

Efficacy, safety, and real-world access to PD-1 inhibitors in the treatment of Hodgkin lymphoma in Latin America in first- or second-line therapy: a prospective cohort study in LATAM 2025

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3. INTRODUCTION

Hodgkin lymphoma (HL) is a lymphoid neoplasm with response rates close to 85% with first-line therapy. The 15% of patients who do not respond to first-line treatment represent a high-risk group with poor prognosis. Historically, these patients received combination chemotherapy as second-line therapy, and those achieving partial or complete response underwent consolidation with autologous hematopoietic stem cell transplantation (AHSCT). (1–3)

Since 1975, the classical first-line treatment has consisted of ABVD or BEACOPP followed by radiotherapy to residual lesions. Over time, therapeutic strategies have evolved in an effort to improve outcomes while reducing toxicity. Current approaches aim to minimize pulmonary toxicity, secondary malignancies—particularly breast cancer in female patients—and ischemic heart disease. This has been achieved, in part, through PET-CT-adapted therapy, which avoids overtreatment, especially in residual lesions previously interpreted as refractory disease (4). In parallel, advances in the understanding of HL pathophysiology have enabled the incorporation of more targeted therapies, such as anti-CD30 antibodies and immune checkpoint inhibitors (ICIs), which act on alterations associated with amplification of chromosome 9p24.1 (5,6).

The ECHELON-1 trial introduced the use of brentuximab vedotin (BV) in first-line treatment for CD30-positive HL, combined with AVD and omitting bleomycin, thereby reducing the risk of pneumonitis. This regimen demonstrated high overall response rates, particularly in younger patients, those with stage IV disease, and those with involvement of more than two extranodal sites. At 2 years, progression-free survival (PFS) was 82% versus 77% compared with standard ABVD, and overall survival (OS) was 96.6% versus 94.2%. With 6 years of follow-up, OS was 93% and 89%, respectively. The most frequent adverse events were neutropenia and neuropathy, limiting its use in patients older than 65 years (7–9).

Expression of PD-L1 on Reed–Sternberg cells in HL, due to amplification of chromosome 9p24.1, enables the use of agents that block the interaction between PD-L1 on tumor cells and PD-1 on lymphocytes, thereby enhancing antitumor immune activity. Initially, PD-1 inhibitors were used in patients with relapsed or refractory HL; since 2024, they have been incorporated into U.S. guidelines as first-line therapy due to their excellent results (10).

The phase II CheckMate 205 study (2018) evaluated nivolumab in patients with relapsed/refractory HL after AHSCT across three cohorts, demonstrating overall response rates of approximately 69%, with a median response duration of 16 months in a high-risk population and an acceptable toxicity profile (11).

The phase III KEYNOTE-204 trial (2018) compared pembrolizumab versus brentuximab vedotin monotherapy in patients with relapsed or refractory HL, showing improved PFS at 2 years (13.2 vs 8.3 months, respectively) (12).

In 2022, Dr. Moskowitz proposed the use of pembrolizumab combined with GVD in patients who relapsed after first-line therapy. Forty-one percent were primary refractory and 38% relapsed within one year. Complete response was achieved in 95% of patients, with the remaining 5% achieving at least partial remission. With a median follow-up of 13.5 months, OS was 100%, and 95% of patients underwent AHSCT consolidation after 2–4 cycles. Adverse events included transaminitis, rash, mucositis, and neutropenia (13).

Following these results, in 2024 Dr. Herrera presented a phase III trial comparing BV-AVD with nivolumab-AVD in newly diagnosed stage III–IV HL (n=970). At 2 years, PFS was 92% versus 83% and OS 99% versus 98%, favoring the ICI-based regimen. Adverse events were similar. Patients over 60 years derived particular benefit, achieving 2-year PFS of 88% versus 65% (10).

In 2023, the GELL group presented a 10-year retrospective cohort at ASH, showing that 98% of HL patients in LATAM were treated with ABVD as first-line therapy (14).

We believe that describing the real-world role of ICIs in HL patients in LATAM, both in first and second line, and evaluating outcomes and adverse events in our region is of major importance.

Keywords: Hodgkin lymphoma, PD-1 inhibitors, brentuximab vedotin, LATAM.

4. OBJECTIVES

General Objective

To evaluate, under real-world clinical practice conditions, the efficacy, safety, and access barriers to PD-1 inhibitors in the treatment of Hodgkin lymphoma in Latin America, considering their use across different therapeutic lines.

Specific Objectives

To quantify overall response rate (ORR) and complete response (CR) at 6 and 12 months in patients treated with PD-1 inhibitors, stratified by treatment line (1L, 2L) and histological subtype.

To analyze progression-free survival (PFS) and overall survival (OS) at 2 years and identify prognostic factors associated with response to PD-1 inhibitors.

To determine the incidence and severity of adverse events associated with PD-1 inhibitors and document management strategies in resource-limited settings.

Secondary Objectives

To identify the positioning of PD-1 inhibitors within LATAM treatment algorithms, stratified by country, and explore access barriers.

To describe access to AHSCT after PD-1 therapy and evaluate its impact on OS.

5. MATERIALS AND METHODS

Design

A prospective, multicenter cohort study including patients with confirmed Hodgkin lymphoma receiving first- or second-line therapy at specialized LATAM centers belonging to the GELL group between 2026 and 2028.

Population

Patients with histologically confirmed Hodgkin lymphoma receiving first-, second-, or subsequent-line therapy at participating centers during the study period.

Inception Cohort

Patients initiating PD-1 inhibitor therapy between 2026 and 2028 at GELL-affiliated centers.

Time Zero

Defined as the date of initiation of PD-1 inhibitor therapy.

Follow-up

Patients will be followed for up to 2 years or until death, loss to follow-up, study closure, or administrative censoring.

Survival analyses will appropriately handle censoring. Median follow-up will be estimated using the reverse Kaplan–Meier method.

Eligibility Criteria

Inclusion Criteria

1. Age ≥ 18 years
2. Histologically confirmed Hodgkin lymphoma (WHO 2022)

3. Receipt of first-, second-, or subsequent-line therapy
4. Relapsed/refractory disease receiving PD-1 inhibitors

Exclusion Criteria

1. Active synchronous solid or hematologic malignancy within 3 years
2. Pregnancy or breastfeeding

Competing Risks

Competing events will be analyzed using Fine and Gray subdistribution hazard models, with cumulative incidence curves.

6. SAMPLING AND SAMPLE SIZE CALCULATION

A minimum sample size of 549 participants (1,098 person-years) was estimated, assuming a global event rate of 15% (165 events). This yields an events-per-predictor value of 16.47, ensuring model stability. Calculations were performed using the pmsampsize package in R.

7. VARIABLES TO BE EVALUATED

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8. STUDY PROCEDURES

Coordination with Investigators

A preliminary meeting will be held with the board of directors, the lymphoma committee, and investigators from the Latin American Group of Lymphoproliferative Disorders (GELL) to launch a collaborative research initiative involving specialized centers managing patients with Hodgkin lymphoma (HL) across Latin America (19 countries). A prior formal invitation will be sent via email. A coordinating committee will be established to oversee the coordination, execution, and monitoring of the present study. Research activities will be conducted outside the investigators' regular working hours.

Regulatory Approvals

The research protocol and the data collection database will be shared with the principal investigator at each participating center. Each center, if required, will submit the study protocol to its local research ethics committee and institutional board to obtain the corresponding approvals.

Data Collection

A data collection database designed according to the study objectives will be shared using Microsoft Excel version 2019 to ensure compatibility with the operating systems used by investigators across participating centers. The data collection form and codebook will be provided to the principal investigator at each center. General and individualized guidance will be offered upon request to support data management and collection at each site. Upon completion of the data collection period, each principal investigator will be requested to submit their center-specific database, which will then be integrated into a centralized dataset for subsequent statistical analysis.

Quality Control

If missing or incorrectly entered data are identified, the principal investigator at the corresponding center will be contacted to perform the necessary corrections or, if applicable, to contact the patient to complete missing information. If missing data cannot be retrieved from clinical records or patient contact, data imputation procedures will be applied.

Data Imputation

The presence, nature, and proportion of missing data will be assessed in advance (ideally <10%). The missing data pattern and the relationships between variables with missing values will be evaluated. Little's test ($p\text{-value} > 0.05$) will be used to assess whether data are missing completely at random, at random, or not at random. Based on the identified distribution, a machine learning–based imputation procedure using Random Forest algorithms will be applied to both quantitative and qualitative variables. These procedures will be performed using the statistical packages “mice,” “VIM,” and “naniar” within the R programming language, using the latest version of RStudio. Once the final complete dataset is obtained, it will be submitted for the corresponding statistical analyses.

9. STATISTICAL ANALYSIS

Definitions

- Response Assessment following Immune Checkpoint Inhibitor (ICI) Therapy
- Overall Response Rate (ORR): Defined according to Lugano criteria, or CT-based response assessment when PET-CT is unavailable. Proportion of patients achieving complete response (CR) plus partial response (PR).
- Complete Response (CR): Defined according to Lugano criteria, or CT-based assessment when PET-CT is unavailable. Complete disappearance of all lesions on PET/CT and physical examination.

Assessment Timepoints

- Primary: At 3, 12, and 24 months after initiation of PD-1 inhibitor therapy. Adverse events (AEs) will be recorded.
- Secondary: Every 6 months until disease progression or death, with long-term outcome reporting.

Follow-up (Time-to-Event Outcomes)

Progression-Free Survival (PFS):

- Time from initiation of PD-1 inhibitor therapy to radiological or clinical progression or death due to HL. Date of progression will be documented using imaging (PET/CT) or clinical criteria (e.g., recurrence of B symptoms).

Overall Survival (OS):

- Time from diagnosis to death from any cause. Data sources include death certificates and confirmation by the treating oncologist.

Software

Data will be processed using the R statistical programming language with the RStudio graphical interface (latest version), employing the packages “readXL,” “gtsummary,” “survival,” and “survminer.” Statistical significance will be defined as $p < 0.05$, according to the statistical test applied.

Descriptive Analysis

Descriptive statistics will be performed based on clinical variables. Categorical variables will be summarized as frequencies and percentages. For quantitative variables, the Kolmogorov–Smirnov test will be used to assess normality ($p > 0.05$). Quantitative variables with normal distribution will be summarized as means with standard deviations, while variables with non-normal distribution will be reported as medians with ranges.

Bivariate Analysis

For inferential analysis of progression-free survival and overall survival, both time-to-event outcomes, survival curves will be estimated using the semi-parametric Kaplan–Meier method and compared using the log-rank test ($p < 0.05$). Survival probabilities will be estimated at the first and second year of follow-up. For independent quantitative variables with normal distribution between two groups, Student’s t-test will be used. For non-normally distributed quantitative variables, the Mann–Whitney U test or Welch’s test will be applied when homoscedasticity cannot be assumed. For qualitative variables, the chi-square (χ^2) test will

be used, with appropriate corrections based on degrees of freedom (Fisher's exact test or Yates' correction). Statistical significance will be defined as $p < 0.05$.

Multivariable Analysis

Univariable Cox proportional hazards regression analyses will be conducted to identify associations between clinical variables and the outcomes of interest. Variables with clinical relevance and literature support will be included in the multivariable model regardless of p-value. The multivariable Cox model will estimate adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs). The proportional hazards assumption will be assessed using Schoenfeld residuals, and potential non-linear relationships of continuous variables will be explored using restricted cubic splines. Model performance will be evaluated using the concordance index (C-index) and calibration curves. Internal validation will be performed using bootstrap resampling (1,000 repetitions) with estimation of the shrinkage factor.

Stratification

A stratified analysis by histological subtype of Hodgkin lymphoma will be performed to explore prognostic differences, provided that sample size permits, with the aim of achieving cohort homogeneity.

Competing Risks

Given that certain outcomes of interest, such as progression or sustained response, may be affected by competing events (e.g., death from unrelated causes, treatment discontinuation due to toxicity), competing risk-adjusted survival methods will be applied. Cumulative incidence functions will be estimated, and subdistribution regression models (Fine-Gray model) will be fitted. The classical Cox model will be reserved for analyses in which censoring is non-informative.

Safety

Treatment-related adverse events will be recorded, focusing on adverse reactions graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4. Safety outcomes will be reported in terms of frequency and severity of adverse events.

10. PROCEDURES TO ENSURE ETHICAL CONSIDERATIONS

Participants in this study will not be exposed to foreseeable risks nor will they receive direct benefits from participation. All collected information will be managed according to the highest standards of security and confidentiality and will be stored in a protected, fully anonymized database. As part of the inclusion process, written informed consent will be obtained,

ensuring that each participant fully understands the scope of the study and participates voluntarily.

This study strictly adheres to international ethical guidelines established by the Council for International Organizations of Medical Sciences (CIOMS, 2016) and the Declaration of Helsinki, ensuring protection of the fundamental principles of respect for participant autonomy, beneficence through minimization of potential harm, and justice in the equitable selection of study subjects.

11. STUDY TIMELINE

	Month 1-24	Month 12	Month 26
Data collection	X		
Interim analysis and presentation of results		X	
Final data analysis and manuscript writing			X

12. FUNDING

The conduct of this study will not generate costs requiring external funding. As this is an observational study, investigators will perform medical record review and subsequent analyses without remuneration. No additional diagnostic tests will be required, and no extra costs will be incurred by patients or their health insurance providers.

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