haematologica
Journal of the Ferrata Storti Foundation

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

by Loic Renaud, Juliette Wencel, Arnaud Pages, Ahmad Al Jijakli, hannah Moatti, Laurent Quero, Vincent Camus, and Pauline Brice

Received: December 15, 2023.
Accepted: April 22, 2024.

Citation: Loic Renaud, Juliette Wencel, Arnaud Pages, Ahmad Al Jijakli, hannah Moatti, Laurent Quero, Vincent Camus, and Pauline Brice. Nivolumab combined with brentuximab vedotin with or without mediastinal radiotherapy for relapsed/refractory primary mediastinal large B-cell lymphoma. Haematologica. 2024 May 2. doi: 10.3324/haematol.2023.284689 [Epub ahead of print]

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

Loic Renaud[1], Juliette Wencel[2], Arnaud Pagès[3], Ahmad AL JIJAKLI[4], Hannah Moatti[5], Laurent Quero[6, 7], Vincent Camus[8], Pauline Brice[2].

[1]Gustave Roussy, Université Paris-Saclay, Département d'Hématologie, 94800 Villejuif, France.
[2]AP-HP, Hôpital Saint-Louis, Hemato-oncologie, DMU DHI ; Université de Paris, F-75010 Paris, France.
[3]Gustave Roussy, Université Paris-Saclay, Service de Biostatistique et d'Epidémiologie, et Inserm, CESP U1018, Oncostat, 94800 Villejuif, France
[4]Centre Hospitaliser d'Argenteuil, service d'hématologie, Argenteuil, France.
[5]Centre Hospitalier Annecy-Genevois, service d'hématologie, Epagny-Metz-Tessy, France.
[6]AP-HP, Hôpital Saint-Louis, service de Cancérologie-Radiothérapie, Paris, France.
[7]INSERM U1160, Université Paris Cité, Paris, France.
[8]Centre Henri Becquerel, Département d'Hématologie et INSERM U1245, Rouen, France.

Short running title: BV-Nivolumab +/- Radiotherapy for RR PMBL.

Key words: Primary mediastinal large B-cell lymphoma, Mediastinal grey zone lymphoma, nivolumab, brentuximab vedotin, radiotherapy.

Author Contributions: L.R, J.W and P.B contributed to data collection. L.R, J.W, A.P and P.B contributed to data analysis and interpretation. L.R and A.P contributed for data analysis and statistical analysis. L.R, J.W, A.P, A.A, H.M, V.C, L.Q, PB. Contributed development and revision of the manuscript, and provision of final approval of the submitted content

Disclosures: LR: Honorarium: Astra Zeneca, Jansen, Takeda, Travel fees : Kite, a Gilead Company LQ: Honorarium: Ipsen, Sanofi, Merck Serono, Travel fee: Ipsen, Research funding : Astra Zeneca VC: Honorarium : Kite, a Gilead Company, Bristol Myers Squibb, Novartis, Incyte, Kyowa Kirin, Abbvie, Ideogen, Takeda. Travel fees : Pfizer, Kite, a Gilead Company, Bristol Myers Squibb, Novartis; Research funding paid to institution : Astra Zeneca, Bristol Myers Squibb, Novartis, Ideogen CT : Amgen: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; Roche: Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses, Research Funding; Novartis: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; Janssen: Honoraria, Other: Travel Expenses; Takeda: Honoraria, Membership on an entity's Board of Directors or advisory committees; BMS/Celgene: Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses, Research Funding; Incyte: Honoraria, Membership on an entity's Board of Directors or advisory committees; Kite: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; Cellectis: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; Hospira: Research Funding; Gilead Sciences: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; AbbVie: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; Bayer: Honoraria; Paris University, Assistance Publique, hopitaux de Paris (APHP): Current Employment; Kyte, Gilead, Novartis, BMS, Abbvie, F. Hoffmann-La Roche Ltd, Amgen: Honoraria J.W, H.M, A.P, A.A, P.B have no financial interest to report

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

Corresponding author:

Loïc Renaud (MD), Department of Hematology, Gustave Roussy, 14 Rue Edouard Vaillant, 94805 Villejuif,

Telephone number: +33 1 42 11 42 29, email: loic.renaud@gustaveroussy.fr

Nb of words: 1493/1500

Article summary:

- R/R PMBL responds poorly to salvage therapy, promising results of the BV-nivolumab combination have been reported with a significant proportion of responding patients receiving subsequent auto or allo-SC.
- With a 3-year PFS of 65%, Bv-nivo +/- radiotherapy is an effective option with sustained responses.

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, CAR-T cells have been proposed for R/R PMBL, with an ORR of 78% and a 2-year PFS rate of 54% to 64%(3,4). Similar results have been reported with the combination of Nivolumab and brentuximab-Vedotin (BV-nivo), 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-nivo received subsequent autologous (auto, n=6) or allogeneic (allo, n=6) hematopoietic stem cell transplantation (SCT), and only four patients remained progression-free without SCT. Nivolumab is FDA-approved as single agent since 2016 for the treatment of patients with classical Hodgkin lymphoma (cHL) who have relapsed or progressed after auto-SCT, but is still unapproved for PMBL patients. Pembrolizumab is FDA-approved since 2018 as single agent for r/r PMBL after two or more prior lines of treatment. Brentuximab-Vedotin is curently FDA-approved for six indications including cHL, but is still unapproved for PMBL patients. Here, we report the results of 11 patients, two of them who were enrolled in the CheckMate436 study, and 9 who were treated with BV-nivo in a real-life, off-label compassionate use. None received auto or allo-SCT, but five received consolidation radiotherapy (CRT). After a median follow-up of 44.0 months, median PFS and OS were not reached, 3-years progression-free survival (PFS) and OS were 65 and 71% respectively. These data suggest that BV-nivo, eventually 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) and MGZL (n=1) were treated with BV-nivo at St Louis Hospital. PMBL diagnosis was performed by expert hematopathologists following the diagnostic criteria established by previous pathologic 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 Brentuximab-Vedotin 1.8 mg/Kg intravenously every 21 days as previously reported(9). Response assessment was performed using PET-CT and CT-scans according to 2014 Lugano criteria(10). Best ORR (BORR) was defined as the proportion of patients achieving complete response (CR) or partial response (PR) during treatment. Overall survival (OS) and PFS were estimated using Kaplan-Meier method. The study was conducted in accordance with the declaration of Helsinki; institutional board approval was obtained. All patients received written information.

Baseline Patient characteristics are presented in Table 1. Median age was 33 (19-82) years. Patients had received a median of 2(1-6) previous lines of therapy, including one patient treated in first relapse, one patient who received an auto-SCT, and 9 patients were considered to have refractory disease to the most recent therapy.

After a median follow-up of 44 (9.6 - 58.5) months, median PFS and OS were not achieved, 3-years PFS and OS rates were 65% and 71% respectively (Figure 1A, Figure 1B). Patients received a median of 5(2-10) cycles. After four cycles, the ORR was 64% including 36% (n=4) CR and 27 % (n=3) PR, three patients were in stable disease (SD) and one patient was in progressive disease (PD). One patient with MGZL obtained a persistent CR with a 22.3 months follow-up. For the ten

patients with PMBL, the ORR after 4 cycles was 60% and the 3 years PFS was 64%. For the six PMBL with localized disease, five underwent radiotherapy, the ORR after 4 cycles was 67% the 3-y PFS was 83%. For the three disseminated PBML, ORR was 33%, the 3-y PFS was: 67% (Table 2). Two patients achieved SD including one with durable SD (no relapse event after 58 months of follow-up) and one who was lost to follow-up. Only one patient progressed on therapy and died from lymphoma eight months later. None of the patients received consolidation with auto or allo-SCT. Of the six patients with localized disease, five (all PMBL) received mediastinal involved-site radiotherapy (ISRT). Among them, none had received prior radiotherapy, one had received prior ASCT, two were disseminated at diagnosis (stage III and IV), but all were localized (mediastinal stage IE or I) at relapse prior to initiation of BV-nivo. These patients received a radiation dose of 30 Gy (n=3), 36 Gy (n=1) and 50 Gy (n=1), 5 fractions of 2 Gy per week. Status of the disease before CRT was: CR (n=3), PR (n=1) and SD (n=1), after 4-6 cycles of BV-nivo (Figure 1C). None received subsequent cycles of BV-nivo after CRT.

Among patients who did not received CRT, two achieved CR with 8-10 cycles of BV-nivo without consolidation. One of them was still in CR after 44 months of follow-up, while the second died of cardiac complication at age 86, in CR, 33 months after the start of treatment.

Treatment tolerance was good with ~~a~~ limited number of cycles administered; one patient developed peripheral neuropathy grade 2. 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 spontaneous favourable evolution without intervention. No significant acute toxicity was observed after CRT.

After a median follow-up of 44 months, our report of a monocentric use of BV-nivo for the treatment of R/R PMBL and MGZL was effective, in line with previous reports (CheckMate 436(5)). We reported 3-year PFS and OS rates of 65% and 71%, respectively, which testified of a sustained efficacy of this strategy as a salvage treatment. Safety data was consistent with previous reports using this combination (5).

The main difference between our report and the CheckMate436 trial is in the consolidation after BV-nivo. In the CheckMate436 trial, 40% of patients underwent transplantation, including 20% auto-SCT and 20% allo-SCT, while no patients underwent transplantation in our study. In contrast, 23% of patients in the CheckMate436 trial received non-palliative CRT, while 50% of PMBL patients in our report received CRT. The results were excellent for the five patients with relapsed localised PMBL, who were treated with BV-nivo for 4 to 6 cycles, 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 progression-free survival (PFS) of 29% after a first relapse (1,2), these results are consistent with the CheckMate436 trial and suggest a better efficacy than chemotherapy for this population. However, the administration of 4 to 6 cycles followed by CRT is a less restrictive and more cost-effective option and could be discussed for these patients from the first relapse, especially in the rare case of elderly patients, although validation in a larger subset is needed, especially for MGZL patients.
While the median number of cycles was the same in both series (5 cycles), the maximum number of cycles administered was 10 in our cohort, compared to 22 for Nivo and 20 for BV, with 4

patients still on treatment in theCheckMate436 trial. Given the good results in both cohorts, a lower number of cycles doesn't seem to affect the results, especially in patients receiving CRT.
As the CheckMate436 study, these results compare favorably in this setting to BV monotherapy with an ORR of 13% (2/12)(11) or to PD-1 inhibition alone with an ORR of 41.5%(12), but in the absence of a comparative clinical trial, ~~it is~~ it's 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 abscopal effect in several tumor subtypes, including Hodgkin's lymphoma (13). The involvement of this synergistic mechanism may partly explain the good results in patients treated with BV-nivo followed by CRT, and the conversion of PR or SD to CR 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 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 cfDNA may be of particular interest for this specific population (14).
Limitations of our study are inherent to monocentric 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, follow-up is not long enough to assess the late toxicity of radiotherapy in a young population, in particular valvular and coronary calcifications.
According to our data and in line with the CheckMate436 trial, BV-nivo 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 auto or allo-SCT, especially in local relapse due to its favourable safety profile and durability of responses obtained. An open question is the possibility of using this combination as a bridge to CAR-T-cells, which has not been reported to our knowledge.

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. S203: 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 of Haematol. 2021;193(5):867-881.

Characteristics	Overall cohort (n=11)	PMBL patients (n=10)	Checkmate 436 (n=30)
Female, n (%)	4 (36)	3 (27)	17 (56,7)
Age, years			
median (range)	33 (19-82)	34 (19-82)	36 (19 – 83)
Age < 65	10 (91%)	9 (90%)	29 (97)
Disease stage at initial diagnosis, n (%)			
I-II	4 (36)	3 (30)	16 (53)
III-IV	7 (64)	7 (70)	13 (44)
Extranodal localizations at diagnosis	6 (55)	5 (50)	UK
Disease stage at inclusion, n (%)			
I	6 (55)	6 (60)	UK
II	0	0	UK
III	2 (18)	2 (20)	UK
IV	1 (9)	1 (10)	UK
Unknown	2 (18)	1 (10)	UK
Prior lines of systemic therapy, median (range)	2 (1-6)	2 (1 -3)	2 (2-5)
Patients receiving only 1 line before inclusion	1 (9)	1 (10)	0
First-line therapy, n (%)			
R-CHOP	4 (36)	3 (30)	8 (26,7)
R-CHOP 14	1 (9)	1 (9)	UK
R-CHOP 21	3 (27)	2 (18)	UK
R-mini CHOP	1 (9)	1 (9)	0
R-ACVBP	5 (45)	5 (50)	UK
R-EPOCH	1 (9)	1 (10)	9 (30)

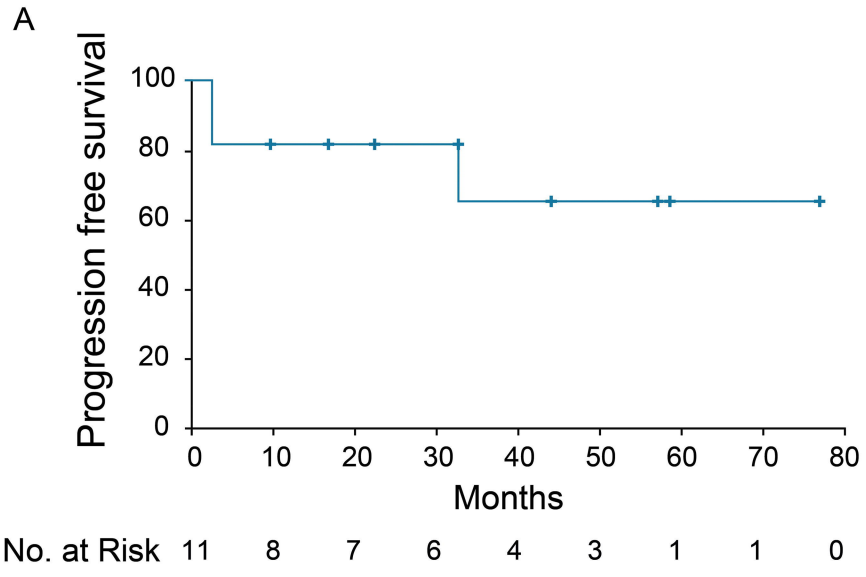
Other, n (%)	0	0	13 (43,3)
Prior Rituximab	11 (100)	10 (100)	30 (100)
Disease Status, n (%)			
Refractory	9 (82)	8 (80)	20 (67)
Relapsed	2 (18)	2 (20)	6 (20)
Best response to most recent systemic therapy, n (%)			
CR	2 (18)	2 (20)	0
PR	0	0	6 (20)
Stable disease	4 (36)	4 (40)	6 (20)
Relapse/progressive disease	5 (45)	4 (40)	16 (53)
Unknown	0	0	2 (7)
Prior ASCT, n (%)	1 (9)	1 (10)	4 (13)
Prior radiotherapy, n (%)	1 (9)	1 (10)	3 (27)

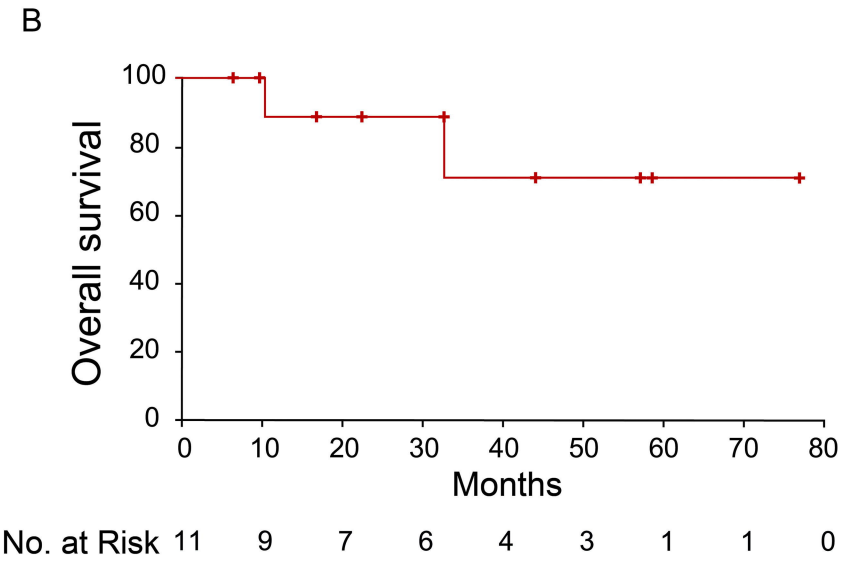
Table 1: Baseline Demographic and Clinical Characteristics. PMBL: primary mediastinal large B-cell lymphoma, CR: complete response, PR: partial response, ASCT: autologous stem cell transplantation, UK: unknown

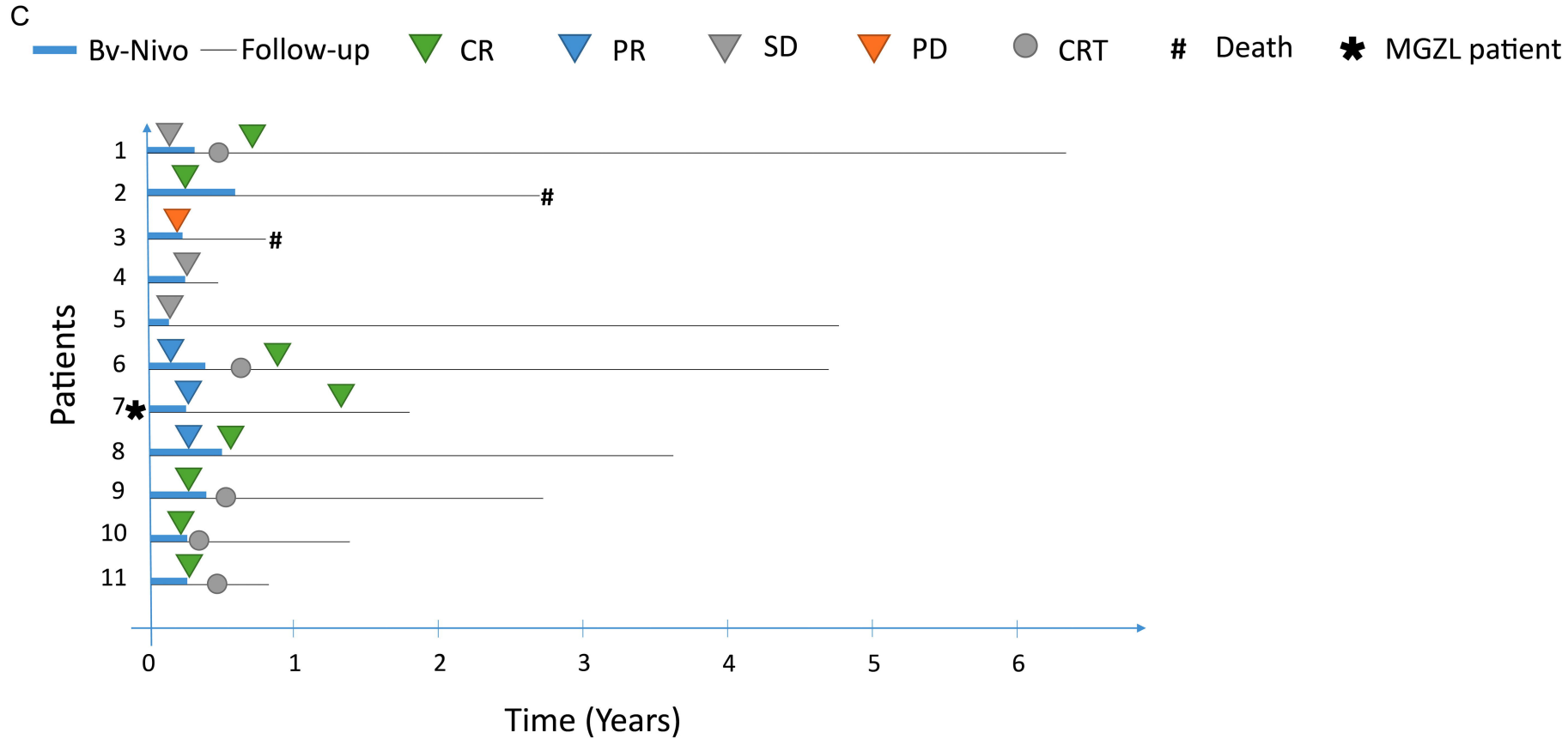
Characteristics	Overall cohort (n=11)	PMBL patients (n = 10)	PMBL patients excluding CM436 pts (n=8)	Localized PMBL patients (n=6)	Localized PMBL patients Receiving CRT As consolidation (n=5)	Disseminated PMBL patients (n= 3)
ORR (%) post C4 and before CRT [IC95%]	64 [31-89]	60 [26-88]	63 [24-91]	67 [22-96]	80 [28-99]	33 [8-90]
CR (%) post C4 and before CRT [IC95%]	36 [11-69]	40 [12-73]	38 [9-76]	50 [12-88]	60 [15-95]	33 [8-90]
Best ORR (%) [IC95%]	73 [39-93]	70 [35-93]	63 [24-91]	83 [36-99]	100 [48-100]	33 [8-90]
3 y PFS (%) [IC95%]	65 [32-88]	64 [31-88]	75 [41-93]	83 [44-97]	100	67 [21-94]
OS (%) [IC95%]	71 [34-92]	70 [33-92]	83 [44-97]	80 [38-96]	100	100

Table 2: Responses of the overall cohort and by patient category including response after 4 cycles and before radiotherapy (ORR) and best response (BORR). PMBL: primary mediastinal large B-cell lymphoma, CR: complete response, PFS: progression free survival, OS: overall survival.

Figure 1**: Time to response, duration of response and Kaplan–Meier Estimates of Efficacy End Points.** Progression free survival (A) and overall survival (B). Symbols represent censored observations. Waterfall plot (A): Each bar represents one patient. CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, CRT: received consolidation radiotherapy, MGZL: mediastinal grey zone lymphoma


A
Progression free survival
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80
Months
No. at Risk 11 8 7 6 4 3 1 1 0


B
Overall survival
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80
Months
No. at Risk 11 9 7 6 4 3 1 1 0


C
Bv-Nivo
Follow-up
CR
PR
SD
PD
CRT
Death
MGZL patient
Patients
1
2
3
4
5
6
7
8
9
10
11
0 1 2 3 4 5 6
Time (Years)