Nivolumab combined with brentuximab vedotin with or without mediastinal radiotherapy for relapsed/refractory primary mediastinal large B-cell lymphoma

Patients with relapsed/refractory primary mediastinal large B-cell lymphoma (R/R PMBL) respond poorly to salvage therapy. After the first relapse, the objective response rate (ORR) is 25%[1] and a second study reported a 2-year progression-free survival (PFS) of 29%.[2] More recently, chimeric antigen receptor T cells have been proposed for the treatment of R/R PMBL, producing an ORR of 78% and a 2-year PFS rate of 54% to 64%.[3,4] Similar results have been achieved with the combination of nivolumab and brentuximab vedotin (BV), with an ORR of 73.3% and a 2-year PFS of 55.5%.[5] However, in this trial, 12 of the 29 patients treated with BV-nivolumab subsequently underwent autologous (N=6) or allogeneic (N=6) hematopoietic stem cell transplantation (SCT), and only four patients remained progression-free without SCT. Nivolumab has been approved by the Food and Drug Administration (FDA), since 2016, as a single agent for the treatment of patients with classical Hodgkin lymphoma who have relapsed or progressed after autologous SCT, but is not yet approved for PMBL patients. Pembrolizumab has had FDA approval since 2018 for use as a single agent for R/R PMBL after two or more prior lines of treatment. BV is currently FDA-approved for six indications, including classical Hodgkin lymphoma, but is still unapproved for PMBL patients. Here, we report the results of 11 patients, two of whom were enrolled in the CheckMate 436 study, and nine of whom were treated with BV-nivolumab in the setting of real-life, off-label, compassionate use. None of these patients underwent autologous or allogeneic SCT, but five received consolidation radiotherapy (CRT). After a median follow-up of 44.0 months, the median PFS and overall survival (OS) had not been reached, while the 3-year PFS and OS rates were 65% and 71%, respectively. These data suggest that BV-nivolumab, possibly followed by CRT, may be a reasonable approach for the treatment of R/R PMBL, without the need for SCT, especially for patients with localized relapse.

Between May 2017 and October 2023, 11 patients with R/R PMBL (N=10) or mediastinal gray zone lymphoma (MGZL, N=1) were treated with BV-nivolumab at St. Louis Hospital. The diagnosis of PMBL was made by expert hematopathologists following the diagnostic criteria established by previous pathologyl descriptions of PMBL from the literature and international classifications[6,7] with support of the French Lymphopath network.[8] All patients received nivolumab 240 mg and BV 1.8 mg/kg intravenously every 21 days, as previously reported.[9] Response was assessed, using computed tomography (CT) scans with or without positron emission tomography (PET), in accordance with the 2014 Lugano criteria.[10] Best ORR was defined as the proportion of patients achieving complete response (CR) or partial response (PR) during treatment. OS and PFS were estimated using the Kaplan-Meier method. The study was conducted in accordance with the Declaration of Helsinki; institutional board approval was obtained. All patients received written information.

The patients' baseline characteristics are presented in Table 1. Their median age was 33 years (range, 19-82). The patients had received a median of two (range, 1-6) previous lines of therapy, including one patient treated in first relapse and one patient who underwent autologous SCT; nine were considered to have disease that was refractory to the most recent therapy.

After a median follow-up of 44 months (range, 9.6 - 58.5), the median PFS and OS had not been achieved, while the 3-year PFS and OS rates were 65% and 71%, respectively (Figure 1A, B). Patients received a median of five (range, 2-10) cycles of treatment. After four cycles, the ORR was 64% including four patients (36%) with complete responses and three (27%) with partial responses; three patients had stable disease and one patient had progressive disease. The one patient with MGZL obtained a complete response that persisted over a 22.3-month follow-up. For the ten patients with PMBL, the ORR after four cycles of treatment was 60% and the 3-year PFS was 64%. Of the six PMBL patients with localized disease, five underwent radiotherapy; their ORR after four cycles of treatment was 67% and their 3-year PFS was 83%. The ORR of the three patients with disseminated PBML was 33% and their 3-year PFS was 67% (Table 2). Two patients had stable disease, of whom one had durable stability (no relapse event after 58 months of follow-up) and the other was lost to follow-up. Only one patient progressed on therapy and died from lymphoma 8 months later. None of the patients underwent consolidation with autologous or allogeneic SCT. Of the six patients with localized disease, five (all with PMBL) received mediastinal involved-site radiotherapy. Among them, none had received prior radiotherapy, one had previously undergone autologous SCT, and two had had disseminated disease at diagnosis (stage III and IV), but all had localized disease (mediastinal stage IE or I) at relapse prior to initiation of BV-nivolumab therapy. These patients received a radiation dose of 30 Gy (N=3), 36 Gy (N=1) and 50 Gy (N=1), five fractions of 2 Gy per week. Disease status before CRT was complete remission in three patients, partial remission in one patient and sta-

Table 1. Baseline demographic and clinical characteristics of the patients in this study and the CheckMate 436 trial.

Characteristics	This study		Checkmate 436 patients N=30
	Overall cohort N=11	PMBL patients N=10	
Female, N (%)	4 (36)	3 (27)	17 (56.7)
Age in years Median (range) <65, N (%)	 33 (19-82) 10 (91)	 34 (19-82) 9 (90)	 36 (19-83) 29 (97)
Disease stage at initial diagnosis, N (%) I-II III-IV	 4 (36) 7 (64)	 3 (30) 7 (70)	 16 (53) 13 (44)
Extranodal localizations at diagnosis, N (%)	6 (55)	5 (50)	Unknown
Disease stage at inclusion, N (%) I II III IV Unknown	 6 (55) 0 2 (18) 1 (9) 2 (18)	 6 (60) 0 2 (20) 1 (10) 1 (10)	 Unknown Unknown Unknown Unknown Unknown
Prior lines of systemic therapy, median (range)	2 (1-6)	2 (1-3)	2 (2-5)
Patients who received only 1 line of treatment before inclusion, N (%)	1 (9)	1 (10)	0
First-line therapy, N (%) R-CHOP R-CHOP 14 R-CHOP 21 R-mini-CHOP R-ACVBP R-EPOCH Other, N (%) Prior rituximab	 4 (36) 1 (9) 3 (27) 1 (9) 5 (45) 1 (9) 0 11 (100)	 3 (30) 1 (9) 2 (18) 1 (9) 5 (50) 1 (10) 0 10 (100)	 8 (26.7) Unknown Unknown 0 Unknown 9 (30) 13 (43.3) 30 (100)
Disease status, N (%) Refractory Relapsed	 9 (82) 2 (18)	 8 (80) 2 (20)	 20 (67) 6 (20)
Best response to most recent systemic therapy, N (%) Complete response Partial response Stable disease Relapse/progressive disease Unknown	 2 (18) 0 4 (36) 5 (45) 0	 2 (20) 0 4 (40) 4 (40) 0	 0 6 (20) 6 (20) 16 (53) 2 (7)
Prior ASCT, N (%)	1 (9)	1 (10)	4 (13)
Prior radiotherapy, N (%)	1 (9)	1 (10)	3 (27)

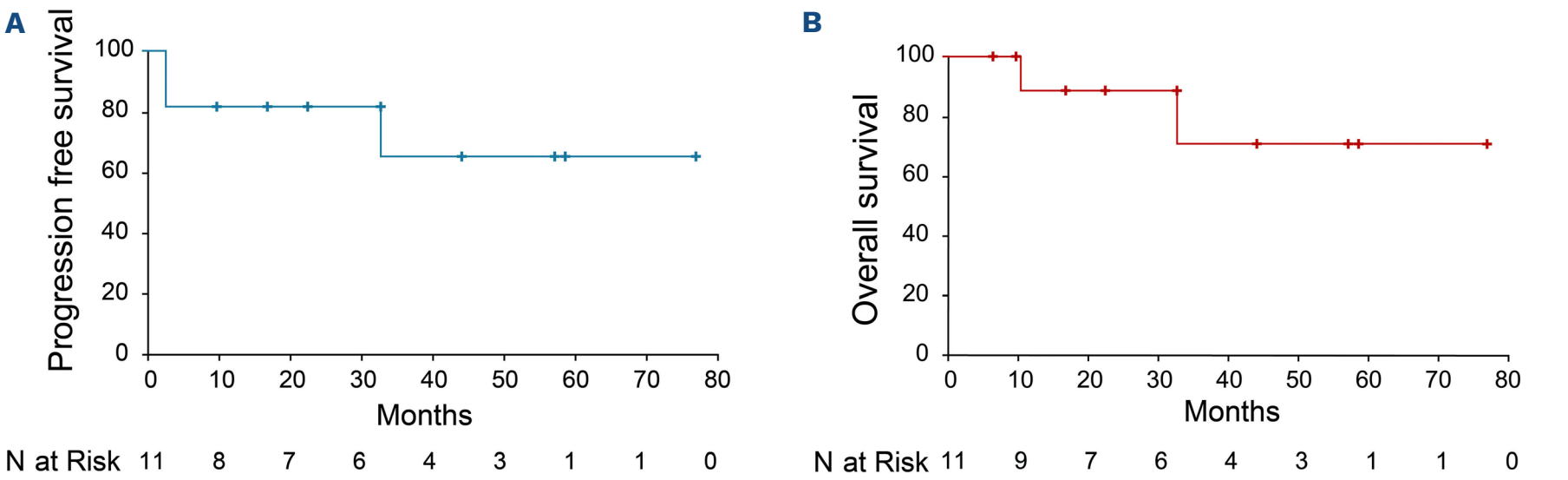
PMBL: primary mediastinal large B-cell lymphoma; R-CHOP: rituximab, cyclosphosphamide, doxorubicin, vincristine, prednisone; R-CHOP-14: R-CHOP every 14 days; R-CHOP-21: R-CHOP every 21 days; R-mini-CHOP: rituximab and reduced dose CHOP; R-ACVBP: rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; ASCT: autologous stem cell transplantation.

ble disease in the other patients, after four to six cycles of BV-nivolumab (Figure 1C). None received subsequent cycles of BV-nivolumab after CRT.

Among patients who did not receive CRT, two achieved complete responses with eight to ten cycles of BV-nivolumab without consolidation. One of them was still in complete remission after 44 months of follow-up, while the second died of cardiac complications at the age of 86, in complete remission, 33 months after the start of treatment.

Treatment tolerance was good with a limited number of cycles administered. One patient developed grade 2 peripheral neuropathy, one patient developed grade 1 thyroiditis related to nivolumab, and another developed multilocular granulomatosis (lymph nodes, pulmonary condensation and spleen invasion) confirmed by lung biopsy, with a spontaneous favorable evolution without intervention. No significant acute toxicity was observed after CRT.

After a median follow-up of 44 months, in our single-center



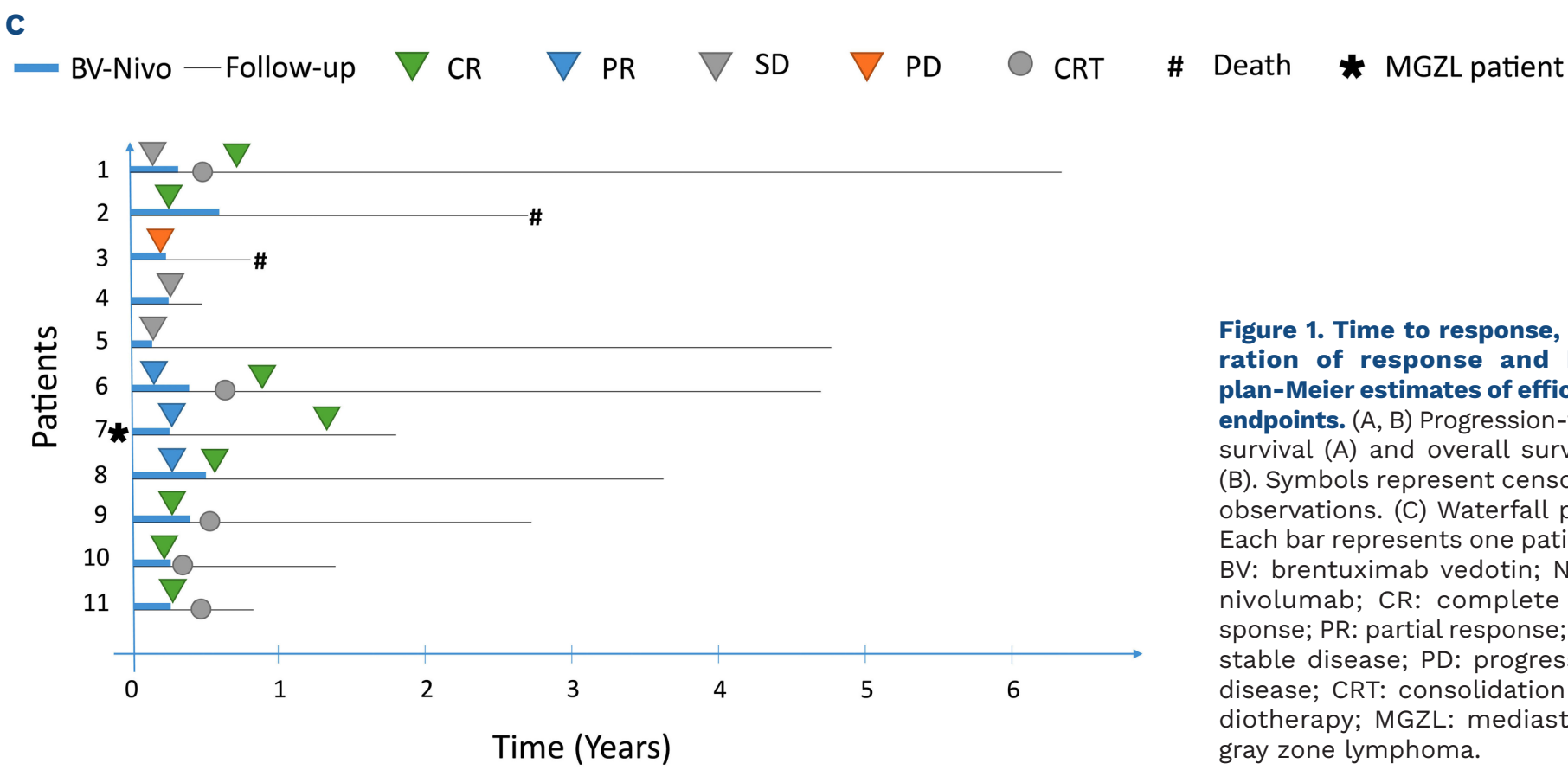


Figure 1. Time to response, duration of response and Kaplan-Meier estimates of efficacy endpoints. (A, B) Progression-free survival (A) and overall survival (B). Symbols represent censored observations. (C) Waterfall plot. Each bar represents one patient. BV: brentuximab vedotin; Nivo: nivolumab; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; CRT: consolidation radiotherapy; MGZL: mediastinal gray zone lymphoma.

experience we found that BV-nivolumab for the treatment of R/R PMBL and MGZL was effective, in line with previous reports (CheckMate 436).[5] We observed 3-year PFS and OS rates of 65% and 71%, respectively, which testify to the sustained efficacy of this strategy as a salvage treatment. Safety data were consistent with previous reports on this combination.[5]

The main difference between our study and the CheckMate 436 trial lies in the consolidation after BV-nivolumab. In the CheckMate 436 trial, 40% of patients underwent transplantation, with 20% receiving autologous and 20% allogeneic transplants, while no patients in our study underwent transplantation. In contrast, in the CheckMate 436 trial, 23% of patients received non-palliative CRT, while 50% of PMBL patients in our study received CRT. The results were excellent for the five patients with relapsed, localized PMBL who were treated with four to six cycles of BV-nivolumab, followed by CRT. All of these patients showed persistent responses after several years of follow-up.

Compared with the previously reported results of salvage therapy for this population with an ORR of 25% and a 2-year PFS of 29% after a first relapse,[1,2] our results are more consistent with those of the CheckMate 436 trial and suggest a better efficacy than chemotherapy for this population. However, the administration of four to six treatment cycles followed by CRT is a less restrictive and more cost-effective option and could be discussed for these patients from first relapse, especially in the rare cases of elderly patients, although validation in a larger subset is needed, especially for patients with MGZL.

While the median number of cycles was the same in both our study and the CheckMate 436 trial (5 cycles), the maximum number of cycles administered was ten in our cohort, compared to 22 for nivolumab and 20 for BV, with four patients still on treatment, in the CheckMate 436 trial. Given the good results in both cohorts, a lower number of cycles does not seem to have affected the results, especially in patients receiving CRT.

Table 2. Responses of the overall cohort and by patient category including response after four cycles of brentuximab vedotin plus nivolumab and before radiotherapy.

Characteristics	Overall cohort N=11	PMBL pts N=10	PMBL pts excluding CM436 cases N=8	Pts with localized PMBL N=6	Pts with localized PMBL who received CRT N=5	Pts with disseminated PMBL N=3
ORR after C4 and before CRT, % (95% CI)	64 (31-89)	60 (26-88)	63 (24-91)	67 (22-96)	80 (28-99)	33 (8-90)
CR after C4 and before CRT, % (95% CI)	36 (11-69)	40 (12-73)	38 (9-76)	50 (12-88)	60 (15-95)	33 (8-90)
Best ORR, % (95% CI)	73 (39-93)	70 (35-93)	63 (24-91)	83 (36-99)	100 (48-100)	33 (8-90)
3-year PFS, % (95% CI)	65 (32-88)	64 (31-88)	75 (41-93)	83 (44-97)	100	67 (21-94)
3-year OS, % (95% CI)	71 (34-92)	70 (33-92)	83 (44-97)	80 (38-96)	100	100

PMBL: primary mediastinal large B-cell lymphoma; pts: patients; CM436: Checkmate 436 trial; CRT: consolidative radiotherapy; ORR: overall response rate; C4: cycle 4; 95% CI: 95% confidence interval; CR: complete response; PFS: progression-free survival; OS: overall survival.

Our results, like those of the CheckMate 436 study, compare favorably in this setting to BV monotherapy, for which an ORR of 13% (2/12) has been reported,[11] or to inhibition of programmed cell death protein 1 (PD-1) alone with an ORR of 41.5%,[12] but in the absence of a comparative clinical trial, it is difficult to draw definitive conclusions on the benefit of the combination, compared to PD-1 inhibition alone.

Anti-PD1 and local radiotherapy may be associated with an abscopal effect in several tumor subtypes, including Hodgkin lymphoma.[13] The involvement of this synergistic mechanism may partly explain the good results in patients treated with BV-nivolumab followed by CRT, and the conversion of partial responses or stable disease to complete responses after CRT.

Assessing the response of PMBL patients with bulky mediastinal disease using PET-CT is challenging, and mediastinal biopsy should be considered as often as possible before initiating a new line of therapy to avoid overtreatment of patients with persistent hypermetabolic mediastinal masses without active disease. In this study, most patients underwent biopsy at relapse, but the procedure was not systematic. The development of the use of cell-free DNA for the purposes of assessment may be of particular interest in this specific population.[14]

The limitations of our study are those inherent to single-center, real-life, retrospective studies in a rare disease, including small number of patients, unsystematic reporting of treatment-emergent adverse events, different number of cycles and different doses of radiation administered. Moreover, the follow-up is not yet long enough to assess the late toxicity of radiotherapy in a young population, in particular with regard to valvular and coronary calcification.

According to our data and in line with the findings of the CheckMate 436 trial, BV-nivolumab appears to be safe and effective for the treatment of R/R PMBL. Consolidation after this therapy seems to be a preferred option for most clinicians in the community; our data suggest that CRT could be considered as an alternative to autologous or allogeneic SCT, especially following a local relapse, due to its favorable safety profile and durability of the responses obtained. An interesting question is whether this combination could be used as a bridge to chimeric antigen receptor T-cell therapy, which has not, to our knowledge, been reported.

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Contributions

LR, JW, and PB collected data. LR, JW, AP, and PB contributed to the data analysis and interpretation. LR and AP contributed to the data analysis and statistical analysis. LR, JW, AP, AA, HM, VC, LQ, and PB contributed to the development and revision of the manuscript, and provided final approval of the submitted content.

Data-sharing statement

Data are available in excel format upon request by email to the corresponding author.

References

1. Camus V, Rossi C, Sesques P, et al. Outcomes after first-line immunochemotherapy for primary mediastinal B-cell lymphoma: a LYSA study. Blood Adv. 2021;5(19):3862-3872.
2. Kuruvilla J, Pintilie M, Tsang R, Nagy T, Keating A, Crump M. Salvage chemotherapy and autologous stem cell transplantation are inferior for relapsed or refractory primary mediastinal large B-cell lymphoma compared with diffuse large B-cell lymphoma. Leuk Lymphoma. 2008;49(7):1329-1336.
3. Crombie JL, Nastoupil LJ, Redd R, et al. Real-world outcomes of axicabtagene ciloleucel in adult patients with primary mediastinal B-cell lymphoma. Blood Adv. 2021;5(18):3563-3567.
4. Schubert ML, Bethge WA, Ayuk FA, et al. Outcomes of axicabtagene ciloleucel in PMBCL compare favorably with those in DLBCL: a GLA/DRST registry study. Blood Adv. 2023;7(20):6191-6195.
5. 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.
6. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390.
7. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117(19):5019-5032.
8. Laurent C, Baron M, Amara N, et al. Impact of expert pathologic review of lymphoma diagnosis: study of patients from the French Lymphopath Network. J Clin Oncol. 2017;35(18):2008-2017.
9. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma: efficacy and safety from the phase II CheckMate 436 study. J Clin Oncol. 2019;37(33):3081-3089.
10. 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):3059-3067.
11. Zinzani PL, Pellegrini C, Chiappella A, et al. Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: results from a phase 2 clinical trial. Blood. 2017;129(16):2328-2330.
12. Zinzani PL, Thieblemont C, Melnichenko V, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma: final analysis of KEYNOTE-170. Blood. 2023;142(2):141-145.
13. Bröckelmann P, Bühnen I, Zijlstra J, et al. Abscopal effect of radiotherapy and nivolumab in relapsed or refractory Hodgkin lymphoma: pre-planned interim analysis of the international GHSG phase II AERN trial. HemaSphere. 2022;6:104-105.
14. Lakhotia R, Roschewski M. Circulating tumour DNA in B-cell lymphomas: current state and future prospects. Br J Haematol. 2021;193(5):867-881.