Advances in Treatment for Small Cell Lung Cancer in Federal Medicine

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NOW IN THE VA LUNG CANCER CLINICAL PATHWAY[1]

A bispecific treatment option for patients with extensive-stage SCLC[2,3]

Veterans are at risk of rapid disease progression[4]

~ 75% of patients with locally advanced disease and > 90% of patients with metastatic disease progress within 2 years of 1L treatment[4]

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1L, first line; SCLC, small cell lung cancer; VA, Veterans Affairs.

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Front page image: U.S. Air Force Senior Airman Ashley Rodriguez and Staff Sgt. Malika Roberts, 81st Healthcare Operations Squadron respiratory therapists, provide lung cancer screening information to Chief Master Sgt. Sarah Esparza, 81st Training Wing command, during the 10th Annual 81st Medical Group Health Expo at Keesler Air Force Base, MS, in 2021. Military exposures increase the risk of small cell lung cancer. U.S. Air Force photo by Kemberly Groue

Veterans Face Unique Risks for Small Cell Lung Cancer, Prompting Advances in VA Treatment

WASHINGTON, DC—Lung cancer remains the leading cause of cancer death in the U.S. and among veterans, who face an increased risk of developing the malignancy. Consequently, the VA actively screens for the disease and continues to expand access to new treatment options.

Lung cancer has two primary types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). While the names distinguish the two types based on the distinctive appearance of the cancer cells under a microscope, the differences between SCLC and NSCLC extend into their incidence, location, aggressiveness and treatments as well.

Nationally, NSCLC represents 85% of all lung cancers; SCLC accounts for 10% to 15%, with a small number of cancers exhibiting characteristics of both NSCLC and SCLC.

The same split is seen in the veteran population. Of the nearly 8,000 veterans who are diagnosed with lung cancer each year, about 7,000 have NSCLC, and 1,000 have SCLC, according to the VA Cooperative Studies Program Epidemiology Analytics Resource.

Like NSCLC, SCLC is a presumptive condition for veterans exposed to Agent Orange or other herbicides during the Vietnam era and in the Korean Demilitarized Zone, as well as those exposed to radiation. SCLC is also presumed to be service-related in veterans who served in Southwest Asia and other combat zones where they were exposed to fine particulate matter and burn pits.

Veterans are also at particular risk for SCLC due to older average age and higher rates of smoking than the general population. Among veterans with all types of lung cancer, 53.8% were former smokers, and 39.9% were current smokers at the time of diagnosis. Exposure to carcinogens like asbestos and per- and polyfluoroalkyl substances as well as air pollution, also increases risk.[1]

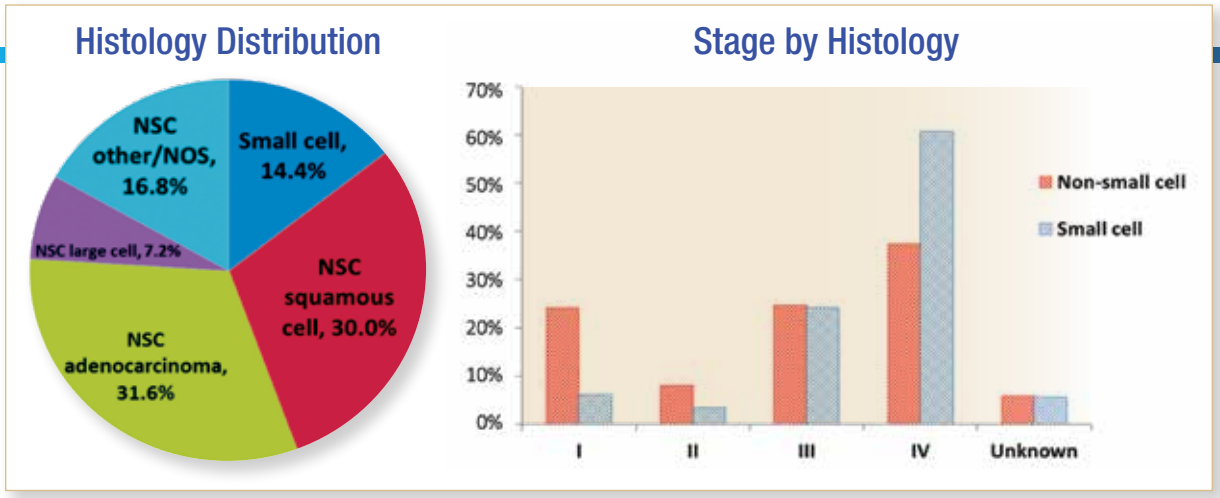
The U.S. Preventive Services Task Force and VA guidelines recommend screening for all lung cancers with low-dose CT scans in adults aged 50 to 80 years who have a 20 pack-per-year history of smoking, regardless of whether they continue to smoke or when they quit. Implementation of the screening guidelines has increased the diagnosis of lung cancer in the VA and enabled more veterans with early stage NSCLC to receive curative treatment.

The SCLC Challenge

The situation is less rosy with SCLC. SCLC stands out for its rapid spread and often late diagnosis. While SCLC can be treated, it often recurs as it has frequently metastasized before it is detected. A new therapy, tarlatamab-dlle, recently gained U.S. FDA approval and offers a powerful option for patients facing recurrence.

SCLC typically starts in the bronchi and then often spreads quickly to the lymph nodes and beyond. Common locations for metastases include the adrenal glands, bones, brain and liver.

As part of staging the disease, SCLC is categorized as being either limited stage or extensive stage at diagnosis. In limited-stage disease, the cancer remains in one lung, though it may have invaded lymph nodes on the same side or the nearby supraclavicular or mediastinal lymph nodes. Most importantly, the cancer is confined to a small enough region that it can be treated with radiation



The two major lung cancer histology groups are non-small cell lung cancer (NSCLC), accounting for 86% of all lung cancer cases, and small cell (SCLC). Adenocarcinoma and squamous cell are predominant subtypes of NSCLC. Lung cancer is typically diagnosed at an advanced stage. For NSCLC, ~30% are early-stage (I/II) disease, 25% stage III, and 40% stage IV. The majority (85%) of SCLC cases are advanced stage. Source: VA

treatment in just one area.

In extensive-stage disease, the cancer spreads throughout the lung, to both sides or metastasizes to other parts of the body. Extensive-stage SCLC may also involve the fluid surrounding the heart and lungs.

Common symptoms of SCLC include a persistent cough, difficulty breathing, chest pain, hoarseness and weight loss. Some patients may also cough up blood or experience swelling in the face and neck or neurological issues due to metastasis. Diagnosing SCLC involves imaging such as chest X-rays or CT scans, followed by a biopsy to confirm the presence of cancer cells. Additional tests, like PET scans, help stage the cancer and determine how far it has spread.

Despite advances, long-term survival for SCLC remains poor, with most patients surviving two to four months without treatment.

Patients with limited-stage disease who undergo chemotherapy and thoracic radiation therapy (TRT) experience significantly longer survival, a median survival of 16 to 24 months, but the five-year survival rate remains low at 14%. For those with extensive-stage SCLC, median survival drops to 6 to 12 months, and long-term survival is rare.

Among veterans diagnosed with SCLC, nearly 15% are diagnosed with limited disease (stage I or II); 85% already have extensive-stage, advanced disease when first detected.

Treatment for SCLC at VA

The VA offers veterans a wide range of treatments for SCLC, from chemotherapy and radiation therapy to cutting-edge immunotherapy and combinations of these modalities. Because most cases have already spread, surgery is not recommended in SCLC. Many patients with SCLC initially respond well to therapy, but the malignancy tends to return and become treatment-resistant.

A new therapy, tarlatamab-dlle, that addresses this gap gained FDA accelerated approval in May. Tarlatamab-dlle is indicated for treatment of extensive-stage small cell lung cancer in patients who experienced disease progression after platinum-based chemotherapy. A bispecific T-cell engager (BiTE) immunotherapy, tarlatamab-dlle, received approval based on its overall response rate and duration of response in clinical trials. Prior to approval, the FDA granted tarlatamab-dlle priority review, breakthrough drug designation and orphan drug designation, demonstrating its significance for patients with limited options.

The VA's Precision Oncology Program and partnerships with leading cancer research institutions help ensure that veterans receive state-of-the-art care for SCLC. These collaborations have increased access to genetic testing, allowing doctors to tailor treatments to individual patients. New treatments, like tarlatamab-dlle, reflect the VA's commitment to bringing cutting-edge therapies to veterans with advanced SCLC.

While the outlook for SCLC remains challenging, especially for veterans with extensive-stage disease, the VA's focus on improving diagnostic tools, early detection and integrating new therapies offers hope for better outcomes.

[1] VA Cooperative Studies Program Epidemiology Analytics Resource. Lung Cancer Fact Sheet: Data on Veterans Using VA Health Care.

Treatment of Small Cell Lung Cancer:
Emerging Therapies After Decades of Stagnation

SILVER SPRING, MD—Small cell lung cancer (SCLC) is a highly aggressive form of lung cancer, characterized by rapid growth and early metastasis. Accounting for roughly 1 in 7 lung cancers, SCLC presents unique challenges in treatment due to its biologically aggressive nature and the rapid development of resistance to therapies.

For more than four decades, SCLC treatment remained largely static, relying largely on platinum-based chemotherapy to which patients typically respond very well initially and nearly always relapse. Consequently, mortality rates have remained stunningly poor, with most patients dying within two years. Recent advances in immunotherapy and targeted therapies in the last few years have provided new hope for improving outcomes, especially in the relapsed or metastatic setting.

The combination of cisplatin or carboplatin with etoposide remains the cornerstone of SCLC treatment. In limited-stage disease, in which tumors have remained in the hemithorax of origin or spread only to the mediastinum or supraclavicular lymph nodes, platinum therapy, etoposide and concurrent chemoradiotherapy (CCRT) provides an objective response rate as high as 94.8%, as demonstrated in the control arm of the STIMULI trial.[1] The trial reported two-year and three-year overall survival rates of 66.4% and 49.3%, respectively, showcasing the impressive initial responses and representing a very substantial increase in overall survival compared to the median overall survival (OS) of 10.3 months and 18-month OS of 25% seen with just chemotherapy and etoposide.[2]

In addition to CCRT, prophylactic cranial irradiation is commonly used to prevent the development of brain metastases, which are present in 10% to 25% of SCLC patients at diagnosis and arise in up to half as the cancer progresses.

A small subset of patients with limited-stage SCLC may benefit from surgery, recent research found. Using data from patients with stage 1 SCLC from the National VA Cancer Care Cube Registry, researchers compared patients who had undergone surgery (223) with or without chemotherapy, radiation or a combination to those who had concurrent chemoradiotherapy (CRT). Median overall survival for patients whose treatment included surgery reached 3.87 years vs. 2.45 years median overall survival for the CRT cohort. The improvement was independent of the location of the tumor.[3]

Unfortunately, despite these high response rates, relapse remains common, reflecting the paradox of SCLC—the bright promise of its initial chemosensitivity belies its fleeting response.

Increasingly, however, researchers have focused on immunotherapy as a novel means to both control and extend survival in SCLC, especially in the relapsed and extensive-stage settings.

Immunotherapy: A New Frontier in SCLC Treatment

In the extensive-stage setting, standard of care includes a combination of platinum-based chemotherapy and immune checkpoint inhibitors (ICIs), such as atezolizumab or durvalumab. This has been particularly beneficial for veterans with extensive-stage SCLC, who often have comorbidities that limit treatment options and who are more prone to early recurrence of disease. By enhancing the body's immune response against the tumor, ICIs offer an additional line of defense and extend survival beyond the initial effects of chemotherapy.

For patients with relapsed or refractory SCLC, treatment options remain limited, and responses to subsequent lines of therapy are often less durable than in the frontline setting. The standard salvage treatment for relapsed SCLC has been topotecan, which offers modest benefits, with overall survival outcomes remaining suboptimal. Lurbinectedin was approved in this setting in 2020.

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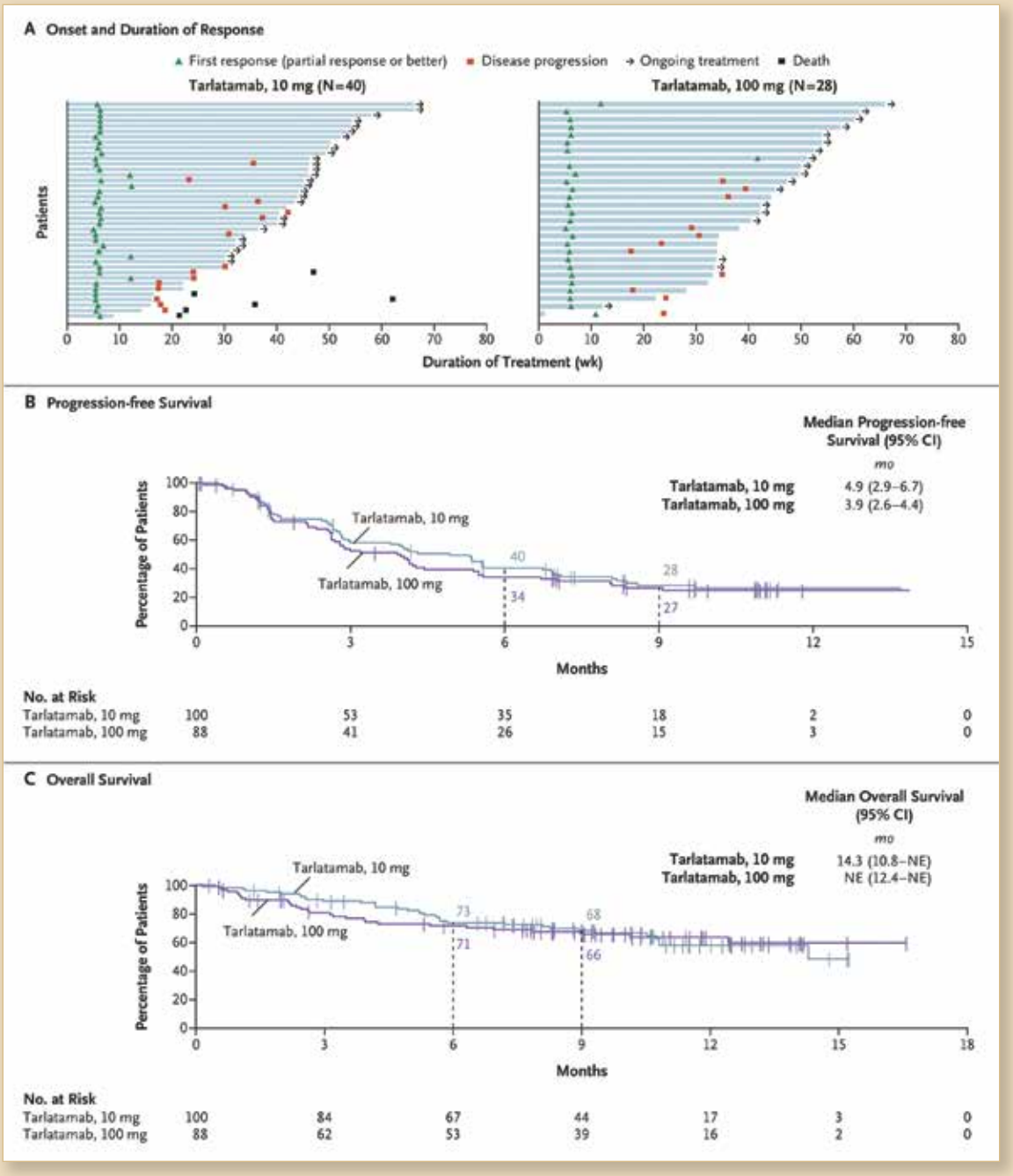
Anti-Tumor Activity of Tarlatamab



Panel A shows the time to response, the duration of response and patient status as of the data cutoff date for all the patients who were assessed as having an objective response (complete or partial response; primary end point) to 10 mg or 100 mg of tarlatamab, as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Panel B shows the Kaplan–Meier curve of progression-free survival in the analysis population for anti-tumor activity, which included 100 patients who had been assigned to receive 10 mg of tarlatamab in part 1 or part 2 of the trial and 88 patients who had been assigned to receive 100 mg of tarlatamab in part 1 of the trial. Panel C shows the Kaplan–Meier curve of overall survival in the analysis population for anti-tumor activity. The tick marks in Panels B and C indicate censored data. NE denotes not evaluable.

Source: Ahn MJ, Cho BC, Felip E, Korantzis I, et. Al.; DeLLphi-301 Investigators. Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. N Engl J Med. *2023 Nov 30;389(22):2063-2075. doi: 10.1056/NEJMoa2307980. Epub 2023 Oct 20. PMID: 37861218.*

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Tarlatamab: A Breakthrough for Relapsed and Metastatic SCLC

One of the most promising recent developments in the treatment of SCLC is the approval of tarlatamab, a bispecific T-cell engager (BiTE) targeting delta-like ligand 3 (DLL3). This immunotherapy represents a novel approach to treating relapsed or metastatic SCLC.

Tarlatamab engages the immune system more directly in the fight against SCLC by binding to two targets simultaneously: DLL3, which is highly expressed on the surface of SCLC cells, and CD3, a receptor on T cells. By bringing these two cell types into close proximity, tarlatamab enables the T cells to attack and destroy the cancer cells. This mechanism is particularly promising for SCLC, as DLL3 is expressed in approximately 85% of real-world SCLC cases.

DeLLphi-301 Clinical Trial

The Food and Drug Administration based its May 2024 approval of tarlatamab on the results of the DeLLphi-301 phase II clinical trial. The trial enrolled 220 patients who had previously received at least two prior therapies, including chemotherapy and immune checkpoint inhibitors. Researchers tested two doses, 10 mg and 100 mg of tarlatamab administered intravenously every two weeks.

Results from the trial were hopeful, particularly for the lower-dose (10 mg) group, where a 40% overall response rate (ORR) was observed—far surpassing the historical response rate of 15% seen with standard treatments in this setting. Further, responses were durable. At 10.6 months of follow-up, 57.5% of responders experienced 6 months or more of response. Subsequent analysis found 30% of responders sustained disease control for at least nine months. The median overall survival for patients in the 10 mg group reached 14.3 months, a significant improvement over the 6 to 12 months seen with previous treatments. Median duration of response was not reached.

In the DeLLphi-301 trial, the most common side effects were cytokine release syndrome (CRS) and neurologic toxicities, which are characteristic of T-cell engager therapies. CRS was generally mild and manageable, with only 0.8% of patients experiencing grade 3 events on the 10 mg dose and 5.7% on the 100 mg dose. There were no grade 4 or 5 events. Neurologic toxicities, including headache and dizziness, were similarly manageable with appropriate monitoring and dose adjustments.

The 10 mg dose demonstrated similar efficacy to the higher dose with fewer adverse events. As a result, the 10 mg dose has been selected for further study in ongoing clinical trials.

"After decades of minimal advancements in the SCLC treatment landscape, there is now an effective and innovative treatment option available," Laurie Fenton Ambrose, co-founder, president, and CEO of GO2 for Lung Cancer, said in an Amgen press release. "Today's FDA approval marks a significant milestone for the SCLC community as the availability of a targeted bispecific therapy brings forward new possibilities to those living with this aggressive disease."

GO2 for Lung Cancer is the result of a 2019 merger between two of the most effective and influential nonprofit organizations serving the lung cancer community, the Bonnie J. Addario Lung Cancer Foundation (ALCF) and Lung Cancer Alliance (LCA). It provides a wide range of support for cancer patients, including research updates.

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[5] Sands J, Cho BC, Ahn MJ, et al. Tarlatamab sustained clinical benefit and safety in previously treated SCLC: DeLLphi-301 phase 2 extended follow-up. Presented at: 2024 World Conference on Lung Cancer; September 7-10, 2024; San Diego. Abstract OA10.03.

Military Exposures and Small Cell Lung Cancer in Deployed Veterans

BALTIMORE—Military service often places individuals in environments where they may be exposed to hazardous substances with potential for long-term consequences. A particularly concerning health outcome for veterans exposed to Agent Orange, burn pits and other environmental toxins common during military service is small cell lung cancer (SCLC).

SCLC is an aggressive form of lung cancer characterized by small, round cells that multiply rapidly. SCLC has two main subtypes: small cell carcinoma (often referred to as oat cell cancer because it looks like oat flakes under a microscope), the classic and more common form of SCLC and combined small cell carcinoma, which features a mix of small cell and non-small cell lung cancer cells.

Both subtypes are recognized by the VA as presumptive cancers for certain Vietnam, Gulf War, post-9/11 and other veterans. This designation means that veterans diagnosed with these conditions are assumed to have developed the disease as a result of their service-related exposures, qualifying them for VA health benefits and disability compensation.

Those included in the presumptive coverage for SCLC include "atomic veterans," who may have been exposed to ionizing radiation during the occupation of Japan while held as a prisoner of war in Japan or through nuclear weapons testing, while working at Long-Range Navigation stations or at McMurdo Station in Antarctica's nuclear power plant. In addition, the Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics Act of 2022, known as the Honoring our PACT Act of 2022, added servicemembers involved in the clean-up operations on Enewetak Atoll; in Palomares, Spain; and on Thule Air Force Base in Greenland.

SCLC is also presumed to be service-related in veterans deployed in Vietnam, Cambodia, Laos, Thailand, Guam, American Samoa, Johnston Atoll, the Korean demilitarized zone or who regularly served aboard or maintained a C-123 aircraft used for spraying herbicides. All of these individuals are assumed to have sustained exposure to Agent Orange.

Burn Pit Exposure Increased SCLC Risk for Young Vets

Veterans who served in combat zones during and after the Gulf War or the post-9/11 period were often exposed to a variety of substances that could damage lungs or contribute to the development of lung malignancies in later life, and SCLC in this cohort is also a presumed condition.

Burn pits have been a central focus in understanding veterans' exposure to toxic substances. These open-air disposal sites were widely used in combat settings to incinerate everything from plastics and electronics to human waste and chemicals, creating thick, toxic smoke that directly affected burn pit workers. Smoke drift also exposed others at the site to the toxins.

The pits were used in areas where other methods of waste disposal were impractical. However, the incomplete combustion of materials in these pits led to the release of harmful chemicals, including volatile organic compounds (VOCs), such as benzene and dioxins, which are known carcinogens. Burn pits also released polycyclic aromatic hydrocarbons (PAHs), which can cause lung cancer upon prolonged exposure. In addition, the fires, materials and environmental setting generated a great deal of particulate matter, which can damage lung tissue and contribute to the development of cancer.

The exposure to these hazardous materials was often prolonged, with many veterans experiencing daily or near-daily exposure during deployments. Studies have linked exposure to these toxins with an increased risk of respiratory illnesses, including lung cancers of all types.

Many of these exposures occurred in specific locations known to have had a higher risk of contamination,

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including Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, Yemen and the airspace above these areas after Sept. 11, 2001. Veterans of previous conflicts in Southwest Asia, including those serving in Bahrain, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, Somalia, the United Arab Emirates (UAE) and the airspace above these areas after Aug. 2, 1990, are also considered at high risk.

Other locations of concern include the Arabian Sea, Gulf of Aden, Gulf of Oman, the neutral zone between Iraq and Saudi Arabia, the Persian Gulf and the Red Sea. Veterans who served in these areas are presumed to have been exposed to burn pits and other toxins and thus to have a higher likelihood of developing diseases such as SCLC as a result of their service, though the malignancy might not develop for decades.

Many veterans also regularly encountered other environmental toxins that increase the risk of SCLC, such as particulate matter, chemicals from munitions and industrial emissions as well as common occupational hazards in military work including diesel exhaust, solvents and chemical agents.

Exposures, Period of Service and Lung Cancer Type

To better understand the association of lung cancer histological subtypes and specific exposures among veterans, a recent VA study analyzed service locations and exposures among veterans seen in the lung mass clinic at the Baltimore VAMC between 2015 and 2022.[1]

"Veterans' unique occupational, operational and environmental exposures during and post service constitute additional risk factors," Grace Faith Salacup, MD, of the Baltimore VAMC and the division of Pulmonary, Critical Care and Sleep at the University of Maryland School of Medicine and colleagues noted.

The analysis included 293 veterans with cancer who had an average age of 69.3 +/- 7.7 years. The study population was 96.3% male, 53.6% white, 44.7% Black and 1.7% other. Of the participants, 57.3% were former smokers, 40.3% were current smokers, and 2.4% had never smoked. Among the smokers, 91.5% currently or previously smoked at least 20 packs of cigarettes per year.

Consistent with the age of the veterans in the study, 65% served in Vietnam, 9% in Korea, 6% were Persian Gulf war veterans, and 20% were locally deployed or served elsewhere. The most common exposures were asbestos (170), Agent Orange (111) and radiation (103). Twenty-six participants in the study reported exposure to oil fumes, 25 to pesticides and 11 to burn pits, with these lower numbers in keeping with the age and location of service of the veterans studied.

Nine percent of the veterans had SCLC, 85% had non-small cell lung cancer (NSCLC) and 6% had no tissue analyzed or were lost to follow-up.

At diagnosis, 32.76% of the veterans had stage I cancer, 11.95% had stage II, 26.28% had stage III, and 22.53% had stage IV disease. The researchers did not break down the stage at diagnosis by type of lung cancer.

Their analysis revealed that, after adjusting for smoking history, Agent Orange exposure quadrupled the relative risk of developing SCLC (RR:4.17, 95% CI: 1.03-16.87, p 0.045).

"As a single-center case control study, these exposures cannot establish causality to a specific type of lung cancer and/or bronchiolitis," the researchers noted. However, they did find "burn pit exposure is associated with increased odds of bronchiolitis in histopathology (OR 6.14 CI: 1.06 35.55, p 0.043)." Bronchiolitis, a chronic lung inflammation, elevates the risk of SCLC. The 19 veterans with bronchiolitis in the study also had SCLC, though the study did not identify the timing of their diagnoses.

Based on these findings, the researchers recommended "education and training among the VA providers on standardizing exposure screening among veterans in their clinic visits" and development of a standardized questionnaire to enable objective quantification of exposures.

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As Small Cell Lung Cancer Rates Drop, Understanding of Disease Increases

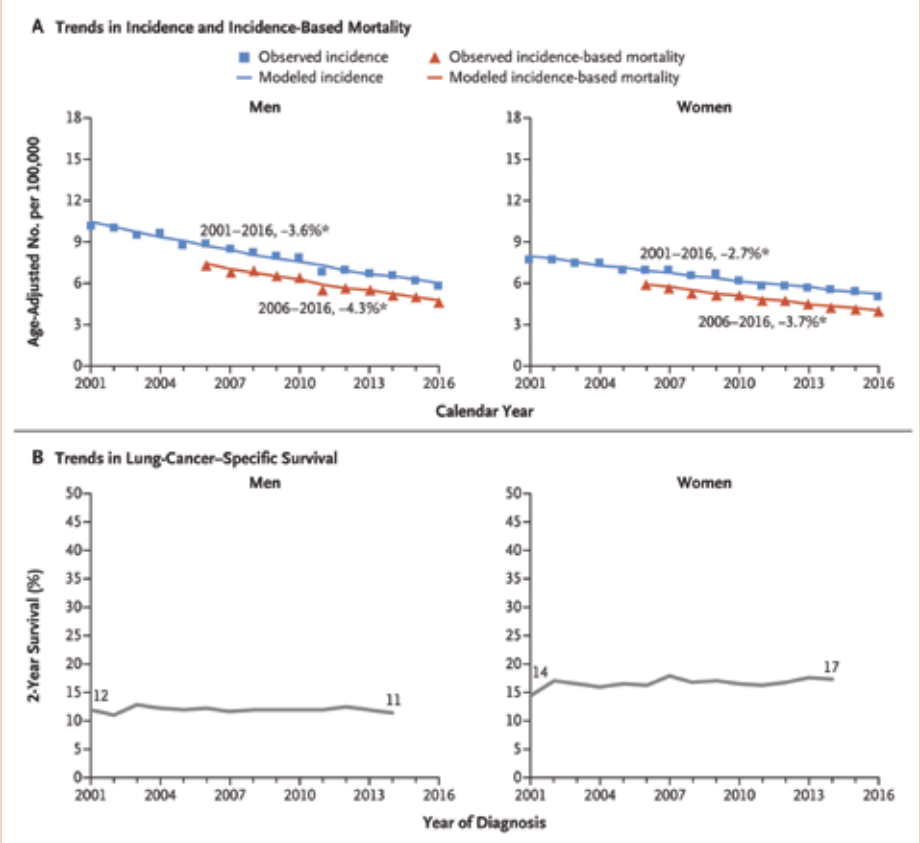
CLEVELAND—"The more things change, the more they stay the same" could be a tagline for small cell lung cancer (SCLC). In recent decades, the epidemiology of SCLC has shifted substantially, as have the understanding of the disease, screening options and the treatments available. The malignancy, however, remains both challenging and highly lethal.

Worldwide, SCLC now accounts for approximately 15% of all lung cancers, down from 25% with smoking as a well-established etiological factor in up to 90% of cases.[1,2] Increased public awareness of the association between smoking and lung cancer over the last 50 years and dramatic drop in the number of smokers in most countries drove down incidence rates for all lung cancers, including SCLC.

Where the overall survival rate for non-small cell lung cancer improved faster than the incidence of the malignancy declined as a result of more effective therapies, SCLC mortality declined in tandem with its incidence, while survival remained both dismal and largely unchanged.[3]

Still, the overall decrease in SCLC incidence is encouraging, though the impact varies significantly across demographics. Where males historically accounted for two-thirds of SCLC cases globally and three-quarters in the U.S., today they represent less than half, though what has driven the change is unclear. Further, while the cancer typically occurs in individuals over age 60, an increasing number

Non–Small-Cell Lung-Cancer (NSCLC) Incidence, Incidence-Based Mortality and Survival Trends Among Men and Women



Source: The Effect of Advances in Lung-Cancer Treatment on Population Mortality. Published August 12, 2020. N Engl J Med *2020;383:640-649.DOI: 10.1056/NEJMoa1916623*

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of women under the age of 50 have been diagnosed with SCLC in the last two decades.[4]

Advances in Genetic and Molecular Pathology

A comprehensive understanding of SCLC's genetic landscape has emerged only recently, thanks to next-generation sequencing (NGS) technologies. While historically limited by scarce tissue samples due to the aggressive nature of SCLC and the tendency toward small biopsy specimens, recent studies have identified characteristic mutations in genes involved in cell cycle regulation, DNA repair and apoptosis.

The most frequently mutated genes in SCLC are *TP53* and *RB1*, present in nearly all cases. The loss of function in these tumor suppressor genes is a hallmark of SCLC, underpinning the cancer's propensity for rapid proliferation and early metastasis. Additionally, aberrations in MYC family genes, including *MYC, MYCL* and *MYCN*, are observed in certain subsets of SCLC and are associated with particularly aggressive disease courses.[5] These findings suggest a heterogeneous SCLC landscape, with distinct genetic subtypes that may eventually guide individualized therapeutic approaches.

Beyond driver mutations, recent research also has elucidated the role of epigenetic changes in SCLC pathogenesis. Histone modifications and aberrant methylation patterns have been implicated in SCLC, impacting gene-expression profiles and contributing to chemotherapy resistance.[6]

Improved Screening and Early Detection Strategies

The challenge of early SCLC detection is compounded by its aggressive progression and asymptomatic onset in initial stages. Low-dose computed tomography (LDCT) has been a breakthrough for lung cancer screening in high-risk populations, reducing mortality in non-small cell lung cancer; however, its efficacy for SCLC is limited due to the rapid development and spread of SCLC lesions.[7]

Emerging technologies, such as liquid biopsies, offer promising alternatives for early SCLC detection. Liquid biopsies analyze circulating tumor DNA (ctDNA) and other cancer-derived components in the bloodstream, providing a minimally invasive means of identifying tumor-specific mutations. In recent studies, ctDNA analysis has demonstrated high sensitivity and specificity for detecting SCLC-associated genetic alterations, even at early disease stages.[8] These findings suggest that liquid biopsy may complement existing imaging modalities for more comprehensive lung cancer screening, especially in high-risk individuals where LDCT alone may not suffice.

In addition to ctDNA, biomarker panels that include microRNAs, protein signatures and autoantibodies are under investigation for their potential in SCLC screening. For example, microRNAs such as miR-375 and miR-92a have been shown to correlate with SCLC presence and progression, offering insight into tumor biology and possible disease monitoring.[9]

The landscape of SCLC is shifting due to changes in epidemiological trends, deeper insights into genetic and molecular pathogenesis, and innovations in screening technologies. While SCLC remains challenging to detect and treat, these advancements provide hope for improved outcomes through earlier diagnosis and potentially targeted therapies. As research progresses, continued integration of genetic profiling and novel biomarker-driven strategies into clinical practice may redefine the approach to SCLC, ultimately bridging gaps in survival for this aggressive cancer.

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Lung Cancer Survival Rates in Federal Medicine Compare Well to Community

SCLC Survival Looking Up but Lags Behind NSCLC

LOS ANGELES—Survival rates appear to be somewhat better for veterans and military healthcare beneficiaries diagnosed with small cell lung cancer (SCLC) but are not as improved as with non-small cell lung cancer (NSCLC), according to recent studies.

A key advantage, according to the report in *Clinical Lung Cancer*, is that both the VA and MHS are universal healthcare systems that provide equal care despite race, ethnicity or ability to pay. So, unlike in the general population, Black veterans are benefiting as much or more than white ones from any increased lung cancer survival rates.[1]

In addition to equal access healthcare systems in federal medicine, the studies lauded an increase in the percentage of patients diagnosed at earlier stages, improved diagnostic technologies and advancements in medical, surgical and radiation therapies.

Using data from the VA Central Cancer Registry, the study team identified 54,922 veterans with lung cancer diagnosed from 2010-2017. Most of the veterans, 64.2%, had NSCLC, with other histologies, including small cell lung cancer SCLC (12.9%) and "other" (22.9%).

"The proportion with stage I increased from 18.1% to 30.4%, while stage IV decreased from 38.9% to 34.6% (both p<0.001)," wrote the VA Greater Los Angeles Healthcare System-led researchers. "The 3-year overall survival (OS) improved for stage I (58.6% to 68.4%, p<0.001), stage II (35.5% to 48.4%, p<0.001), stage III (18.7% to 29.4%, p<0.001), and stage IV (3.4% to 7.8%, p<0.001)."

For NSCLC, the median OS increased from 12 to 21 months (p<0.001), and 3-year OS increased from 24.1% to 38.3% (p<0.001), the investigators reported. For SCLC, the median OS remained unchanged (8 to 9 months, p=0.10), while the 3-year OS increased from 9.1% to 12.3% (p=0.014)."[1]

The authors pointed out that, compared to white veterans, Black veterans with NSCLC had similar OS (p=0.81), and those with SCLC had higher OS (p=0.003). "The observed racial equity in outcomes within a geographically and socioeconomically diverse population warrants further investigation to better understand and replicate this achievement in other healthcare systems," they added. The VHA is the largest integrated healthcare system in the U.S. and serves approximately 9 million enrollees.

The MHS, which serves approximately 9.6 million beneficiaries through TRICARE, also has reported that its patient population—active-duty servicemembers, National Guard/Reserve members, military retirees and their families—fared better than those receiving civilian care when diagnosed with lung cancer.[2]

A report in the journal *Cancer Causes & Control* noted that, in contrast to the MHS and VA, healthcare access varies in the U.S. general civilian population by insurance status/type.

A study team led by researchers from the Murtha Cancer Center Research Program and the Uniformed Services University of the Health Sciences, both in Bethesda, MD, divided the patients from the U.S. general

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population by insurance status/type and compared them to the MHS patients in survival.

The military health system patients were identified from the DoD's Automated Central Tumor Registry (ACTUR). Patients from the U.S. general population were identified from the Surveillance, Epidemiology, and End Results (SEER) program. The focus of the study was overall survival.

"Compared to ACTUR patients with non-small cell lung cancer (NSCLC), SEER patients showed significant worse survival," the authors pointed out.

The adjusted hazard ratios (HRs) were 1.08 [95% Confidence Interval (CI) = 1.03-1.13], 1.22 (95% CI = 1.16-1.28), 1.40 (95% CI = 1.33-1.47), 1.50 (95% CI = 1.41-1.59), for insured, insured/no specifics, Medicaid and uninsured patients, respectively. "The pattern was consistently observed in subgroup analysis by race, gender, age, or tumor stage," according to the study. "Results were similar for small cell lung cancer (SCLC), although they were only borderline significant in some subgroups."

The authors advised that the "survival advantage of patients receiving care from a universal healthcare system over the patients from the general population was not restricted to uninsured or Medicaid as expected, but was present cross all insurance types, including patients with private insurance. Our findings highlight the survival benefits of universal health care system to lung cancer patients."

Background information recounted how a *New England Journal of Medicine (NEJM)* report in 2020 showed improving survival rates for lung cancer patients in the United States. That study identified increasing 2-year survival rates for men (26%-35%) and women (35%-44%) diagnosed between 2001 and 2014. On the other hand, the rates of lung cancer survival increase were found to accelerate between 2013 and 2016. Unlike in the VHA, "while these increases were observed across different racial and ethnic groups, survival rates remained inferior throughout the study period for non-Hispanic Black men and women demonstrating the persistence of lung cancer racial disparities in the U.S.," the authors wrote.[2]

That is in contrast to the findings at the VA, where, according to the more recent study, "Survival rates for veterans with lung cancer who received healthcare through the VHA increased significantly during the study period. This observation was made across all stages and histological subtypes and was coincident with the identification of a 68% relative increase in stage I at diagnosis and an 11% relative decrease in stage IV diagnosis. Further, compared to white Veterans, we observed Black Veterans with NSCLC and SCLC had better or similar survival rates, respectively"

Authors of the *NEJM* report from the National Cancer Institute, Harvard Medical School and the University of Michigan credited the decreases to the then-recent introduction of recommendations for routine testing of molecular alterations in epidermal growth factor receptor and anaplastic lymphoma kinase, as well as commercial use of related FDA-approved targeted therapies.

The VA authors agreed with that assessment and suggested even more contributors, such as:

1) increasing utilization of low-dose chest computed tomography (LDCT) scans for early detection,
2) advances in biopsy techniques to increase the likelihood of obtaining a positive biopsy and correctly staging patients at the time of initial diagnosis (e.g., endobronchial ultrasound and robotic bronchoscopy guided systems),
3) incorporation of nurse navigators to improve the timeliness of care,
4) technological advances improving the safety of lung cancer surgery and radiation therapy delivery systems (e.g., minimally invasive surgery and image guided radiation therapy),
5) access to newly FDA-approved targeted therapies and immunotherapies,
6) better integration of palliative care for patients with metastatic lung cancer, which has been shown to not only prolong survival but also improve the quality of life for people at the end of their lung cancer journey, and
7) decreased wait times for healthcare within VHA since passage of the 2014 Veterans Choice Program.

"Given the complex coordination of healthcare required to successfully work up and manage patients with newly diagnosed lung cancer, further research into

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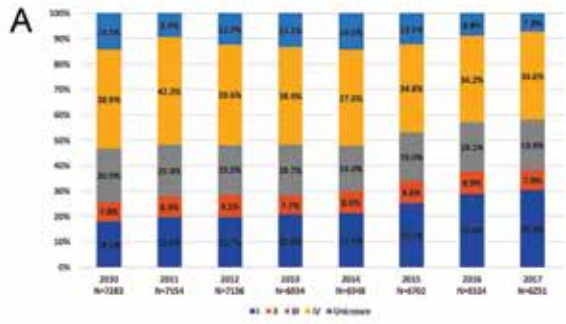
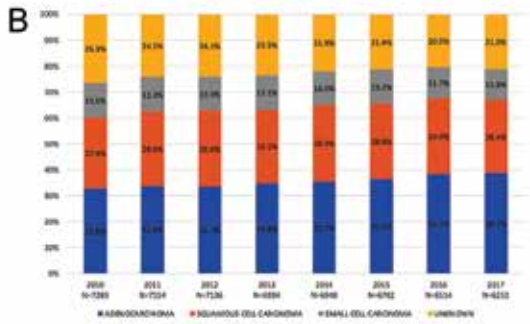
Trends in Baseline Distributions at Diagnosis for (A) Stage, (B) Histology and (C) Race

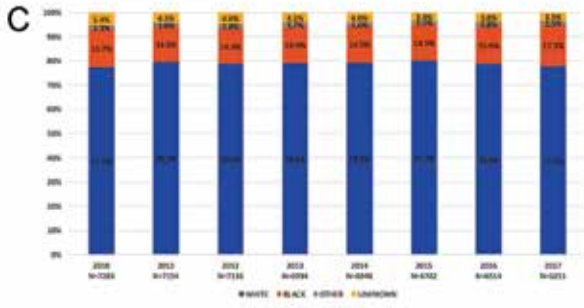
Newly Diagnosed Lung Cancer Cases by Stage



Newly Diagnosed Lung Cancer Cases by Histology



Newly Diagnosed Lung Cancer Cases by Race



Source: Lung Cancer Survival Trends in the Veterans Health Administration. Clin Lung Cancer. *2024 Mar 2:S1525-7304(24)00035-4. doi: 10.1016/j.cllc.2024.02.009. Epub ahead of print. PMID: 38553325.*

the relative contributions of each of these diagnostic and therapeutic factors is necessary to replicate the VHA's success in other healthcare systems," they added.

The researchers also noted that the achievement of better or similar survival rates in Black versus white veterans with lung cancer existed in both the VHA and MHS healthcare systems. "Collectively, these findings align with the US Military and VHA's long-standing culture of ensuring healthcare equity which dates back to Executive Order 9881, written by President Harry S. Truman, which was declared in 1948: 'There shall be equality of treatment and opportunity for all persons in the armed services without regard to race, color, religion or national origin.'"

[1] Moghanaki D, Taylor J, Bryant AK, Vitzthum LK, et. Al.. Lung Cancer Survival Trends in the Veterans Health Administration. *Clin Lung Cancer*. 2024 Mar 2:S1525-7304(24)00035-4. doi: 10.1016/j.cllc.2024.02.009. Epub ahead of print. PMID: 38553325.

[2] Lin J, Shriver CD, Zhu K. Survival among lung cancer patients: comparison of the U.S. military health system and the surveillance, epidemiology, and end results (SEER) program by health insurance status. *Cancer Causes Control*. 2024 Jan;35(1):21-31. doi: 10.1007/s10552-023-01765-0. Epub 2023 Aug 2. PMID: 37532916

[3] Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, Mariotto AB, Lowy DR, Feuer EJ. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. *N Engl J Med*. 2020 Aug 13;383(7):640-649. doi: 10.1056/NEJMoa1916623. PMID: 32786189; PMCID: PMC8577315.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