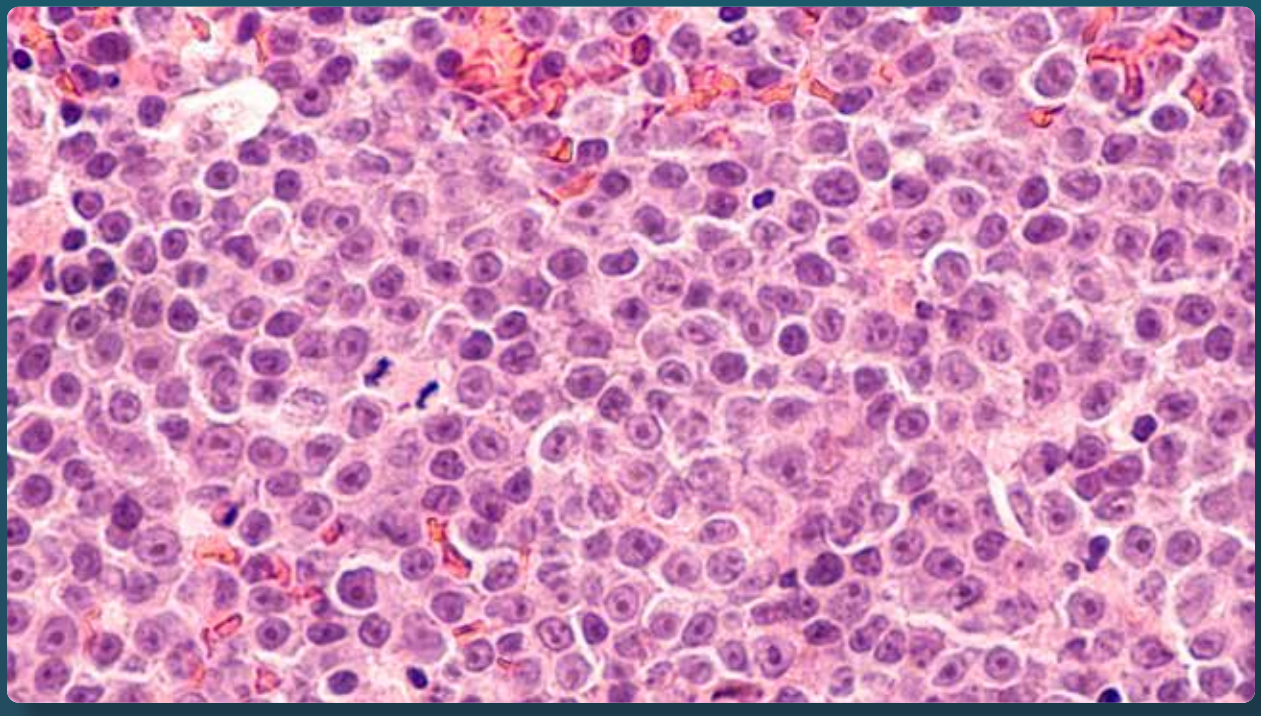
ADVANCES IN TREATMENT FOR DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)



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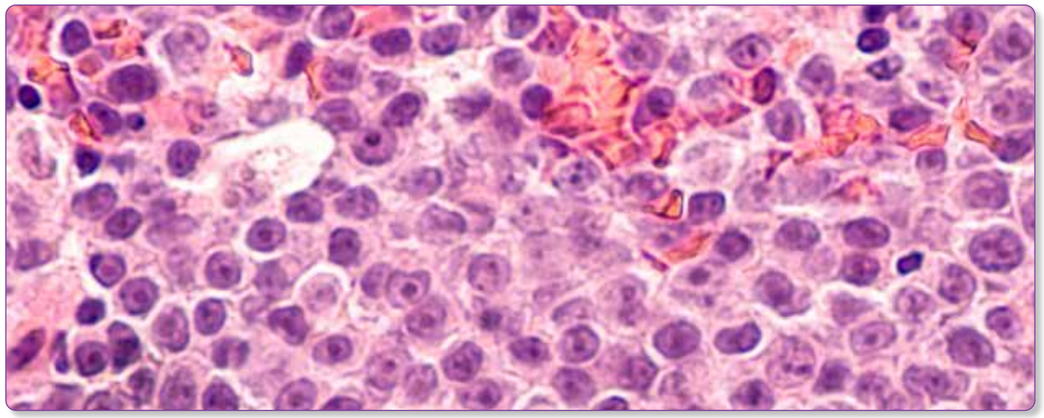

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Front Cover and Table of Contents image: photomicrograph of a diffuse large B-cell lymphoma (DLBCL) Photo by © iStockphoto rightdx

Survival Improving for Most Common Lymphoma Diagnosed in Veterans

BETHESDA, MD—Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma diagnosed in active-duty servicemembers and veterans. Fortunately, advances in understanding of the disease are leading to more targeted and effective therapies and improved survival rates.

DLBCL accounts for approximately 30% of all non-Hodgkin lymphomas. In the United States, about 25,000 people receive a new diagnosis of this aggressive disease each year, and DLBCL is responsible for 5,600 deaths annually.

For decades, the five-year survival rate for DLBCL hovered in the low-40% range before beginning to rise in the late 1990s, reaching 62% by 2003. This notable improvement resulted from the incorporation of the first targeted therapies into the standard treatment regimens. In the last two decades, the five-year survival rate has risen modestly and now stands at 64.7%.[1]

A spate of recent U.S. Food & Drug Administration approvals of new agents, including tafasitamab, axicabtagene ciloleucel, glofitamab, polatuzuma vedotin, and epcoritamab could significantly improve those results in the coming years.

As with other cancers, early diagnosis substantially expands treatment options and influences the length of survival. Individuals diagnosed with stage I disease have a nearly 80% five-year survival rate, while those who have stage IV DLBCL at diagnosis have a less than 60% 5-year survival rate.

Unfortunately, the often painless and frequently swift progression of the disease results in nearly twice as many people being diagnosed after the disease has spread significantly than when it remains localized. Twenty percent of patients receive their diagnosis at Stage I, 19% at Stage II, 19% at Stage III and 38% at Stage IV.

Veterans at Increased Risk

Veterans who receive treatment through the VA have a high rate of risk factors for DLBCL, including older age and male sex. More than 3 out of 4 patients are older than age 55 when diagnosed with DLBCL, and more than half are over age 65. In patients younger than age 45, males are 2 to 5 times more likely to develop the disease than females, although, across all ages, males are 50% more likely to be diagnosed with DLBCL.[2]

Chronic infection with hepatitis B, which is more common in veterans than in the general U.S. population, is also associated with an increased risk of DLBCL. Chronic hepatitis C (HCV) infection also increases the risk, and while the VA's aggressive treatment of HCV has made that less of an issue among veterans, the rates are still higher than in the general population.[3]

In addition, veterans exposed to certain environmental hazards, such as Agent Orange and ionizing radiation, are at an increased risk for developing DLBCL. The VA recognizes DLBCL as a presumptive condition for these veterans. (Please see accompanying article, Page 7).

Other common risk factors include having a first-degree relative who has had DLBCL, chronic immune dysregulation and obesity.

Presentation and Symptoms

DLBCL typically presents as a rapidly enlarging mass, either in lymph nodes or extranodal sites. Common symptoms include painless swelling of lymph nodes in the neck, armpit or groin. Extranodal symptoms such as abdominal pain or diarrhea, cough or shortness of breath may be initially confused with other common conditions such a gastrointestinal or respiratory infections.

Approximately 30% of patients experience systemic issues known as B symptoms such as unexplained fevers above 103°F (39.5°C), rapid weight loss exceeding more than 10% of body weight and drenching night sweats.[4]

Diagnosis

Diagnosing DLBCL can be challenging due to its heterogeneous presentation and nonspecific symptoms. The disease may mimic other lymphomas, reactive lymphadenopathies or inflammatory condition, leading to potential misdiagnosis. A definitive diagnosis requires a comprehensive approach, including histopathological examination, immunophenotyping

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and molecular studies. Clinicians are urged to maintain a high index of suspicion when patients present with rapidly enlarging lymph nodes, systemic "B symptoms" and extranodal involvement.

In addition to clinical evaluation and imaging studies to assess organomegaly and lymphadenopathy, a definitive diagnosis of DLBCL requires an excisional core needle biopsy. Additional immunohistochemistry and genetic studies are typically undertaken to identify specific subtypes of DLBCL, which can influence treatment decisions. Bone marrow biopsy may also be required to confirm limited stage disease.[5]

Standard Treatments

First-line treatment for most DLBCL cases relies on immunochemotherapy that combines rituximab with cyclosphosphamide, doxorubicin, vincristine and prednisone (R-CHOP). About 60% of patients achieve remission with this treatment. In certain cases, especially with localized disease, radiation may be used in conjunction with chemotherapy.[6]

Eventually, about half of patients develop relapsed or refractory DLBCL, however. For these patients, high-dose chemotherapy followed by autologous stem cell transplantation has been considered the standard a second-line therapy for those who can withstand it.[7]

For those for whom a stem cell transplant is not an option, novel agents including monoclonal antibodies such as tafasitamab and CAR T-cell therapies offer new hope for extended survival.[8]

[1]NIH. National Cancer Institute SEER Program. Cancer Stat Facts: NHL—Diffuse Large B-Cell Lymphoma (DLBCL).

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Incidence Rate Ratios (IRR) by Race and Sex, 2011-2020

		Lymphoid neoplasms, total	B-cell lymphoid neoplasms, total	DLBCL
		IRR*	IRR*	IRR*
Male:Female IRR	White	1.6	1.6	1.5
	Black	1.5	1.5	1.7
	Asian	1.2	1.5	1.4
White:Black IRR	Males	1.1	1.1	1.4
	Females	1.0	1.0	1.6
White:Asian IRR	Males	1.7	1.8	1.2
	Females	1.6	1.7	1.1

DLBCL: diffuse large B-cell lymphoma

*All incidence rates are age-adjusted to the 2000 U.S. population and expressed per 100,000 person-years

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER Research Data, 12 Registries, Nov 2022 Sub (1992–2020) - Linked to County Attributes - Time Dependent (1990–2021) Income/Rurality, 1969–2021 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission.

Source: Epidemiology and etiology of diffuse large B-cell lymphoma. Semin Hematol. *2023 Nov;60(5):255-266. doi: 10.1053/j.seminhematol.2023.11.004. Epub 2023 Nov 27.*

New Treatment Options Extend Survival for Veterans With DLBCL

SILVER SPRING, MD—Diffuse large B-cell lymphoma (DLBCL) is the most prevalent subtype of non-Hodgkin lymphoma (NHL), characterized by its aggressive nature. While frontline therapies achieve remission in the majority of patients, many of those diagnosed with the lymphoid malignancy will ultimately experience relapsed or refractory (R/R) disease, necessitating novel therapeutic approaches.

The standard initial treatment for DLBCL involves a combination chemotherapy regimen that includes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). This regimen induces durable remission in approximately 60% of patients. However, about 40% of patients either do not respond to initial therapy or relapse after an initial response, with about 15% not responding at all and 20% to 25% relapsing, typically within 24 months following initial response.

For these individuals, one of several high-dose chemotherapy regimens followed by autologous stem cell transplantation (ASCT) has been the standard treatment recommendation.

Yet, only 10% of patients with R/R DLBCL receive long-term benefit from ASCT. The math is brutal: Up to half of patients with R/R DLBCL are ineligible for ASCT because of advanced age, comorbidities or poor performance status. Of those eligible for ASCT, about half prove refractory to the salvage chemotherapy and are unable to continue to transplantation. Of those who complete the grueling treatment, 40% achieve lasting remission.[1]

Patients who do not respond or cannot withstand the intensive chemotherapy required before transplantation or become ineligible for ASCT after the salvage therapy, have had few options, little hope and less time until recently.

A burst of U.S. Food and Drug Administration approvals for novel therapies in the last 5 years has significantly expanded options for patients with R/R DLBCL and for selected patients in the first line.

In a change for initial treatment, the VA Oncology Clinical Pathways for DLBCL and the National Comprehensive Cancer Network (NCCN) now recommend using polatuzumab plus vedotin piiq, rituximab, cyclophosphamide, doxorubicin, prednisone (pola-R-CHP) for most patients diagnosed with Stage III or IV disease who have International Prognostic Index of 2 or higher and nongerminal center B-cell cell of origin.

Polatuzumab, a monoclonal antibody, received FDA approval in this setting in April 2023 based on the POLARIX trial. While the 879-person study did not demonstrate a difference in overall survival or complete response rate for Pola-R-CHP compared to R-CHOP, progression-free survival was 27% longer.[2]

For patients with R/R DLBCL who relapsed within 12 months of initial treatment or had primary refractory disease, NCCN recommends chimeric antigen receptor T-cell (CAR-T)-mediated therapies using axicabtagene ciloleucel or lisocabtagene maraleucel, both CD19-directed therapies, with several options for bridging therapies.

CAR-T therapies face numerous challenges, however. Physicians are often reluctant to use them in patients over age 70 or 75 or in those with significant comorbidities because of their toxicity and the high risk of cytokine release syndrome and potentially life-threatening neurological events. In addition, because they are customized to the patient, they are very expensive and are not available outside of major academic centers. These therapies are only available through Risk Evaluation and Mitigation Strategy (REMS) programs because of their risks. Further, they can take 3 to 4 weeks to produce, which is often too long for a patient with a quickly progressing disease that has already been demonstrated to be refractory to high-intensity immunochemotherapy.

For patients who are not eligible for or choose not to proceed with CAR T-cell therapy, the NCCN recommends five newer therapies.

Tafasitamab-cxix

Tafasitamab-cxix is a humanized monoclonal antibody targeting the CD19 antigen on B cells. In July 2020, the FDA granted accelerated approval for tafasitamab-cxix in combination with lenalidomide for adult patients with R/R DLBCL

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who are not eligible for ASCT. The VA added tafasitamab to its formulary in 2024 for patients who meet the agency's criteria for use.

This approval was based on the L-MIND study, which demonstrated an overall response rate of 57.5% at a median of 44 months follow-up, including a complete response rate of 41.3%. The median duration of response was 21.7 months. Median progression-free survival was 11.6 months, and overall survival was 33.5 months. Neutropenia and thrombocytopenia were the most common adverse events.[3]

A subsequent real-world analysis of 181 patients supported these findings, reporting a progression-free survival of 11.3 months and an overall survival of 24.8 months in patients treated with tafasitamab-cxix and lenalidomide. The overall response rate (ORR) was 73.5%, of which 23.2% achieved complete response. Factors such as treatment line, disease stage and comorbidities significantly influenced outcomes, with use of the tafasitamab-cxix/lenalidomide combination in earlier lines associated with better results than in later lines.[4]

Epcoritamab-bysp

A bispecific antibody that engages CD3 and CD20, epcoritamab-bysp received accelerated approval from the FDA in May 2023 for patients with R/R DLBCL after two or more lines of systemic therapy. NCCN recommends using epcoritamab-bysp with gemcitabine and oxaliplatin (GemOx) as a second-line therapy.

The EPCORE NHL-1 trial supported the agency's decision. The multicenter, single-arm trial included 148 patients with R/R DLCBL who had previously received at least two lines of systemic therapy including at least one with an anti-CD20 antibody-containing therapy. The ORR was 61%, with 38% of patients achieving complete response and median duration of response of 15.6 months at a median of 9.8 months of follow-up.[5]

At three years, EPCORE NHL-1 had an ORR of 59%, complete response of 41% and median duration of response of 20.8 months.[6]

Epcoritamab carries a black box warning for cytokine response syndrome (CRS) and life-threatening immune effector cell-associated neurotoxicity syndrome (ICANS). The FDA noted that more than half of the patients in the trial developed CRS, and 6% developed threatening immune effector cell-associated neurotoxicity syndrome.[7]

Glofitamab-gxbm

Glofitamab-gxbm is another bispecific antibody targeting CD20 and CD3. It gained FDA accelerated approval in June 2023 for relapsed or refractory DLBCL following two or more lines of systemic therapy. As with epcoritamab, NCCN recommends its use in combination with GemOx.

In its pivotal study, 154 patients received glofitamab, of which 52% had an objective response and 39% had complete response. At a median follow-up of 11.6 months, the ORR was 56% with complete response in 43%. The estimated median duration of response was 18.4 months.[8]

Glofitamab-gxbm has a boxed warning for serious or fatal CRS and a warning for ICANS, serious infections, and tumor flare. Among 145 patients with relapsed or refractory LBCL evaluated for safety, CRS occurred in 70%, ICANS in 4.8%, serious infections in 16%, and tumor flare in 12%, the FDA noted. Nearly two-thirds of patients had an adverse event of grade 3 or higher.

Polatuzumab

Polatuzumab is also listed by NCCN as a preferred a second-line therapy either in combination with bendamustinem with or without rituximab or in combination with mosunetuzumab-axgb.

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[7]US FDA. FDA grants accelerated approval to epcoritamab-bysp for relapsed or refratory diffuse large B-cell lymphoma nad high-grad B-cell lymphoma. May 19, 2023.

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Exposures Significantly Increase DLBCL Risks for Veterans, Servicemembers

WASHINGTON, DC—Exposure to a wide range of chemicals and radiation has long been known to increase the risk of developing diffuse large B-cell lymphoma (DLBCL). As research has identified new agents associated with increased risk, the U.S. Congress and the VA have responded by facilitating access to healthcare for veterans who were exposed to these agents during their service.

Over more than three decades, the VA has progressively expanded the recognition of certain lymphomas, including DLBCL, as presumptive conditions.

Atomic Veterans

In 1990, Congress enacted the Radiation-Exposed Veterans Compensation Act, establishing a presumptive service connection for specific cancers linked to ionizing radiation exposure. Non-Hodgkin lymphoma (NHL) was among the conditions recognized under this legislation. DLBCL is the most common subtype of NHL. This act primarily benefited "atomic veterans" who participated in atmospheric nuclear tests, occupied Hiroshima or Nagasaki or were held as prisoners of war in Japan during World War II.

The Sergeant First Class Heath Robinson Honoring Our Promise to Address Comprehensive Toxics Act (PACT Act) of 2021 expanded coverage for DLBCL for several groups of veterans exposed to radiation, including those involved in clean up of radiactive sites from 1966 to 1980. More than 8,000 veterans are thought to be eligible for the benefits, but, thus far, a high percentage have been denied.

Agent Orange

The Agent Orange Act of 1991 acknowledged a presumptive service connection for NHL related to Agent Orange exposure for veterans who served on land or on the inland waterways of Vietnam between Jan. 9, 1962, and May 7, 1975.

Agent Orange combined two highly toxic chemicals: 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. The highly toxic dioxin contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin, a byproduct of Agent Orange production, is widely considered the most carcinogenic component of the herbicide used extensively during the Vietnam War.

The publication of the National Academy of Sciences, formerly the Institutes of Medicine, report, "Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam" definitively established a positive association between herbicide exposure and NHL in 1994.[1]

Burn Pit Exposures

The PACT Act expansion by the VA also added lymphomas of any kind as a presumptive condition for veterans exposed to burn pits, which were commonly used to dispose of waste during conflicts over the last 35 years in the Persian Gulf and southwest Asia. In addition to the chemicals released by the burning materials, JP-8 jet fuel, which contains benzene, was often used as an accelerant for burn pits. Benzene exposure, in particular, is a known risk factor for NHL.

While the PACT Act covers all lymphomas, a recent study of individuals who served in Afghanistan or Iraq between 2001 and 2022 found that deployment to these locations particularly increased DLBCL and related malignancies. "Prior deployment was associated with more aggressive B-cell lymphoma than military personnel who had never deployed," noted researchers from Walter Reed National Military Medical Center, Wright Patterson Air Force Base and Brooke Army Medical Center, in their study that included 2,599 active duty servicemembers and retirees diagnosed with NHL during the study period.[2]

Contaminated Water

All NHLs, including DLBCL, are also presumptive conditions for veterans who served for at least 30 days at either Marine Corps Base Camp Lejeune or Marine Corps Air Station New River between Aug. 1, 1953, and Dec. 31, 1987 under the Camp Lejeune Justice Act of 2022, which is section 804 of the PACT Act. These veterans experienced exposure to water contaminated with benzene, cidhlorethylene, tetrachoroethylene, trichloroethylene, vinyl chloride and other contaminants.

[1] Institute of Medicine (US) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam. Washington (DC): National Academies Press (US); 1994.

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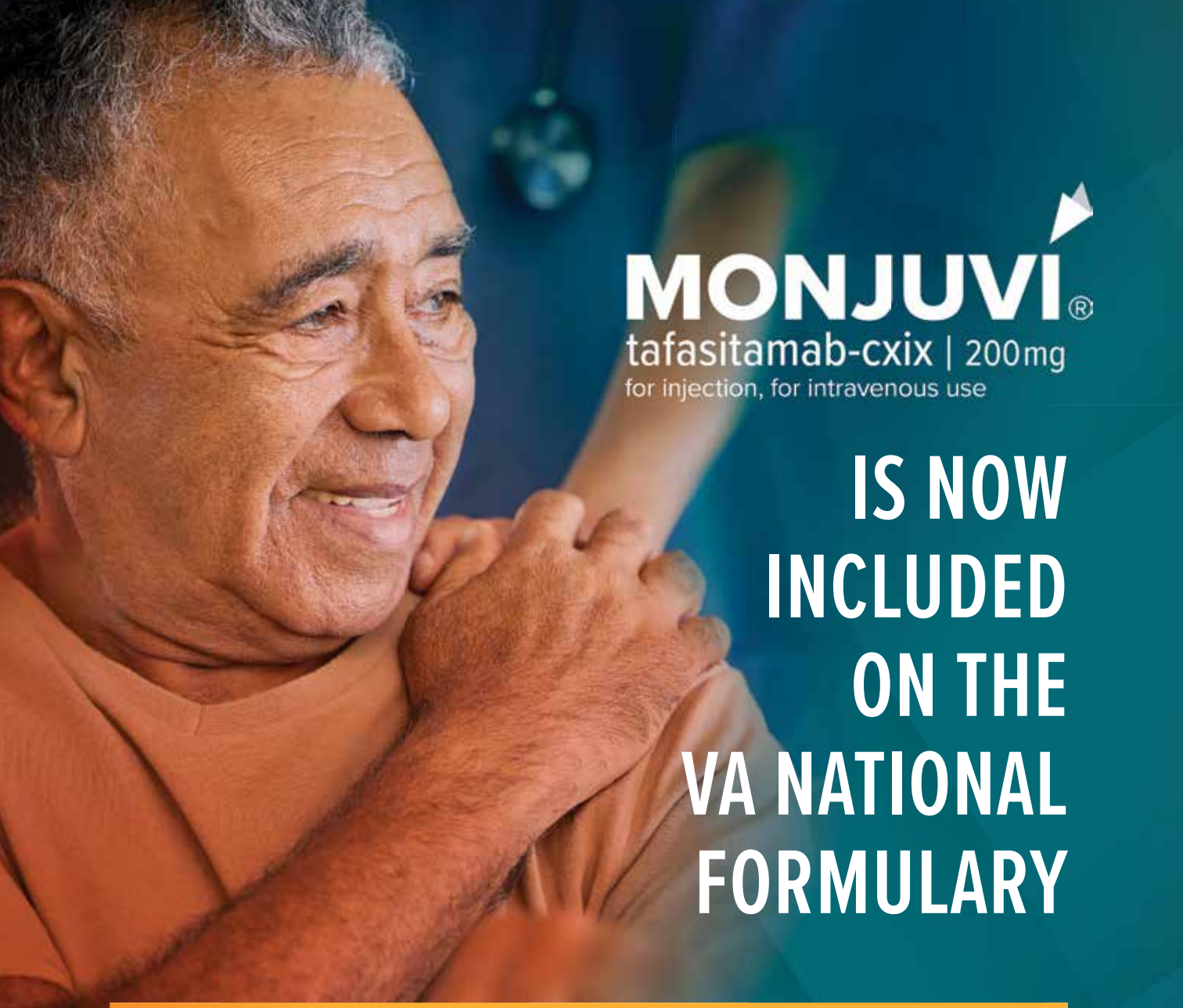

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