small cell/other lung cancer histology; (II) multiple primary cancers in SEER; (III) any Medicare Part C coverage or disenrollment from Medicare Part A or B from 6 months before diagnosis till index treatment date (to determine healthcare services use) because Medicare database does not have Part C claims; (IV) receipt of any oral targeted therapy medications (afatinib dimaleate, alectinib HCl, ceritinib, crizotinib, erlotinib HCl, cabozantinib s-m, ceritinib, crizotinib, dabrafenib mesylate, erlotinib HCl, gefitinib, osimertinib mesylate, sunitinib malate, trametinib dimethyl, vandetanib) to ensure uniformity in prognosis and tumor characteristics of the patient cohort; (V) died within 30 days of lung cancer diagnosis or diagnosed at autopsy; and (VI) previously treated with ICI as first-line treatment before second-line ICI. We further excluded patients (n<11) who received nivolumab and ipilimumab combinations since the combination is formally approved for first-line treatment only and the approval was on May 26, 2020 (31), which falls outside our study period.

Treatment exposure

Based on previous literature (32,33), and input from

clinician co-authors, systemic agents received within 21 days from systemic treatment initiation after diagnosis were considered as part of the first-line regimen. Receipt of an ICI or a new chemotherapy agent not included in the first-line systemic regimen was labeled as a switch and the start of second-line treatment. Similarly, initiation of a new agent 21 days after the start of the second-line treatment was considered as a treatment switch and initiation of the third-line treatment. However, there were some exceptions, and further details about the determination of the line of treatment are provided in Appendix 1. Using this algorithm, patients who received ICIs as second- or third-line treatment were classified in the "ICI" group. Since the FDA first approved ICI as a subsequent treatment for NSCLC after platinum-based chemotherapy in 2015, the index dates for all patients in the ICI group were 2015 and beyond. For comparison, we identified a historical cohort of patients who received second- or third-line chemotherapy with index dates before 2015 and never received any ICIs during the study period (hereafter "chemotherapy" group). SEER does not have information on the proportion of PD-L1 expression on cancer cells, an important predictor of immunotherapy responses. Patients with higher tumor expression of PD-L1 may be more likely to receive subsequent ICI treatment. Thus using historical cohort of patients who initiated subsequent chemotherapy treatment before 2015 as the comparison group will help mitigate confounding by indication bias as these patients did not have the opportunity to receive ICI treatment at the time of subsequent treatment initiation regardless of their PD-L1 status.

Survival outcome

OS was measured as time (in days) from the index treatment date till death. Patients were censored at disenrollment from Medicare Part A or B, or enrollment in Medicare Part C, or the end of data availability (December 31, 2019), whichever occurred first.

Covariates

The following covariates were selected through a review of published literature (34-36) that used SEER-Medicare data, based on their relevance to the survival and/or receipt of treatment, and input from our clinical collaborators. Patients' demographic characteristics at diagnosis included age, sex, race, ethnicity, marital status, percent poverty level in each patient's census tract of residence, and rurality of each patient's county of residence. Cancer and treatment-related covariates included the presence of any lung, bone, or liver metastasis at diagnosis, primary tumor grade and size at diagnosis, histology of NSCLC, receipt of cranial radiation before subsequent treatment (ICI/chemotherapy), and any neurosurgical resection within 1 year of diagnosis. Cranial radiation [stereotactic radiosurgery (SRS) or non-SRS] was identified using current procedural terminology (CPT)/HCPCS codes for radiation treatment delivery (30) combined with an ICD-9/10-CM code (198.3x/C79.31) for secondary malignant neoplasm of the brain to confirm radiation was received for BM. Baseline comorbidity and PS were assessed using the Charlson comorbidity index (CCI) (excluding cancer) (37,38) and a proxy of Eastern Cooperative Oncology Group (ECOG) PS scale (39,40) using Medicare claims within 6 months before the diagnosis date of NSCLC to account for different health status among the patient population. Additional information regarding the calculation of the proxy ECOG PS scale has been provided in the Appendix 1. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

To compare patients' characteristics between the matched groups (ICI and chemotherapy), we used the Wilcoxon signed-rank test for continuous variables (age) and Cochran's Q test for categorical variables (all other covariates). We generated survival curves using the Kaplan-Meier (KM) method and compared them between treatment groups using a log-rank test. HR between groups were estimated using the Cox's proportional hazards (CPH) model, adjusting for covariates. To account for the clustering effect of the matched patients (41), we used two approaches commonly used in the literature: (I) robust sandwich covariance matrix to account for correlations within matched pairs or (II) shared frailty model with a random effect for matched pairs (42). Choice between the approaches usually depends on the study perspective and relevance of the inferences as the former approach provides an average response of the entire population while the latter allows the hazard to vary by matched pairs (43). In our study, HRs obtained from the two approaches were similar (Table S1); hence only estimates from the robust sandwich method are included in the main text.

As a sensitivity analysis, we conducted propensity score matching using the 1:1 greedy matching method. The

propensity score was estimated using the aforementioned covariates, line of treatment, and time from diagnosis to index treatment. Balance in these covariates before and after matching was assessed using absolute standardized differences (ASD), with ASD <0.1 indicating proper balance. After the appropriate balance was achieved, we used the KM method to estimate and compare survival curves. A CPH model was used to estimate the HR and 95% CI using the matched cohorts without covariates, adjusting for matched pairs using the robust sandwich method.

Several other secondary analyses were conducted. We observed the initial crossing of KM curves, similar to those presented in KM curves of clinical trials (2-5). Since crossing of survival curves indicates a violation of the proportional hazard assumption, we further compared the overall KM curves using the "MaxCombo" test, a combination weighted log-rank test (44,45), and additionally used a CPH model with a change point (46) of 114 days from the index date. The change point was selected by comparing the range of Akaike's information criterion and Schwartz's Bayesian Criterion values generated by models analyzed around the survival time when KM curves were seen to cross. Further, we separately compared ICI and chemotherapy patients in second-line and third-line groups using the KM method and log-rank test. Subgroup analyses by pre-selected demographic (age, sex, and race) and clinical characteristics (any bone/liver/lung metastasis at diagnosis and CCI score) were also conducted to assess treatment heterogeneity using unadjusted CPH models. Due to sample size concerns, non-White categories were combined for analysis. Sensitivity analysis excluding those who did not receive cranial radiation before subsequent treatment was conducted using adjusted CPH models from a robust sandwich method.

SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Figure 1 shows the sample selection flow chart. There were 14,661 patients aged 65 years or older with a diagnosis of NSCLC + SBM in SEER. After applying the inclusion and exclusion criteria, 716 patients remained with 350 patients in the ICI group and 366 patients in the chemotherapy group. After matching on time to treatment, the final sample included a total of 546 patients; 273 ICI patients were matched to 273 chemotherapy patients.

The median age of the matched sample was 71 (range, 66–87) years. *Table 1* displays the characteristics of the matched sample. Comparing to the chemotherapy group, patients receiving ICI treatment were older {mean 72.11 [standard deviation (SD): 5.03] *vs.* 71.25 (SD: 4.56) years, P=0.03}, more likely to be non-Hispanic (P=0.02), and have liver metastasis at diagnosis (20.15% *vs.* 11.36%, P=0.003). Majority of patients in both groups had adenocarcinoma (63.37% *vs.* 62.64%); however, patients receiving ICI treatment were more likely to have squamous cell carcinoma (16.85% *vs.* 9.16%, P=0.009) compared to the chemotherapy group, but similar concerning all other covariates. Median time to second-line (241 *vs.* 227 days, P=0.29) or third-line (259 *vs.* 267 days, P=0.80) treatment from diagnosis was similar between the ICI and chemotherapy groups.

The median follow-up time was 206 days (range, 2–1,607 days) for the ICI group and 151 days (range, 6–3,240 days) for the chemotherapy group after the index treatment date. KM survival curves show that patients receiving subsequent ICI treatment had longer survival than those receiving subsequent chemotherapy treatment [median OS: 209 days (95% CI: 160–275) for the ICI group and 155 days (95% CI: 135–187) for chemotherapy group, log-rank test P<0.001] (*Figure 2A*). After adjusting for covariates, subsequent ICI treatment had a lower risk of death than subsequent chemotherapy treatment (HR =0.63; 95% CI: 0.52–0.75) using the robust sandwich method (*Table 2*). Secondary analyses using the MaxCombo test also showed an overall significant difference in survival time between groups (P<0.001) and when applying higher weights to early (P=0.03) or later (P<0.001) survival times (Figure S1). Robust sandwich method CPH with a change point showed that subsequent ICI was associated with a significantly higher hazard of death (HR =1.48; 95% CI: 1.09–2.02) before 114 days from index date, and a significantly lower hazard of death (HR =0.53; 95% CI: 0.42–0.68) after 114 days from index date when compared to subsequent chemotherapy (Table S2).

Using the propensity score matching method, we found 259 matched pairs. After matching, all variables were well balanced with ASD <0.1 (Table S3). KM survival curves comparing propensity matched groups show that patients receiving subsequent ICI treatment had longer survival than those receiving subsequent chemotherapy treatment [median OS: 209 days (95% CI: 161–284) for the ICI group and 152 days (95% CI: 133–172) for chemotherapy group, log-rank test P<0.001] (Figure S2). Cox's regression model estimated a lower risk of death in subsequent ICI treatment *vs.* chemotherapy (HR =0.63; 95% CI: 0.52–0.76) using a

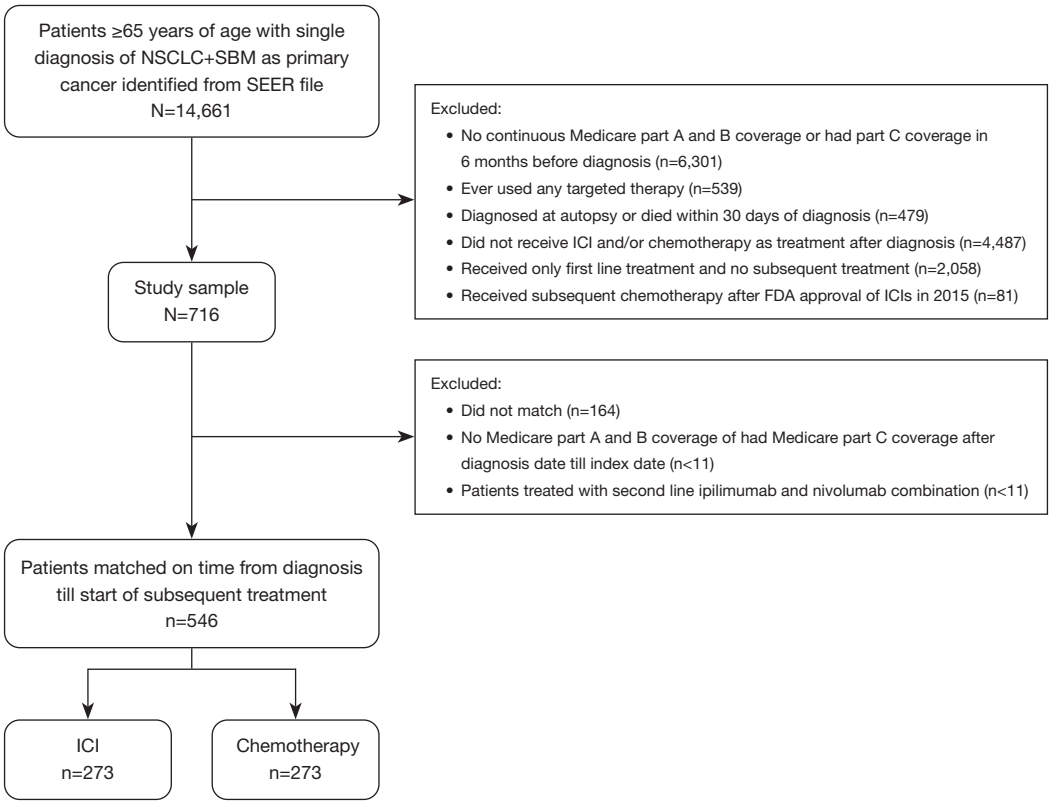

Figure 1 Study sample selection flowchart. According to the SEER-Medicare data use agreement, counts <11 are masked. NSCLC, non-small cell lung cancer; SBM, synchronous brain metastasis; SEER, Surveillance Epidemiology and End Results; ICI, immune checkpoint inhibitor; FDA, Food and Drug Administration.

robust sandwich method.

Stratified analysis by lines of subsequent treatment showed similar survival benefits in second-line ICI use over chemotherapy as in the main analysis (Figure S3, top figure). However, no statistically significant difference was found (HR =1.50; 95% CI: 0.58–3.90) for third-line ICI use *vs.* chemotherapy (Figure S3, bottom figure), a finding consistent with the subgroup analysis using clinical trial data (8). In subgroup analyses, HRs for OS favored subsequent ICI over chemotherapy across all pre-specified subgroups, although estimates for patients with any other (bone/live/lung) metastasis at diagnosis and CCI ≥2 were not statistically significant (*Figure 2B*). Sensitivity analyses excluding those who did not receive cranial radiation before subsequent treatment showed similar survival benefits as in the main analysis (Table S4).

Discussion

Using population-based real-world data of older patients, we found that subsequent ICI treatment was associated with improved survival compared to chemotherapy in NSCLC patients with SBM previously treated with chemotherapy. Although the survival benefit of subsequent ICI treatment over chemotherapy has been shown in previous clinical trials (2-5), patients with BMs, those with poor PS (ECOG PS ≥2), and older adults (especially those age ≥75 years) were under-represented.

In this cohort of older patients with NSCLC and SBM previously treated with chemotherapy, we found the median OS was 6.8 months in patients receiving ICI as second or third-line treatment. This median OS is shorter than those reported in previous trials involving second-line ICI use (9.2 months in CheckMate 017, 12.2 months in CheckMate 057, 10.4 months in KEYNOTE-010). This difference likely reflected the generally younger and healthier patients included in clinical trials. The median age in our study was 71 years, which was 8–10 years older than patients included in the clinical trials (2-5,27), but more comparable to the average age at diagnosis of real-world lung cancer patients

Table 1 Patient demographic and clinical characteristics of matched samples

Variables	Chemotherapy (n=273)	ICI (n=273)	P value
Age (years) at diagnosis, mean ± SD	71.25±4.56	72.11±5.03	0.03
Sex, n (%)			0.79
Male	129 (47.25)	133 (48.72)	
Female	144 (52.75)	140 (51.28)	
Race, n (%)			0.20
White	>234[†] (–[†])	236 (86.45)	
Black	28 (10.26)	20 (7.33)	
Other	<11[†] (–[†])	17 (6.23)	
Ethnicity, n (%)			0.02
Non-Hispanic	254 (93.04)	<262[†] (–[†])	
Hispanic	19 (6.96)	<11[†] (–[†])	
Marital status at diagnosis, n (%)			0.60
Non-married	114 (41.76)	109 (39.93)	
Married	159 (58.24)	164 (60.07)	
Census tract poverty indicator level, n (%)			0.25
0–<5%	57 (20.88)	72 (26.37)	
5–<10%	71 (26.01)	78 (28.57)	
10–<20%	72 (26.37)	63 (23.08)	
20–100%	47 (17.22)	33 (12.09)	
Unknown	26 (9.52)	27 (9.89)	
Rurality, n (%)			0.06
Metropolitan	220 (80.59)	236 (86.45)	
Non-metropolitan	53 (19.41)	37 (13.55)	
Index year, n (%)			–
2010	27 (9.89)	–	
2011	54 (19.78)	–	
2012	70 (25.64)	–	
2013	53 (19.41)	–	
2014	69 (25.27)	–	
2015	–	24 (8.79)	
2016	–	117 (42.86)	
2017	–	82 (30.04)	
2018–2019	–	50 (18.31)	
Lung metastasis at diagnosis, n (%)			0.55
No	207 (75.82)	200 (73.26)	
Yes	66 (24.18)	73 (26.74)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Chemotherapy (n=273)	ICI (n=273)	P value
Bone metastasis at diagnosis, n (%)			0.11
No	197 (72.16)	181 (66.30)	
Yes	76 (27.84)	92 (33.70)	
Liver metastasis at diagnosis, n (%)			0.003
No	242 (88.64)	218 (79.85)	
Yes	31 (11.36)	55 (20.15)	
Charlson comorbidity index, n (%)			0.94
0	162 (59.34)	160 (58.61)	
1	65 (23.81)	69 (25.27)	
≥2	46 (16.85)	44 (16.12)	
ECOG performance status proxy, n (%)			0.50
ECOG PS 0–2	>262[†] (–[†])	261 (95.60)	
ECOG PS 3–4	<11[†] (–[†])	12 (4.40)	
Cranial radiation before index treatment, n (%)			0.63
No	106 (38.83)	108 (39.56)	
Yes	167 (61.17)	165 (60.44)	
Neurosurgical resection within 1 year from diagnosis, n (%)			0.91
No	224 (82.05)	223 (81.68)	
Yes	49 (17.95)	50 (18.32)	
NSCLC histology, n (%)			0.009
Adenocarcinoma	171 (62.64)	173 (63.37)	
Squamous cell carcinoma	25 (9.16)	46 (16.85)	
Other	77 (28.21)	54 (19.78)	
Tumor size at diagnosis, n (%)			0.97
<30 mm	66 (24.18)	62 (22.71)	
30 to <50 mm	79 (28.94)	77 (28.21)	
50 to <70 mm	59 (21.61)	57 (20.88)	
≥70 mm	37 (13.55)	41 (15.02)	
Missing/unknown	32 (11.72)	36 (13.19)	
Primary tumor grade, n (%)			0.27
Grade I/Grade II (well differentiated/moderately differentiated)	41 (15.02)	31 (11.36)	
Grade III/Grade IV (poorly differentiated/undifferentiated; anaplastic)	87 (31.87)	80 (29.30)	
Cell type not determined	145 (53.11)	162 (59.34)	
Primary tumor laterality, n (%)			0.32
Bilateral involvement/midline/one side/lateral origin unknown	14 (5.11)	<11[†] (–[†])	
Right: origin of primary	153 (55.84)	>151[†] (–[†])	
Left: origin of primary	106 (38.83)	111 (40.66)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Chemotherapy (n=273)	ICI (n=273)	P value
Agents used as first-line chemotherapy treatment, n (%)			–
Platinum only	24 (8.79)	>10† (–†)	
Pemetrexed only	17 (6.23)	<11† (–†)	
Platinum + taxane	105 (38.46)	83 (30.40)	
Platinum + pemetrexed	102 (37.36)	149 (54.58)	
Other combinations	25 (9.16)	20 (7.33)	
Agents used as subsequent chemotherapy treatment (second line), n (%)	N=273	N=14‡	–
Taxane only	111 (40.66)	<11† (–†)	
Gemcitabine only	48 (17.58)	<11† (–†)	
Pemetrexed only	84 (30.77)	<11† (–†)	
Other combinations	30 (10.99)	<11† (–†)	
Agents used as second-line ICI, n (%)		N=259	–
Pembrolizumab	–	57 (22.01)	
Nivolumab	–	189 (72.97)	
Atezolizumab	–	13 (5.02)	
Agents used as third-line ICI, n (%)		N=14	–
Pembrolizumab/atezolizumab	–	<11† (–†)	
Nivolumab	–	>4† (–†)	

All P values significant at $\alpha \leq 0.05$. †, according to the SEER-Medicare data use agreement, cell counts and percentages in this row are masked/concealed due to a cell having a case count of <11; ‡, this number represents the 14 third-line ICI patients that received previous second-line chemotherapy treatment. ICI, immune checkpoint inhibitor; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NSCLC, non-small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results.

(70 years) (47). Only 7–8% of the population in clinical trials were older than 70 years. Additionally, we focused on patients with SBM and included both patients who were previously treated with cranial radiation and those who were not, but trials only included a small number of patients (6–16%) with previously treated and stable BM. Thus, our patient population is likely more frail and has poorer prognoses. However, even among these older and more frail patients, our findings indicate that subsequent ICI treatment after failed chemotherapy can improve survival in patients with NSCLC and BM.

We found a 37% overall reduction and a 47% reduction after 114 days post-index treatment in OS of patients who received subsequent ICI treatment compared to chemotherapy after previous chemotherapy. These estimates are comparable to the 44% reduction in OS favoring subsequent atezolizumab treatment compared to chemotherapy in a subgroup of BM patients (n=85) from the OAK trial (5). It is also consistent with findings from a large meta-analysis of 102 trials that compared second-line ICI treatment with chemotherapy in lung cancer patients (n=36,058) (48). This study separately reported HRs for specific second-line ICI agents compared to docetaxel (nivolumab: HR =0.69, 95% CI: 0.56–0.83; pembrolizumab: HR =0.71, 95% CI: 0.56–0.90; atezolizumab: HR =0.73, 95% CI: 0.62–0.87). However, no separate analysis of patients with BM was reported and the analysis included both phase 2 and 3 trials, with some conducted only in SCLC patients, or with EGFR/KRAS gene mutations. Our finding of a significant OS benefit of subsequent ICI treatment over chemotherapy in older patients with NSCLC and BM further strengthened the evidence that ICI is possibly as effective as the subsequent treatment over chemotherapy in NSCLC, even in the presence of BM.

We found a lower hazard of death using subsequent ICI treatment compared to chemotherapy in both males

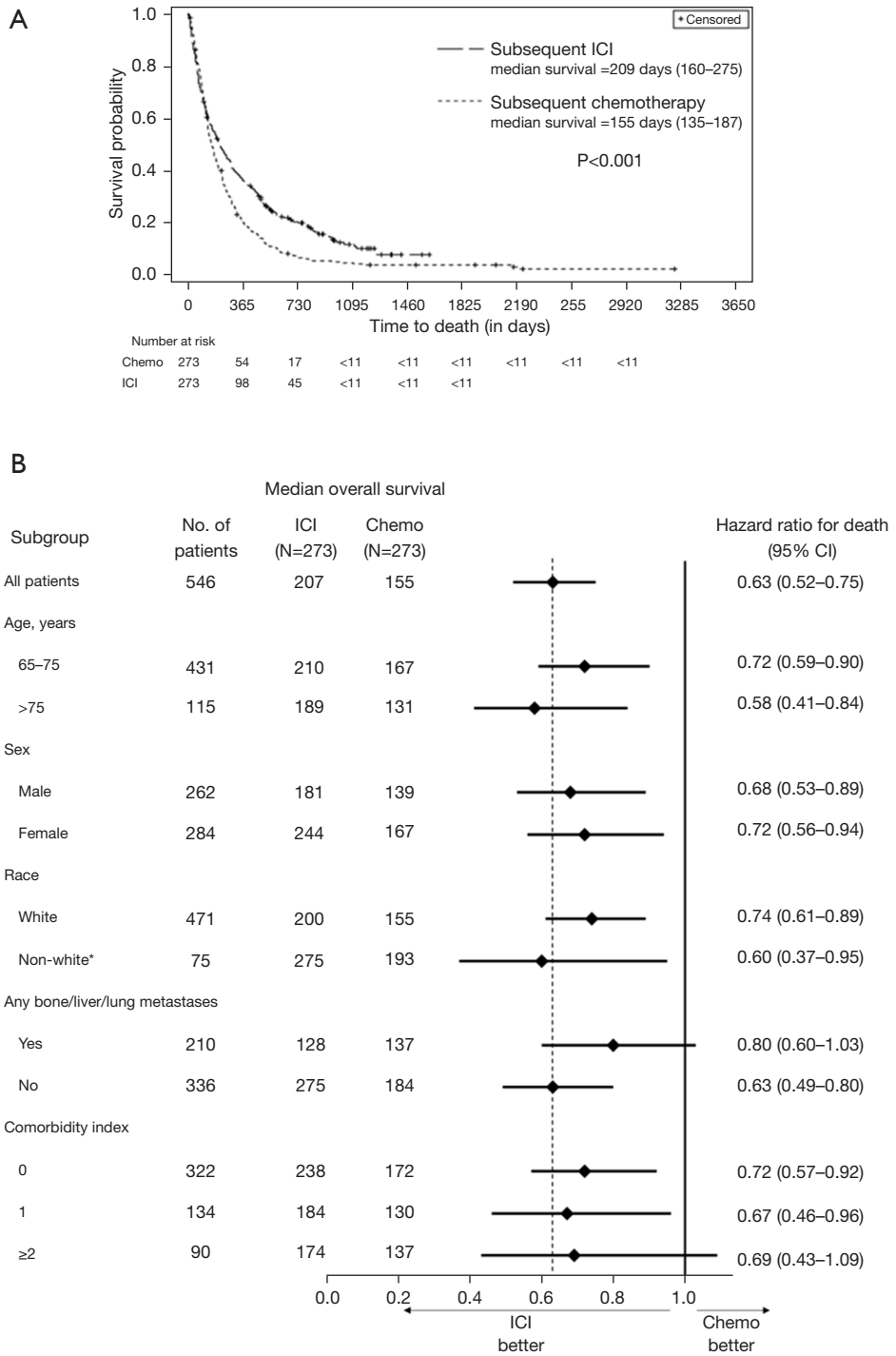

Figure 2 Overall survival. (A) Kaplan-Meier survival curves of subsequent ICI *vs.* chemotherapy only; (B) hazard ratio (95% CI) for subsequent ICI *vs.* chemotherapy only in selected subgroups from unadjusted CPH model. Vertical dotted line in (B) denotes the hazard ratio in the overall population. *, non-White group has <30 patients with subsequent ICI treatment; thus, the estimate may not be reliable. All P values are significant at α <0.05 except non-White. According to the SEER-Medicare data use agreement, counts <11 are masked. Chemo, chemotherapy; ICI, immune checkpoint inhibitor; CI, confidence interval; CPH, Cox's proportional hazards; SEER, Surveillance, Epidemiology, and End Results.

Table 2 Adjusted hazard ratios of overall survival from multivariate Cox's proportional hazards regression analysis using robust sandwich method

Variables	HR (95% CI)	P value
Subsequent ICI *vs.* chemotherapy	0.63 (0.52–0.75)	<0.001
Age	1.03 (1.01–1.05)	0.004
Married *vs.* non-married	1.13 (0.93–1.37)	0.22
Female *vs.* male	0.87 (0.74–1.03)	0.11
Race		
Black *vs.* White	0.86 (0.64–1.16)	0.33
Other *vs.* White	0.85 (0.58–1.24)	0.38
Hispanic *vs.* non-Hispanic	1.09 (0.75–1.58)	0.65
Census tract poverty indicator level		
5–<10% *vs.* 0–<5%	1.25 (0.98–1.60)	0.07
10–<20% *vs.* 0–<5%	1.06 (0.80–1.41)	0.68
20–100% *vs.* 0–<5%	1.18 (0.86–1.62)	0.31
Unknown *vs.* 0–<5%	1.04 (0.73–1.48)	0.83
Non-metropolitan area *vs.* metropolitan area	0.89 (0.67–1.18)	0.41
Bone metastasis *vs.* no bone metastasis	1.27 (1.06–1.53)	0.01
Liver metastasis *vs.* no liver metastasis	1.57 (1.19–2.05)	0.001
Lung metastasis *vs.* no lung metastasis	1.22 (1.01–1.49)	0.04
Charlson comorbidity index		
1 *vs.* 0	1.35 (1.08–1.68)	0.008
≥2 *vs.* 0	1.25 (0.98–1.59)	0.07
ECOG PS proxy 3–4 *vs.* ECOG PS proxy 0–2	1.21 (0.70–2.07)	0.49
Primary tumor grade		
Poorly differentiated/undifferentiated *vs.* well/moderately differentiated	1.06 (0.79–1.43)	0.67
Not determined *vs.* well/moderately differentiated	1.11 (0.84–1.47)	0.47
NSCLC histology		
Squamous cell *vs.* adenocarcinoma	1.83 (1.41–2.36)	<0.001
Other type *vs.* adenocarcinoma	1.05 (0.84–1.31)	0.66
Primary tumor size		
30 to <50 *vs.* <30 mm	1.13 (0.89–1.42)	0.31
50 to <70 *vs.* <30 mm	1.03 (0.79–1.34)	0.85
≥70 *vs.* <30 mm	1.34 (0.97–1.84)	0.07
Missing *vs.* <30 mm	0.94 (0.70–1.26)	0.69
Neurosurgical resection within 1 year of diagnosis (yes *vs.* no)	0.82 (0.64–1.06)	0.13
Cranial radiation before index treatment date (no *vs.* yes)	0.64 (0.42–0.96)	0.03

HR, hazard ratio; CI, confidence interval; ICI, immune checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer.

and females, consistent with clinical trials (2-5). A survival benefit was also seen in patients 65–74 years and those ≥75 years. Only trials of subsequent nivolumab had conducted subgroup analysis in very old patients ≥75 years and reported a statistically insignificant HR in squamous (HR =1.53; 95% CI: 0.65–3.62) (7) and non-squamous (HR =0.90; 95% CI: 0.43–1.87) NSCLC compared to docetaxel (8). However, the number of patients ≥75 years was small in both trials (29 and 43 respectively) (7,8), compared to 115 patients in our study. We also found that subsequent ICI was associated with a survival benefit over chemotherapy among both White and non-White patients. None of the trials of subsequent ICI use had reported subgroup analysis by race (7-10). However, both clinical trials and our study have a small number of patients from racial minorities. This finding should be interpreted with caution and should be confirmed in larger studies.

Strength and limitation

The strength of our study is that it included a large sample of older NSCLC patients with BM aged 65 years or older, a population commonly underrepresented and more frail than those included in clinical trials. Nonetheless, some important limitations should be noted. First, we do not have information on some important prognostic factors such as the proportion of PD-L1 on cancer cells, patient PS, and smoking status. To reduce potential confounding bias due to missing PD-L1 status, we used a historical cohort of patients who received subsequent chemotherapy treatment before 2015, the year when the FDA first approved ICIs as a subsequent treatment for NSCLC, as the comparison group. However, using a historical cohort might introduce time bias as patients treated with ICIs more recently may benefit from improved supportive care, potentially influencing survival outcomes. We also do not have information on the driver mutation testing results, which were not in wide use during the time period of this study and therefore was not likely a consideration for physician's treatment choice between ICI and chemotherapy. Although a direct measure of patients' PS was unavailable, we used a proxy measure derived from using previously validated study (39). However, this measure can only categorize patients into ECOG 0–2 *vs.* 3–4 and could not distinguish ECOG =2 from ECOG 0–1; most trials of subsequent ICIs included only patients with ECOG 0–1 (7-10). Thus, patients with worse PS (ECOG ≥2), a population excluded from clinical trials, could not be studied separately. Second, although we used matched cohorts to ensure comparison of patients with similar prognoses to minimize survival bias, there may exist other biases and residual confounding that may lead to over or underestimation. Third, due to the inability to directly observe the line of therapy from SEER-Medicare data, we employed a modified algorithm to delineate the treatment line, the validity of which has not been evaluated. Fourth, in our matched sample, the number of patients who received ICI as third-line treatment or who did not receive cranial radiation before subsequent treatment was small. Further, subgroups by ethnicity or rurality could not be compared and some subgroups were combined to form larger groups for comparison [e.g., race, any (liver/lung/bone) metastasis]. Caution is warranted to interpret these findings and future larger studies with more patients in those subgroups should be conducted to confirm the findings. Finally, we used a variable in SEER to identify NSCLC patients who were presented with BM at diagnosis (SBM). Although additional NSCLC patients who developed BM later (metachronous BM) may be identified using diagnosis codes for secondary cancer in Medicare claims, these codes do not provide information on primary cancer. Literature suggests that SBM and metachronous BM have different prognoses and outcomes (49). Thus, our study may not generalize to NSCLC patients with metachronous BM.

Conclusions

In this population-based study of older patients ≥65 years with NSCLC and SBM who were previously treated with chemotherapy, we found subsequent ICI treatment was associated with improved survival compared to subsequent chemotherapy. These findings add to the evidence that ICIs likely confer a survival advantage in the second-line treatment of NSCLC over chemotherapy in older, more frail patients with BM.

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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-24-205/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-205/coif). B.C.M. receives royalties from Trestle Tree LLC for the commercialization of an opioid risk prediction tool that is unrelated to this investigation and receives honoraria for his service on the Midwest CEPAC which assesses the clinical and economic value of new health technologies. A.R. has obtained grant funding from Bristol Myers Squibb, Nico Corporation and the NIH which are not related to this work. She serves on multiple advisory boards (Nico Corporation, Medexus, and UCSC) which are not in conflict with this work. C.L. is supported by the American Cancer Society under award number RSGI-23-1039245-01-HOPS, and was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1 TR003107-02S2. Support of data acquisition was provided by the Arkansas Biosciences Institute, the major research component of the Arkansas Tobacco Settlement Proceeds Act of 2000. C.L. received research support (payment to the university) for unrelated projects sponsored by University of Utah/AstraZeneca, and received honoraria from PCORI for grant review. The other authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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