Outcomes of refractory or relapsed Hodgkin lymphoma patients with post-autologous stem cell transplantation brentuximab vedotin maintenance: a French multicenter observational cohort study

The majority of patients with Hodgkin lymphoma (HL) are cured with first-line therapy, but 10-20% of patients still experience refractory or relapsing (R/R) disease. The current standard of care for R/R HL is salvage chemotherapy, followed by autologous hematopoietic stem cell transplantation (ASCT) and brentuximab vedotin (BV) maintenance, based on the results of AETHERA. This study demonstrated that R/R HL patients with refractory disease, or experiencing early (less than 12 months from chemotherapy completion) or extranodal relapse (at any time) have a lower risk of progression or death when receiving BV maintenance compared to placebo.[1,2] These results led to the approval of post-transplant BV maintenance for high-risk R/R HL patients in 2017.

In AMAHRELIS (Adcetris Maintenance after Autologous stem cell transplantation in Hodgkin lymphoma: a Real-Life Study), a retrospective nationwide French cohort study, we investigated the real-life outcome of patients with R/R HL who received post-transplant BV maintenance. Notably, most patients received BV during salvage, in contrast to the AETHERA cohort in which prior BV exposure represented an exclusion criterion. We also performed a central review of 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging at relapse and before transplantation, by two independent experts, with a complete evaluation of 79% of the cohort.

We included patients 16 years and older with R/R HL who received at least two infusions of BV maintenance after ASCT. Patients who received BV for progression after transplant were excluded. Among 1,134 patients included in the French Society of Bone Marrow Transplantation databases who underwent ASCT for R/R HL between 2012 and 2017 in France, we received responses for 835 patients (73%) from 25 centers. Finally, 115 patients met eligibility criteria for our study (Figure 1A).

The patients' characteristics are summarized in Table 1. The median age was 34 years (range, 16-68 years), and 62 (54%) were male. Sixty-nine (60%) patients had stage III or IV disease at diagnosis. ABVD was the first line of treatment for 64 patients (56%), escalated BEACOPP was administered to 42 (37%) and nine patients received other regimens. Fifty (43%) patients had primary refractory disease, 32 (28%) experienced early relapse (before 12 months) and 33 (29%) relapsed later than 12 months. At relapse, histological confirmation was obtained for half of the patients. Sixty-seven (58%) patients had stage III-IV disease, 19 (17%) had B symptoms and extranodal disease occurred in half of them. A BV-based salvage regimen was used in 34 (29.5%) patients during the first salvage and 29 of them (85%) achieved a complete response (CR), while 81 did not receive BV and 24 (29%) of them achieved a CR. The difference in CR rate between patients who did or did not receive a BV-based salvage regimen was highly significant (Figure 1B). Among 57 patients who did not receive a BV-based regimen at first salvage, 46 (81%) were given BV during the second salvage and 37 of them (80%) achieved CR. Pre-transplant FDG-PET status was reported for 111 (97%) patients and among them, 93 (84%) were reported to be in CR. Among 91 patients (79% of the cohort) with centrally reviewed FDG-PET data, 82.4% (75/91) achieved metabolic CR (defined as a Deauville score 1-3) before ASCT. According to AETHERA, 95% of patients met inclusion criteria for BV maintenance due to primary refractory disease (43%), early relapse (28%) or extranodal involvement (49%). The mean number of BV injections after ASCT was 11 (range, 3-18), without difference between patients who did or did not receive salvage BV. The median time between ASCT and the first BV maintenance cycle was 70 days (range, 18-223), and 88 (77%) patients were treated within 3 months from ASCT. The main reported adverse event was neuropathy, which occurred in 50 (43%) patients, with complete resolution in half of them. Treatment-related events led to BV maintenance discontinuation in 10% of patients, and included neuropathy (6 patients), infections (3 patients), thrombocytopenia (1 patient), and pancreatitis (1 patient). Neuropathy was more frequent in patients who received pre-transplant BV, without impact on treatment discontinuation rate.

The median follow-up period was 35 months. The 2-year progression-free survival (PFS) and overall survival (OS) for the whole cohort were 75.3% (95% confidence interval: 68.4-84.3%) and 96.4% (95% confidence interval: 94.2%-100%), respectively (Figure 1C, D). Seven patients died: three from disease progression, two from a second cancer (1 acute myeloid leukemia and 1 pancreatic cancer), and two from infection (meningitis due to *Streptococcus pneumoniae* in both cases). The non-relapse mortality rate was 3.5% (4 patients) during the follow-up of our study. During or after BV maintenance, 30 (26%) patients relapsed and among them, 21 (70%) received an immune checkpoint

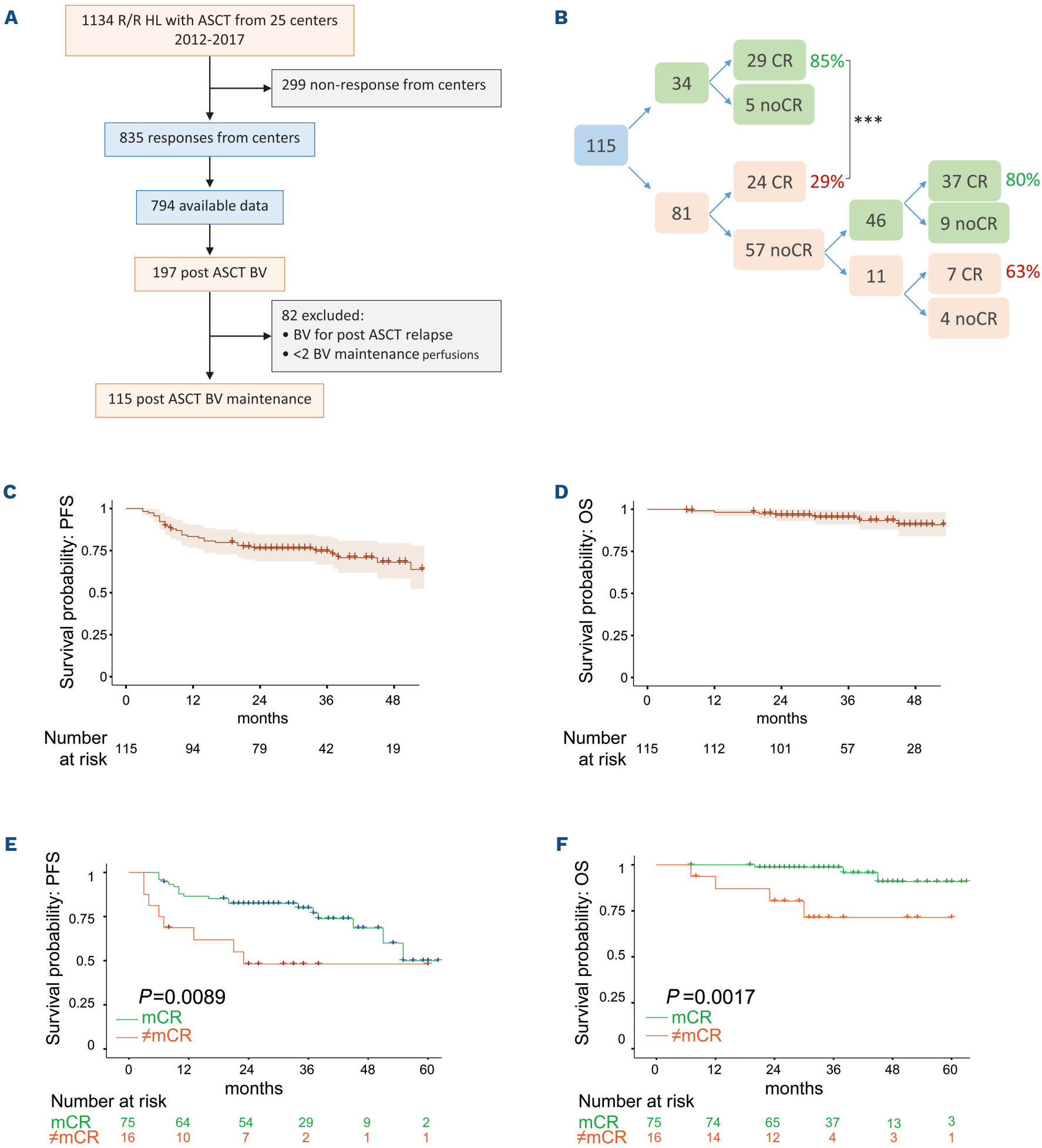

Figure 1. Impact of post-transplant brentuximab vedotin maintenance therapy in real-life practice: the AMAHRELIS study. (A) Flow chart of patients entering the study. (B) Proportion of patients who did or did not receive brentuximab vedotin during the first and second lines of salvage therapy. The percentage of patients in complete remission is indicated. ***P<0.001 (Fisher test). (C, D) Progression-free and overall survival of the 115 patients of the AMAHRELIS cohort since transplant. The 95% confidence intervals are shown by the pale shaded areas on both sides of the survival curves. (E, F) Progression-free and overall survival probabilities dependent on the achievement of a complete metabolic response among 91 patients of the AMAHRELIS cohort after central review of the 18-fluorodeoxyglucose-positron emission tomography data. R/R HL: relapsed-refractory Hodgkin lymphoma; ASCT: autologous hematopoietic stem cell transplantation; BV: brentuximab vedotin; CR: complete remission; noCR: not in complete remission; PFS: progression-free survival; OS: overall survival; mCR: metabolic complete response; ≠mCR: not in metabolic complete response.

blocker of whom 15 (71%) had a response, including 13 CR. Using a univariate Cox regression model, we tested several variables listed in Table 2 for correlation with survival. We found that refractory status, early relapse (less than 12 months), high-risk LYSA prognostic score (primary refractory disease, or early relapse and disseminated disease),[3] and absence of pre-transplant metabolic CR (after central FDG-PET review) were significantly predictive of reduced

Table 1. Characteristics of the 115 patients from the AMAHRELIS cohort and the 165 patients from AETHERA.

	AMAHRELIS N=115		AETHERA N=165	
	N	%	N	%
Male	62	54	76	46
Age in years (mean, min-max)	34	16-68		
Frontline chemotherapy				
ABVD	64	56	119	72
Escalated BEACOPP	42	37	26	16
other	9	8	20	12
Time to relapse				
Primary refractory disease (≤ 3 months)	50	43	99	60
Early relapse (> 3 or ≤ 12 months)	32	28	53	32
Late relapse (> 12 months)	33	29	13	8
Histological confirmation at relapse				
Yes	67	58		
No	48	42		
Stage at relapse				
I-II	45	39		
III-IV	67	58		
Unknown	3	3		
B symptoms at time of relapse				
Yes	19	17		
No	85	74		
Unknown	11	10		
Bulky disease at relapse				
Yes	11	10	47	28
No	90	78		
Unknown	14	12		
Extranodal relapse				
Yes	56	49	54	33
No	54	47		
Unknown	5	4		
LYSA score				
Low	9	8		
Intermediate	38	33		
High	68	59		
Salvage lines (n)				
1	56	49	94	57
2	50	43		
≥ 3	9	8		
Pre-transplant BV				
Yes	81	70		
No	34	30	165	100
Pre-transplant FDG-PET*			Unknown 45	27
No metabolic CR	16	17.6	FDG positive 64	39
Metabolic CR (DS 1,2,3)	75	82.4	FDG negative 56	34
Not centrally reviewed	24	-		100
Time to BV in days (median, min-max)	70	18-223	41	28-49

Data are number and percentage unless otherwise indicated. *Tomography percentages are based on the 91 patients for whom central review of imaging was available. ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; LYSA: Lymphoma Study Association; FDG: 18-fluorodeoxyglucose; PET: positron emission tomography; CR: complete remission; DS: Deauville score; BV: brentuximab vedotin.

Table 2. Univariate and multivariate Cox regression analyses on AMAHRELIS.

		Progression-free survival						Overall survival					
		Univariate			Multivariate			Univariate			Multivariate		
	N	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Sex	115	1	0.51-2	0.98				0.35	0.068-1.8	0.21			
Age*	115	1	0.98-1	0.58				1	0.98-1.1	0.18			
Refractory	115	2.1	1.1-4.2	0.033	0.68	0.29-1.61	0.378	0.59	0.11-3	0.53			
Rel.<12	115	3.4	1.2-9.8	0.021	3.84	0.75-19.69	0.107	2.3	0.28-19	0.44			
ECOG*	94	1	0.63-1.8	0.85				1.4	0.51-3.9	0.5			
Stage*	112	1	0.74-1.4	0.91				1.6	0.69-3.6	0.28			
B-symptoms*	104	0.56	0.19-1.6	0.28				0.62	0.074-5.2	0.66			
Bulk*	101	1.5	0.51-4.2	0.48				1.9	0.22-17	0.55			
Extra.*	110	0.82	0.41-1.6	0.57				0.38	0.074-2	0.25			
Irrad.	112	1.1	0.42-2.8	0.85				2.5	0.48-13	0.28			
AETHERA	104	1.3	0.89-2	0.16				1.9	0.81-4.2	0.14			
LYSA	115	0.32	0.14-0.75	0.008	0.67	0.18-2.54	0.557	0.58	0.11-3	0.51			
Pre-BV	115	0.89	0.43-1.8	0.75				0.6	0.12-2.4	0.43			
Salvage	115	1.1	0.63-1.8	0.84				1.8	0.75-4.3	0.18			
FDG-PET	91	2.9	1.3-6.6	0.013	3.34	1.41-7.9	0.006	7.7	1,7-35	0.0079	7.68	1.71-34.51	0.008

HR: hazard ratio; 95% CI: 95% confidence interval (min-max); *: at the time of relapse; Rel<12: relapse before 12 months; Extra.: extranodal relapse; Irrad: irradiated field relapse; Pre-BV: pre-transplant use of brentuximab vedotin; FDG-PET: results of central 18-fluorodeoxyglucose positron emission tomography analysis with Deauville scores 1, 2 and 3 classified as metabolic complete remission, and scores 4 and 5 classified as no metabolic complete remission.

PFS, while FDG-PET status was the only variable significantly correlated with OS (Table 2). Notably, survival probability was similar between patients who did or did not receive a BV-based regimen before transplantation (Table 2). PFS and OS probabilities at 24 months dependent on significant variables, including LYSA prognostic score, refractory status or relapse timing, are provided in *Online Supplementary Figure S1*. Using a multivariate Cox model for significant variables identified in univariate analysis, we found that only absence of metabolic CR (i.e., Deauville score 4 and 5) before transplantation correlated significantly with reduced PFS and OS (Table 2), which was confirmed by the log-rank test (Figure 1E, F). Currently, evaluation of pre-transplant response to salvage therapy by FDG-PET is recommended,[4–6] although not allowing post-transplant therapeutic guidance. Our results showed that FDG-PET response after salvage is strongly associated with survival, and thus a next step could be to assess FDG-PET-driven post-transplant strategies in clinical trials.

In our study, R/R HL patients treated with post-transplant BV maintenance had a 2-year PFS of 75%, similar to the results of AETHERA, although a direct comparison between AETHERA and our current study would not be correct, since the patients' characteristics were different (Table 1). More patients received first-line escalated BEACOPP in our cohort. Moreover, a majority of patients in our cohort (70%) received off-label BV-based salvage regimens, while patients with pre-transplant exposure to BV were excluded from AETHERA. Notably, pre-transplant BV use had no impact on the completion of BV maintenance in our study, and was associated with a high pre-transplant CR rate (82% metabolic CR rate according to FDG-PET central review). We observed that achievement of metabolic CR before transplant was predictive of improved PFS and OS, also after multivariate analysis. Indeed, recent studies have attempted to increase metabolic CR rate by incorporating BV into initial salvage therapy, including bendamustine, DHAP, ESHAP and gemcitabine.[7–10] In particular, the BRAVE study,[9] a phase II trial of BV-DHAP without post-transplant BV maintenance, resulted in a 2-year PFS rate of 74%, similar to our results. These observations suggest that the optimal timing of BV use, as salvage or as maintenance, remains to be determined in future prospective clinical trials.

Despite accurate risk stratification and generalization of BV use, the prognosis of high-risk R/R HL patients remains a matter of concern. However, the excellent OS results ob-

served in our cohort highlight the generalization of use of efficient salvage therapies in post-transplant relapse. In particular, 70% of patients who relapsed during BV maintenance received an immune checkpoint blocker, and 71% of them responded. We may thus hypothesize that selected patients may benefit from immune checkpoint blockade earlier on, as currently being investigated in clinical trials using immune checkpoint blockers as part of salvage or post-transplant maintenance therapy.[11–13] During first-line salvage, a combination of BV and nivolumab resulted in a CR rate of 61% after four cycles, without unexpected toxicity,[11] and pembrolizumab combined with gemcitabine, vinorelbine and liposomal doxorubicin led to CR in 95% of patients.[12] In the post-transplant setting, consolidation with eight cycles of pembrolizumab resulted in an 82% PFS rate at 18 months.[13] Thus, incorporating immune checkpoint blockers into salvage and/or post-transplant strategies represents a promise for R/R HL patients at high risk of treatment failure or progression which should be investigated further in clinical trials. On the other hand, identification of a subgroup of patients with a more favorable profile in the context of these new therapies may enable omission of consolidative ASCT thereby avoiding the risk of early and late toxicities. In this perspective, FDG-PET-based risk stratification at relapse could benefit from quantitative analysis and the assessment of the dynamic evolution of metabolic tumor volume.[14]

In conclusion, our real-life nationwide study confirmed the improved survival of R/R HL patients receiving post-transplant BV compared to historical cohorts. The exact timing of BV administration, and the place of new therapies such as immune checkpoint blockers in current salvage strategies remain to be determined in future clinical trials.

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AM, PD, PF, DS, TG, CB, MH, GS, RG, DC, AS, LF, JL, AC, LF, SA, MR, NR, BB, MTR, DB, PQ, OC, PB, HG, JT and BD performed the research, BD designed the study, ASC, SK, MM, CA performed the PET review, AM, JT and BD analyzed the data, JT and BD wrote the paper.

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Original data can be made available on reasonable request to the authors.

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