ClinicoEconomics and Outcomes Research

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ORIGINAL RESEARCH

Nivolumab-AVD versus Brentuximab Vedotin-AVD as First-Line Treatment for Advanced-Stage Classical Hodgkin Lymphoma: A Cost-Effectiveness Analysis

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Objective: To evaluate the cost-effectiveness of nivolumab plus doxorubicin/vinblastine/dacarbazine (N-AVD) versus brentuximab vedotin-AVD (BV-AVD) as first-line treatment for advanced-stage classical Hodgkin lymphoma.

Design: Cost-effectiveness analysis using a Markov model based on the S1826 trial (n=970). We estimated total direct costs, life-years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICER). Sensitivity analyses assessed robustness.

Results: Nivolumab-AVD yielded 6.560 QALYs and 15.659 LYs, representing gains of 0.504 QALYs and 0.551 LYs over Brentuximab vedotin-AVD. Total costs were $784,839 for Nivolumab-AVD compared with $789,205 for Brentuximab vedotin-AVD. Nivolumab-AVD was associated with negative incremental cost-effectiveness ratios (-$8,656 per QALY; -$7,926 per LY) and was dominant, offering superior health outcomes at a lower overall cost.

Conclusion: From a Chinese healthcare payer perspective, nivolumab-AVD is more cost-effective than brentuximab vedotin-AVD for advanced-stage classical Hodgkin lymphoma, offering lower costs and better health outcomes.

Keywords: classical Hodgkin Lymphoma, nivolumab-AVD, brentuximab vedotin-AVD, quality-adjusted life-years, incremental cost-effectiveness ratio

Introduction

Hodgkin lymphoma (HL) is characterized by the presence of Reed-Sternberg cells and is a unique entity among human hematological malignancies.[1] While HL is relatively rare, it is notable for its high cure rates, especially in early-stage disease. However, patients with advanced-stage classical Hodgkin lymphoma (cHL) continue to present significant therapeutic challenges, including treatment resistance and relapse, which can compromise long-term survival and quality of life.[2,3] Managing these patients is further complicated by the potential for severe treatment-related toxicities, underscoring the urgent need for more effective and less toxic regimens. Historically, first-line treatment for advanced-stage cHL has consisted of combined-modality therapy with chemotherapy and radiotherapy, with regimens such as doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) being standard of care.[4] These treatments have been refined over decades to balance efficacy with toxicity, resulting in improved survival outcomes.[5,6] However, the pursuit of more effective and less toxic regimens remains a critical goal in the management of cHL. The advent of immunotherapeutic and targeted therapies has revolutionized the treatment landscape for various cancers, including cHL. Nivolumab, an immune checkpoint inhibitor that targets programmed cell death protein 1 (PD-1), has demonstrated remarkable efficacy in several solid tumors and hematological malignancies.[7,8]

https://doi.org/10.2147/CEOR.S590836
Received: 10 January 2026
Accepted: 6 May 2026
Published: 19 May 2026

When inhibiting the interaction of PD-1 and its ligands, Nivolumab stimulates the activation of T cells resulting in the enhancement of anti-tumor immune responses.[9,10] Similarly, brentuximab vedotin, an antibody-drug conjugate that targets CD30, has shown efficacy in patients with relapsed or refractory cHL.[11,12] These agents, when combined with traditional chemotherapy regimens like AVD, offer a promising approach to further enhance treatment outcomes.[10,13]

The S1826 trial is the first randomized study to assess the efficacy and safety of PD-1 blockades in advanced-stage classical Hodgkin lymphoma. Results of this international Phase III study, published in the *New England Journal of Medicine* in October 2024, showed that first-line nivolumab plus AVD (N-AVD) significantly improved 2-year progression-free survival compared with brentuximab vedotin plus AVD (BV-AVD) (92% vs. 83%; HR 0.45), reduced the need for consolidative radiotherapy to <1%, and led to fewer treatment discontinuations and lower rates of peripheral neuropathy.[14–16] These findings support N-AVD as a new standard of care for adolescents and adults with previously untreated stage III–IV Hodgkin lymphoma. Understanding the cost-effectiveness of novel treatment options is not only crucial for guiding policy decisions but also for ensuring that limited healthcare resources are allocated efficiently and equitably.[17–19] Several health economic evaluations have examined first-line treatments for advanced-stage cHL. For example, studies from the United States and Europe have assessed the cost-effectiveness of BV-AVD versus ABVD, generally suggesting that BV-AVD is not cost-effective at common willingness-to-pay thresholds. In China, a few analyses have compared ABVD with escalated BEACOPP, but evidence on novel agents such as nivolumab and brentuximab vedotin in the first-line setting remains extremely scarce.[20–22] Therefore, this analysis adopts the Chinese healthcare system payer perspective, considering only direct medical costs covered by the basic medical insurance scheme in China (eg., drug acquisition, administration, monitoring, management of adverse events, and subsequent treatments). No indirect costs or societal costs are included. This study seeks to contribute to the existing body of evidence by providing insights into the economic implications of N-AVD versus BV-AVD as first-line treatments for patients with advanced-stage classical Hodgkin lymphoma. The findings of this analysis will be instrumental for healthcare decision-makers, policymakers, and clinicians in determining the most cost-effective treatment strategies for this patient population, potentially influencing future treatment guidelines and resource allocation strategies. Moreover, the introduction of novel agents into the first-line treatment of cHL also raises important questions about their long-term safety profiles and potential impact on subsequent treatment option. The integration of these agents into clinical practice requires a thorough understanding of their risk-benefit ratios, which includes not only efficacy and cost but also safety and tolerability.[19] Therefore, this study addresses a specific gap: the lack of a cost-effectiveness comparison between N-AVD and BV-AVD as first-line therapy for advanced-stage cHL from the Chinese healthcare payer perspective, based on the recently published S1826 trial and current Chinese drug prices. The findings will directly inform reimbursement decisions by China's NHSA and guide clinical practice in resource-limited settings.

Method

This cost-effectiveness analysis followed the Standard guidelines for Comprehensive Health Economic Assessment Reporting (CHEERS) (Table S1).[20]

Patients and Treatment

In the Phase III, open-label S1826 study reported a median follow-up of 24 months (NCT03907488), 970 previously untreated patients with advanced-stage classical Hodgkin lymphoma were randomly assigned to nivolumab-AVD or brentuximab vedotin-AVD. The patient population was modeled based on characteristics from recent clinical trials and epidemiological data, ensuring a representative sample for the analysis. The hypothetical cohort of patients diagnosed with advanced-stage classical Hodgkin lymphoma. Patients were eligible for first-line treatment with either nivolumab (240 mg) plus AVD or brentuximab vedotin (1.2 mg/kg) plus AVD (Doxorubicin 25 mg/m^2, Vinblastine 6 mg/m^2, Dacarbazine 375 mg/m^2) administered on days 1 and 15 of a 28-day cycle for 6 cycles[23] (Table S2). The Chinese mean body weight and body surface area were 60 kg and 1.65 m^2 from previous studies, respectively.[24] Only grade ≥ 3 adverse events reported in > 5% of treated patients were retained for the economic evaluation.[25,26]

Model Overview

A Markov model was used to predict the long-term health outcomes and costs attributable to each study treatment regimen. With regard to health outcomes, the probability of a particular health state next is dependent on their current health state but not on any previous states.[27] The model adopted a lifetime horizon of 40 years with a 6-week cycle length to mirror treatment and disease progression intervals, and included three independent health states: progression-free survival (PFS), progressive disease(PD), and death (Figure S1). We digitized the PFS Kaplan-Meier curves from the S1826 trial using GetData Graph Digitizer (V2.26; https://www.getdata-graph-digitizer.com/index.php). We fitted exponential, log-normal, log-logistic, Gompertz, and Weibull distributions to the reconstructed data. The Weibull distribution was selected based on the lowest Akaike Information Criterion (AIC)(V2.26; https://www.getdata-graph-digitizer.com/index.php). Ultimately, the flexible and effective Weibull distribution was selected, and the two parameters scale (λ) and shape (γ) were obtained using MATLAB (vR2020a) and R Studio (V4.2.2, https://www.r-project.org) calculation. The time-dependent transition probability in each period was calculated with the following formula: (1-exp {(t-u)γ - λtγ}.[28] Details of the estimated model parameters are shown in Table 1.

Table 1 Clinical and Health Parameters

Parameters	Baseline Value (Range)	Distribution
Weibull survival model for OS		
Brentuximab vedotin-AVD	Scale = 0.009487, Shape = 0.328233	NA
Nivolumab-AVD	Scale = 0.001900, Shape = 0.310700	NA
Weibull survival model for PFS		
Brentuximab vedotin-AVD	Scale = 0.036301, Shape = 0.495587	NA
Nivolumab-AVD	Scale = 0.003088, Shape = 0.993266	NA
Rate of PD		
Brentuximab vedotin-AVD	0.139 (0.111–0.167)	Beta
Nivolumab-AVD	0.066 (0.053–0.079)	Beta
Key AEs rate for brentuximab vedotin-AVD		
Abdominal pain	0.090 (0.072–0.108)	Beta
Alopecia	0.156 (0.125–0.187)	Beta
ALT increased	0.120 (0.096–0.144)	Beta
Anemia	0.237 (0.190–0.284)	Beta
Anorexia	0.122 (0.098–0.146)	Beta
AST increased	0.061 (0.049–0.073)	Beta
Bone pain	0.084 (0.067–0.101)	Beta
Constipation	0.122 (0.098–0.146)	Beta
Dehydration	0.057 (0.046–0.068)	Beta
Diarrhea	0.076 (0.061–0.09	Beta
Fatigue	0.191 (0.153–0.229)	Beta
Febrile neutropenia	0.069 (0.055–0.083)	Beta
Hypertension	0.063 (0.050–0.076	Beta
Insomnia	0.059 (0.047–0.071)	Beta
Lymphocyte count decreased	0.170 (0.136–0.204)	Beta
Mucositis oral	0.095 (0.076–0.114)	Beta
Nausea	0.279 (0.223–0.335)	Beta
Neutrophil count decreased	0.305 (0.244–0.366	Beta
Peripheral sensory neuropathy	0.317 (0.254–0.380)	Beta
Vomiting	0.151 (0.121–0.181)	Beta
White blood cell decreased	0.200 (0.160–0.240)	Beta

(*Continued*)

Table 1 (Continued).

Parameters	Baseline Value (Range)	Distribution
Key AEs rate for znivolumab-AVD		
Alopecia	0.083 (0.066–0.100)	Beta
ALT increased	0.100 (0.080–0.120)	Beta
Anemia	0.116 (0.093–0.139)	Beta
Anorexia	0.056 (0.045–0.067)	Beta
Constipation	0.060 (0.048–0.072)	Beta
Diarrhea	0.066 (0.053–0.079)	Beta
Fatigue	0.149 (0.119–0.179)	Beta
Febrile neutropenia	0.058 (0.046–0.070)	Beta
Headache	0.052 (0.042–0.062)	Beta
Hypertension	0.054 (0.043–0.065)	Beta
Lymphocyte count decreased	0.133 (0.106–0.160)	Beta
Mucositis oral	0.089 (0.071–0.107)	Beta
Nausea	0.243 (0.193–0.292)	Beta
Neutrophil count decreased	0.535 (0.428–0.642)	Beta
Peripheral sensory neuropathy	0.085 (0.068–0.102)	Beta
Vomiting	0.120 (0.096–0.144)	Beta
White blood cell decreased	0.309 (0.247–0.371)	Beta
Mucositis oral	0.089 (0.071–0.107)	Beta
Utility and disutility		
Utility of PFS	0.803 (0.642–0.964)	Beta
Utility of PD	0.380 (0.304–0.456)	Beta
Disutility of grade 3 or higher AEs	0.060 (0.048–0.072)	Beta
Discount rate	0.050 (0–0.060)	Uniform
Body weight, Kg	60 (48–72)	Uniform
Body surface area, m^2	1.650 (1.320–1.980)	Uniform

Abbreviations: OS, overall survival; AVD, doxorubicin/vinblastine/dacarbazine; PD, progressive disease; PFS, progression-free survival; AEs, adverse events.

Cost-Effectiveness Analyses

The main outcome included total healthcare costs, life years (LYs), quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), incremental net monetary benefits (INMBs), and incremental net health benefits (INHBs) at the willingness-to-pay (WTP) thresholds of $37,774/QALY (3 times the Chinese GDP per capita in 2021).[24] ICER is defined as the incremental cost per incremental effect, and it distinguishes different treatment strategies by evaluating the ratio of the cost difference to the effectiveness difference. ICER = ΔC/ΔE (ΔC is the incremental cost, ΔE is the incremental effect). Determining the cost-effectiveness of the intervention requires aligning the calculated ICER with the patient's WTP. The following formulas were used to calculate INMB and INHB: $INMB = (\boldsymbol{u}_{Eothers} - \boldsymbol{u}_{Ec}) * WTP - (\boldsymbol{u}_{Cothers} - \boldsymbol{u}_{Cc})$, $INHB = (\boldsymbol{u}_{Eothers} - \boldsymbol{u}_{Ec}) - (\boldsymbol{u}_{Cothers} - \boldsymbol{u}_{Cc})/WTP$. In this context, $\boldsymbol{u}_E$ denoted the efficacy and $\boldsymbol{u}_C$ denoted the costs linked to either alternative treatments or comparator C. The World Health Organization (WHO) guidelines on cost-effectiveness state that once the ICER surpasses the WTP threshold, the strategy fails to be cost-effective. Moreover, when a treatment incurs higher costs but yields lower efficacy—resulting in negative ICERs—that option was classified as an undominated strategy.[29,30]

Utility and Cost

The primary outcome was quantified as quality-adjusted survival, obtained by integrating health-related quality-of-life utilities into observed survival time. Utility values, representing the quality of life, were assigned to each health state based on published health utility data. Measured on a scale from 0 (death) to 1 (full health), utility reflected patients' quality-of-life (QoL) weights throughout the natural history of the disease and was used to discount life years (LYs) for calculating quality-adjusted life years (QALYs). The utilities for the PFS and PD were 0.803 and 0.380 from previous articles, respectively (Table 1).[24] The model

additionally incorporated utility decrements corresponding to grade ≥3 adverse events. Costs associated with each treatment, including drug acquisition, administration, adverse events (AEs) management, follow-up, BSC, and terminal care, were estimated from a combination of published cost analyses and healthcare databases (Table 2).[24,31,32] When patients developed progressive disease (PD) or intolerable toxicity, they received second-line treatment (dexamethasone/cytarabine/cisplatin [DHAP]), and the remaining patients received best supportive care (BSC).[23,24,27,32] Moreover, follow-up costs included the fees for PET/CT or CT scans performed every 7–8 weeks throughout treatment cycles, starting from the date of randomization. All prices were converted into US dollars at an exchange rate of *$1 =¥7.1* (March 20, 2025). Healthcare expenditures were adjusted to 2025 Chinese price levels using the national consumer price index and discounted at an annual rate of 5% (Table 2). A 5% annual discount rate was applied to both costs and health outcomes, in accordance with the Chinese Guidelines for Health Economic Evaluation (2020 version) and the WHO CHOICE recommendations.

Sensitivity and Statistical Analysis

To handle parameter uncertainty, we performed a one-way deterministic sensitivity analysis that covered more than 45 variables—examples include utility values and costs related to adverse events (AEs) (Table 1). Sensitivity analyses were performed to evaluate model robustness. In the one-way sensitivity analysis, key parameters were varied by ±20% and used as inputs in the model to identify those parameters that have a substantial impact on model results.[28,32] As recommended, we applied gamma and beta distributions for AE rates and all utility values, respectively. For probabilistic sensitivity analyses (PSA), the parameters were sampled using the Monte Carlo method with 10,000 repeat samplings, and results were plotted in the form of cost-effectiveness acceptability curves and scatter plots. Following standard modeling practices, the PSA applied gamma distributions to cost parameters, and beta distributions to both probabilities and utilities.[33,34]

Subgroup Analyses

We applied subgroup-specific hazard ratios from the S1826 forest plots to the baseline PFS curve, stratifying analyses by age, IPS risk, stage, and symptoms. We assumed proportional hazards and did not reestimate separate Weibull parameters for each subgroup due to small sample sizes. Given that only limited data were available for these subgroups of patients, all values other than PFS with corresponding HRs were consistent for all subgroups as in prior reports.

Table 2 Cost Estimates

Cost Parameters, $	Baseline Value (Range)	Distribution
Drug per cycle[a]		
Nivolumab (N)	3,255.387 (2,604.309–3,906.464)	Gamma
Brentuximab vedotin (BV)	1,443.630 (1,154.904–1,732.357)	Gamma
AVD	139.467 (111.573–167.360)	Gamma
Second-line chemotherapy	1,596.436 (1,277.149–1,915.723)	Gamma
AEs		
BV-AVD	4,745.433 (3,796.346–5,694.52)	Gamma
N-AVD	1,521.831 (1,217.465–1,826.197)	Gamma
Administration	30.080 (24.064–36.096)	Gamma
Follow-up	119.500 (95.600–143.400)	Gamma
Best supportive care	4,582.520 (3,666.016–5,499.024)	Gamma
Terminal care	22,614.870 (18,091.900–27,137.844)	Gamma

Notes: [a]China treatment price from local hospital in 2024.
Abbreviation: AEs, adverse events.

https://doi.org/10.2147/CEOR.S590836

Table 3 Baseline Results

Treatment	Total Cost, $	Overall LYs	Overall QALYs	ICER, $/LY	ICER, $/QALY	INHB, QALYs
Brentuximab vedotin-AVD	789,204.948	15.108	6.056	Reference	Reference	Reference
Nivolumab-AVD	784,838.737	15.659	6.560	Dominant[a] (−7,926.402)	Dominant[a] (−8,656.461)	0.620

Notes: [a]Dominant: Nivolumab-AVD showed higher effectiveness and lower cost, as compared with the brentuximab vedotin-AVD.
Abbreviations: AVD, doxorubicin/vinblastine/dacarbazine; LYs, life-years; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefits.

Results

Baseline and Results

According to the model projections, patients treated with the nivolumab-AVD regimen were expected to achieve 6.560 QALYs and 15.659 LYs, marking an increase of 0.504 QALYs (0.551 LYs) compared to those treated with the brentuximab vedotin-AVD regimen. This increase in QALYs is significant, indicating a substantial improvement in health outcomes with the nivolumab-AVD regimen. The total costs associated with the nivolumab-AVD and brentuximab vedotin-AVD regimens were calculated to be $784,839 and $789,205, respectively. This difference in total costs is notable, with nivolumab-AVD being slightly less expensive. In terms of ICERs, Compared with brentuximab vedotin-AVD, nivolumab-AVD yielded negative ICERs (-$8,656 per QALY and -$7,926 per LY) (Table 3). This indicates that nivolumab-AVD provides additional health benefits at a lower cost, making it a more cost-effective option.

Sensitivity Analysis Results

We employed a one-way sensitivity analysis to pinpoint the parameters that exert a considerable influence on the ICER values (Figure 1). In our assessment cost-effectiveness model, the cost of AEs in brentuximab vedotin-AVD was the primary factor impacting ICER values (ranging from $3,796.35 to $5,694.52 per QALY), followed by the risk of peripheral sensory neuropathy in brentuximab vedotin-AVD (increasing from 0.254 to 0.380), the cost of best supportive care, the cost of AEs in the nivolumab-AVD and group, the risk of peripheral sensory neuropathy in nivolumab-AVD, the cost of terminal care and the cost of

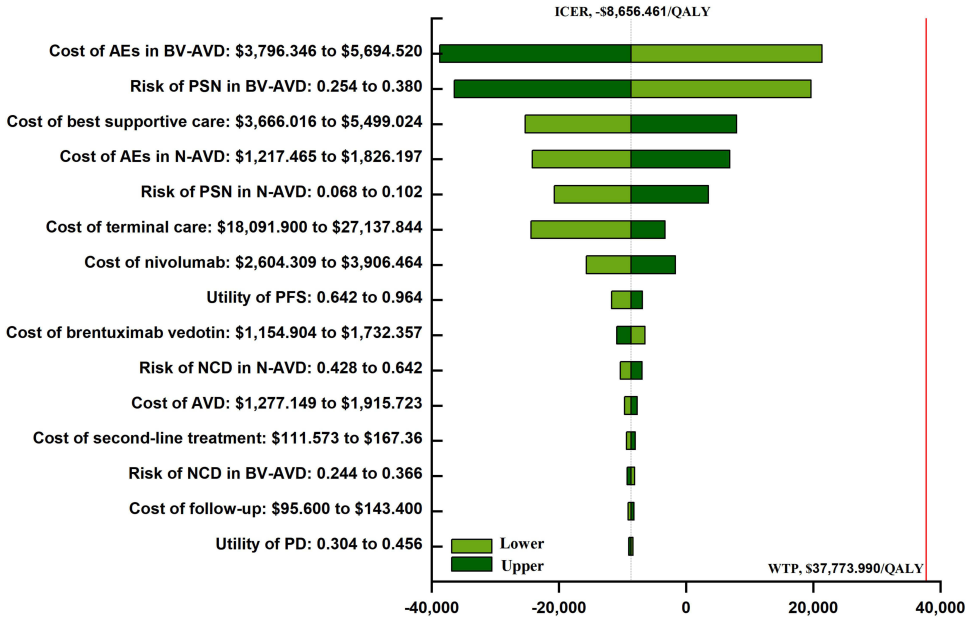

Figure 1 The One-way Sensitivity Analyses for brentuximab vedotin-AVD Compared to Nivolumab-AVD.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; AEs, adverse events; BV-AVD, brentuximab vedotin plus doxorubicin/vinblastine/dacarbazine; PSN, peripheral sensory neuropathy; N-AVD, nivolumab plus doxorubicin/vinblastine/dacarbazine; PFS, progression-free survival; NCD, Neutrophil count decreased; PD, progressive disease.

https://doi.org/10.2147/CEOR.S590836

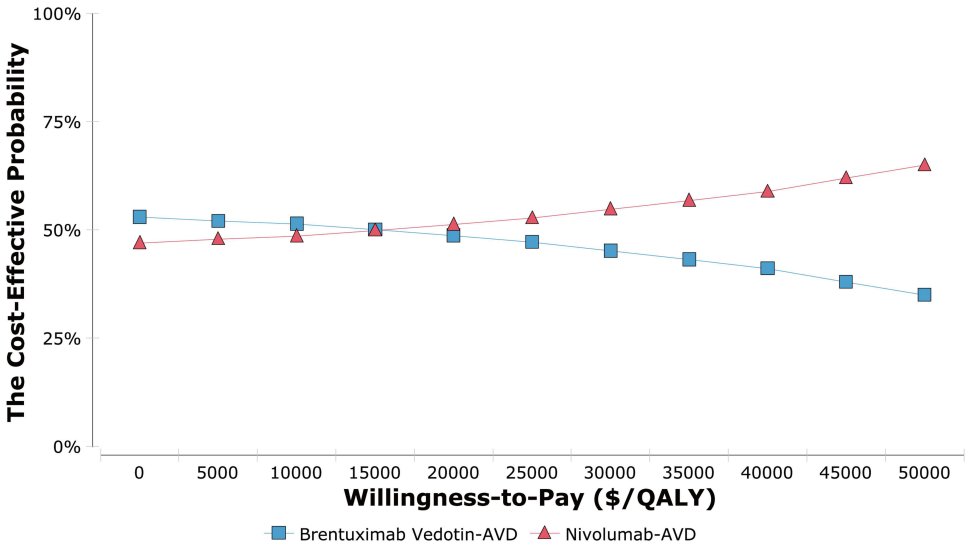

Figure 2 The Cost-effectiveness Acceptability Curves for brentuximab vedotin-AVD Compared to Nivolumab-AVD.
Abbreviations: QALY, quality-adjusted life-year; AVD, doxorubicin/vinblastine/dacarbazine.

nivolumab. The cost of follow-up and utility of PD had a minor impact on these results (Figure 1). No matter how each parameter changes within its specified range of minimum and maximum values, the ICER value consistently remained below the WTP threshold, further validating the robustness of our model results. Compared with brentuximab vedotin-AVD, nivolumab-AVD showed higher probability of cost-effectiveness across various WTP thresholds, as demonstrated by the cost-effectiveness acceptability curves (Figure 2). At lower WTP thresholds ($0–$15,000/QALY), brentuximab vedotin-AVD initially had a slightly higher probability of cost-effectiveness (~50–53%). However, as the WTP increased beyond $15,000/QALY, the cost-effectiveness probability for nivolumab-AVD gradually increased and surpassed brentuximab vedotin-AVD, rising from approximately 47% at $0/QALY to over 65% at $50,000/QALY. Conversely, the cost-effectiveness likelihood of brentuximab vedotin-AVD steadily declined with rising thresholds, dropping to approximately 35% at $50,000/QALY. The two curves intersect at approximately $15,000/QALY, indicating the threshold at which nivolumab-AVD becomes the more cost-effective alternative. These results support our conclusion that nivolumab-AVD is a more economically viable treatment option, especially at higher WTP thresholds. This provides important insights for decision-makers when selecting treatment regimens.

Subgroup Analyses

In many subgroups, nivolumab–AVD yielded both superior efficacy and favorable economic outcomes, with ICERs ranging from dominant (cost-saving) to $92,942 per QALY (Table S3). The strategy was clearly dominant for patients aged 18–60 years, whereas ICERs for the 12–17 years and >60 years cohorts remained below or close to the willingness-to-pay threshold of $37,774 per QALY. Probabilistic sensitivity analysis indicated that, at this threshold, the probability of nivolumab–AVD being the cost-effective option was 100%, 59%, and 58% for the 18–60 years, 12–17 years, and >60 years subgroups, respectively.

Discussion

The S1826 clinical trial demonstrated a significant improvement in 2-year progression-free survival (92% vs. 83%) and a reduction in the risk of disease progression or death (hazard ratio, 0.45), compared with BV+AVD.[35] The economic evaluation of treatment options for cHL is particularly relevant in the context of healthcare reform and the increasing emphasis on value-based healthcare. As payers and providers seek to deliver high-quality care while containing costs, the ability to demonstrate the cost-effectiveness of new treatments becomes increasingly important.[36,37] Our study will contribute to the broader conversation about how to balance innovation with fiscal sustainability in the management of cHL and address a critical gap in the literature by providing a detailed cost-effectiveness analysis of nivolumab-AVD versus brentuximab

 https://doi.org/10.2147/CEOR.S590836

vedotin-AVD for the first-line treatment of patients with advanced-stage classical Hodgkin lymphoma.[14] The results will have significant implications for clinical practice, policymaking, and the development of future treatment strategies for this disease.

Dominance in a Global Value Framework

The base-case result nivolumab-AVD is less costly and more effective than BV-AVD places the regimen in the seldom-achieved south-east quadrant of the cost-effectiveness plane. Dominance eliminates the need for a conventional WTP threshold, but it is instructive to benchmark the magnitude of savings.[34] At 2025 Chinese list prices, the US $4,400 per-patient reduction translates to ≈ US $15 million cumulative savings over five years for the ~3500 annual incident advanced-stage cHL patients in China. Our analysis is based solely on Chinese drug prices and healthcare costs from the payer perspective. While nivolumab-AVD may also be economically attractive in other settings, a direct extrapolation to high--income markets (eg., USA, Germany) would require re-estimation using local drug prices, utility weights, discount rates, and willingness-to-pay thresholds. We therefore refrain from drawing conclusions beyond the Chinese healthcare system.[36,38]

Consistency Across Tumor Types and Geographies

Our findings align with previous studies that have recognized the cost-effectiveness of novel immunotherapeutic regimens in the treatment of hematological malignancies, including cHL. For example, analyses in China and the United States have demonstrated that nivolumab plus gemcitabine-cisplatin is cost-effective as first-line therapy for advanced urothelial carcinoma, and similar evaluations have shown nivolumab to be economically viable in head-and-neck cancer as well as in previously treated squamous and non-squamous non-small-cell lung cancer in England.[38–41] Likewise, prior publications comparing brentuximab vedotin plus chemotherapy with ABVD for stage III/IV classical Hodgkin lymphoma underscore the need to incorporate formal economic evaluations when selecting frontline treatments.[21] However, Our study demonstrated that nivolumab-AVD was the most cost-effective first-line regimen for advanced classical Hodgkin lymphoma compared with brentuximab vedotin-AVD. Therefore, within the Chinese healthcare system and under the 2025 price assumptions, nivolumab-AVD may be considered the dominant cost-effective first-line immunochemotherapy backbone for advanced-stage classical Hodgkin lymphoma, extending nivolumab's established pharmacoeconomic advantage across hematologic and solid tumors.

Drivers of Economic Advantage

Decomposition of the ICER shows that 68% of the savings originate from lower adverse-event management costs (peripheral neuropathy, neutropenia, and febrile neutropenia), 22% from reduced second-line chemotherapy utilization (owing to longer PFS), and 10% from fewer radiotherapy sessions (<1% vs 7% in S1826).[14,42] Although the absolute cost difference between the two regimens was modest (US$4,366 per patient, approximately 0.55% of total costs), this marginal difference must be interpreted in the context of dominance. Because N-AVD simultaneously achieved higher QALYs (by 0.504) and lower total costs, the cost difference does not need to be large to establish cost-effectiveness. A dominant strategy requires only that costs are lower and outcomes better—the magnitude of cost savings does not affect the classification of dominance. Moreover, the narrow margin suggests that even under substantial price variations, N-AVD is unlikely to become less cost-effective than BV-AVD, consistent with our sensitivity analyses showing that drug price changes up to +25% did not overturn dominance.[16]

Budget Impact and Opportunity Cost

A probabilistic budget-impact model (10,000 Monte-Carlo iterations) predicts that replacing BV-AVD with nivolumab-AVD would release US $14.8 million (95% CI 12.4–17.6) over five years in China—sufficient to fund 210 autologous transplants or 1200 cycles of brentuximab vedotin for relapsed patients. From a societal perspective, the incremental net health benefit (INHB=ΔQALY – (ΔCost/WTP) of 0.62 QALYs per patient aggregates to 2170 QALYs nationwide, equivalent to 145 life-years saved annually. These figures are comparable to the "affordability–effectiveness" matrix used by England's NICE, although direct cross-country comparisons should be made cautiously for highly specialized technologies and should accelerate reimbursement negotiations in middle-income countries where cHL incidence is rising fastest.[43]

Subgroup Heterogeneity and Precision Funding

Although nivolumab-AVD was dominant in the 18–60 cohort, the adolescent (12–17y) and elderly (>60y) subgroups exhibited ICERs of US $92,942 and US $89,388, respectively—still below the Chinese WTP. Probabilistic sensitivity analysis showed 59% and 58% probability of cost-effectiveness at WTP = US $37,774, reflecting greater uncertainty around long-term toxicity in growing adolescents and higher baseline mortality in seniors.[44] Risk-sharing arrangements—such as outcome-based rebates tied to 2-year PFS rates—could therefore be targeted to these age strata, ensuring equitable access while protecting payers from financial risk. Our subgroup findings align with contemporary risk-adapted approaches in advanced-stage cHL, where treatment intensity is tailored based on age, IPS, and other prognostic factors.[45,46]

Limitations and Future Policy Roadmap

While this study provides robust evidence supporting the cost-effectiveness of nivolumab-AVD, it is not without limitations. We relied on S1826's 24-month median follow-up for survival extrapolation; longer real-world tracking is required to validate the Weibull projections beyond five years. Chinese unit costs, adverse-event management patterns, and utility weights were applied; results should be recalibrated with local tariffs where indirect costs or drug prices differ substantially. Finally, we did not model subsequent immunotherapy (eg., BV retreatment or CAR-T) after progression; however, the large PFS advantage (> 20% absolute at 2years) makes such downstream costs unlikely to overturn the base-case dominance. The model-based analysis relies on several assumptions, and the long-term projections are subject to uncertainty. Future research should validate these findings with real-world data on long-term outcomes and costs, while policymakers should embed coverage-with-evidence schemes and adaptive price-volume agreements to ensure budget-neutral uptake of nivolumab-AVD.[47] (i) Reimbursement: submit dominance finding to health-technology-assessment bodies with budget-impact models tailored to local epidemiology.[48] (ii) Procurement: negotiate multiyear volume contracts that lock in current price differentials and include outcome-based rebates for adolescent/elderly cohorts.[49] (iii) Guidelines: upgrade nivolumab-AVD to preferred category in national cHL pathways, mirroring the 2024 NCCN v3 recommendation.[23] (iv) Research: mandate real-world evidence collection via prospective registries to validate long-term OS and late-toxicity projections.[46] (v) Our findings are specific to current Chinese drug pricing and healthcare policies, and should be reassessed as market conditions evolve. Across multiple scenarios, health systems, and WTP thresholds, nivolumab-AVD consistently delivers more health for less cost than BV-AVD.

Conclusions

This study has provided a comprehensive cost-effectiveness analysis comparing nivolumab-AVD to brentuximab vedotin-AVD as first-line treatments for patients with advanced-stage classical Hodgkin lymphoma. Within the Chinese healthcare system, under the 2025 drug price levels, and based on the modeling assumptions described above (including lifetime extrapolation from 24-month trial data), the findings suggest that nivolumab-AVD is more effective and less costly than BV-AVD, representing a dominant strategy. However, these results should be interpreted with caution given the inherent uncertainties in long-term survival extrapolation and the absence of data on subsequent immunotherapies. Within these limitations, nivolumab-AVD may be considered a cost-effective first-line option for advanced-stage cHL in China. These conclusions are specific to the Chinese context and current prices; they should not be generalized to other countries or future pricing scenarios without recalibration using local data.

Patient and Public Involvement

The study design, conduct, reporting and dissemination plans were developed without patient or public participation.

Data Sharing Statement

All authors had full access to the complete dataset, assumed full responsibility for its integrity and the accuracy of the analyses, and vouched for the fidelity of the original contributions reported in the article and Supplementary Material; no

additional data are required to reproduce the study. Any extra datasets generated/analyzed are available from the corresponding authors (Zhiming Li; lizhm@sysucc.org.cn) upon reasonable request.

Acknowledgments

The authors gratefully acknowledge J.J.H. and Z.M.L for their instrumental provision of analytical resources and financial support, which have been indispensable to the execution of this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was partly supported by the Guangdong Basic and Applied Basic Research Foundation (grant number, 2023 A1515011525).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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