

CheckMate 436: extended follow-up from the phase 2 study investigating nivolumab plus brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma

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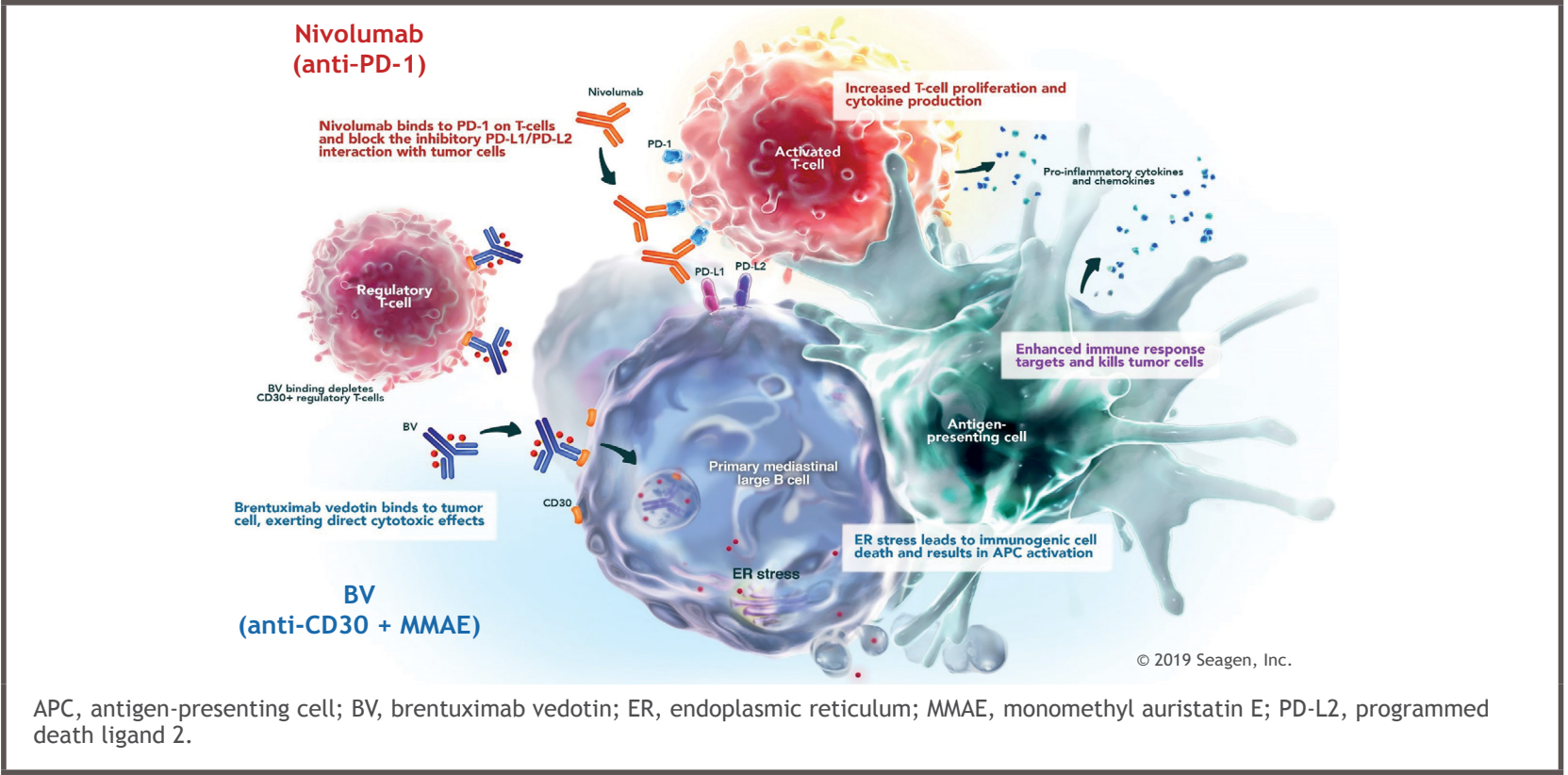
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Introduction

- Patients with relapsed/refractory (R/R) primary mediastinal B-cell lymphoma (PMBL) have poor outcomes¹
- The overall response rate (ORR) to salvage chemotherapy is approximately 25% and 2-year overall survival (OS) after diagnosis of R/R disease is 15%¹
- With no standard of care for R/R PMBL, new treatment strategies are urgently needed
- Gene expression profiling has shown that PMBL and classical Hodgkin lymphoma (cHL) share many molecular and genetic features including CD30 expression and abnormalities on chromosome 9p, which expresses programmed death ligand 1 (PD-L1)²
- PD-L1 binds programmed death-1 (PD-1) on T cells, causing evasion of the antitumor immune response (Figure 1)³

Figure 1. Simultaneous targeting of PD-1 and CD30 by nivolumab and BV



- The efficacy and safety of nivolumab, which targets PD-1, in combination with BV, which targets CD30, have been evaluated in phase 1/2 studies of R/R cHL^{3,4}
- In R/R PMBL, BV and PD-1 blockade are associated with ORRs of 13% and 48%, respectively^{5,6}
- Considering the common features between PMBL and cHL, the CheckMate 436 study (NCT02581631) was designed to evaluate the efficacy and safety of nivolumab + brentuximab vedotin in patients with R/R non-Hodgkin lymphoma
- The primary analysis of CheckMate 436 (median follow-up 11.1 months) showed an ORR of 73% and complete remission (CR) rate of 37% in a cohort of patients with R/R PMBL⁷

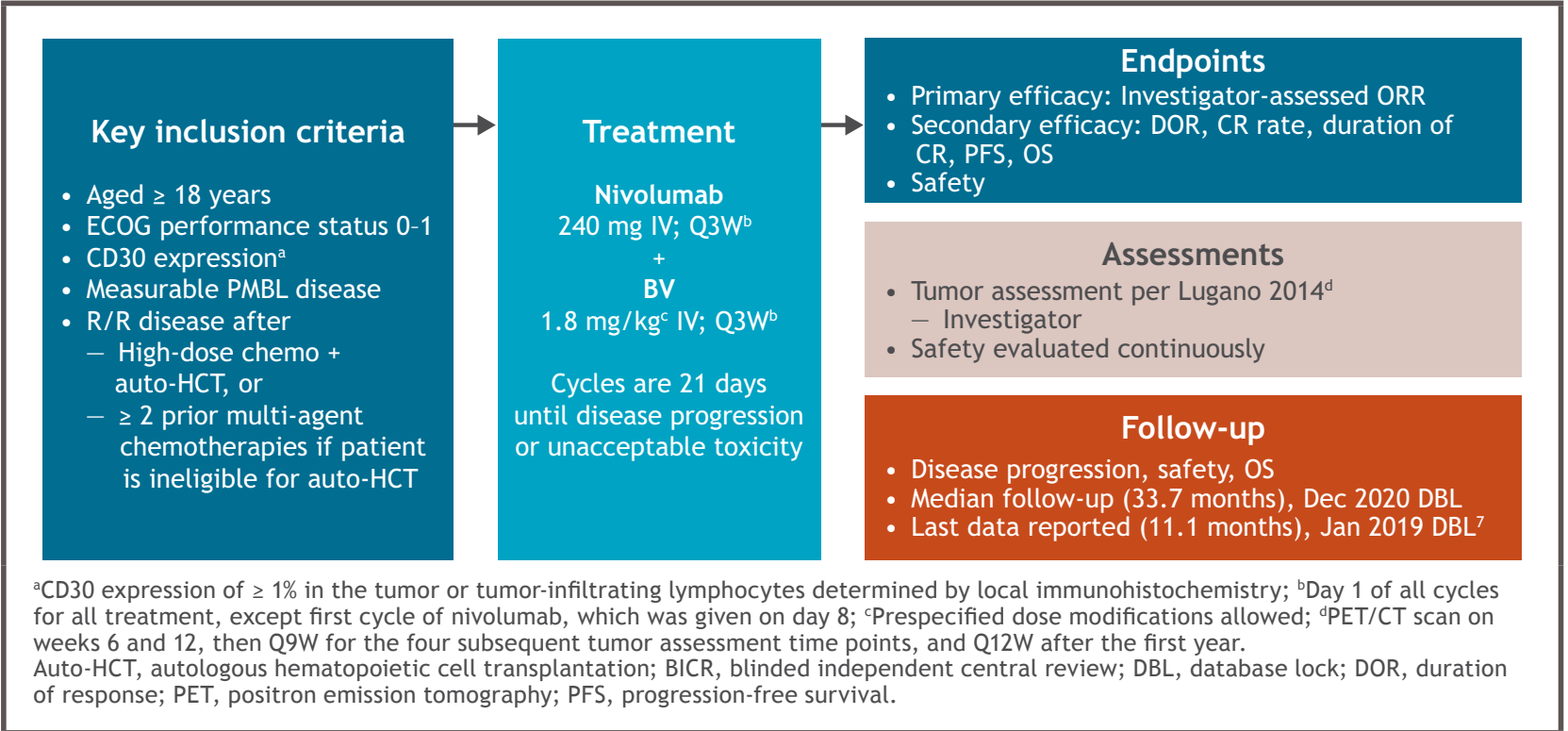
Objective

- To report the extended follow-up data from CheckMate 436 in a cohort of patients with R/R PMBL (median follow-up 33.7 months)

Methods

- CheckMate 436 is an open-label, phase 1/2 study (Figure 2) that enrolled patients with various subtypes of R/R non-Hodgkin lymphoma, including PMBL

Figure 2. Phase 2 CheckMate 436: PMBL cohort (NCT02581631)



Results

Patients

- At database lock (December 2020), among 30 patients enrolled in the R/R PMBL cohort of CheckMate 436, the median age was 36. Patients received a median of 2 prior lines of systemic therapy (Table 1)
- At database lock (median follow-up of 33.7 months, interquartile range [IQR] 12.0-39.5), all 30 patients had discontinued treatment (Table 2)
 - The most common reason for discontinuation was maximum clinical benefit, experienced by 13 patients, 12 of whom received subsequent HCT
- In all, 29 patients received nivolumab + BV, and 1 patient received BV only
 - Patients received a median of 5 doses of nivolumab (range 1-35) and 5 of BV (range 1-20)
 - One patient received BV on day 1 cycle 1 but discontinued before the scheduled first dose of nivolumab

Table 1. Baseline demographics and clinical characteristics

Characteristic	Patients (n = 30)
Age, median (range), years	36 (19-83)
Female	17 (57)
Disease stage at initial diagnosis,* n (%)	
I-II	16 (53)
III-IV	13 (43)
Disease status at enrollment, n (%)	
Relapsed	7 (23)
Refractory	18 (60)
Relapsed and refractory ^b	5 (17)
Prior lines of systemic therapy, median (range) ^{c,d}	2 (2-5)
First-line therapy, ^e n (%)	
R-CHOP	8 (27)
R-EPOCH	9 (30)
Other	13 (43)
Prior rituximab, n (%)	30 (100)
Prior auto-HCT, n (%)	4 (13)

*Disease stage at initial diagnosis not reported for one patient; ^bRelapse after prior line of therapy and no response to most recent prior therapy; ^cThese data are from database lock January 2019; ^dR-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH, rituximab + etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin.

Table 2. Patient disposition

Disposition, n (%)	Patients (n = 30)
Patients still on treatment	0
Discontinued treatment	30 (100)
Maximum clinical benefit	13 (43)
Received stem cell transplant	12 (40)
Disease progression	8 (27)
Study drug toxicity	3 (10)
AEs unrelated to study drug	2 (7)
Patient request to discontinue	1 (3)
Other	3 (10)

AE, adverse event.

Efficacy

- The ORR was 73% (90% CI, 54-88), with 11 patients each achieving a best overall response (BOR) of CR and partial remission (Table 3)
- The median DOR was 31.6 months (Table 4). Median duration of CR was not reached
- Median time to first response was 1.3 months and median time to CR was 3.2 months (Figure 3)
- Four patients remained progression-free in follow-up without consolidation for 137+, 273+, 372+, and 606+ days after the last dose of nivolumab + BV (Figure 3)
- Subsequent radiotherapy for treatment of tumors was administered to 8 patients, 6 of whom also received HCT (1 before and 5 after radiotherapy)
- Among the 22 responders, 12 (55%) received subsequent HCT (Table 5)

Table 3. BOR per investigator

BOR, n (%)	Patients (n = 30)
Objective response rate ^a	22 (73)
90% CI	54-88
CR	11 (37)
PR	11 (37)
Stable disease	3 (10)
Relapsed or progressive disease	3 (10)
Unable to determine (death prior to disease assessment)	2 (7)

Assessment was per Lugano 2014. ^aCR + PR values may not total ORR due to rounding. PR, partial remission.

Table 4. DOR and time to response

Assessment	Time, months
Duration of follow-up, median (IQR)	33.7 (12.0-39.5)
Time to response, median (IQR)	
First response	1.3 (1.3-1.6)
CR	3.2 (2.5-5.6)
DOR, median (95% CI)	31.6 (23.3-NA)
Duration of CR, median (IQR)	NR

NA, not available; NR, not reached.

Figure 3. Patient response to treatment

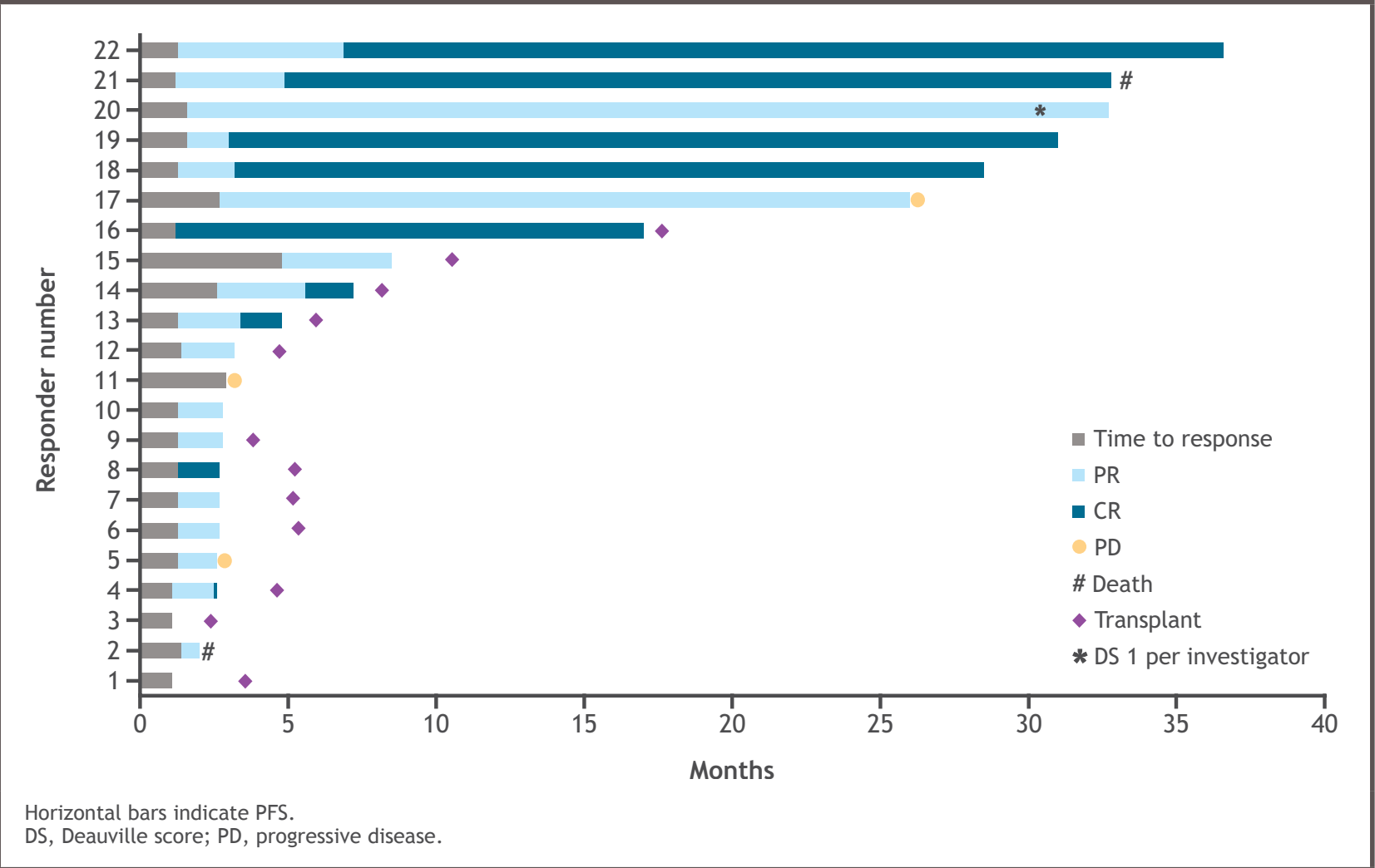


Table 5. Subsequent stem cell transplant therapy

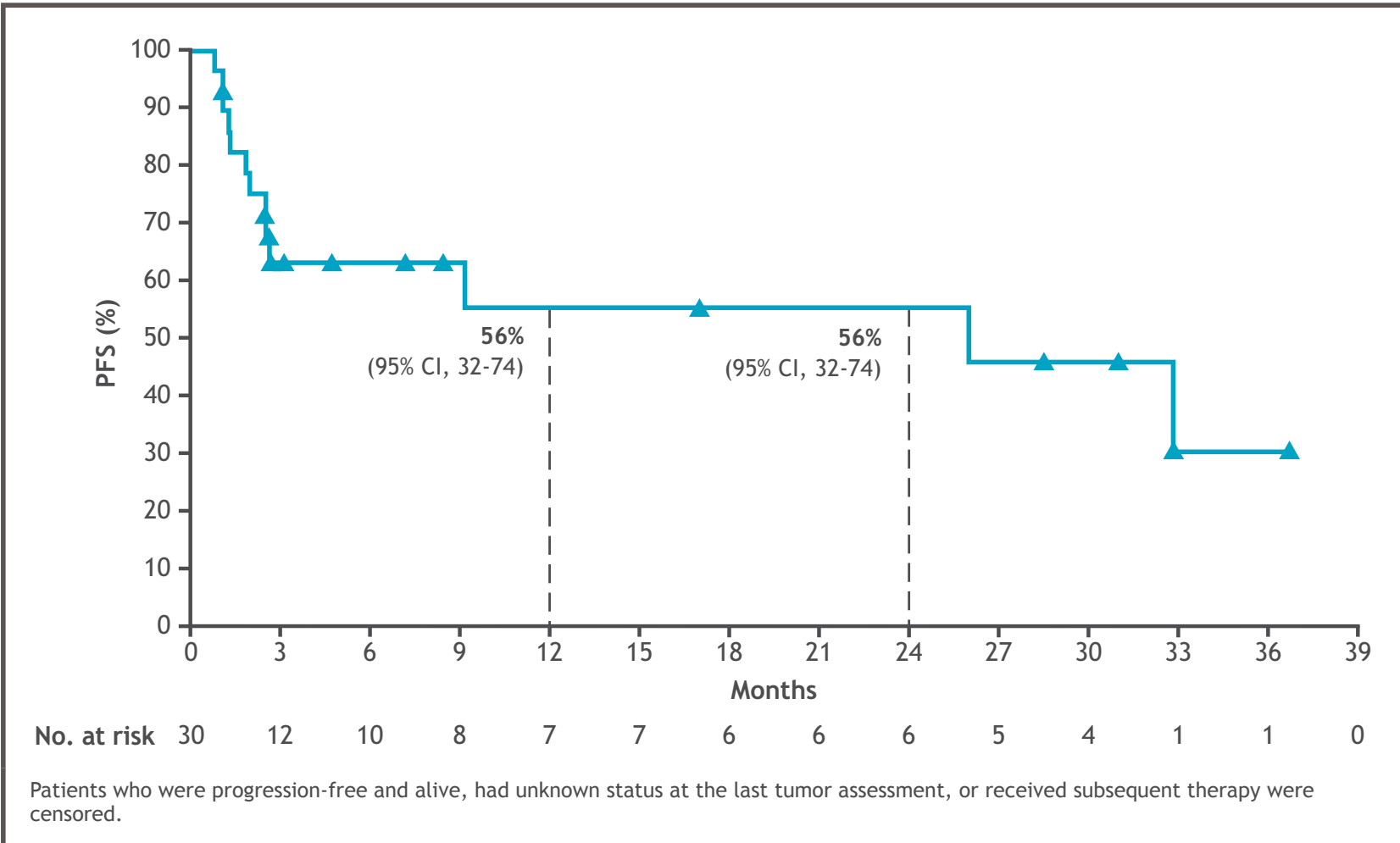
Subsequent transplant and response	Autologous HCT	Allogeneic HCT
Patients receiving transplant therapy, n	6	6
Response at the time of transplant, n (%)		
CR	3 (50)	3 (50)
Non-CR	3 (50)	3 (50)
Response post-transplant,* n (%)		
100 days		
CR	6 (100)	5 (100)
6 months		
CR	6 (100)	5 (100)
1 year		
CR	5 (83)	5 (100)
Non-CR	1 (17)	0
2 years		
CR	4 (100)	5 (100)
3 years		
CR	2 (67)	2 (100)
Unable to determine/not applicable	1 (33)	0

*Percentages calculated based on number of patients who reached the post-transplantation assessment.

Progression-free survival

- Median PFS was 26.0 months (Figure 4)
- PFS rate was 56% at 12 months and 24 months

Figure 4. PFS per investigator



Overall survival

- Median OS was not reached
- OS rate was 79% at 12 months and 76% at 24 months (Figure 5)

Figure 5. OS

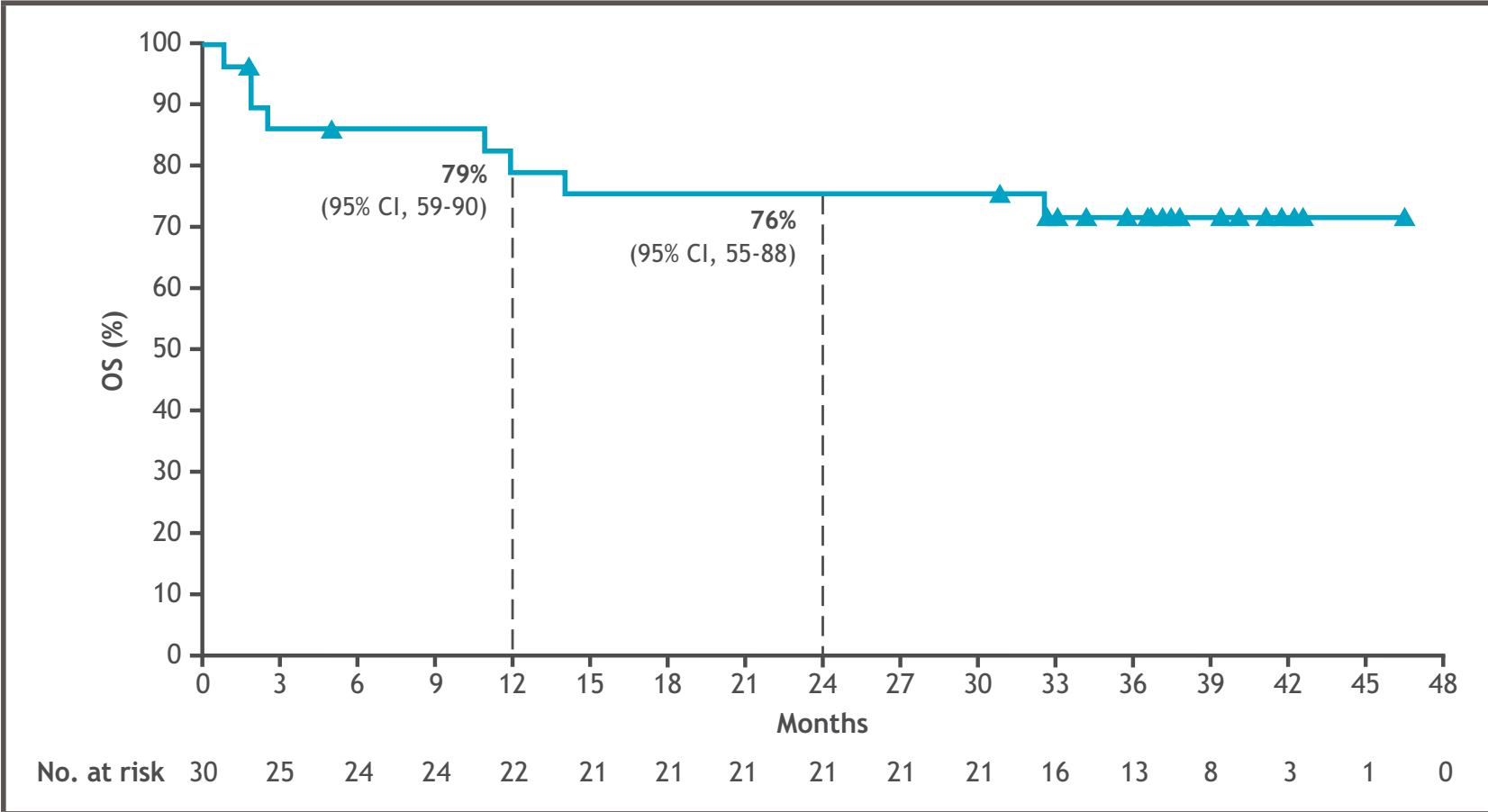


Table 6. TRAEs in ≥ 10% of patients

Event (n = 30)	Any grade	Grade 3/4
Patients with TRAEs, n (%)	25 (83)	16 (53)
Neutropenia	9 (30)	9 (30)
Peripheral neuropathy	8 (27)	3 (10)
Thrombocytopenia	4 (13)	3 (10)
Rash	4 (13)	1 (3)
Peripheral sensory neuropathy	4 (13)	0
Hyperthyroidism	4 (13)	0
Pyrexia	3 (10)	0
Patients with treatment-related SAEs, n (%)	4 (13)	2 (7) ^a
Colitis	1 (3)	1 (3)
Maculopapular rash	1 (3)	1 (3)
Immune-mediated hepatitis	1 (3)	1 (3)
Fall	1 (3)	0
Acute kidney injury	1 (3)	0
Pyrexia	1 (3)	0

^aTwo patients experienced three grade 3/4 treatment-related SAEs; 1 had grade 3 colitis and maculopapular rash and 1 had grade 4 immune-mediated hepatitis. SAE, serious adverse event.

Table 7. TRAEs leading to discontinuation

Event (n = 30)	Any grade	Grade 3/4	Grade 5
Patients with an event, n (%)	6 (20)	5 (17)	0
Peripheral neuropathy	4 (13)	3 (10)	0
Immune-mediated hepatitis	1 (3)	1 (3)	0
Pulmonary toxicity	1 (3)	0	0
Rash	1 (3)	1 (3)	0

Conclusions

- For patients with R/R PMBL, nivolumab plus BV treatment resulted in an investigator-assessed ORR of 73%, with a 37% CR rate
 - After a median follow-up of 33.7 months, median PFS was 26.0 months, median DOR was 31.6 months, and median OS was not reached
- Treatment-related AEs were consistent with the safety profiles of nivolumab and BV treatment alone
 - The most frequently reported treatment-related AEs were neutropenia (30%) and peripheral neuropathy (27%)
 - There were no treatment-related deaths
- Four patients remained progression-free without consolidation for 137+, 273+, 372+, and 606+ days after the last dose of treatment with nivolumab plus BV
- The combination of nivolumab and BV may be synergistic and is highly active in patients with R/R PMBL

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Disclosures

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