Section Editors: Lindsey Lyle and Wendy H. Vogel

Understanding PD-1 Inhibitors in Hodgkin Lymphoma: A Guide for the Oncology Advanced Practitioner

MARIA D. GUERRERO, DNP, NP-C, AOCNP, and
VAN NGUYEN, DNP, MS, APRN, AGACNP-BC, FNP-C, PMGT-BC

From The University of Texas MD Anderson Cancer Center, Houston, Texas

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Maria D. Guerrero, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030

E-mail: mdguerre@mdanderson.org

https://doi.org/10.6004/jadpro.2026.17.5.3

Abstract

Classical Hodgkin lymphoma (cHL) is a rare cancer, usually affecting young adults and those over 55 years. A subset of patients experiences relapsed or refractory disease, which remains a treatment challenge. Understanding molecular biomarkers, especially programmed cell death protein 1 (PD-1), is increasingly important for developing new therapies. PD-1 is an immune checkpoint that controls T-cell activation, and its overexpression in cHL enables tumors to evade immune detection. Immune checkpoint inhibitors, such as nivolumab, have shown promise in treating relapsed or refractory cHL by blocking PD-1 and restoring immune responses. This developing landscape requires oncology advanced practitioners to be aware of PD-1 as both a therapeutic target and a predictive biomarker, allowing for personalized treatment plans. Additionally, ensuring equitable access to these innovations remains a major concern, particularly for underserved populations. Oncology advanced practitioners play a critical role in closing care gaps, advocating for broader access, and maintaining ethical standards.

Lymphoma is a group of blood cancers that originate from lymphocytes, a type of white blood cell involved in the body's immune defense. These cancers most often affect the lymph nodes or other lymphoid tissues (Lymphoma Research Foundation, 2025). One specific and relatively rare subtype is classical Hodgkin lymphoma (cHL), which develops from B cells and displays a characteristic bimodal age distribution, with incidence peaking in young adults aged 15 to 30 years and again in those aged 55 years and up (Brice et al., 2021). According to the National Cancer Institute, approximately 8,920 new cases of HL are expected to be diagnosed in the United States in 2026, resulting in approximately 1,100 deaths. Although cHL is considered highly curable with standard front-line

J Adv Pract Oncol 2026;17(5):192–195

therapy, approximately 10% to 20% of patients experience relapses or develop refractory disease, which poses additional challenges and worsens prognosis (Randall & Spinner, 2023).

PD-1 AND ITS RELEVANCE IN cHL

In this evolving therapeutic landscape, it is increasingly important for oncology advanced practitioners (APs) to understand emerging genomic markers/biomarkers and their implications for treatment. One such biomarker is programmed cell death protein 1 (PD-1), an immune checkpoint receptor located on T cells. Under normal physiological conditions, PD-1 functions as a regulatory mechanism to prevent excessive immune activation (Chamoto et al., 2023). When PD-1 binds to its ligands, PD-L1 or PD-L2, T cell activity is suppressed. Many cancers, including HL, exploit this pathway by overexpressing PD-L1 (Hudson et al., 2020). This interaction effectively turns off the immune response, allowing the tumor to evade detection and destruction by the immune system (Ansell et al., 2015).

This knowledge has led to the development of therapies targeting the PD-1 pathway. Drugs such as nivolumab (Opdivo), a PD-1 inhibitor, are now being used in the treatment of relapsed or refractory cHL. These immune checkpoint inhibitors restore immune function by blocking the PD-1 receptor, thereby enabling T cells to recognize and attack cancer cells. Clinical trials have shown that these therapies produce durable responses and are generally well tolerated. Using PD-1 as both a therapeutic and a predictive biomarker emphasizes the expanding role of precision medicine in oncology. Instead of a one-size-fits-all approach, treatments can now be tailored to the specific biological characteristics of a patient's tumor. For patients whose tumor tissue demonstrates PD-1 pathway activation, PD-1 inhibitors may be particularly effective. This approach helps maximize treatment benefits while reducing exposure to the toxic effects of chemotherapy, which is especially important for younger individuals, older patients, or those with comorbidities who may not tolerate intensive regimens (Burton et al., 2024).

PD-1 Inhibitors in the Treatment Landscape

Herrera (2018) raised an important question that continues to shape modern management of cHL: Where do PD-1 inhibitors fit within the treatment landscape? Historically, front-line treatment for cHL has consisted of combination chemotherapy with or without radiation therapy. As described by Burton et al. (2024), standard regimens such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or BV (brentuximab vedotin) plus AVD (doxorubicin, vinblastine, and dacarbazine) have been widely used, with treatment intensity tailored to clinical risk factors. More recently, PD-1 inhibitors have moved into the frontline setting in combination regimens, such as nivolumab plus AVD (Nivo-AVD), demonstrating promising efficacy and improved tolerability.

The role of PD-1 inhibitors becomes even more prominent in the relapsed or refractory setting. Traditionally, patients with relapsed or refractory cHL were treated with non–cross-resistant cytotoxic chemotherapy regimens followed by autologous stem cell transplant (ASCT) in those with chemosensitive disease. BV was later introduced and initially approved as a single agent for patients with cHL who relapsed after multiple prior therapies. Its use subsequently expanded to include pre-ASCT salvage therapy, both as monotherapy and in combination regimens (Burton et al., 2024).

Today, anti–PD-1 therapies have reshaped this space. Nivolumab and pembrolizumab (Keytruda) have demonstrated superior outcomes compared with BV in several clinical settings (Table 1). These agents, used either as monotherapy or in combination approaches, are now standard treatment options for patients who relapse after ASCT and are increasingly being incorporated earlier in the treatment algorithm.

Despite these advances, salvage chemotherapy followed by ASCT remains a cornerstone of care for eligible patients with relapsed or refractory cHL. However, the integration of PD-1 inhibitors across multiple lines of therapy reflects a shift toward immunotherapy-based strategies that are improving both disease control and tolerability for patients.

Role of Oncology APs

For oncology APs, staying informed about molecular targets such as PD-1 is essential to advancing patient-centered care. Knowing when to order biomarker testing, interpreting results in collaboration with the care team, managing adverse effects,

Table 1. Approved PD-1 Inhibitors and Regimens for cHL

Medication	Mechanism of action	Indication
Nivolumab	PD-1 inhibitor	Frontline, relapsed/refractory cHL, after ASCT
Pembrolizumab	PD-1 inhibitor	Relapsed/refractory cHL

Note. ASCT = autologous stem cell transplantation; cHL = classical Hodgkin lymphoma; PD-1 = programmed cell death protein 1.

and educating patients on immunotherapy options are critical responsibilities (Table 2). Furthermore, understanding new treatment standards is key. Nivolumab in combination with AVD was recently established as a new front-line regimen for advanced-stage cHL. This combination has demonstrated a 92% 2-year progression-free survival rate and a reduced toxicity profile compared with older regimens (Montgomery, 2025). Notably, it has reduced the use of radiation therapy and minimized long-term side effects such as peripheral neuropathy, addressing long-standing concerns about late effects in cHL survivors (Montgomery, 2025).

However, access to these innovations may be limited. Many of the advanced diagnostic tests required to determine eligibility for PD-1 targeted therapy are primarily available at large academic centers. Patients in rural or underserved areas may face barriers such as limited local infrastructure, lack of health insurance, or providers who are not familiar with managing PD-1 targeted therapies. Oncology APs are uniquely positioned to help bridge this gap by raising awareness among both patients and community health-care providers, coordinating referrals, and advocating for comprehensive care strategies. Disparities in access to cancer research through clinical trials and treatment remain a complex issue, influenced by systemic inequities and a lack of inclusive research that accounts for underrepresented populations, including those affected by cHL (Dent et al., 2025; Nayak et al., 2024).

Ethical Considerations

Ethical considerations play a central role in the use of immunotherapies. Informed consent must be comprehensive so that patients fully understand the potential benefits, risks, and uncertainties associated with PD-1 identification for PD-1 blocking agents. This can be especially challenging in immuno-oncology, where science is evolving rapidly, and individual responses can vary greatly. Additionally, not all patients have equal access to these tests and treatments. Socioeconomic factors, educational background, geographic location, and health literacy can all influence a patient's ability to understand and access cutting-edge care. The ethical principle of justice demands that all patients have fair and equal access to life-saving therapies. Therefore, health-care providers, policymakers, and pharmaceutical companies must collaborate to reduce disparities and improve access to innovative treatments and diagnostic markers (Garg et al., 2025). Future research in cHL includes combining PD-1 inhibitors with other immune checkpoint inhibitors or chemotherapy to further improve outcomes. Simultaneously, the application of artificial intelligence (AI) and machine learning in diagnostic pathology is expanding. These tools hold the potential to assist in biomarker identification, improve diagnostic accuracy, and make advanced testing more accessible in community settings that may lack expert hematopathologists. Although AI tools are not yet a replacement for experienced clinicians, they may soon serve as valuable support for decision-making and quality assurance in biomarker testing (Huss et al., 2023; Moran-Sanchez et al., 2021).

While cHL is often curable, a portion of patients will require advanced, targeted approaches due to relapses or resistance. Identifying PD-1 and using PD-1 inhibitors such as nivolumab and pembrolizumab offer a promising therapeutic option, shifting care toward a more personalized, biomarker-driven model. Oncology APs play a crucial role in implementing these advances, ensuring that care is delivered in an ethical, informed, and equitable manner. As the field continues to evolve, combining targeted therapies with digital technologies will likely play an increasingly important role in improving patient outcomes and expanding access to high-quality cancer care.

Table 2. Common Adverse Events With PD-1 Inhibitors

Nivolumab	Pembrolizumab
• Fatigue • Hypersensitivity/ infusion-related reaction • Rash • Pruritus • Nausea • Diarrhea/colitis • Hepatitis • Pneumonitis • Nephritis • Renal dysfunction • Endocrine-related events (hypothyroidism, thyroiditis, diabetes mellitus, adrenal insufficiency)	• Fatigue • Nausea • Vomiting • Diarrhea • Pruritus • Pyrexia • Neutropenia • Hypothyroidism • Hyperthyroidism • Pneumonitis

Note. Information from Ansell et al. (2023); Manji et al. (2022).

References

Ansell, S. M., Bröckelmann, P. J., von Keudell, G., Lee, H. J., Santoro, A., Zinzani, P. L., Collins, G. P., Cohen, J. B., de Boer, J. P., Kuruvilla, J., Savage, K. J., Trněný, M., Provencio, M., Jäger, U., Willenbacher, W., Wen, R., Akyol, A., Mikita-Geoffroy, J., Shipp, M. A.,...Armand, P. (2023). Nivolumab for relapsed/refractory classical Hodgkin lymphoma: 5-year survival from the pivotal phase 2 CheckMate 205 study. *Blood Advances, 7*(20), 6266–6274. https://doi.org/10.1182/bloodadvances.2023010334

Ansell, S. M., Lesokhin, A. M., Borrello, I., Halwani, A., Scott, E. C., Gutierrez, M., Schuster, S. J., Millenson, M. M., Cattry, D., Freeman, G. J., Rodig, S. J., Chapuy, B., Ligon, A. H., Zhu, L., Grosso, J. F., Kim, S., Timmerman, J. M., Shipp, M. A., & Armand, P. (2015). PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *New England Journal of Medicine*, *372*(4), 311–319. https://doi.org/10.1056/nejmoa1411087

Brice, P., de Kerviler, E., & Friedberg, J. W. (2021). Classical Hodgkin lymphoma. *The Lancet*, *398*(10310), 1518–1527. https://doi.org/10.1016/s0140-6736(20)32207-8

Burton, C., Allen, P., & Herrera, A. F. (2024). Paradigm shifts in Hodgkin lymphoma treatment: From frontline therapies to relapsed disease. *American Society of Clinical Oncology Educational Book*, *44*(3), e433502. https://doi.org/10.1200/edbk_433502

Chamoto, K., Yaguchi, T., Tajima, M., & Honjo, T. (2023). Insights from a 30-year journey: Function, regulation and therapeutic modulation of PD1. *Nature Reviews Immunology*, *23*, 682–695. https://doi.org/10.1038/s41577-023-00867-9

Dent, J., Jorge, M., Sobrevilla, N., Uldrick, T. S., Adoubi, I., Bajpai, J., Burotto, M., Bulhan, H., Dosunmu, G. T., Ekpo, L., Gopal, S., Espinoza-Gutarra, M. R., Homian, N., Kingham, T., Mathias, C., Ngwa, W., Niyonzima, N., Nkegoum, B., Olopade, O. I.,...Kaufman, D. R. (2025). Cancer immunotherapy clinical trials to support urgently needed access in low- and middle-income countries: A report from the SITC global access and impact committee. *Journal for ImmunoTherapy of Cancer*, *13*(6), e011258. https://doi.org/10.1136/jitc-2024-011258

Garg, A., Pandey, P., Singh, V., & Ashique, S. (2025). Ethical considerations of cancer immunotherapy and patient perspectives on the benefits and risks of treatment. In R. Sharma, V. Pandey, & N. Mishra (Eds.), *Nanotechnology based strategies for cancer immunotherapy* (pp. 419–438). Springer. https://doi.org/10.1007/978-981-97-7022-9_16

Herrera, A. F. (2018). Where does PD-1 blockade fit in HL therapy? *Hematology*, *2018*(1), 213–220. https://doi.org/10.1182/asheducation-2018.1.213

Hudson, K., Cross, N., Jordan-Mahy, N., & Leyland, R. (2020). The extrinsic and intrinsic roles of PD-L1 and its receptor PD-1: Implications for immunotherapy treatment. *Frontiers in Immunology*, *11*. https://doi.org/10.3389/fimmu.2020.568931

Huss, R., Raffler, J., & Märkl, B. (2023). Artificial intelligence and digital biomarker in precision pathology guiding immune therapy selection and precision oncology. *Cancer Reports*, *6*(7). https://doi.org/10.1002/cnr2.1796

Lymphoma Research Foundation. (2025). *Understanding lymphoma.* https://lymphoma.org/understanding-lymphoma/aboutlymphoma/

Manji, F., Laister, R. C., & Kuruvilla, J. (2022). An evaluation of pembrolizumab for classical Hodgkin lymphoma. *Expert Review of Hematology*, *15*(4), 285–293. https://doi.org/10.1080/17474086.2022.2061947

Montgomery, R. M. (2025). *Hodgkin's lymphoma: Integrating epidemiological patterns, genomic landscapes, environmental determinants, and contemporary therapeutic advances in the era of precision medicine* [PDF]. Research Gate.

Moran-Sanchez, J., Santisteban-Espejo, A., Martin-Piedra, M., Perez-Requena, J., & Garcia-Rojo, M. (2021). Translational applications of artificial intelligence and machine learning for diagnostic pathology in lymphoid neoplasms: A comprehensive and evolutive analysis. *Biomolecules*, *11*(6), 793. https://doi.org/10.3390/biom11060793

National Cancer Institute. (2026). *Cancer stat facts: Hodgkin lymphoma.* National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/hodg.html

Nayak, R. K., Aiello, M., Maldonado, L., Clark, T. Y., Buchwald, Z. S., & Chang, A. (2024). Impact of race, ethnicity, and social determinants on outcomes following immune checkpoint therapy. *Journal for ImmunoTherapy of Cancer*, *12*(10), e010116. https://doi.org/10.1136/jitc-2024-010116

Randall, M. P., & Spinner, M. A. (2023). Optimizing treatment for relapsed/refractory classic Hodgkin lymphoma in the era of immunotherapy. *Cancers*, *15*(18), 4509. https://doi.org/10.3390/cancers15184509