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

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Running title: Anti-PD1 and transplantation in Hodgkin lymphoma

Highlights:

- The majority of R/R HL patients eventually progressed during anti-PD1 therapy.
- In responding patients, the relapse rate was lower in patients consolidated with allo-HSCT.
- Among responders, subsequent allo-HSCT was not associated with a greater overall survival.

Keywords: Immunotherapy; Hodgkin Lymphoma; Checkpoint inhibitors; anti-PD1; nivolumab; Allogenic hematopoietic stem cell transplantation.

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1 **Abstract**

2 **Introduction:** Long term efficacy of anti-PD1 therapy and the need for a consolidation with
3 allogenic stem cell transplantation (alloHSCT) remain unclear in patients with
4 relapsed/refractory (R/R) Hodgkin lymphoma (HL).

5 **Methods:** We retrospectively analyzed 78 patients with R/R HL treated with nivolumab in the
6 French Early Access Program and compared their outcome according to subsequent
7 alloHSCT.

8 **Results:** After a median follow-up of 34.3 months, the best overall response rate was 65.8%,
9 including 38.2% complete responses (CR). The median progression-free survival (PFS) was
10 12.1 months. Patients reaching a CR upon nivolumab had a significantly longer PFS than
11 those reaching a partial response (PR) (median = not reached vs 9.3 months, $p < 0.001$). In
12 our cohort, 13 patients who responded (*i.e.* in CR or PR) to nivolumab monotherapy
13 underwent consolidation with alloHSCT. Among responding patients, none of those who
14 underwent subsequent alloHSCT (N=13) relapsed, whereas 62.2% of those who were not
15 consolidated with alloHSCT (N=37) relapsed ($p < 0.001$). There was no difference in overall
16 survival (OS) between the two groups. Five out of 6 patients who were not in CR at the time
17 of transplantation (4 PR and 1 PD) converted into a CR after alloHSCT.

18 **Conclusion:** Most R/R HL patients treated with anti-PD1 monotherapy eventually
19 progressed, notably those who did not achieve a CR. Patients undergoing consolidation with
20 alloHSCT after anti-PD1 therapy experienced prolonged disease-free survival compared to
21 non-transplanted patients, but this difference did not translate into a benefit in OS. This
22 information should be considered when evaluating the risk/benefit ratio of alloHSCT after
23 anti-PD1 therapy.

24

1 **Introduction**

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

10 In recent years, checkpoint blockade with anti-PD1 antibodies demonstrated remarkable
11 efficacy in patients with R/R HL[7–10]. Studies evaluating anti-PD1 therapy in these patients,
12 which account for more than 450 patients in total, showed overall response rates (ORR) of
13 around 70% and complete remissions (CR) of up to 20%. These results led to the approval of
14 nivolumab and pembrolizumab for R/R HL by the Food and Drug Administration in 2016 and
15 2017, respectively. In 2015, an Early Access Program (EAP) was started in France allowing
16 treatment of R/R HL patients with nivolumab.

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

24 There is limited data regarding the long term efficacy of anti-PD1 therapy since the median
25 follow-up of previously published studies was rather short (median = 7-18 months[10,12,13]).
26 Furthermore, the role of alloHSCT after anti-PD1 therapy remains poorly defined. A

1 retrospective study by Merryman *et al* (N=31 HL patients) suggested that patients
2 undergoing alloHSCT after nivolumab might experience a lower relapse rate compared to
3 historical controls[14]. However, this strategy was not compared to patients receiving anti-
4 PD1 treatment without subsequent alloHSCT.

5 Here, we report the results of R/R HL patients consolidated with alloHSCT after nivolumab
6 treatment in comparison to patients treated with nivolumab monotherapy alone in the French
7 EAP.

8

9 **Methods**

10 We conducted a retrospective, nationwide study of patients aged ≥ 18 years with R/R HL
11 who were treated with nivolumab in the French EAP. EAP included patients with HL
12 relapsing or refractory after three lines of chemotherapy (including Brentuximab-Vedotin) and
13 autoHSCT, or four lines of chemotherapy if the patient was not eligible for HSCT due to age,
14 insufficient stem-cell collection or chemorefractory disease. Patients with active auto-immune
15 disease and/or steroid or immunosuppressive treatment-requiring disease were not eligible.
16 All patients who had received at least one dose of nivolumab as part of the French EAP were
17 eligible for the study. Nivolumab was administered at 3 mg/kg IV over 60 min every 2 weeks
18 in an outpatient setting until progression, death of any cause, unacceptable toxicity, consent
19 withdrawal, or treating physician's decision. Patients were allowed to undergo subsequent
20 alloHSCT according to primary physician's decision.

21 Primary endpoint was best response (ORR, CR, partial response (PR), stable disease (SD)
22 and progressive disease (PD) as defined by the primary physician using the Cheson
23 1999[15] or Cheson 2007[16] criteria depending on the current practice in each center at the
24 time of evaluation) at any time during nivolumab treatment.

25 Secondary endpoints included other efficacy parameters (including duration of response,
26 progression-free survival, and overall survival), safety analysis and the impact of alloHSCT.

1 OS and progression-free survival (PFS) were defined as the duration from the first dose of
2 nivolumab to death of any cause and disease progression or death of any cause, whichever
3 occurred first, respectively. Both OS and PFS were censored at the date of last information
4 and were estimated using the Kaplan–Meier method. Exact 95% confidence intervals (CI)
5 were used when appropriate. All data analysis was carried out using SAS v.9.3 software.
6 Safety and tolerability were evaluated and reported by investigators according to the National
7 Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

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

11

12 **Results**

13 Patients' characteristics

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

25 Outcome of the entire cohort

1 Among evaluable patients (n=76), the best ORR was 65.8% (90% CI [55.82; 74.80]),
2 including 38.2% CR and 27.6% PR. The median time to response was 2.6 months (95% CI
3 [2.0; 4.0]) and the median time to best response was 2.7 months (6 patients reached CR at
4 the second evaluation and 2 others later). The median duration of response was 24.3 months
5 (95% CI [9.9; not evaluable]). Median PFS was 12.1 months (95% CI [7.3; 26.2]) and median
6 OS was 38.7 months (95% CI [38.7; not evaluable]). At three years of follow-up, the PFS and
7 OS rates were 32% and 65%, respectively (Figure 1 A & B). Patients achieving a CR upon
8 nivolumab had a significantly longer PFS than those reaching a PR (median PFS = not
9 reached vs 9.3 months, $p < 0.001$). There was no difference in OS between those two groups
10 (Figure 1 C & D). Among 50 responders (CR or PR), 23 (46%) patients had
11 relapsed/progressed at the time of analysis: 7 out of 29 (24%) CR patients, 16 out of 21
12 (76%) PR patients, and up to 94% of the PR patients who did not undergo subsequent
13 alloHSCT. Overall, 45 (57.7%) patients relapsed or progressed after nivolumab treatment.
14 Thirty-six (80%) of them received a salvage therapy. Among 23 patients evaluated, 13
15 (56.6%) experienced an objective response and 8 (34.8%) achieved CR.

16 A total of 107 adverse events (AE) were reported in 40 (51.3%) patients. Among these, there
17 were 62 AE of grade ≥ 3 in 29 (37%) patients and 28 serious AE (SAE) in 16 (20.5%)
18 patients. Most frequent clinically relevant, immune-related and serious AE are summarized in
19 Supplementary Table 1.

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

22 Outcome of patients according to subsequent alloHSCT consolidation

23 In our cohort, 17 patients proceeded to alloHSCT after nivolumab therapy (Figure 2 & 3,
24 Supplementary Table 2). One patient reached a PR upon nivolumab then progressed before
25 starting the conditioning regimen and thus received radiotherapy before transplantation.
26 Three patients had a PD upon nivolumab therapy of whom 2 received a salvage therapy

1 before transplantation. Characteristics of allo-transplanted patients are summarized in
2 Supplementary Table 2.

3 At the time of analysis, 14 out of the 17 transplanted patients were alive and 13 remained
4 disease-free after a median follow-up of 34.0 months from nivolumab initiation and 29.2
5 months from transplantation (Figure 3). The PFS and OS at one year from alloHSCT were
6 76% and 82%, respectively.

7 In order to assess the benefit of alloHSCT consolidation, we compared the outcome of
8 patients who achieved an objective response (CR or PR) upon nivolumab monotherapy and
9 underwent (N=13) or not (N=37) immediate subsequent alloHSCT. Characteristics of these
10 patients are summarized in Table 2. At nivolumab initiation, patients with subsequent
11 alloHSCT were younger (median age = 30.5 vs 38.0 years, $p=0.029$). There was no
12 significant difference between the two groups regarding disease stage or number of prior
13 lines of systemic therapy. The duration of treatment with nivolumab was shorter in patients
14 receiving subsequent alloHSCT (median duration = 2.89 vs 6.1 months, $p=0.012$) probably
15 due to the initiation of the allograft procedure. The median time to response from nivolumab
16 initiation was not significantly different between the two groups (2.0 vs 1.8 months, $p=0.420$)
17 but the time to best response was shorter in the transplanted group (2.4 vs 1.8 months,
18 $p=0.039$). Indeed, all patients who underwent alloHSCT, except one, achieved a CR at first
19 evaluation. At the time of analysis, 23 out of 37 (62.2%) patients without subsequent
20 alloHSCT had relapsed (7 out of 20 CR patients and 16 out of 17 PR patients) whereas all
21 patients who underwent alloHSCT remained disease-free after a median follow-up of 33.3
22 months from nivolumab initiation ($p<0.001$). Median PFS was 22.4 (95% CI [7.3; 32.0])
23 months for the non-transplanted group and was not reached for the transplanted group
24 ($p=0.003$; Figure 2A). In terms of PFS, alloHSCT consolidation tended to benefit both CR
25 ($p=NS$) and PR ($p=0.01$) patients (Supplementary Figure 2 A & C). In the non-transplanted
26 group, 12 out of 20 (60%) patients in CR and 0 out of 17 patients in PR were alive and
27 progression-free at the time of analysis. In the transplanted group, 2 patients died of toxicity

1 at day 155 and 192 after alloHSCT, respectively (causes of death are described below).
2 There was no difference in OS between the transplanted and non-transplanted groups
3 (Figure 2B). In the non-transplanted group, 19 out of 23 relapsed patients received a salvage
4 therapy. Among 12 patients evaluated, 9 (75%) experienced an objective response including
5 5 CR (41.7%).

6 All the 17 transplanted patients experienced acute and/or chronic-GVHD (Supplementary
7 Table 2). Fourteen patients experienced acute GVHD (4 grade IV), 5 of which were steroid-
8 refractory and required second line treatment with anti-IL2R antibody (inolimomab and
9 basiliximab), anti-thymocyte globulin, or extra-corporal photopheresis. Seven patients
10 experienced chronic GHVD, 5 of which were steroid-refractory and had not resolved at the
11 time of analysis (4 cutaneous and 1 hepatic GVHD). One patient experienced veno-occlusive
12 disease which resolved after defibrotide treatment and 2 patients presented a non-infectious
13 febrile syndrome responding to corticosteroids. Treatment-Related Mortality (TRM) was
14 5.9%, 11.8% and 17.6% at day 100, 6 months and 12 months, respectively. Three patients
15 died: one patient had undergone prior alloHSCT and received a second (haploidentical) graft
16 after reaching a PR upon nivolumab. He presented with a grade IV cutaneous and hepatic
17 GHVD, and an unexplained encephalitis leading to death 5 months after transplantation. The
18 second death occurred in a patient who underwent geno-identical alloHSCT after reaching a
19 CR upon nivolumab. He first presented a non-infectious febrile syndrome that was efficiently
20 treated with corticosteroids and then developed a steroid-refractory cutaneous and
21 gastrointestinal GVHD. He died of massive and unexplained hemoptysis 6 months after
22 transplantation. The third death occurred in a patient with infectious acute pneumonia.

23

24 **Discussion**

25 Our study has a particularly long follow-up compared to previously published studies (median
26 = 34.3 months *versus* 7-18 months[10,12,13]). This gave us the opportunity to evaluate long

1 term efficacy of anti-PD1 therapy in 78 R/R HL patients. Although initial response to anti-PD1
2 was high (ORR=65.8%), our results show that most patients eventually relapse/progress,
3 notably those who are unable to achieve a CR (76% of all PR patients and 94% of PR
4 patients without subsequent alloHSCT). In responding (CR or PR) patients, the relapse rate
5 was significantly lower in patients consolidated with alloHSCT (0% vs 62.2%, $p<0.001$).
6 Furthermore, five out of 6 patients who were not in CR at the time of transplantation (4 PR
7 and 1 PD) converted into a CR after alloHSCT.

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

12 We were also able to analyze the outcome of patients who underwent consolidation with
13 alloHSCT and compare them to patients who were not consolidated with alloHSCT. To
14 reduce the bias, we limited the final comparison to patients who experienced an objective
15 response after nivolumab monotherapy.

16 In our cohort, 17 patients had undergone alloHSCT after nivolumab therapy (Figure 3).
17 Among them, 13 patients were transplanted after reaching an objective response upon
18 nivolumab monotherapy (9 CR and 4 PR). Of note, 4 additional patients were transplanted:
19 one with a progressive disease and 3 after salvage therapy. Interestingly, 5 out of 6 patients
20 who were not in CR at the time of transplantation (4 PR and 1 PD) converted into a CR after
21 alloHSCT. Among the 17 transplanted patients, 14 are alive and 13 remain disease-free after
22 a median follow-up of 29.2 months from transplantation. One-year PFS and OS from
23 alloHSCT were 76% and 82%, respectively. All patients experienced graft-versus-host
24 disease (GVHD), either acute (N=14, 82%) and/or chronic (N=7, 41%) GVHD, including 7
25 (41%) patients with grade III-IV GVHD. At the time of analysis, GVHD had resolved in 9 out
26 of 13 disease-free patients. Two patients experienced non-infectious febrile syndrome which

1 resolved with corticosteroids and one patient experienced a sinusoidal obstructive syndrome.
2 The 6 or 12 months TRM was 11.8% and 17.6%.

3 Although the number of transplanted patients is limited, our results are consistent with other
4 previously published studies (Supplementary Table 4). In their study, Merryman *et al*
5 reported the outcome of 39 patients (31 HL and 8 NHL) who underwent alloHSCT after PD1
6 blockade[14]. Among HL patients, one-year PFS and OS were 74% and 90%, respectively.
7 Incidence of grade III-IV GVHD was 23% and 4 patients died of treatment-related toxicity.
8 Seven patients (18%) presented a non-infectious febrile syndrome requiring corticosteroids
9 and 3 patients (8%) a sinusoidal obstructive syndrome. In Checkmate-205, 44 patients out of
10 243 patients proceeded to alloHSCT, with a median follow-up of 5.5 months after
11 alloHSCT[10]. The 6-months cumulative incidence of TRM and disease-progression were
12 13% and 7%, respectively. All grade incidence of acute and chronic GVHD were 48% and
13 15%, respectively.

14 To assess whether responding patients should be consolidated with alloHSCT or continue
15 treatment with anti-PD1, we compared the outcome of patients in CR or PR upon nivolumab
16 monotherapy with (n=13) and without (N= 37) subsequent alloHSCT. Although the patients in
17 the transplanted group were younger (median age = 30.5 vs 38.0 years, p=0.029), and with a
18 trend for more CR, the other characteristics at baseline were not significantly different
19 between the 2 groups (Table 2). Twelve out of 20 patients (60%) who achieved a CR upon
20 nivolumab monotherapy and did not undergo alloHSCT remained disease-free at the time of
21 analysis, suggesting that some of them may be cured with anti-PD1 alone, even after
22 nivolumab discontinuation[11]. Conversely, 16 out of 17 (94.1%) patients who were unable to
23 reach a CR upon nivolumab and did not undergo alloHSCT eventually progressed
24 (Supplementary Figure 2). In transplanted patients, the relapse rate was markedly lower
25 compared to non-transplanted patients (0% vs 62.2%, p<0.001, Figure 2A), both in CR and
26 PR patients (Supplementary Figure 2). Interestingly, 5 out of 6 patients who were not in CR
27 at the time of transplantation (4 PR and 1 PD) converted into a CR after alloHSCT. There

1 was no significant difference in OS between the transplanted and non-transplanted groups
2 (Figure 2B). Whether the benefit observed in PFS may eventually translate into an increase
3 in OS remains uncertain and should be re-evaluated after a longer follow-up. Emerging data
4 suggest that anti-PD1 therapy may “re-sensitize” Hodgkin lymphoma tumors to standard
5 chemotherapy[17]. Thus, patients who relapse or progress after anti-PD1 therapy may
6 respond to salvage chemotherapy even if they were previously refractory. In our cohort,
7 despite a great number of prior lines of treatment, most patients who progressed/relapsed
8 after anti-PD1 were able to receive a salvage therapy (80%), most of whom achieved an
9 objective response (56.5% among evaluated patients). These results suggest that a subset
10 of patients who fail anti-PD1 therapy may still be rescued.

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

15 Although our study suggests a benefit of alloHSCT consolidation, these results should be
16 interpreted with caution given the retrospective nature of this analysis. Despite our attempt to
17 limit the bias associated with the response to anti-PD1 therapy by limiting the comparison to
18 responding patients, other biases - including age and proportion of complete responders -
19 may have influenced the differences observed between transplanted and non-transplanted
20 groups. The decision to perform an alloHSCT was left to the decision of the primary
21 physician and thus could not be controlled. Finally, the number of patients in the two sub-
22 groups is limited and may have reduced the power of the study.

23 Overall, our results show that, with a long follow-up (median = 34.3 months), most R/R HL
24 patients eventually progress during anti-PD1 therapy, notably patients who are unable to
25 achieve a CR. Conversely, consolidation with alloHSCT can convert incomplete responses
26 into CR and is associated with a very low relapse-rate. Although patients undergoing
27 alloHSCT after anti-PD1 may experience increased toxicities, these adverse events

1 appeared manageable and reversible in most patients. Thus, consolidation with alloHSCT
2 may be considered in R/R HL treated with anti-PD1, particularly in those not reaching a CR.
3 However, the absence of benefit in OS and the possibility to induce a response with salvage
4 chemotherapy after anti-PD1 “re-sensitization” should be considered when evaluating the
5 risk/benefit ratio. Prospective studies are needed to further define which patients may benefit
6 from consolidation with alloHSCT after anti-PD1 therapy.

7

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Authorship contributions

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

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Figure 1: PFS (A & C) and OS (B & D) of the entire cohort (A & B) and according to best response upon nivolumab monotherapy (C & D)

Figure 2: PFS (A) and OS (B) of patients in CR or PR after nivolumab monotherapy according to subsequent allogenic-HSCT

Figure 3: Outcome of patients who underwent allogenic HSCT after nivolumab therapy

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 Nivo initiation, median [range]	2.6 [0.5 – 34.1]
Time to best response from Nivo 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

NE, Not evaluable

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

Characteristics at nivolumab initiation	No alloHSCT consolidation (N=37)	AlloHSCT consolidation (N=13)	p
Age, years, median [range]	38.0 [19 – 77]	30.5 [21 – 44]	0.029
Sex, No (%)			
• Male	20 (54.1%)	9 (69.2%)	0.515
• Female	17 (45.9%)	4 (30.8%)	
Performance status (ECOG)			
• 0 - 1	21 (75.0%)	8 (80%)	0.329
• ≥ 2	7 (26.9%)	2 (20%)	
• Missing	9	3	
Stage disease, No (%)			
• I/II	8 (25%)	2 (16.7%)	0.794
• III/IV	25 (75.7%)	10 (83.3%)	
• missing	4	1	
B symptoms, No (%)			
• No	27 (77.1%)	8 (66.7%)	0.471
• 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%)	12 (100%)	-
	2 missing	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			
• Disease progression	15 (50%)	0	<0.001
• 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 (%)			
- CR	20 (54.1%)	9 (69.2%)	
- PR	17 (45.9%)	4 (30.8%)	
- SD	0	0	0.515
- 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%)*	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	-	

*Three of these patients underwent alloH SCT after salvage therapy

BOR, Best Overall Response

Figure 1. PFS (A & C) and OS (B & D) of the entire cohort (A & B) and according to best response upon nivolumab monotherapy (C & D)

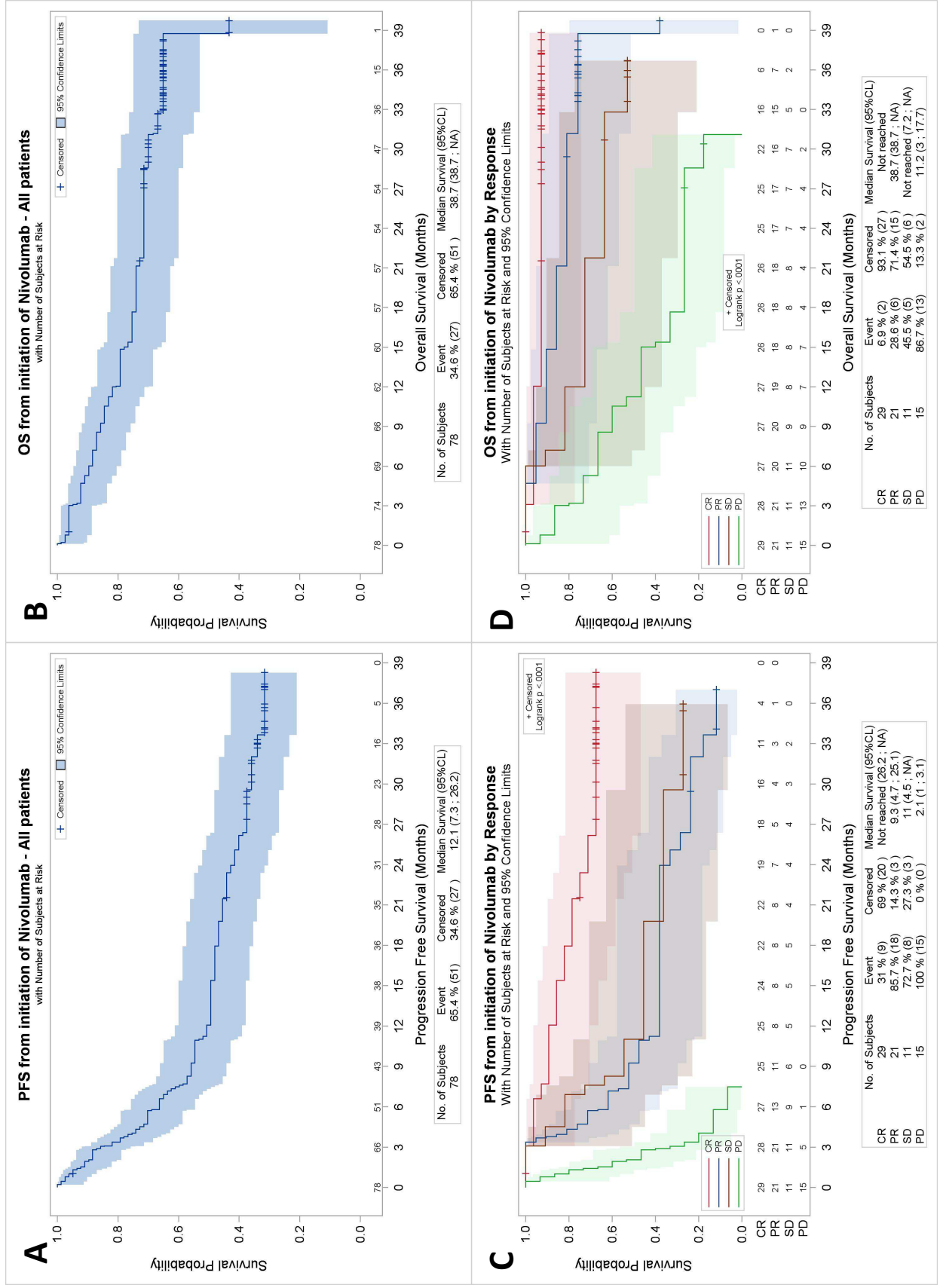


Figure 2. PFS (A) and OS (B) of patients in CR or PR after nivolumab monotherapy according to subsequent allogeneic-HSCT

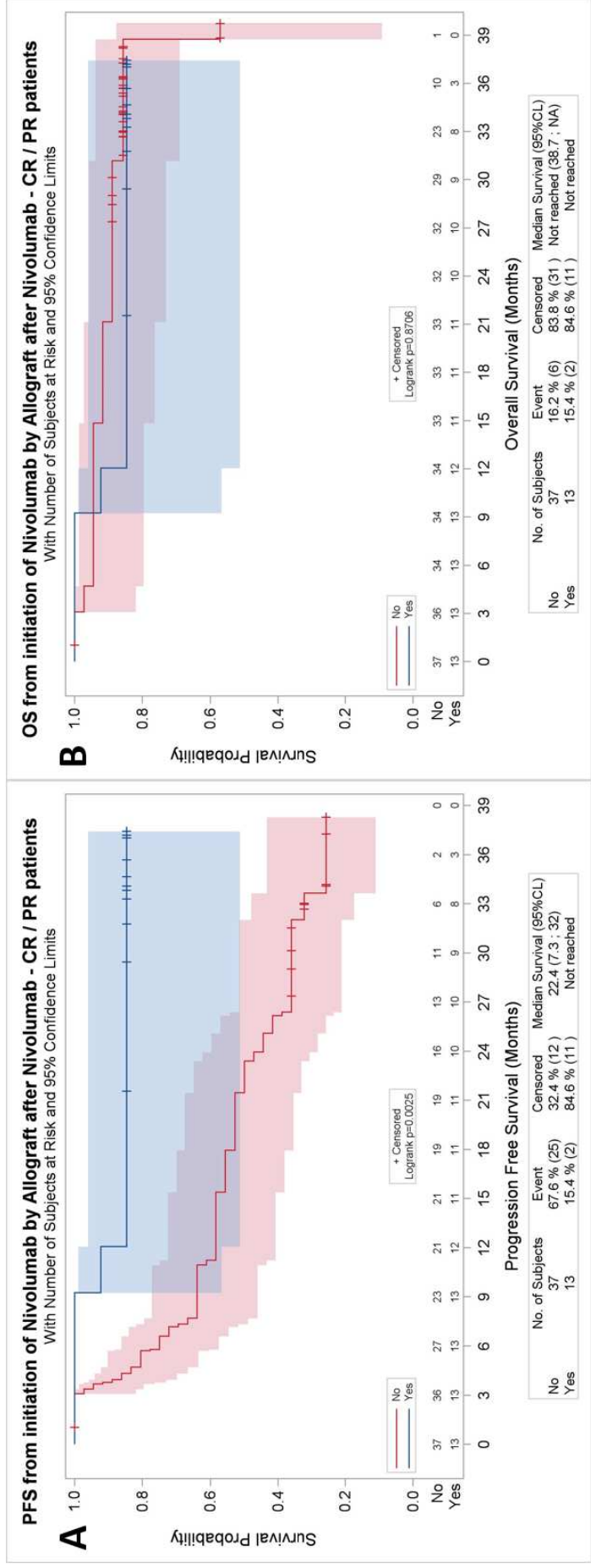


Figure 3. Outcome of patients who underwent allogeneic HSCT after nivolumab therapy

