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Original Research

Long-term efficacy of anti-PD1 therapy in Hodgkin lymphoma with and without allogenic stem cell transplantation

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Abstract ***Introduction:*** Long-term efficacy of anti-PD1 therapy and the need for a consolidation with allogenic haematopoietic stem cell transplantation (allo-HSCT) remain unclear in patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL).
Methods: We retrospectively analysed 78 patients with R/R HL treated with nivolumab in the French Early Access Program and compared their outcomes according to subsequent allo-HSCT.
Results: After a median follow-up of 34.3 months, the best overall response rate was 65.8%, including 38.2% complete responses (CRs). The median progression-free survival (PFS) was 12.1 months. Patients reaching a CR upon nivolumab had a significantly longer PFS than those reaching a partial response (PR) (median = not reached *vs* 9.3 months, $p < 0.001$). In our cohort, 13 patients who responded (*i.e.* in CR or PR) to nivolumab monotherapy underwent consolidation with allo-HSCT. Among responding patients, none of those who underwent subsequent allo-HSCT (N = 13) relapsed, whereas 62.2% of those who were not consolidated with allo-HSCT (N = 37) relapsed ($p < 0.001$). There was no difference in overall survival (OS) between the two groups. Five of 6 patients who were not in CR at the time of transplantation (4 PRs and 1 progressive disease) converted into a CR after allo-HSCT.
Conclusion: Most patients with R/R HL treated with anti-PD1 monotherapy eventually progressed, notably those who did not achieve a CR. Patients undergoing consolidation with allo-HSCT after anti-PD1 therapy experienced prolonged disease-free survival compared with non-transplanted patients, but this difference did not translate into a benefit in OS. This information should be considered when evaluating the risk/benefit ratio of allo-HSCT after anti-PD1 therapy.

1. Introduction

Classical Hodgkin lymphoma (HL) is highly curable with standard treatments. However, relapse can occur in up to 30% of patients with advanced disease [1,2]. In relapsed patients, salvage therapy followed by autologous haematopoietic stem cell transplantation (auto-HSCT) can induce prolonged remissions [3]. Patients who relapse after auto-HSCT have a poor outcome with a median overall survival (OS) ranging from 10.5 to 27.6 months in the pre–brentuximab vedotin era [4,5]. Although brentuximab vedotin has shown encouraging overall response rates (ORRs) in relapsed or refractory (R/R) HL, only ~20% of patients might be cured with this single-agent therapy [6].

In recent years, checkpoint blockade with anti-PD1 antibodies demonstrated remarkable efficacy in patients with R/R HL [7–10]. Studies evaluating anti-PD1 therapy in these patients, which account for more than 450 patients in total, showed ORRs of around 70% and complete responses (CRs) of up to 20%. These results led to the approval of nivolumab and pembrolizumab for R/R HL by the Food and Drug Administration in 2016 and 2017, respectively. In 2015, an Early Access Program (EAP) was started in France allowing treatment of patients with R/R HL with nivolumab.

Despite remarkable immediate efficacy, many questions remain unanswered regarding the long-term efficacy and optimal management of patients with HL treated with anti-PD1, including the duration of treatment and the need for a consolidation with allogenic haematopoietic stem cell transplantation (allo-HSCT). We have previously addressed the first issue and demonstrated that prolonged remissions can be achieved after nivolumab discontinuation in patients with CR [11]. Here, we evaluated the role of allo-HSCT consolidation in patients with HL treated with anti-PD1.

There are limited data regarding the long-term efficacy of anti-PD1 therapy because the median follow-up of previously published studies was rather short (median = 7–18 months [10,12,13]). Furthermore, the role of allo-HSCT after anti-PD1 therapy remains poorly defined. A retrospective study by Merryman *et al.* [14] (N = 31 patients with HL) suggested that

patients undergoing allo-HSCT after nivolumab might experience a lower relapse rate than historical controls. However, this strategy was not compared with patients receiving anti-PD1 treatment without subsequent allo-HSCT.

Here, we report the results of patients with R/R HL consolidated with allo-HSCT after nivolumab treatment in comparison with those of the patients treated with nivolumab monotherapy alone in the French EAP.

2. Methods

We conducted a retrospective, nationwide study of patients with R/R HL aged ≥18 years who were treated with nivolumab in the French EAP. The EAP included patients with HL relapsing or refractory after three lines of chemotherapy (including brentuximab vedotin) and auto-HSCT or four lines of chemotherapy if the patient was not eligible for HSCT because of age, insufficient stem cell collection or chemorefractory disease. Patients with active autoimmune disease and/or steroid or immunosuppressive treatment–requiring disease were not eligible. All patients who had received at least one dose of nivolumab as part of the French EAP were eligible for the study. Nivolumab was administered at 3 mg/kg intravenously over 60 min every 2 weeks in an outpatient setting until progression, death of any cause, unacceptable toxicity, consent withdrawal or treating physician's decision. The patients were allowed subsequent allo-HSCT to be undergone according to primary physician's decision.

The primary end-point was best response (ORR, CR, partial response [PR], stable disease [SD] and progressive disease [PD] as defined by the primary physician using the criteria defined by Cheson et al [15,16] depending on the current practice in each centre at the time of evaluation) at any time during nivolumab treatment.

Secondary end-points included other efficacy parameters (including duration of response, progression-free survival [PFS] and OS), safety analysis and the impact of allo-HSCT. OS and PFS were defined as the duration from the first dose of nivolumab to death of any cause and disease progression or death of any cause, whichever occurred first, respectively. Both OS and PFS were censored at the date of last information and were estimated using the Kaplan–Meier method. Exact 95% confidence intervals (CIs) were used when appropriate. All data analyses were carried out using SAS version 9.3 software. Safety and tolerability were evaluated and reported by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

The protocol was approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé—CCTIRS (approval n° 16.861). All patients have been informed and consented before registration.

3. Results

3.1. Patients' characteristics

Seventy-eight patients from 35 French centres were included (Supplementary Fig. 1). The characteristics of the patients are summarised in Table 1. The median age at nivolumab initiation was 37 (range, 18–77) years. *Performance status* was ≥2 in 27% of the patients, 27% of them had B symptoms and 77.5% had stage III/IV disease. The median number of prior lines of treatment was 6 (range, 2–13). All patients had been previously treated with brentuximab vedotin; 62% and 28% of them had undergone prior autologous or allogenic HSCT, respectively. The median exposure to nivolumab was 5.2 (range, 0–38.3) months, and the median number of cycles was 9.5 (range, 1–84). The median follow-up was 34.3 months (range, 0.1–39.7). At the time of analysis, 85.9% of patients had discontinued nivolumab, mostly because of progression (50.7%), consolidation with allo-HSCT (19.4%) or toxicity (9.0%).

3.2. Outcome of the entire cohort

Among evaluable patients (n = 76), the best ORR was 65.8% (90% CI [55.82; 74.80]), including 38.2% CR and 27.6% PR. The median time to response was 2.6 months (95% CI [2.0; 4.0]), and the median time to best response was 2.7 months (6 patients reached CR at the second evaluation and 2 others later). The median duration of response was 24.3 months (95% CI [9.9; not evaluable]). The median PFS was 12.1 months (95% CI [7.3; 26.2]), and the median OS was 38.7 months (95% CI [38.7; not evaluable]). At three years of follow-up, the PFS and OS rates were 32% and 65%, respectively (Fig.1 A and B). Patients achieving a CR upon nivolumab had a significantly longer PFS than those reaching a PR (median PFS = not reached *vs* 9.3 months, $p < 0.001$). There was no difference in OS between those two groups (Fig. 1C and D). Among 50 responders (CR or PR), 23 (46%) patients had relapsed/progressed at the time of analysis: 7 of 29 (24%) CR patients, 16 of 21 (76%) PR patients and up to 94% of the PR patients who did not undergo subsequent allo-HSCT. Overall, 45 (57.7%) patients relapsed or progressed after nivolumab treatment. Thirty-six (80%) of them received a salvage therapy. Among 23 patients evaluated, 13 (56.6%) experienced an objective response, and 8 (34.8%) achieved CR.

A total of 107 adverse events (AEs) were reported in 40 (51.3%) patients. Among these, there were 62 AEs of grade ≥3 in 29 (37%) patients and 28 serious AEs (SAEs) in 16 (20.5%) patients. Most frequent clinically

Table 1
Patients' characteristics for the entire cohort.

Characteristics at nivolumab initiation	All N = 78
Age, years, median (range)	37.0 (18–77)
Sex, no. (%)	
Male	44 (56.4%)
Female	34 (43.6%)
Performance status (ECOG)	
0 - 1	45 (72.6%)
≥2	17 (27.4%)
Missing	16
Stage disease, no. (%)	
I/II	16 (22.5%)
III/IV	55 (77.5%)
Unknown	7
B symptoms, no. (%)	
No	54 (73%)
Yes	20 (27%)
Missing	4
Prior lines of systemic therapy, no. (%)	
Median (range)	6 (2–13)
2	2 (2.6%)
3	9 (11.5%)
4	11 (14.1%)
5	11 (14.1%)
6	13 (16.7%)
≥7	32 (41.0%)
Prior radiation therapy, no. (%)	42 (53.8%)
Prior treatment with brentuximab vedotin, no. (%)	74 (100%) 4 missing
Prior autologous HSCT, no. (%)	48 (61.5%)
Prior allogenic HSCT, no. (%)	22 (28.2%)
Nivolumab treatment and response	
Number of nivolumab injections, median (range)	9.5 (1–84)
Duration of anti-PD1 therapy, months, median (range)	5.2 (0–38.3)
Permanent treatment discontinuation	67 (85.9%)
Reason for treatment discontinuation	
Disease progression	34 (49.3%)
Toxicity	6 (9.0%)
Consolidation with allogenic HSCT	13 (20.9%)
Consolidation with autologous transplant	1 (1.5%)
Decision of the clinician with no further treatment	7 (10.4%)
Death	2 (3.0%)
Other	4 (6.0%)
Concomitant radiotherapy, no. (%)	7 (9.6%)
Concomitant chemotherapy, no. (%)	5 (6.8%)
Follow-up, months, median (range)	34.3 (0.1–39.7)
BOR among evaluated patients, no. (%)	
- CR	29 (38.2%)
- PR	21 (27.6%)
- SD	11 (14.5%)
- PD	15 (19.7%)
- Non-evaluated/missing	2
Time to response from nivolumab initiation, median (range)	2.6 (0.5–34.1)
Time to best response from nivolumab initiation, median (range)	2.7 (0.5–28.8)
DOR, median (95% CI)	24.3 (9.9 – NE)
PFS, median (95% CI)	12.1 (7.3–26.2)
OS, median (95% CI)	38.7 (38.7 – NE)
Relapse/progression	45 (57.7%)
If relapse/progression, salvage therapy	36 (80%)
Response after salvage therapy	
CR	8 (34.8%)
PR	5 (21.7%)
SD	1 (4.3%)
PD	9 (39.1%)
Non-evaluated/missing	13

BOR, best overall response; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response; CI, confidence interval; PFS, progression-free survival; OS, overall survival; HSCT, haematopoietic stem cell transplantation; SD, stable disease; PD, progressive disease; NE, not evaluable; DOR, duration of response.

relevant, immune-related and SAEs are summarised in Supplementary Table 1.

At the time of analysis, 54 (69.2%) patients were alive. The main cause of death was lymphoma progression in 14 (58.3%) patients.

3.3. Outcome of patients according to subsequent allo-HSCT consolidation

In our cohort, 17 patients proceeded to allo-HSCT after nivolumab therapy (Figs. 2 and 3, Supplementary Table 2). One patient reached a PR upon nivolumab, then progressed before starting the conditioning regimen and thus received radiotherapy before transplantation. Three patients had a PD upon nivolumab therapy; of whom, 2 received a salvage therapy before transplantation. Characteristics of allogenic transplanted patients are summarised in Supplementary Table 2.

At the time of analysis, 14 of the 17 transplanted patients were alive, and 13 remained disease-free after a median follow-up of 34.0 months from nivolumab initiation and 29.2 months from transplantation (Fig. 3). The PFS and OS at one year from allo-HSCT were 76% and 82%, respectively.

To assess the benefit of allo-HSCT consolidation, we compared the outcome of patients who achieved an objective response (CR or PR) upon nivolumab monotherapy and underwent (N = 13) immediate subsequent allo-HSCT or not (N = 37). Characteristics of these patients are summarised in Table 2. At nivolumab initiation, patients with subsequent allo-HSCT were younger (median age = 30.5 vs 38.0 years, p = 0.029). There was no significant difference between the two groups regarding disease stage or number of prior lines of systemic therapy. The duration of treatment with nivolumab was shorter in patients receiving subsequent allo-HSCT (median duration = 2.89 vs 6.1 months, p = 0.012) probably because of the initiation of the allograft procedure. The median time to response from nivolumab initiation was not significantly different between the two groups (2.0 vs 1.8 months, p = 0.420),

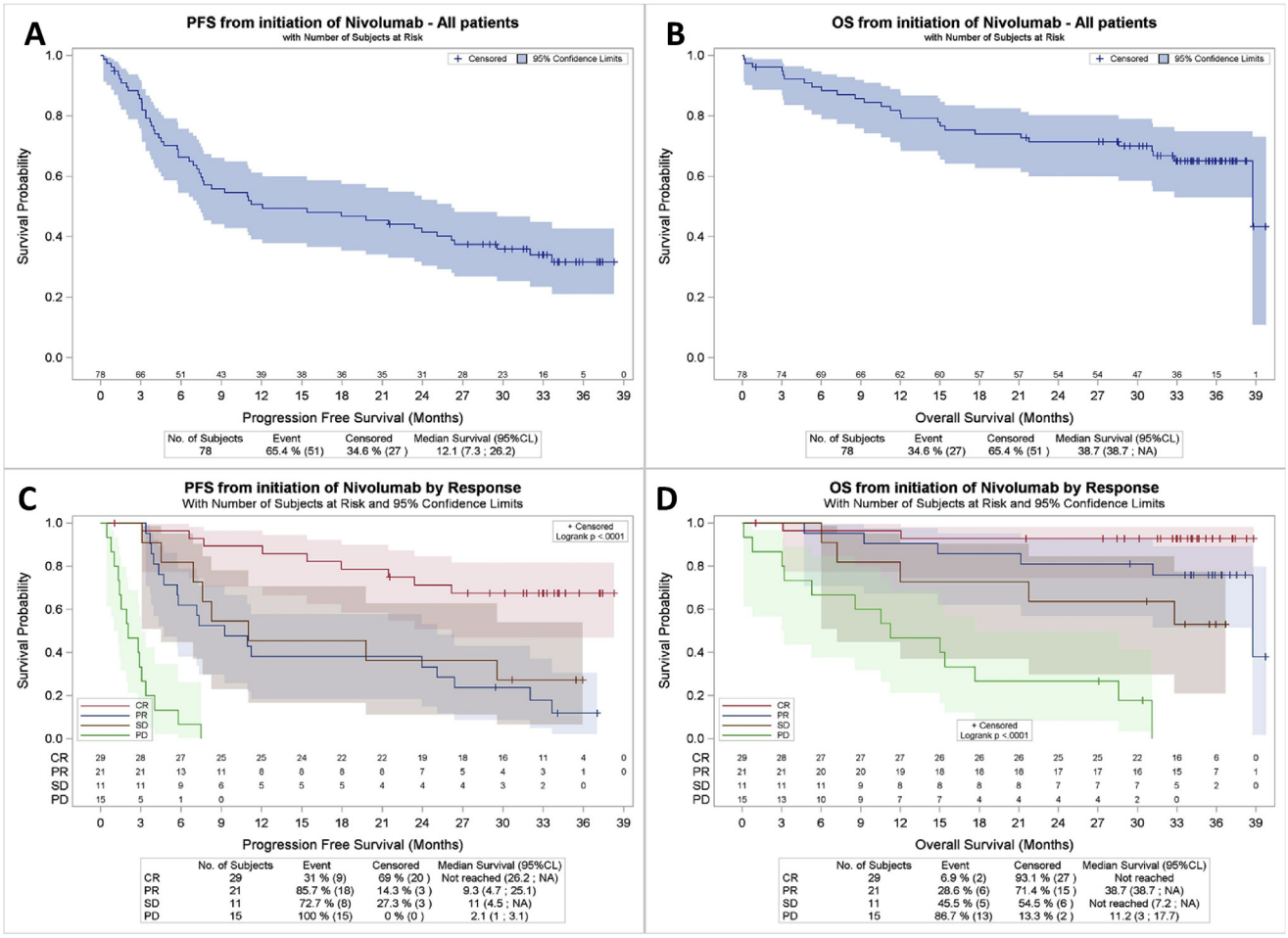

Fig. 1. PFS (A and C) and OS (B and D) of the entire cohort (A and B) and according to best response upon nivolumab monotherapy (C and D). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival.

but the time to best response was shorter in the transplanted group (2.4 vs 1.8 months, p = 0.039). Indeed, all patients who underwent allo-HSCT, except one, achieved a CR at first evaluation. At the time of analysis, 23 of 37 (62.2%) patients without subsequent allo-HSCT had relapsed (7 of 20 CR patients and 16 of 17 PR patients), whereas all patients who underwent allo-HSCT remained disease-free after a median follow-up of 33.3

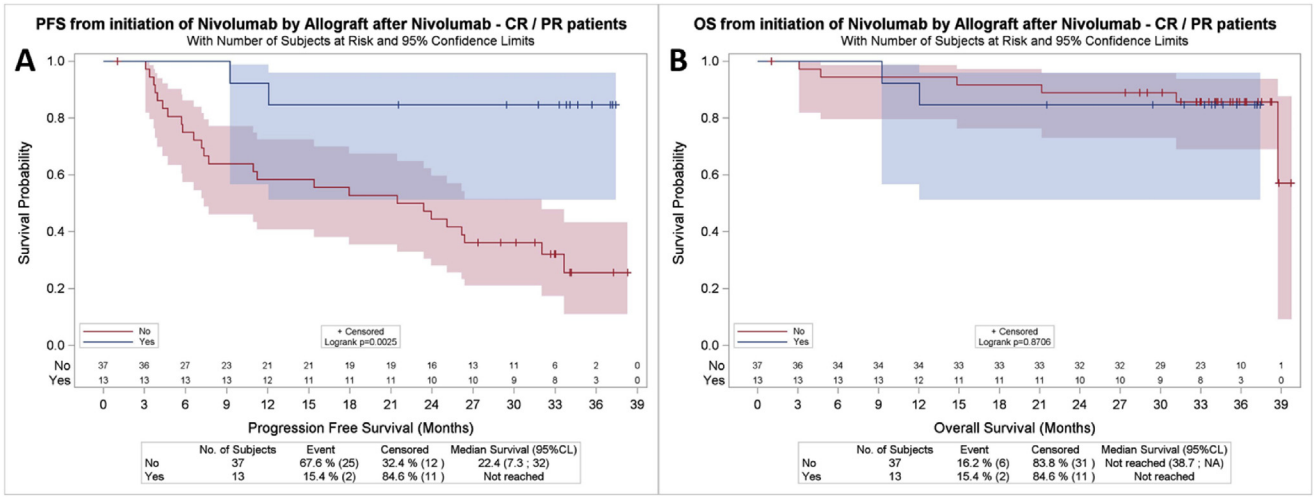

Fig. 2. PFS (A) and OS (B) of patients in CR or PR after nivolumab monotherapy according to subsequent allogenic HSCT. CR, complete response; PR, partial response; HSCT, haematopoietic stem cell transplantation; PFS, progression-free survival; OS, overall survival.

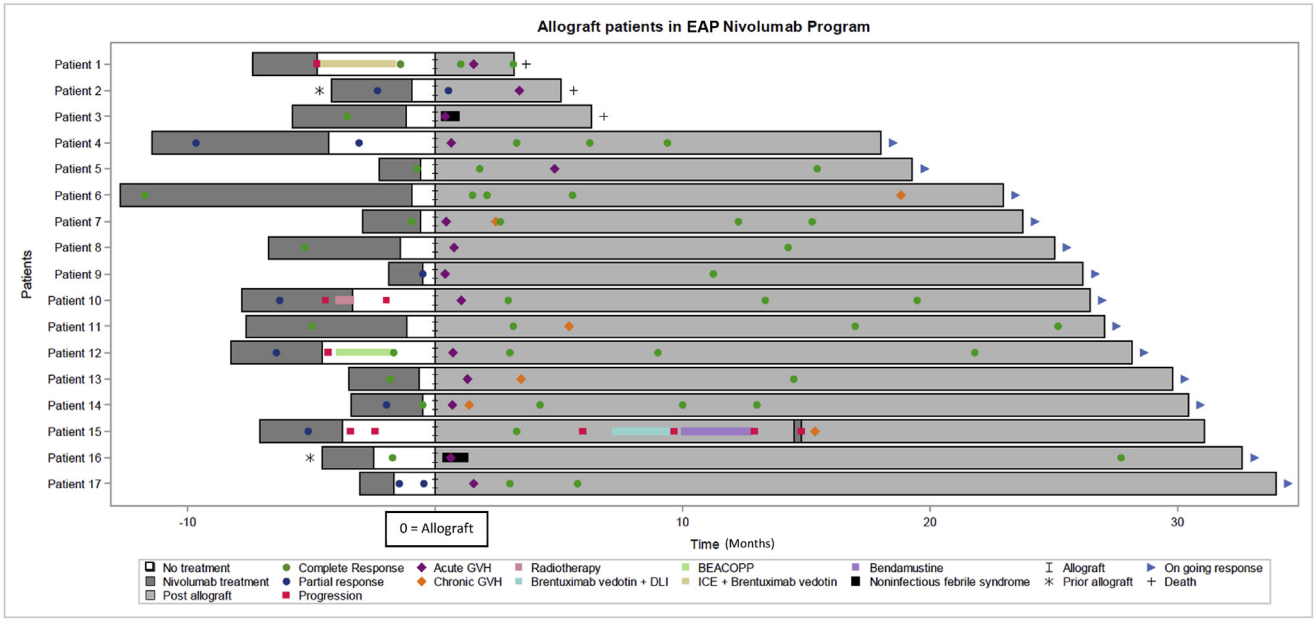

Fig. 3. Outcome of patients who underwent allogenic HSCT after nivolumab therapy. HSCT, haematopoietic stem cell transplantation; GVH, graft-versus-host; EAP, early access program; ICE, Ifosfamide, carboplatine and etoposide; BEACOPP, bleomycine, etoposide, adriamycine, cyclosphophamide, oncovin®, procarbazine and prednisone.

months from nivolumab initiation ($p < 0.001$). The median PFS was 22.4 (95% CI [7.3; 32.0]) months for the non-transplanted group and was not reached for the transplanted group ($p = 0.003$; Fig. 2A). In terms of PFS, allo-HSCT consolidation tended to benefit both CR (p = NS) and PR ($p = 0.01$) patients (Supplementary Fig. 2 A and C). In the non-transplanted group, 12 of 20 (60%) patients in CR and 0 of 17 patients in PR were alive and progression-free at the time of analysis. In the transplanted group, 2 patients died of toxicity on day 155 and 192 after allo-HSCT, respectively (causes of death are described in the following sections). There was no difference in OS between the transplanted and non-transplanted groups (Fig. 2B). In the non-transplanted group, 19 of 23 relapsed patients received a salvage therapy. Among 12 patients evaluated, 9 (75%) experienced an objective response including 5 CRs (41.7%).

All the 17 transplanted patients experienced acute and/or chronic graft-versus-host disease (GVHD) (Supplementary Table 2). Fourteen patients experienced acute GVHD (4 grade IV), 5 of whom were steroid-refractory and required second-line treatment with anti-interleukine-2 receptor (anti-IL2R) antibody (inolimomab and basiliximab), anti–thymocyte globulin or extracorporeal photopheresis. Seven patients experienced chronic GVHD, 5 of whom were steroid-refractory and had not resolved at the time of analysis (4 cutaneous and 1 hepatic GVHD). One patient experienced veno-occlusive disease which resolved after defibrotide treatment, and 2 patients presented a non-infectious febrile syndrome responding to corticosteroids. Treatment-related mortality (TRM) was 5.9%, 11.8% and 17.6% on day 100 and at 6 months and 12 months, respectively. Three patients died: one patient had undergone prior allo-HSCT and received a second (haploidentical) graft after reaching a PR upon nivolumab. He presented with grade IV cutaneous and hepatic GVHD and unexplained encephalitis, leading to death 5 months after transplantation. The second death occurred in a patient who underwent geno-identical allo-HSCT after reaching a CR upon nivolumab. He first presented a non-infectious febrile syndrome that was efficiently treated with corticosteroids and then developed steroid-refractory cutaneous and gastrointestinal GVHD. He died of massive and unexplained haemoptysis 6 months after transplantation. The third death occurred in a patient with infectious acute pneumonia.

4. Discussion

Our study has a particularly long follow-up compared with previously published studies (median = 34.3 months *versus* 7–18 months [10,12,13]). This gave us the opportunity to evaluate long-term efficacy of anti-PD1 therapy in 78 patients with R/R HL. Although initial response to anti-PD1 was high (ORR = 65.8%), our results show that most patients eventually relapse/progress, notably those who are unable to achieve a CR (76% of all PR patients and 94% of PR patients without subsequent allo-HSCT). In responding (CR or PR) patients, the relapse rate was significantly lower in patients consolidated with allo-HSCT (0% vs 62.2%, $p < 0.001$).

Table 2
Characteristics of patients in CR or PR after nivolumab monotherapy according to subsequent allogenic HSCT.

Characteristics at nivolumab initiation	No allo-HSCT consolidation (N = 37)	AlloHSCT consolidation (N = 13)	p
Age, years, median (range)	38.0 (19–77)	30.5 (21–44)	**0.029**
Sex, no. (%)			0.515
Male	20 (54.1%)	9 (69.2%)	
Female	17 (45.9%)	4 (30.8%)	
Performance status (ECOG)			0.329
0 - 1	21 (75.0%)	8 (80%)	
≥2	7 (26.9%)	2 (20%)	
Missing	9	3	
Stage disease, no. (%)			0.794
I/II	8 (25%)	2 (16.7%)	
III/IV	25 (75.7%)	10 (83.3%)	
missing	4	1	
B symptoms, no. (%)			0.471
No	27 (77.1%)	8 (66.7%)	
Yes	8 (22.9%)	4 (33.3%)	
Missing	2	1	
Number of prior lines of systemic therapy, median (range)	6.0 (2–7)	6.0 (3–7)	0.872
Prior radiation therapy, no. (%)	19 (51.4%)	7 (53.8%)	1.000
Prior treatment with brentuximab vedotin, no. (%)	35 (100%) 2 missing	12 (100%) 1 missing	–
Prior autologous SCT, no. (%)	21 (56.8%)	9 (69.2%)	0.522
Prior allogenic SCT, no. (%)	9 (24.3%)	2 (15.4%)	0.704
Nivolumab treatment and response			
Number of nivolumab injections, median (range)	13.0 (1–84)	7.0 (4–23)	**0.011**
Duration of anti-PD1 therapy, months, median (range)	6.1 (0–38.3)	2.89 (1.4–11.8)	**0.012**
Permanent treatment discontinuation	30 (81.1%)	13 (100%)	0.168
Reason for treatment discontinuation			**< 0.001**
Disease progression	15 (50%)	0	
Toxicity	4 (13.3%)	0	
Consolidation with allogenic HSCT	0	13 (100%)	
Consolidation with autologous transplant	1 (3.3%)	0	
Decision of the clinician with no further treatment	7 (18.9%)	0	
Death	0	0	
Other	3 (8.1%)	0	
Concomitant radiotherapy, no. (%)	6 (17.6%)	0	0.167
Concomitant chemotherapy, no. (%)	2 (5.9%)	0	1.000
Follow-up from nivolumab initiation, months, median	34.5	34.1	–
BOR among evaluated patients, no. (%)			0.515
- CR	20 (54.1%)	9 (69.2%)	
- PR	17 (45.9%)	4 (30.8%)	
- SD	0	0	
- PD	0	0	
- Non-evaluated	0	0	
Time to response from nivolumab initiation, median	2.0	1.8	0.420
Time to best response from nivolumab initiation, median	2.4	1.8	**0.039**
DOR, median (95% CI)	16.6 (4.1–24.6)	Not reached	**0.002**
PFS, median (95% CI)	22.4 (7.3–32.0)	Not reached	**0.003**
OS, median (95% CI)	Not reached	Not reached	0.871
Relapse/progression	23 (62.2%)[a]	0	**< 0.001**
If relapse/progression, salvage therapy	19 (82.6%)	0	-
Response after salvage therapy			-
CR	5 (41.6%)	–	
PR	4 (33.3%)	–	
SD	0	–	
PD	3 (25%)	–	
Non-evaluated/missing	7	–	

BOR, best overall response; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response; CI, confidence interval; PFS, progression-free survival; OS, overall survival; allo-HSCT, allogenic haematopoietic stem cell transplantation; SD, stable disease; PD, progressive disease; DOR, duration of response.
Numbers in bold correspond to values below 0.05 and therefore statistically significant.
[a] Three of these patients underwent allo-HSCT after salvage therapy.

Furthermore, five of 6 patients who were not in CR at the time of transplantation (4 PR and 1 PD) converted into a CR after allo-HSCT.

Our results are consistent with the results of the studies previously published by Armand *et al.* [10], Chen *et al.* [12] and Beköz *et al.* [13] showing an ORR of 69%, 69%, and 64%, respectively (Supplementary Table 3). Similarly, the median PFS in our study was comparable with the one in the study by Armand *et al.* (12.1 months *versus* 14.7 months, respectively).

We were also able to analyse the outcome of patients who underwent consolidation with allo-HSCT and compare that with patients who were not consolidated with allo-HSCT. To reduce the bias, we limited the final comparison with patients who experienced an objective response after nivolumab monotherapy.

In our cohort, 17 patients had undergone allo-HSCT after nivolumab therapy (Fig. 3). Among them, 13 patients were transplanted after reaching an objective response upon nivolumab monotherapy (9 CR and 4 PR). Of note, 4 additional patients were transplanted: one with a PD and 3 after salvage therapy. Interestingly, 5 of 6 patients who were not in CR at the time of transplantation (4 PR and 1 PD) converted into a CR after allo-HSCT. Among the 17 transplanted patients, 14 are alive and 13 remain disease-free after a median follow-up of 29.2 months from transplantation. One-year PFS and OS from allo-HSCT were 76% and 82%, respectively. All patients experienced GVHD, either acute (N = 14, 82%) and/or chronic (N = 7, 41%) GVHD, including 7 (41%) patients with grade III-IV GVHD. At the time of analysis, GVHD had resolved in 9 of 13 disease-free patients. Two patients experienced non-infectious febrile syndrome which resolved with corticosteroids, and one patient experienced a sinusoidal obstructive syndrome. The 6- or 12-month TRM was 11.8% and 17.6%, respectively.

Although the number of transplanted patients is limited, our results are consistent with the results of other previously published studies (Supplementary Table 4). In their study, Merryman *et al.* [14] reported the outcome of 39 patients (31 HL and 8 Non-Hodgkin Lymphoma (NHL)) who underwent allo-HSCT after PD1 blockade. Among patients with HL, one-year PFS and OS were 74% and 90%, respectively. Incidence of grade III-IV GVHD was 23%, and 4 patients died of treatment-related toxicity. Seven patients (18%) presented a non-infectious febrile syndrome requiring corticosteroids, and 3 patients (8%), a sinusoidal obstructive syndrome. In Checkmate 205, 44 of 243 patients proceeded to allo-HSCT, with a median follow-up of 5.5 months after allo-HSCT [10]. The 6-month cumulative incidence of TRM and disease progression were 13% and 7%, respectively. All grade incidence of acute and chronic GVHD was 48% and 15%, respectively.

To assess whether responding patients should be consolidated with allo-HSCT or continue treatment with anti-PD1, we compared the outcome of patients in CR or PR upon nivolumab monotherapy with (n = 13) and without (N = 37) subsequent allo-HSCT. Although the patients in the transplanted group were younger (median age = 30.5 vs 38.0 years, p = 0.029), and with a trend for more CR, the other characteristics at baseline were not significantly different between the 2 groups (Table 2). Twelve of 20 patients (60%) who achieved a CR upon nivolumab monotherapy and did not undergo allo-HSCT remained disease-free at the time of analysis, suggesting that some of them may be cured with anti-PD1 alone, even after nivolumab discontinuation [11]. Conversely, 16 of 17 (94.1%) patients who were unable to reach a CR upon nivolumab and did not undergo allo-HSCT eventually progressed (Supplementary Fig. 2). In transplanted patients, the relapse rate was markedly lower than non-transplanted patients (0% vs 62.2%, $p < 0.001$, Fig. 2A), both in CR and PR patients (Supplementary Fig. 2). Interestingly, 5 of 6 patients who were not in CR at the time of transplantation (4 PR and 1 PD) converted into a CR after allo-HSCT. There was no significant difference in OS between the transplanted and non-transplanted groups (Fig. 2B). Whether the benefit observed in PFS may eventually translate into an increase in OS remains uncertain and should be re-evaluated after a longer follow-up. Emerging data suggest that anti-PD1 therapy may 're-sensitize' HL tumours to standard chemotherapy [17]. Thus, patients who relapse or progress after anti-PD1 therapy may respond to salvage chemotherapy even if they were previously refractory. In our cohort, despite a great number of prior lines of treatment, most patients who progressed/relapsed after anti-PD1 were able to receive a salvage therapy (80%), most of whom achieved an objective response (56.5% among evaluated patients). These results suggest that a subset of patients who fail anti-PD1 therapy may still be rescued.

The relapse rate after allo-HSCT following anti-PD1 therapy seems much lower than that of patients who are transplanted after conventional chemotherapy. Indeed, the one-year relapse rate in our study was 5.8% *versus* 26–41% in historical controls [18–24], suggesting that prior anti-PD1 therapy may enhance the graft-versus-lymphoma effect of allo-HSCT.

Although our study suggests a benefit of allo-HSCT consolidation, these results should be interpreted with caution, given the retrospective nature of this analysis. Despite our attempt to limit the bias associated with the response to anti-PD1 therapy by limiting the comparison with responding patients, other biases—including age and proportion of complete responders—may have influenced the differences observed between transplanted and non-transplanted groups. The decision to perform an allo-HSCT was left to the decision of the primary physician and thus could

not be controlled. Finally, the number of patients in the two subgroups is limited and may have reduced the power of the study.

Overall, our results show that, with a long follow-up (median = 34.3 months), most patients with R/R HL eventually progress during anti-PD1 therapy, notably patients who are unable to achieve a CR. Conversely, consolidation with allo-HSCT can convert incomplete responses into CR and is associated with a very low relapse rate. Although patients undergoing allo-HSCT after anti-PD1 may experience increased toxicities, these AEs appeared manageable and reversible in most patients. Thus, consolidation with allo-HSCT may be considered in R/R HL treated with anti-PD1, particularly in those not reaching a CR. However, the absence of benefit in OS and the possibility to induce a response with salvage chemotherapy after anti-PD1 're-sensitization' should be considered when evaluating the risk/benefit ratio. Prospective studies are needed to further define which patients may benefit from consolidation with allo-HSCT after anti-PD1 therapy.

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Conflict of interest statement

R.H. and P.B. have received consulting fees and/or honoraria from Bristol-Myers Squibb. E.N-.V. has received consulting fees from Keocyt, Janssen and Sanofi; A.St. has received consulting fees from Takeda. The remaining authors declare no competing financial interests.

Authorship contributions

G.M. and R.H. designed the research, analysed data and wrote the paper; C.H., J-.M.S, O.C., A.St., B.D., A.Sh., G.G., K.B., M-.P.M-.M., H.G., A.T., R.D., E.N-.V., A.D., C.B., A.C. and P.B. provided the data; and all authors reviewed and approved the final draft.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.04.006.

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