haematologica
Journal of the Ferrata Storti Foundation

Notable clinical activity of immune checkpoint inhibitors with or without brentuximab vedotin in relapsed or refractory gray zone lymphoma

by Ivan Dlouhy, Tiago Maia, Diana Viegas, Nina Abreu, Jose Cabeçadas and Maria Gomes da Silva

Received: April 23, 2026.
Accepted: July 7, 2026.

Citation: Ivan Dlouhy, Tiago Maia, Diana Viegas, Nina Abreu, Jose Cabeçadas and Maria Gomes da Silva. Notable clinical activity of immune checkpoint inhibitors with or without brentuximab vedotin in relapsed or refractory gray zone lymphoma.
Haematologica. 2026 July 16. doi: 10.3324/haematol.2026.301128 [Epub ahead of print]

Notable clinical activity of immune checkpoint inhibitors with or without brentuximab vedotin in relapsed or refractory gray zone lymphoma

Ivan Dlouhy[1], Tiago Maia[2], Diana Viegas[1], Nina Abreu[3], José Cabeçadas[2], Maria Gomes da Silva[1]

[1]Serviço de Hematologia, Instituto Português de Oncologia de Lisboa Francisco Gentil, 1099-023 Lisboa, Portugal

[2]Serviço de Anatomia Patológica, Instituto Português de Oncologia de Lisboa Francisco Gentil, 1099-023 Lisboa, Portugal

[3]Serviço de Pediatria, Instituto Português de Oncologia de Lisboa Francisco Gentil, 1099-023 Lisboa, Portugal

Corresponding author: Ivan Dlouhy (idlouhy@ipolisboa.min-saude.pt)

Data-sharing statement: The dataset generated for the current study is available from the corresponding author upon reasonable request.

Funding: This work benefited from institutional support from the Research Unit UID/04462: iNOVA4Health—Programme in Translational Medicine and the Associated Laboratory LS4FUTURE (https://doi.org/10.54499/LA/P/0087/2020), financially supported by Fundação para a Ciência e Tecnologia/Ministério da Educação, Ciência e Inovação.

Contributions: ID conceptualized the study, analyzed the data, and wrote the first draft of the manuscript. DV and NA collected and analyzed the data. JC and TM performed the pathology analysis and interpretation. M.G.d.S supervised the study. All authors reviewed and edited the manuscript and approved the final version.

Disclosures: MGdS reports research grants from AstraZeneca; advisory board participation for

Roche, Lilly, and Clinical Care Options; non-remunerated consultancy and educational activities for Roche, AbbVie, Johnson & Johnson (Janssen), BeOne Medicines, Lilly, and AstraZeneca; institutional

payments from BeOne Medicines and Lilly; and travel support from AbbVie, Johnson & Johnson (Janssen), Gilead Sciences, Lilly, and BeOne Medicines. The other authors have no conflicts of interest to disclose.

Acknowledgements: Artificial intelligence tools (Anthropic, San Francisco, CA, USA; claude.ai) were used solely to assist with language editing and improvement of manuscript clarity. No AI tools were used for data analysis, interpretation, or generation of results. The authors reviewed and take full responsibility for all content.

Mediastinal gray-zone lymphoma (MGZL) is a rare entity with overlapping features between classic Hodgkin's lymphoma (cHL) and primary mediastinal B-cell lymphoma (PMBCL), typically presenting with bulky mediastinal masses in young adult males. Diagnosis remains challenging due to its rarity, poor interobserver reproducibility, and the frequent reliance on small needle biopsies.[1,2] First-line treatment remains controversial, although non-Hodgkin lymphoma protocols are preferred over those employed for cHL. However, MGZL overall outcomes remain inferior compared with other mediastinal lymphomas.[3]

Management of relapsed or refractory (R/R) disease is particularly challenging, with no established standard of care. Most patients with frontline failure prove to be chemorefractory, and high-dose chemotherapy with stem cell transplant (SCT) is only feasible in a minority.[4] Frequent 9p24.1 amplifications driving PD-L1/PD-L2 overexpression and consistent CD30 expression in both cHL and PMBCL provide a strong biological rationale for PD-1 blockade and anti-CD30 therapy in MGZL.[5–8] The nivolumab-BV combination achieved an ORR of 70% and median PFS of 22 months in an expansion cohort of 10 MGZL patients in the CheckMate 436 trial.[9] However, broader evidence in MGZL remains limited to sparse case reports.[10,11] The objective of this study was to analyze the efficacy and toxicity of immune checkpoint inhibitors (ICI), alone or in combination with BV, in patients with R/R GZL in a real-world setting.

This retrospective, single-center study included patients diagnosed with gray zone lymphoma (GZL) between 2010 and 2025 according to World Health Organization (WHO) classification criteria, who were refractory or relapsed (R/R) after immunochemotherapy and subsequently treated with immune checkpoint inhibitors (ICI). Of 31 identified GZL cases, 15 were excluded: one due to an alternative diagnosis after pathology review, eight with sustained complete remission after first-line treatment, and six R/R patients responding to salvage immunochemotherapy. Baseline evaluation included medical history, physical examination, ECOG performance status, assessment of B symptoms and bulky disease (>10 cm), laboratory tests (including LDH and β2-microglobulin), imaging with CT and/or PET, and bone marrow biopsy. Response was assessed by PET according to Lugano criteria.[12] Toxicities were graded according to CTCAE v5.0.

The study was approved by the Ethics Committee of the Instituto Português de Oncologia de Lisboa (UIC/1657) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective design, in line with national legislation (Law 21/2014, Article 6, paragraph 2).

All diagnoses were established according to WHO criteria at the time of diagnosis and centrally reviewed by two expert pathologists for this study.[1,13,14] Immunohistochemical studies were performed on FFPE tissue sections, in an automated staining instrument (Roche Tissue Diagnostics, Oro Valley, AZ, USA). The antibody panel included CD20, CD79a, CD10, BCL6, BCL2, PAX5, CD15, CD30, MUM1, CD79a, CD23, and Ki-67, as well as EBER in-situ hybridization. We considered as GZL all cases with intermediate features between cHL and PMBCL (N= 12), as well as composite cases (N= 1), where components of cHL and large B-cell lymphoma were present within the same biopsy.[4] Sequential cases were also included (N= 3), namely those with an initial biopsy showing cHL and a subsequent relapse biopsy showing large B-cell lymphoma, or vice-versa, while EBV positive cases were excluded. All patients received first-line and subsequent salvage therapies at our institution. Twelve patients repeated biopsy at first relapse.

Patients received pembrolizumab (200 mg every 3 weeks) until progression or consolidation with stem cell transplantation (SCT). From 2021, treatment was adapted to nivolumab (240 mg on day 8 of cycle 1, then day 1 of subsequent cycles) combined with brentuximab vedotin (1.8 mg/kg every 3 weeks), following the CheckMate 436 protocol, until progression or SCT.[9]

Actuarial survival analysis was performed by the Kaplan–Meier method. All statistical analyses and plots were performed using R (version 4.5) within RStudio IDE (Posit software).

Sixteen patients (pts) were included in the analysis. Initial characteristics are detailed in Table 1. Median age was 30 years (range 15-74) and all patients had received at least two prior lines of therapy before study treatment. Frontline therapy consisted of R-CHOP (N=12), ABVD (N=2), R-CHOEP (N=1), and R-DA-EPOCH (N=1); 62% had primary refractory disease. One patient received consolidation radiotherapy for a residual mediastinal mass. As second line, one elderly patient received R-Gemox, while 15 patients were treated with platinum-based salvage regimens and were intended for consolidation with ASCT (ESHAP 11 pts, DHAP 3 pts, ICE 1 pt). Two were treated with chemotherapy alone, 11 in combination with rituximab and two combined with BV. Only two patients (14%) achieved a CR (of short duration) and one patient a PR after second line.

Eleven patients were treated with nivolumab (10 in combination with BV), and 5 patients were treated with pembrolizumab (1 in combination with BV). A total of 171 ICI cycles were administered (median 9, range 1-20 cycles), including 37 cycles as monotherapy and 134 in combination with BV. ICIs were delivered as third line therapy in 15 patients and as fourth line in one (who had previously received radiotherapy).

Fourteen patients initiated ICI as a bridge to stem-cell transplantation (SCT), of whom 12 (86%) proceeded to transplant (9 allogeneic and 3 autologous) in CR (Figure 1).

The median follow-up time from the start of ICI was 3.8 years (range 0.12-6.6 years). Best overall response rate (ORR) was 87% (95% CI 62%-96%), with a median time to response of 2.7 months (range 1.3 – 7.1). Five patients were treated with ICI monotherapy (including 3 cases without mediastinal mass) with an ORR of 60% (CR 40%). In contrast, ORR of patients treated with ICI-BV combination was 100% (10 obtained a CR and one a PR). PFS and OS at 2 years from the start of PD-1 inhibitor was 55% (95% CI 34-91%) and 71% (95% CI 51-100%), respectively. For patients receiving the ICI-BV combination, 2-year PFS and OS were 61% (95% CI 33-100%) and 74% (95% CI 48-100%), respectively. Two patients that progressed during ICI treatment after 12 and 16 months responded to subsequent therapy with BV plus bendamustine (one proceeded to SCT in CR, the other relapsed after 9 months).

Five patients (31%) eventually died during the study follow up: three due to disease progression (including two patients with early refractoriness to ICI) and two due to toxicities related to allogeneic stem cell transplant, while in remission. At database lock, no relapses after SCT were observed.

The use of ICI in monotherapy was associated with few adverse effects (AE, Table 2. Neutropenia, which was of short duration and reversible with filgrastim, was the most frequent AE (31%, all grade 3-4). Notably, all cases occurred in the ICI–BV combination group, while febrile neutropenia was limited to one patient (in two cycles). Immune-related AEs occurred in 6 patients, mostly grade 1-2, including transaminase elevation (N=5) and hypothyroidism (N=1). No patient discontinued ICI because of AEs, although three patients delayed cycles because of toxicity (grade 4 infections in 3 cycles and cholestasis in 10). Peripheral neuropathy (PN) attributable to BV was also frequent (4 patients, all grade 2) and lead to dose reductions in three patients and permanent discontinuation of BV in one (all cases recovered to normal or grade 1 PN).

In this real-world study, we report outcomes of 16 patients with R/R GZL treated with ICI, representing, to the best of our knowledge, the largest cohort described to date. Despite the inherent limitations of sample size, our findings provide clinically relevant data on both efficacy and tolerability of PD1 blockade, either as monotherapy or in combination with BV, and confirm previous results from the Checkmate 436 expansion cohort.[9]

In the most recent lymphoma classifications, “true” gray zone lymphomas are defined as cases with mediastinal involvement, whereas cases with intermediate histology between Hodgkin and non Hodgkin lymphoma but without a mediastinal mass are now categorized as DLBCL.[1,15] All 16 patients in the current series were diagnosed according the WHO classification applicable at the time of presentation, being all considered GZL and treated accordingly. Three patients had no mediastinal involvement: two were refractory to ICI, and one underwent transplantation in complete remission. By contrast, 11 of 13 patients with mediastinal involvement achieved complete remission to ICI, supporting the biological distinction between mediastinal and non-mediastinal entities as recognized in the current classifications. It should be noted, however, that non-mediastinal cases in this series were all treated with ICI monotherapy, precluding conclusions regarding potential efficacy of the combination with BV in this subgroup.

In conclusion, gray zone lymphomas affect a young patient population and show aggressive behavior with a high rate of chemorefractoriness. Nevertheless, the majority of patients achieved rapid responses to PD-1 inhibitors, particularly when combined with brentuximab vedotin, enabling subsequent response consolidation with SCT in most patients with an acceptable toxicity profile.

Bibliography

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.
2. Pilichowska M, Pittaluga S, Ferry JA, et al. Clinicopathologic consensus study of gray zone lymphoma with features intermediate between DLBCL and classical HL. Blood Adv. 2017;1(26):2600-2609.
3. Kritharis A, Pilichowska M, Evens AM. How I manage patients with grey zone lymphoma. Br J Haematol. 2016;174(3):345-350.
4. Sarkozy C, Molina T, Ghesquières H, et al. Mediastinal gray zone lymphoma: Clinico-pathological characteristics and outcomes of 99 patients from the Lymphoma Study Association. Haematologica. 2017;102(1):150-159.
5. Mottok A, Steidl C. Biology of classical Hodgkin lymphoma: Implications for prognosis and novel therapies. Blood. 2018;131(15):1654-1665.
6. Steidl C, Gascoyne RD. The molecular pathogenesis of primary mediastinal large B-cell lymphoma. Blood. 2011;118(10):2659-2669.
7. Burton C, Allen P, Herrera AF, Stage E. Paradigm Shifts in Hodgkin Lymphoma Treatment: From Frontline Therapies to Relapsed Disease. Am Soc Clin Oncol Educ Book. 2024;44(3):1-8.
8. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for R / R primary mediastinal large B-cell lymphoma: a 3-year follow-up. Blood Adv. 2023;7(18):5272-5280.
9. Santoro A, Moskowitz AJ, Ferrari S, et al. Nivolumab combined with brentuximab vedotin for relapsed/refractory mediastinal gray zone lymphoma. Blood. 2023;141(22):2780-2783.
10. Melani C, Major A, Schowinsky J, et al. PD-1 Blockade in Mediastinal Gray-Zone Lymphoma. N Engl J Med. 2017;377(1):87-89.
11. Rosales Y, Mesquita J, Garcia Y, et al. Use of checkpoint inhibitors in gray zone lymphoma. Hematol Oncol Stem Cell Ther. 2023;16(1):1-5.
12. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.
13. Swerdlow SH, Campo E, Lee Harris N, et al. WHO Classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon (France): Internacional Agency for Research on Cancer (IARC); 2008.
14. Swerdlow SH E. WHO classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon (France): International Agency for Research on Cancer (IARC); 2017.

15. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;11(140):1229-1253.

TABLES

Table 1. Features at diagnosis of 16 relapsed/refractory gray zone lymphoma patients treated with PD-1 inhibitors.

Characteristic	Baseline	At ICI start
Median age	30 (15 - 74)	31 (17 - 76)
Male gender	9 (56%)	
B symptoms	12 (75%)	6 (38%)
PS ≥2	2 (13%)	1 (6.3%)
Stage III/IV	10 (63%)	10 (63%)
Elevated LDH	12 (86%)	9 (56%)
Elevated B2m	5 (50%)	
Extranodal disease (any site)	8 (50%)	9 (56%)
BM infiltration[1]	0 (0%)	
Mediastinal involvement	13 (81%)	14 (88%)
Tumor ≥10 cm	9 (56%)	1 (6.3%)
IPI		
0-2	13 (81%)	14 (88%)
3-5	3 (19%)	2 (13%)
CR rate with frontline therapy	6 (38%)	

[1]Of 13 patients

PS: performance status; BM: bone marrow; CR: complete remission

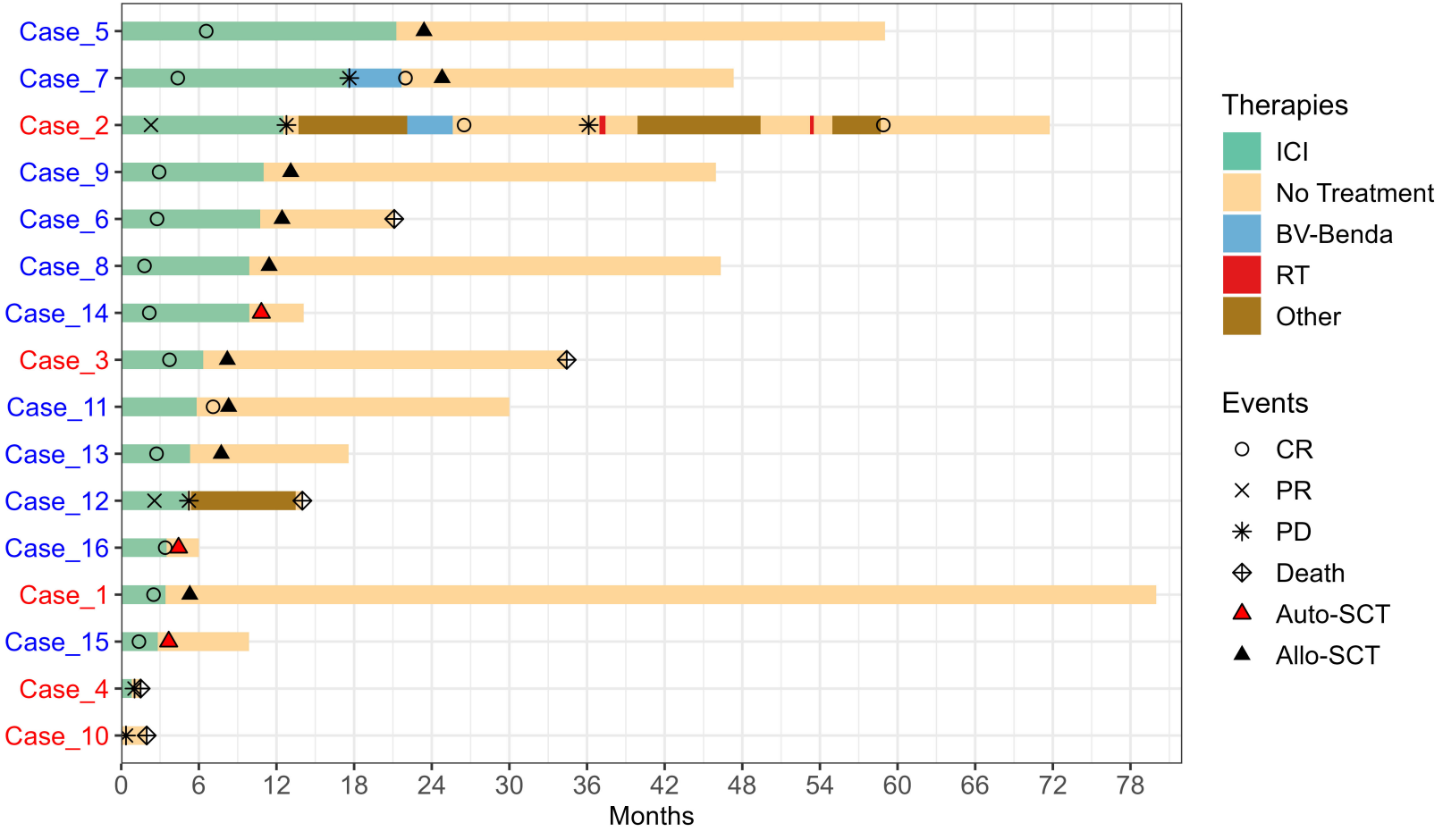
Table 2. Toxicities observed with ICI treatment

	ICI monotherapy (N = 5)		ICI + BV (N = 11)	
Toxicity	Total	Grade 3/4	Total	Grade 3/4
Arthralgias	1	1	1	0
Eczema	1	0	0	0
Infusional Reaction	1	1	0	0
Diarrhea	0	0	3	0
Peripheral Neuropathy	0	0	4	0
Headaches	0	0	1	0
Cholecystitis	1	1	1	1
Infections	0	0	2	1
Covid	0	0	4	0
Hypothyroidism	0	0	1	0
Transaminases	2	0	3	1
Cholestasis	1	1	2	1
Thrombocytopenia	1	0	0	0
Neutropenia	0	0	5	5
Febrile Neutropenia	0	0	1	1
Total	**8**	**4**	**28**	**10**

ICI: immune check-point inhibitor; BV: Brentuximab Vedotin

FIGURE LEGENDS

Fig 1. Swimmer plot showing treatment duration and outcomes for each patient. Bar colors indicate treatment period: green (immune check-point inhibitors, ICI), orange (no treatment), blue (BV-Bendamustine), red (radiotherapy) and brown (other). Time is expressed in months from ICI start.



ICI: Immune check-point inhibitor; BV: Brentuximab vedotin; CR: Complete remission; PR: Partial remission
PD: Progressive disease; SCT: Stem cell transplant; RT: Radiotherapy
Blue: ICI-BV combination; Red: ICI monotherapy