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

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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 study, BD designed the research study, ASC, SK, MM, CA performed the PET review, AM, JT and BD analysed the data, JT and BD wrote the paper.

The majority of patients with Hodgkin lymphoma (HL) are cured with first line therapy, however 10-20% of patients still experience refractory or relapsing (R/R) disease. The current standard of care for R/R HL is a 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.<sup>1,2</sup> These meaningful results led to the approval of post-transplant BV maintenance for high-risk R/R HL patients in 2017.

In the AMAHRELIS (Adcetris maintenance after autologous stem cell transplantation in Hodgkin lymphoma: a real-life study) retrospective nationwide French cohort study, we investigated the real-life outcome of patients with R/R HL having 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 16 years and older R/R HL patients who received at least two infusions of BV maintenance after ASCT. Patients receiving BV for progression after transplant were excluded. Among 1134 patients from 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**).

Patient's characteristics are summarized in **Table 1**. The median age was 34 years (range between 16-68y), and 62 (54%) were male. Sixty-nine (60%) patients were stage III or IV 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, histology confirmation was obtained for half of the patients. Sixty-seven (58%) patients were stage III-IV, 19 (17%) had B symptoms and extranodal disease occurred in half of them. 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 had 24 (29%) CR. The difference in CR rate between patients receiving or not BV-based salvage regimen was highly significant (**Figure 1B**).

Among 57 patients not receiving BV-based regimen at first salvage, 46 (81%) had 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 in CR. Among 91 patients (79% of the cohort) with centrally reviewed FDG-PET data, 82.4% (75/91) achieved metabolic complete response (mCR, being defined as 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 (3-18), without difference between patients who received or not salvage BV. Median time between ASCT and the first BV maintenance cycle was 70 days (18-223), and 88 (77%) patients were treated within three months from ASCT. The main reported adverse event was neuropathy in 50 (43%) patients, with a complete resolution in half of them. Treatment-related event led to BV maintenance discontinuation in 10% of patients, including neuropathy for 6 patients, infections for 3, thrombopenia for 1, and pancreatitis for 1. Neuropathy were more frequent in patients receiving pre-transplant BV, without impact on treatment discontinuation rate.

The median follow-up period was 35 months. The 2 years PFS and OS for the whole cohort were 75.3% (95% CI: 68.4-84.3%) and 96.4% (95% CI: 94.2%-100%), respectively (**Figure 1C-D**). Seven patients died, including three due to disease progression, two due to second cancer (1 acute myeloid leukemia and 1 pancreatic cancer), and two due to 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 blocker (ICB) with a response in 15 (71%) patients, 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)<sup>3</sup>, and absence of pre-transplant mCR (after central FDG-PET review) were significantly predictive of reduced PFS, while FDG-PET status was the only variable significantly correlated with OS (**Table 2**). Notably, survival probability was similar between patients receiving or not BV-based regimen before transplant (**Table 2**). PFS and OS at 24 month dependent on significant variables including LYSA prognostic score, refractory status or relapse timing are provided in **Supplemental Figure 1**. Using a multivariate Cox model for significant variables identified in univariate analysis, we found that only absence of mCR (ie. Deauville score 4 and 5) before transplant significantly correlated 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,<sup>4-6</sup> although not allowing post-transplant therapeutic guidance. Our results identify FDG-PET response after salvage as 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 2y-PFS of 75%, similar to the results of AETHERA. While a direct comparison between AETHERA and our current study was not accurate, we might note that the patient's characteristics were different (**Table 1**). More patients received first-line escalated BEACOPP in our cohort. Moreover, a majority of patients from our cohort (70%) undertook off-label BV-based salvage regimens, while patients with pre-transplant BV exposure 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% of mCR after FDG-PET central review). We observed that achievement of mCR before transplant was predictive of improved PFS and OS, including after multivariate analysis and in fact, recent studies attempted to increase mCR rate by incorporating BV into initial salvage therapy, including bendamustine, DHAP, ESHAP and gemcitabine.<sup>7-10</sup> Particularly, the BRAVE study<sup>9</sup> was a phase II trial of BV-DHAP without post-transplant BV maintenance, resulting in 74% PFS at 2y, similar to our results. These observations suggested that the optimal timing of BV use, as salvage or as maintenance, remained to be determined in future prospective clinical trials.

Despite an accurate risk stratification and the generalization of BV use, the prognostic of high-risk R/R HL patients remains a matter of concern. However, the excellent OS results observed in our cohort underlined the generalization of efficient salvage therapies in post-transplant relapse. Particularly, 70% of patients experiencing a relapse during BV maintenance received an immune check point blocker (ICB), among them 71% responded. We may thus hypothesize that selected patients may benefit from ICB earlier on, as currently investigated in clinical trials using ICB as part of salvage or as post-transplant maintenance.<sup>11-</sup>

<sup>13</sup> During first-line salvage, BV and nivolumab combination resulted in 61% of CR after 4 cycles without unanticipated toxicity,<sup>11</sup> and pembrolizumab combined with gemcitabine, vinorelbine and liposomal doxorubicin led to 95% of CR.<sup>12</sup> In the post-transplant setting, consolidation with eight cycles of pembrolizumab resulted in 82% PFS probability at 18 months.<sup>13</sup> Thus, incorporating ICB to salvage and/or post-transplant strategies represents a promise for R/R HL patients at high-risk for treatment failure or progression that should be

further investigated 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 conduce to the omission of consolidative ASCT to alleviate 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.<sup>14</sup>

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 ICB in current salvage strategies remain to be determined in future clinical trials.

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Table 1. Characteristics of the 115 patients from the AMAHRELIS cohort and the 165 patients from AETHERA.  $\neq$ mCR: not in complete metabolic response; DS: Deauville score. For FDG-PET, percentages are based on the 91 patients with available central review of imaging.

	AMAHRELIS n=115		AETHERA n=165	
Male (n, %)	62	54%	76	46%
Age in years (mean, min-max)	34	16-68		
Frontline chemotherapy				
ABVD	64	56%	119	72%
escBEACOPP	42	37%	26	16%
other	9	8%	20	12%
Time to relapse				
Primary refractory disease ( $\leq 3$ months)	50	43%	99	60%
Early relapse ( $> 3$ or $\leq 12$ months)	32	28%	53	32%
Late relapse ( $> 12$ months)	33	29%	13	8%
Histologic 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%		
Bulk 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%		
$\geq 3$	9	8%		
Pre-transplant BV				
Yes	81	70%		
No	34	30%	165	100%
Pre-transplant FDG-PET*			Unknown 45	27%
$\neq$ mCR	16	17.6%	FDG positive 64	39%
mCR (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

Table 2. Univariate and multivariate Cox regression analysis on AMAHRELIS. HR: hazard ratio; 95% CI: 95% confidence interval (min-max); p-val: p-value; \*: at the time of relapse; ref.: refractory; rel<12: relapse before 12 months; B: B-symptoms; Extra.: extranodal relapse; Irrad: irradiated field relapse; Pre-BV: pre-transplant BV use; Salvage: salvage line number; FDG-PET: results of central FDG-PET analysis with Deauville scores 1, 2 and 3, and 4 and 5 classified mCR and no mCR, respectively.

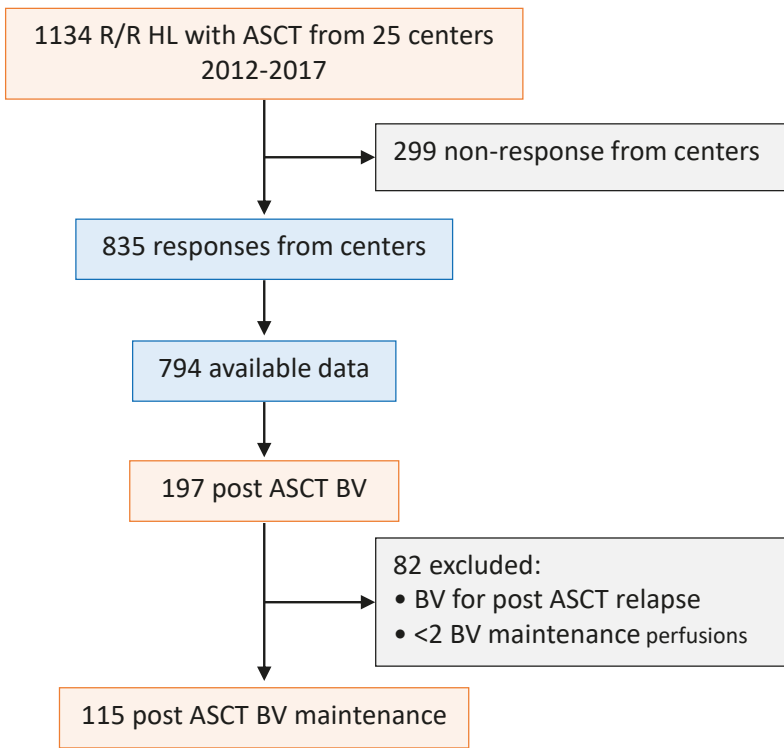
	N	PFS						OS					
		Univariate			Multivariate			Univariate			Multivariate		
		HR	95%	p-	HR	95% CI	p-	HR		p-val	HR	95%	p-
Sex	11	1	0.51-	0.98				0.3	0.068	0.21			
Age*	11	1	0.98-	0.58				1	0.98-	0.18			
Ref.	11	2.1	1.1-	0.03	0.6	0.29-	0.37	0.5	0.11-	0.53			
Rel.<12	11	3.4	1.2-	0.02	3.8	0.75-	0.10	2.3	0.28-	0.44			
ECOG*	94	1	0.63-	0.85				1.4	0.51-	0.5			
Stage*	11	1	0.74-	0.91				1.6	0.69-	0.28			
B*	10	0.5	0.19-	0.28				0.6	0.074	0.66			
Bulk*	10	1.5	0.51-	0.48				1.9	0.22-	0.55			
Extra.*	11	0.8	0.41-	0.57				0.3	0.074	0.25			
Irrad.	11	1.1	0.42-	0.85				2.5	0.48-	0.28			
AETHERA	10	1.3	0.89-	0.16				1.9	0.81-	0.14			
LYSA	11	0.3	0.14-	0.00	0.6	0.18-	0.55	0.5	0.11-	0.51			
Pre-BV	11	0.8	0.43-	0.75				0.6	0.12-	0.43			
Salvage	11	1.1	0.63-	0.84				1.8	0.75-	0.18			
FDG-PET	91	2.9	1.3-	0.01	3.3	1.41-	0.00	7.7	1,7-	0.007	7.6	1.71-	0.00

**Figure 1. Impact of post-transplant BV maintenance in the real-life practice: the AMAHRELIS study. A. Flow chart.** R/R HL: relapse-refractory Hodgkin lymphoma patients; ASCT: autologous hematopoietic stem cell transplantation. **B.** Proportion of patients receiving or not BV during the first and second salvage lines. The percentage of patients in CR is indicated. \*\*\*p<0.001 (Fischer's test). **C-D.** Progression-free (PFS) and overall (OS) survival of the 115 patients of the AMAHRELIS cohort since transplant. The 95% confidence intervals are shown in pale red on both sides of survival curves. **E-F.** PFS and OS probabilities dependent on the achievement of a complete metabolic response among 91 patients of the AMAHRELIS cohort after central reviewing of FDG-PET data. mCR: complete metabolic response; ≠mCR: not in complete metabolic response.

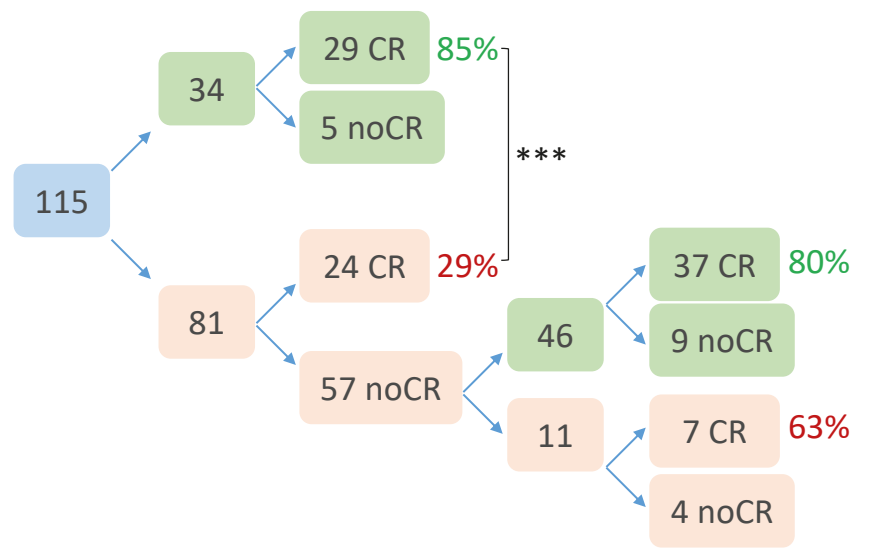
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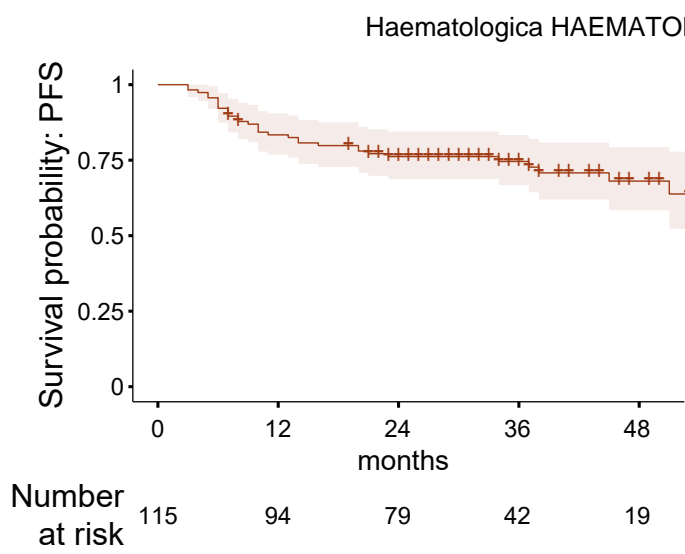
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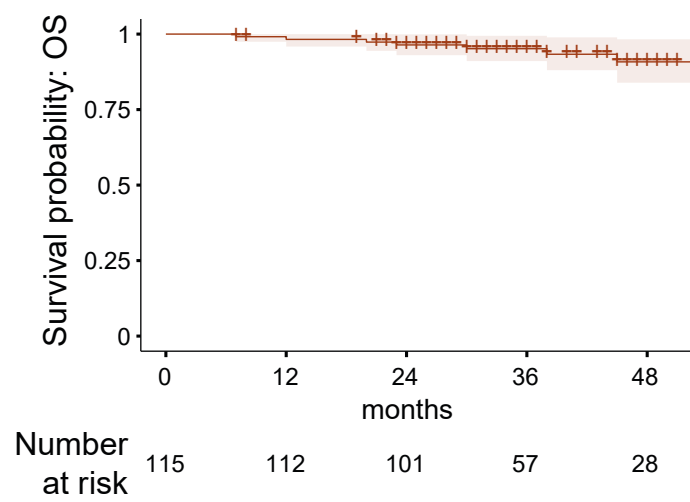
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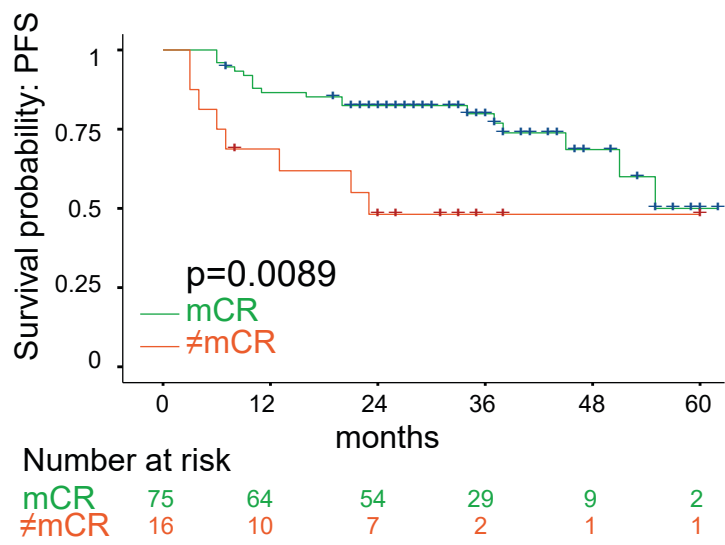
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