

ORIGINAL RESEARCH ARTICLE

Financial toxicity-associated nivolumab dose modifications in lymphoma patients: Real-world cohort from Armenia

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Abstract

Nivolumab is a standard-of-care treatment for relapsed/refractory (r/r) Hodgkin lymphoma (HL) and is approved for selected non-Hodgkin lymphoma (NHL) subtypes. However, high costs significantly restrict nivolumab accessibility, particularly in the developing world. This study aims to report treatment outcomes in patients with r/r HL and r/r NHL treated with standard or reduced doses of nivolumab in Armenia. A total of 16 patients diagnosed with HL and NHL between 2013 and 2023 (follow-up until March 2025) who received at least one nivolumab dose were included in the study. Primary endpoints: overall response rate (ORR), complete response (CR), partial response (PR), and disease progression (PD). Secondary endpoint: overall survival (OS) and safety description. Of the 16 patients, 9 (56.3%) were female. Median age at diagnosis: 37 years. Median follow-up duration: 37 months. Fifteen patients (93.8%) presented with advanced-stage disease. Seven patients (43.8%) were primary resistant. Thirteen (81.3%) experienced financial toxicity, receiving nivolumab at reduced doses. ORR: 9 patients (56.25%), CR: 4 patients (25%), PR: 5 (31.3%), PD: 7 (43.8%). Estimated OS at 12, 24, and 36 months was 91.7%, 81.5%, and 40.7%, respectively. Nivolumab ≥ 100 mg showed superior efficacy, with responses still seen at reduced doses and no severe adverse events. In conclusion, standard-dose nivolumab showed superior effectiveness in this cohort, though ORR was also observed with reduced doses. Approximately half of patients with r/r HL and NHL responded despite dose reduction. OS and safety were comparable to global data. Larger studies are needed to evaluate potential dose reduction in resource-limited settings.

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Citation: Harutyunyan L, Ghahramanyan N, Movsisyan A, *et al.* Financial toxicity-associated nivolumab dose modifications in lymphoma patients: Real-world cohort from Armenia. *Cancer Plus*. doi: 10.36922/CP026050007

Received: January 31, 2026

Revised: March 25, 2026

Accepted: April 1, 2026

Published online: May 8, 2026

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Keywords: Hodgkin's lymphoma; Non-Hodgkin's lymphoma; Nivolumab; Low- and middle-income countries; Financial toxicity; Immunotherapy; PD-1 inhibitors

1. Introduction

Nivolumab is actively prescribed for relapsed and refractory (r/r) Hodgkin lymphoma (HL) and r/r non-Hodgkin lymphoma (NHL), including patients with hematopoietic

stem cell transplantation (HSCT) failure.¹ The elevated expression of programmed death-1 (PD-1) ligands 1 (PD-L1) and PD-L2, due to genetic factors, is a distinguishing feature of HL.² These ligands suppress T-cell immune reactions by binding to PD-1 receptors. Immune checkpoint inhibitors targeting PD-1, such as nivolumab, have exhibited significant efficacy in patients with r/r HL. Nivolumab is a fully human immunoglobulin G4 anti-PD-1 monoclonal antibody that blocks PD-1 signaling pathways by interrupting the interaction between PD-1 and its ligands PD-L1 and PD-L2, thereby alleviating T-cell suppression and bolstering antitumor immune responses.²⁻⁴ It binds to the PD-1 receptor on the surface of T-cells.⁴ Clonality analysis revealed that nivolumab therapy influences the evolutionary dynamics of tumors in complete-response (CR) or partial-response (PR) patients, resulting in the collapse of entire clonal populations, whereas in stable-disease patients, nivolumab treatment may shift the landscape toward specific subclones.⁵

Emerging evidence from retrospective cohorts and observational studies suggests that lower doses of PD-1 inhibitors may retain antitumor activity in r/r HL and other malignancies.⁶ Notably, a phase II study of nivolumab at 40 mg demonstrated clinical responses in patients with r/r HL, supporting the concept that lower exposure may still elicit meaningful immune activation.⁷ Additionally, systematic reviews of low-dose PD-1 inhibition in r/r HL pooled objective response rates, such as standard dosing, further reinforce the potential utility of reduced-dosing strategies in settings where full doses are not feasible.⁸ However, real-world data describing outcomes across a range of patient-driven dosing reductions, particularly in resource-limited environments, remain scarce.^{8,9}

In countries with limited resources, studies have reported real-world data on treatment access; however, most of them highlight the financial toxicity and the potential benefits of dose reductions.^{6,9} In Armenia, data from 10 patients with r/r HL treated with nivolumab have previously been reported.⁶ Immunotherapy was generally not reimbursed locally, and most patients received immunotherapy either through clinical trials or by self-funding. As a result, some patients received individually reduced doses, as full-dose therapy was not financially feasible. Hereby, we aim to report treatment outcomes in patients with r/r HL and NHL treated with standard or reduced doses of nivolumab in Armenia.

2. Methods

This study is a retrospective, single-center, observational cohort study conducted at the Yeolyan Hematology and Oncology Center, Ministry of Health, Republic of

Armenia. Data were acquired from the medical records of patients diagnosed with HL and NHL during 2013–2023 and screened. Data collection was performed using a structured electronic database. Follow-up was continued until March 2025. All patients with r/r HL and NHL who received at least one cycle of nivolumab were enrolled. A Kaplan–Meier analysis was performed. The primary endpoint was overall response rate (ORR), including CR, PR, and progressive disease (PD). The secondary endpoint included overall survival (OS) and safety description. Adverse effects were evaluated with the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

A total of 16 patients who received nivolumab between 2013 and 2023 were identified, including 14 with HL, 1 with primary mediastinal diffuse large B-cell lymphoma (PMBCL), and 1 with anaplastic lymphoma kinase (ALK)+ T-cell lymphoma. All HL patients received first-line therapy with either doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone (BEACOPP, mostly escalated). For second- and third-line treatments, they received liposomal doxorubicin, bleomycin, and vincristine (LABO); vinorelbine, gemcitabine, procarbazine, and prednisone (ViGePP); dexamethasone, cisplatin, and cytarabine (DHAP); brentuximab monotherapy (BV); brentuximab combined with DHAP (BV-DHAP); brentuximab and bendamustine (BV-Bend.); or ifosfamide, carboplatin, and etoposide (ICE, augmented or not). Five patients received autologous HSCT in Armenia; one patient received it abroad. The patient with ALK+ T-cell lymphoma received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, doxorubicin, prednisone, and brentuximab (CHP-BV); and brentuximab monotherapy prior to nivolumab. The patient with PMBCL received rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (R-CHOEP) and rituximab with DHAP (R-DHAP) regimens.

3. Results

3.1. Patient characteristics

Among the 16 patients, 9 (56.25%) were female (Table 1). The median follow-up duration from the start of nivolumab administration until March 2025 was 37 months (range: 11–63 months). The vast majority of patients (15 patients, 93.75%) were diagnosed at advanced stages (III–IV) according to the Ann Arbor classification system. The mean age at diagnosis was 37 years (range: 21–76), and 7 patients (43.75%) had primary refractory disease.

Patients were diagnosed in stages IIB (1 HL patient),

Table 1. Patient information

Patient no.	Diagnosis	Age at diagnosis (years)	Gender	Stage	Chemotherapy treatment regimens	Chemotherapy <3 months before nivolumab treatment	Nivolumab dosage received	Number of injections	Follow-up duration from nivolumab administration until March 2025 (months)	Primary resistant status	Autologous HSCT (yes/no)	If yes, was autologous HSCT before or after nivolumab treatment	Treatment response	Status by December 2024
1	HL	50	F	IVB	BEACOPP; ABVD	Yes	40 mg/week	9	50	No	No	-	PD	Death
2	HL	29	F	IVB	ACOP; ABVD; BEACOPP; LABO	No	40 mg/2 weeks	10	45	No	No	-	PD	Alive
3	HL	25	M	IVB	BEACOPP; ViGeP; DHAP	Yes	100 mg/2 weeks	6	45	Yes	Yes	After	PD	Death
4	HL	52	F	IVB	BEACOPP; BV; BV-DHAP	Yes	100 mg/2 weeks	8	44	No	No	-	PD	Alive
5	HL	28	F	IVB	BEACOPP	No	100 mg/3 weeks	10	40	No	No	-	PR	Alive
6	HL	22	F	IVB	BEACOPP	No	100 mg/2 weeks	8	30	No	No	-	CR	Alive
7	HL	34	F	IVB	ABVD; BEACOPP; DHAP; ICE	Yes	160 mg/2 weeks	3	36	Yes	Yes	After	CR	Alive
8	HL	33	M	IIB	ABVD; BEACOPP; BV-Bend.	No	240 mg/2 week	2	11	No	No	-	PR	Alive

(cont'd...)

Table 1. (Continued)

Patient no.	Diagnosis	Age at diagnosis (years)	Gender	Stage	Chemotherapy treatment regimens	Chemotherapy <3 months before nivolumab treatment	Nivolumab dosage received	Number of injections	Follow-up duration from nivolumab administration until March 2025 (months)	Primary resistant status	Autologous HSCT (yes/no)	If yes, was autologous HSCT before or after nivolumab treatment	Treatment response	Status by December 2024
9	HL	21	F	IVB	BEACOPP	Yes	200 mg/2 weeks	2	53	Yes	No	-	CR	Alive
10	HL	49	M	IVB	ABVD	No	40 mg/2 weeks	2	24	No	No	-	PD	Death
11	HL	41	M	IIIB	BEACOPP	Yes	40 mg/week	8	33	No	No	-	PR	Alive
12	HL	76	F	IVA	ABVD	Yes	40 mg/week	8	55	Yes	No	-	PD	Death
13	HL	42	M	IVB	ABVD; BEACOPP; DHAP	Yes	40 mg/week	2	38	Yes	Yes	After	PD	Death
14	HL	45	M	IIIA	ABVD; R-DHAP	Yes	40 mg/week	2	30	Yes	Yes	Before	PR	Alive
15	ALK+ T-cell lymphoma	29	F	IVB	CHOP; CHP-BV; BV	Yes	200 mg/2 weeks	8	30	No	Yes	After	PR	Alive
16	PMBCL	21	M	IVB	R-CHOP; R-DHAP	Yes	40 mg/week	10	28	Yes	Yes (abroad)	Before	CR	Alive

Note: Refer to Section 2 for the details of the chemotherapy treatment regimens, except for ACOP (doxorubicin [adriamycin], cyclophosphamide, vincristine (oncovin), and prednisone). Abbreviations: ALK: Anaplastic lymphoma kinase; CR: Complete response; F: Female; HL: Hodgkin lymphoma; HSCT: Hematopoietic stem cell transplantation; M: Male; PD: Progressive disease; PMBCL: Primary mediastinal diffuse large B-cell lymphoma; PR: Partial response.

IIIA (1 HL), IIIB (1 HL), IVA (1 HL), and IVB (1 PMBCL, 1 ALK+ T-cell lymphoma, and 10 HL). The median time from diagnosis to initiation of nivolumab treatment was 1.5 years. In four patients, nivolumab was combined with chemotherapy. Most patients had received two prior lines of chemotherapy. Radiotherapy was administered to 9 patients (56.25%), and 6 patients (37.50%) underwent HSCT, with 2 patients receiving HSCT before and 4 after nivolumab therapy.

A total of 11 patients received chemotherapy within three months preceding nivolumab administration, including 9 with HL and 2 with NHL (Table 1; Patients 1, 3, 4, 7, 9, 11, 12, 13, 14, 15, and 16). Among these, four patients received only 2–3 nivolumab injections (Patients 7, 9, 13, and 14), of whom two achieved CR (Patients 7 and 9).

Kaplan–Meier analysis of OS estimated the 12-, 24-, and 36-month OS rates at 91.7% (95% confidence interval [CI]: 77.3–100), 81.5% (95% CI: 61.1–100), and 40.7% (95% CI: 14.7–100), respectively. The median OS follow-up was 24 months (95% CI: 18 months–not reached; Figure 1).

3.2. Safety description

Nivolumab was generally well tolerated. Immune-related adverse events (irAEs) were mild. A Grade 1 rash (per

CTCAE criteria) was observed in two patients (12.50%), both of whom received 40 mg nivolumab over 10 injections (Table 1; Patients 2 and 16). Grade 1 headache, another irAE, occurred in 4 patients (25.00%), of which 2 received 40 mg nivolumab (Patients 2 and 14), and 2 received 100 mg (Patients 3 and 4). No severe irAEs, neurological side effects, or treatment-related hospitalizations were reported.

3.3. Nivolumab dosing and treatment outcomes

Only 3 patients (18.75%) received nivolumab at the standard recommended doses, which in our setting included either 3 mg/kg intravenous (IV) every 2 weeks or 240 mg IV every 2 weeks. Due to financial constraints, the dosing decision was made by clinicians and patients. For patients with lower body weight, 3 mg/kg dosing was often preferred as a more affordable option, whereas patients with sufficient financial resources typically received the fixed 240 mg dose. In our cohort, 1 patient received the 240 mg fixed dose every 2 weeks, and 2 patients received 3 mg/kg every 2 weeks. The remaining 13 patients (81.25%) received reduced doses of nivolumab tailored to their specific circumstances. The dosing details are as follows:

- 40 mg nivolumab: Eight patients received this dose, including 7 with HL and 1 with PMBCL (Patients 1, 2, 10, 11, 12, 13, 14, and 16). The median number of

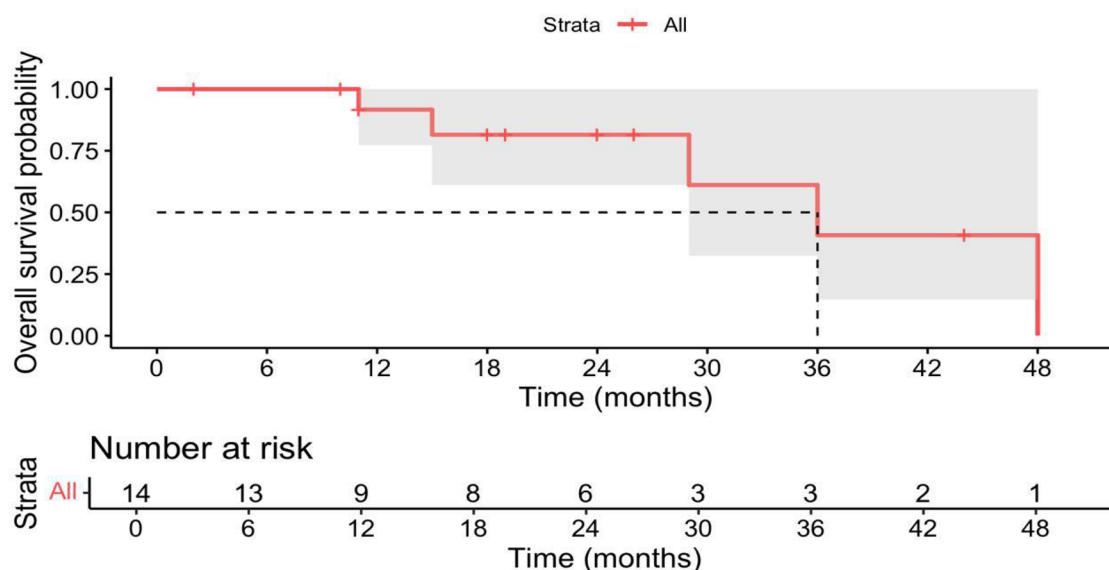


Figure 1. Kaplan–Meier curve for overall survival in patients with relapsed/refractory Hodgkin lymphoma treated with nivolumab

injections was 6 (range: 2–10). Among the HL patients, 4 died, and 3 are alive with the disease. Besides, 6 HL patients received nivolumab weekly, and 1 patient received it every 2 weeks. The patient with PMBCL is alive without disease, received 40 mg weekly for a total of 10 injections, and was assessed with positron emission tomography (PET)/computed tomography (CT), while the other patients were evaluated with contrast-enhanced CT.

- 100 mg nivolumab: Four patients with HL received this dose (Patients 3, 4, 5, and 6). One patient died, one is alive without disease, and two are alive with disease. One patient received nivolumab every 3 weeks, and the remaining three received it every 2 weeks.
- 160 mg nivolumab: One patient with HL (Patient 7) received 160 mg nivolumab every 2 weeks and is alive without disease.
- 3 mg/kg (approximately 200 mg) nivolumab: Two patients received this regimen, one with HL and one with ALK+ T-cell lymphoma (Patients 9 and 15). The ALK+ T-cell lymphoma patient is alive with disease, and the HL patient is alive without disease. Nivolumab was injected every 2 weeks for both of them: 1 received it for 2 weeks (2 doses), and the other for 8 weeks (4 doses). Neither is receiving any treatment now.
- 240 mg nivolumab: One patient with HL (Patient 8) received 240 mg every 2 weeks and is currently alive with disease.

Patients who received ≥ 100 mg had better outcomes (Table 2). Notably, the patient with PMBCL who received 10 injections of 40 mg nivolumab weekly achieved CR, as assessed by PET/CT. Treatment outcomes:

- Complete response: Observed in 4 patients (25%), including 3 with HL and 1 with PMBCL (Patients 6, 7, 9, and 16). Nivolumab dosing was as follows: 40 mg weekly for the PMBCL patient (10 injections), 200 mg every 2 weeks for 1 HL patient (2 injections), 160 mg every 2 weeks for 1 HL patient (3 injections), and 100 mg every 2 weeks for 1 HL patient (8 injections). For patients who had received prior chemotherapy and only a few nivolumab injections, it is unclear which treatment primarily contributed to CR.
- Partial response: Observed in 5 patients (31.25%), including 4 with HL and 1 with ALK+ T-cell lymphoma (Patients 5, 8, 11, 14, and 15). Nivolumab dosing varied: 1 HL patient received 100 mg every 3 weeks (10 injections), 1 HL patient received 240 mg every 2 weeks (2 injections), and 2 HL patients received 40 mg weekly (one for 2 injections and the other for 8 injections).
- Progressive disease: Observed in 7 patients (43.75%),

all with HL (Patients 1, 2, 3, 4, 10, 12, and 13). Nivolumab dosing was as follows: 5 patients received 40 mg (2 weekly and 3 every 2 weeks; 2–10 injections, where 2 patients received 2 injections, 1 received 8, 1 received 9, and 1 received 10), and two patients received 100 mg every 2 weeks (1 for 6 injections and the other for 8 injections).

Overall, clinical responses were observed across different dosing levels. Patients receiving nivolumab doses of ≥ 100 mg appeared to have numerically higher rates of CR and PR compared with those receiving lower doses; however, responses were also documented in patients treated with substantially reduced doses. Notably, the PMBCL patient achieved a metabolic CR. In several patients achieving CR after a limited number of nivolumab doses, prior or concomitant chemotherapy may have contributed to the observed response. Additionally, response assessment was not uniform: only 31% of patients underwent PET/CT, while 69% were assessed by contrast-enhanced CT. Because CT cannot reliably distinguish viable tumors from residual masses, the reported CR and PR rates may be subject to misclassification. Detailed individual patient data are presented in Tables 1 and 2.

4. Discussion

Nivolumab is an established standard treatment for r/r lymphomas; however, access to immune checkpoint inhibitors remains uneven worldwide.⁹⁻¹⁴ High drug costs and lack of reimbursement substantially limit availability in many low- and middle-income countries, resulting in significant financial toxicity and non-standard treatment practices.¹⁴⁻¹⁶ Importantly, financial toxicity is not confined to resource-limited settings: studies report that 20–50% of cancer patients in the United States and 10–30% in Europe experience cancer-related financial distress, with even higher rates reported in middle- and low-income countries.^{9,13} Consequently, nivolumab remains inaccessible or only partially accessible in several regions, including Armenia, Ukraine, India, and parts of Africa.^{6,9,13,14}

In this real-world cohort from Armenia, most patients received reduced, patient-driven doses of nivolumab due to financial constraints. Despite this, nivolumab demonstrated clinically meaningful activity, with an overall CR rate of 25%. Although outcomes appeared numerically better in patients receiving doses of ≥ 100 mg, responses were also observed in patients treated with substantially reduced dosing, suggesting that lower nivolumab doses may still provide antitumor activity in a subset of patients. The 12- and 24-month OS rates in our cohort (91.7% and 81.5%, respectively) are generally

Table 2. Treatment outcomes according to nivolumab dose category

Nivolumab dose category	Patients (n)	Complete response, n (%)	Partial response, n (%)	Overall response rate, n (%)	Progressive disease, n (%)
<100 mg	8	1 (12.50)	2 (25.00)	3 (37.50)	5 (62.50)
≥100 mg	8	3 (37.50)	3 (37.50)	6 (75.00)	2 (25.00)
Total	16	4 (25.00)	5 (31.25)	9 (56.25)	7 (43.75)

Notes: Overall response rate = Complete response + Partial response. Dose categories were defined based on the fixed nivolumab dose administered per injection.

consistent with pivotal nivolumab trials in r/r lymphomas, supporting comparable intermediate-term efficacy in real-world practice (Figure 1). The lower 36-month OS (40.7%) should be interpreted cautiously due to small sample size, patient heterogeneity, and limited follow-up, as reflected by the wide CI. Additionally, nivolumab was well tolerated in this cohort. The irAEs were mild (Grade 1, CTCAE) and manageable, with no severe irAEs or treatment-related hospitalizations observed, supporting the safety of nivolumab in r/r lymphoma patients.

These findings are consistent with emerging evidence supporting dose de-escalation strategies for PD-1 inhibitors. Prior studies have shown that reduced fixed doses of nivolumab, including doses as low as 40 mg, can induce meaningful clinical responses in patients with r/r HL.^{10,12} In other malignancies, such as non-small cell lung cancer, retrospective analyses have demonstrated comparable progression-free survival and OS outcomes with low-dose nivolumab administered at extended intervals, while achieving substantial cost reductions of 50–75%.¹² Together, these data suggest that the pharmacodynamic effects of PD-1 blockade may plateau at lower doses, providing a biological rationale for exploring alternative dosing strategies.

Beyond dose reduction alone, combination strategies may further enhance the feasibility of low-dose immunotherapy. A randomized study in head and neck cancer patients showed that combining 20 mg nivolumab every 3 weeks with metronomic chemotherapy increased 1-year OS by 16.3%.¹⁰ While such strategies have not been systematically evaluated in lymphoma, they warrant consideration, particularly in settings where access to standard-dose immunotherapy is limited. In this context, participation in clinical trials remains a critical pathway to expand access to innovative treatments and to generate robust evidence for optimized dosing approaches.

4.1. Study limitations

Our study has some critical limitations.

4.1.1. Small sample size and heterogeneity

The reported incidence of NHL in Armenia was 4.34 per 100,000 population between 2017 and 2021, while the incidence of HL was 2.3 per 100,000 between 2000 and 2014.¹⁴ Our study cohort, which included HL, PMBCL, and ALK+ T-cell lymphoma, was small and heterogeneous, reflecting the limited number of patients able to access nivolumab treatment on a self-funded basis. This heterogeneity highlights the challenges of accessing high-cost therapies in this setting and precludes reliable conclusions regarding differences in treatment outcomes between standard- and reduced-dose nivolumab. Comparisons across subgroups are therefore descriptive rather than definitive. The small sample size also increases susceptibility to random variation, further limiting the generalizability of these findings to larger patient populations.

4.1.2. Dose selection and potential confounding

The choice of nivolumab dosing in this cohort was largely driven by patient-specific factors, most notably financial constraints and, in some cases, patient body weight. Patients were informed in advance about the long-term nature of nivolumab treatment, and their dosing decisions were influenced by the need to minimize repeated expenses. While patients understood that the standard recommended doses were either 3 mg/kg or 240 mg, those facing financial difficulties often opted for reduced doses, such as 40 mg or other low-dose regimens. In particular, patients with lower body weight sometimes preferred the 3 mg/kg regimen, as the total dose was lower than the 240 mg fixed-dose standard, making treatment more affordable in difficult circumstances. Consequently, comparisons between dosing groups are highly susceptible to selection bias.

Moreover, none of the dose reductions were based on predefined clinical criteria. All patients had r/r disease, and nivolumab was considered their last available therapeutic option locally. In this context, dose reduction was chosen as a feasible alternative to no treatment. Patients were informed that 40 mg nivolumab injections had been studied in low-income settings and might provide some benefit; however, from a clinical perspective, such low doses were not recommended as standard therapy but rather as a palliative-like solution in the absence of other options.^{15,16} Therefore, all reported outcomes must be interpreted in light of these considerations, acknowledging the influence of financial and practical constraints on dosing decisions and the resulting limitations in directly comparing efficacy across dosing groups.

4.1.3. Impact of prior or concomitant chemotherapy

In patients who achieved a response after a limited number of nivolumab cycles, prior chemotherapy may have contributed to tumor regression. The fact that 11 of 16 patients had received prior chemotherapy within three months of nivolumab administration makes it challenging to assess the relative contribution of nivolumab versus delayed chemotherapy. With longer follow-up, the outcomes in four patients appeared more attributable to prior chemotherapy, as they received only two to three nivolumab injections (Table 1). In contrast, in patients who received more than eight nivolumab injections, the reason for treatment effectiveness cannot be fully determined, as both nivolumab and prior chemotherapy may have contributed to the observed response. Given that all patients had r/r disease, it was clinically expected that a new treatment would be initiated promptly following ineffective chemotherapy or disease progression assessed with contrast-enhanced CT or PET/CT. Consequently, the overlap between recent chemotherapy and nivolumab administration, and the resulting confounding in assessing treatment response, are anticipated outcomes in this patient population.

4.1.4. Imaging and response assessment limitations

Disease response in this study was evaluated using either PET/CT or contrast-enhanced CT, depending entirely on patient-specific circumstances, primarily due to financial limitations. From a medical standpoint, PET/CT has always been the preferred modality for assessing treatment response, given its ability to assess both metabolic activity and anatomic tumor burden, providing the most precise evaluation of lymphoma response. However, the high cost of PET/CT in Armenia, which is approximately double the known average monthly salary, posed a substantial barrier for most patients. Consequently, PET/CT was generally

self-funded and accessible to only a few patients, whereas contrast-enhanced CT was provided by the government in almost all cases and thus became the predominant modality for routine follow-up. The medically recommended and expected modality is PET/CT in all cases.

In our cohort, 5 patients underwent PET/CT at least once, while 11 were evaluated exclusively with CT. Importantly, no patient was able to undergo PET/CT at all required stages of treatment, meaning CT scans were the primary tool for monitoring the majority of patients. This situation highlights the dual financial toxicity faced by patients, encompassing both drug access and diagnostic assessment, and emphasizes the unique challenges of conducting real-world oncology research in a resource-limited setting. Patients were therefore often forced to make difficult decisions about which aspects of their care to prioritize, balancing the potential benefit of more accurate imaging with the substantial financial burden.

The uneven use of imaging modalities introduces a major limitation to the interpretation of treatment outcomes. CT alone cannot reliably detect residual metabolic activity, potentially leading to underestimation or overestimation of CR and PR. Borderline or equivocal CT findings may lead to misclassification of disease status, potentially inflating or underestimating progression rates. Such discrepancies are particularly relevant in patients who achieved CR or PR after a limited number of nivolumab cycles, as it becomes difficult to determine whether observed responses reflect true drug efficacy or limitations of the imaging modality. The reliance on CT as the primary modality also limits comparability with international studies, most of which utilize PET/CT for standardized response assessment according to established criteria, such as the Lugano or Cheson guidelines. Accordingly, the response outcomes reported in this study must be interpreted while acknowledging the resource limitations on patient care.

4.2. Potential solutions

The challenges identified in this study, mainly including limited access to standard nivolumab doses, financial constraints affecting dosing decisions, and uneven imaging assessments, highlight the need for systemic solutions to improve lymphoma care in resource-limited settings such as Armenia.

4.2.1. Improving access to standard therapies and diagnosis

One of the primary obstacles in the current setting has been the high cost of nivolumab, which often necessitated dose reductions based on patients' financial capacity.

This situation underscores the importance of developing mechanisms to ensure equitable access to essential therapies. Another major limitation identified in this study was the uneven use of PET/CT versus contrast-enhanced CT for response evaluation. PET/CT remains the gold standard for accurate assessment of lymphoma response, yet its high cost limits accessibility for many patients. In January 2026, Armenia implemented a mandatory government-run medical insurance program to develop local healthcare and reduce out-of-pocket expenses for patients. This can be seen as a potential solution to reduce the financial toxicity in oncology in Armenia.

4.2.2. Improving access to clinical trials

Access to clinical trials has several important implications. First, it reduces financial toxicity for participating patients, enabling them to receive cutting-edge therapy without bearing the full cost. Second, it facilitates local research capacity. Third, it broadened future treatment opportunities, highlighting the importance of clinical trials as a mechanism to expand access to novel therapies in resource-limited settings. Looking forward, the systematic development and expansion of clinical trial opportunities in Armenia could have a substantial impact on patient outcomes. To address this unmet need, some investigator-initiated clinical trials were launched locally, including a study evaluating the PD-1 inhibitor balstilimab in patients with r/r lymphoma (ClinicalTrials.gov: NCT05891821). Such solutions provide access to treatment that would otherwise have been unavailable due to financial constraints.

Integrating clinical trial participation as a standard consideration for eligible patients could therefore serve as a strategic approach to improve treatment outcomes, reduce disparities in care, and build sustainable research infrastructure within the local healthcare system.

4.2.3. Expanding multicenter collaboration

Collaboration among multiple oncology centers across Armenia and neighboring regions could help overcome small sample sizes and provide a broader understanding of treatment patterns and outcomes. Pooling data would allow for a more precise evaluation of dose–response relationships, safety, and long-term efficacy while maintaining relevance to the local healthcare context.

4.2.4. Promoting patient education and support

Improved awareness can empower patients to engage in shared decision-making, potentially improving adherence, follow-up consistency, and overall treatment outcomes.

5. Conclusion

In this study, we present real-world data on nivolumab use in patients with r/r lymphoma in Armenia, highlighting both the clinical potential of this therapy and the practical challenges of its implementation in a resource-limited setting. The findings of this study underscore important systemic barriers to lymphoma care, including financial constraints that influence treatment dosing, limited access to optimal imaging, and variability in prior therapies.

With this publication, our goal is to highlight the existing challenges and facilitate improvements in local practice, contributing to the development of more applicable treatment options and solutions. Ultimately, the current study serves as an initial step toward building a more robust evidence base, encouraging larger, prospective, and multicenter studies. By documenting real-world experience, patient outcomes, and treatment feasibility, we hope this work will inform both clinical practice and healthcare policy, reduce inequities in care, and support better outcomes for lymphoma patients in Armenia and similar resource-limited settings.

Acknowledgments

The authors thank the patients of the Yeolyan Hematology and Oncology Center for their contribution.

Funding

None.

Conflict of interest

The authors declare no conflicts of interest related to this study.

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Writing–review & editing: All authors

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, formal ethical approval and written informed consent were waived according to institutional policies.

Consent for publication

Written informed consent is not applicable due to waiver for de-identified retrospective data. Verbal consent was obtained from all participants.

Availability of data

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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