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# PD-1 blockade and allogeneic hematopoietic stem cell transplantation in Hodgkin lymphoma, a matter of time: a national study on behalf of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire

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Data statement:

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author, [EK], upon reasonable request.

Checkpoint inhibitors such as PD1 blockade (or anti-PD1) are a standard of care for patients with relapsing or refractory (r/R) Hodgkin Lymphoma (HL), mainly in case of relapse after autologous stem cell transplantation and Brentuximab Vedontin therapy.[1] However, as pointed out in the Checkmate cohort, a minority of patients are long term responders, where 38% experience subsequent relapse, with median PFS at 14.7 months. Thus, PD1 Blockade are commonly used as a bridge to allogenic stem cell transplantation (allo-HSCT).[2] In fact, studies highlighted higher frequency of severe Graft Versus Host Disease (GVHD) after allo-HSCT in patients with pre-transplant PD1 Blockade exposure. A meta-analysis reported high rate of aGVHD (56%), and hyperacute GVHD (7%) with mortality attributed to GVHD of 11%.[3] But none compared the occurrence of GVHD between patients who received PD1 Blockade or not before allo-HSCT, impeding risk estimation.

We thus conducted a national retrospective case-control study to measure the risk of GVHD following PD1 Blockade and to explore potential GVHD prophylaxis strategies optimization.

Since PD1 inhibitors have been available in extended accessible program, patients who received allo-HSCT for Hodgkin Lymphoma (HL) between 2015 and 2018 in 21 tertiary care centers of the SFGM-TC (*Société Francophone de greffe de moelle et de thérapie cellulaire*) were included. Data were extracted from the EBMT (European Society for Blood and Marrow Transplantation) registry. All patients who received allo-HSCT signed an informed consent form, authorizing the collection and use for research purposes of their laboratory and clinical data regarding HSCT. The French national ethics board from the SFGM-TC approved this study, which has been declared to the Health Data Hub (number 4610090320).

Conventionally, conditioning was classified into either myeloablative (MAC) or Reduced Intensity Conditioning (RIC). MAC included total body irradiation, with a dose of 12

Gray or a total dose of Busulfan >8 mg/kg orally or >6.4 mg/kg intravenously. All other regimens were considered as RIC.

GVHD was assessed using the modified Glucksberg criteria for acute GVHD (aGVHD)[4] and the 2014 revised National Institutes of Health (NIH) Consensus Conference criteria for chronic GVHD (cGVHD).[5]

Regarding PD1 Blockade management, number of cycles, response to anti-PD1 therapy and time from last injection and allo-HSCT were collected. Because PD1 Blockade half-life is 27 days[6,7], time between last PD1 Blockade infusion and allo-HSCT was ultimately cut in 30 days periods.

The primary endpoint was the cumulative incidence of aGVHD and cGVHD from allo-HSCT. Secondary endpoints included overall survival (OS), progression free survival (PFS), non-relapse mortality (NRM) and GVHD free-relapse free Survival (GRFS). OS was defined as time from HSC infusion to death from any cause from allo-HSCT. We censored patients who either died or were lost to follow up. PFS was determined as survival from allo-HSCT without progression. NRM was defined as the time from HSC infusion to death from any cause other than disease with relapse as competing risk, and GRFS was defined as survival without relapse, severe aGVHD (grade III-IV) nor moderate-severe cGVHD.[8] OS, PFS, NRM and GRFS were estimated using Kaplan-Meier methods and we used log-rank test for comparison between groups. Cumulative incidence was used to estimate the endpoints of aGVHD and cGVHD/relapse/progression, death being the competitive event.

Comparison between two categorical variables was performed using Fisher exact test while continuous variables were compared with non-parametric Mann-Whitney-Wilcoxon test. A Cox proportional hazards model was used for multivariate (MVA) regression. Results are expressed as a hazard ratio (HR) with a 95% confidence interval (CI). All tests were two-

sided. The type-1 error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes.

A p-value <0.05 was considered significant. All analyses were performed using R software (version 4.1.2).[9]

Overall, 149 patients were eligible. Among them 50 (34%) received pre-transplant PD1 Blockade (PD1 group, n=48, 96% for Nivolumab, n=2, 4% for Pembrolizumab) and 99 (66%) were not exposed (no PD1 group).

Baseline patients and allo-HSCT characteristics were comparable between the two groups, except for number of lines before allo-HSCT **(Table 1)**.

Regarding PD1 Blockade exposure, patients received a median of 7.91 (range 1-25) and 9 (range 4-14) cycles of Nivolumab or Pembrolizumab respectively. Median time from last PD1 injection to allo-HSCT was 50 (IQR 33-103) days.

No significant difference was found between the PD1 and no PD1 groups regarding any grade of aGVHD, with respective occurrences of 58% and 57.6% (p=0.73), as depicted in **Figure 1A**. Likewise, median to onset of aGVHD was similar in both groups, with median time at 31.5 days [22;53] in PD1 group and 35.0 days in no PD1 group [23;53], p=0.78. Similarly, no significant differences were observed in the cumulative incidence of grade ≥II and grade III-IV, which were 36% and 12.0% in the PD1 group, and 41.1% and 16.2% in the no PD1 group respectively (p=0.65 for grade ≥II and p=0.67 for grade III-IV).

In addition, there were no significant differences in the cumulative incidence of cGVHD between PD1 and no PD1 patients, with rates of 26% and 34.3%, respectively (p=0.45, **Figure 1B**). Moreover, the proportion of patients requiring systemic therapy for cGVHD did not show any significant difference between the PD1 and no PD1 groups, with rates of 16.1% and 20.2%, respectively (p=0.70). Furthermore, mortality rate from acute and chronic GVHD was

comparable between the two groups (8% and 12% for the PD1 and non-PD1 cohorts, respectively, p=0.4).

Overall, clinical characteristics of aGVHD and cGVHD were comparable between both groups **(Supplementary Table 1)**.

Using Cox analysis, the unique factor associated with aGVHD was the delay between last PD1 blockade injection and allo-HSCT **(Supplementary Table 2)**.

We then compared the impact of time from last PD1 injection on aGVHD and cGVHD occurrence separated in four categories: <30d, 30-60, >60d, no PD1 blockade. We did not identify any difference regarding initial diagnostic characteristics of Hodgkin Lymphoma, nor those of allo-HSCT **(Supplementary Table 3)**. Only one patient who received PD1 blockade was not included due to lack of details concerning the date of last injection.

As depicted in **Figure 2**, we underlined an excess of aGVHD ≥II if last infusion occurred below 60 days (**2A**, p=0.0045) and severe aGVHD (**2B**, p=0.0044) if it occurred below 30 days with incidence of severe aGVHD increased at 41.7% compared to only 2.7% after 30 days (p=0.047). No patients experienced severe aGVHD after 60 days from last PD1 blockade injection. If infusion occurred below 30 days, we observed a trend to higher rate of chronic GVHD (**2C**, p=0.057), lower GRFS (**2D**, p=0.055), but significant higher NRM (**not shown**, p=0.033).

With a median follow-up of 34.7 months (IQR 13.3-52.7), the 2-year OS, PFS and GRFS (**data not shown**) were respectively 75.1% (95CI: 68.3-82.7), 73.2% (95CI: 65.6-81.6) and 44.6% (95CI: 37.0-53.9), without differences between subgroups with PD1 blockade and without anti-PD1.

Herein, we specifically report for the first time that timing of PD1 Blockade before allo-HSCT have a significant impact on rates of aGVHD. Studies regarding impact of delay are

contradictory. A meta-analysis from seven studies conducted on 107 patients, reported higher rate of aGVHD (56%) with median interval from last dose PD1 to allo-HSCT ranging between 28 and 62 days.[3] Merryman and al., reported lower severe aGVHD after median interval of 81 days from the last dose of PD1.[10] Nevertheless, a previous meta-analysis reported higher rate of grade III-IV aGVHD in PD1 blockade cohort (28% versus 8%, p=0.02) without correlation with time of last injection.[11]

The U.S Food and Drug Administration issued a "warning and precaution" after PD1 exposure.[12] These recommendations included PD1 interruption between 6 to 8 weeks before allo-HSCT, without specific studies focusing on the optimal delay of last injection of PD1. There is no clear effect of estimated anti-PD1 concentration or length of interval before allo-HCT on aGVHD or Treatment Related Mortality (TRM).[13] Implication of PD1 axis appears differential between secondary lymphoid organs (SLO) and tissues targeted by GVHD. In targeted organs by GVHD (i.e liver, skin, bowel disease), expression of PDL1 and PDL2 is lower, leading to high cytotoxic activity of LT, and tissue damages.[14]

Nonetheless, our study is constrained by its retrospective nature. The case control study was designed to mitigate this statistical limitation. We closely verified all dataset across all SFGM TC centers. No accurate data on more recent patients have been provided to extend the median follow-up. In light of these limitations, we did observe excess of any grades or severe aGVHD related to timing from last PD1 blockade infusion. This is the largest case-control study whereas other studies provided descriptive accounts of high rate of aGVHD. Presently, no data suggest a specific minimal or optimal delay.

In conclusion, this national case control study reports the safety of PD1 blockade before allo-HSCT. The results highlight the significance of the timing between PD1 blockade exposure and allo-HSCT to alleviate the risk of severe GVHD. It might be reasonable to suggest

a delay of over 60 days from the last PD1 blockade injection when possible. Further studies should be performed to explore the optimal timing of anti-PD1 and allo-HSCT and extend these findings.

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| | Overall N=149 | PD1 blockade exposure N=50 | No PD1 exposure N=99 | p.value |
|---|---|---|---|---|
| **Male Sex (%)** | 97 (65.1) | 35 (70.0) | 62 (62.6) | 0.48 |
| **Mean Age at diagnosis in years (min-max)** | 30.61 (9.4-63.4) | 28.81 (14.1-61.6) | 31.52 (9.4-63.4) | 0.18 |
| **Stage at diagnosis (%):** | | | | 0.25 |
| **I** | 4 (2.7) | 0 (0.0) | 4 (4.0) | |
| **II** | 51 (34.2) | 13 (26.0) | 38 (38.4) | |
| **III** | 31 (20.8) | 11 (22.0) | 20 (20.2) | |
| **IV** | 57 (38.3) | 24 (48.0) | 33 (33.3) | |
| **NA** | 6 (4.0) | 2 (4.0) | 4 (4.0) | |
| **Histology (%):** | | | | 0.68 |
| **Nodular** | 19 (12.8) | 4 (8.0) | 15 (15.2) | |
| **Scleronodular** | 90 (60.4) | 32 (64.0) | 58 (58.6) | |
| **Mix cellularity** | 11 (7.4) | 5 (10.0) | 6 (6.1) | |
| **NOS** | 10 (6.7) | 3 (6.0) | 7 (7.1) | |
| **NA** | 19 (12.8) | 6 (12.0) | 13 (13.1) | |
| **Number of lines before AlloSCT (SD)** | 3.34 (2.0) | 3.79 (2.2) | 3.04 (1.9) | 0.046* |
| **Previous AutoSCT (%)** | 112 (93.3) | 31 (86.1) | 81 (96.4) | 0.09 |
| **Disease Status at AlloSCT (%):** | | | | 0.22 |
| **CR** | 93 (64.1) | 27 (55.1) | 66 (68.8) | |
| **PR** | 42 (29.0) | 18 (36.7) | 24 (25.0) | |
| **Stable** | 8 ( 5.5) | 4 ( 8.2) | 4 ( 4.2) | |
| **Progression** | 2 ( 1.4) | 0 ( 0.0) | 2 ( 2.1) | |
| **Mean Age at AlloSCT in years (min-max)** | 35.14 (18.3-65.1) | 33.57 (19.2-65.1) | 35.93 (18.3-65.1) | 0.27 |
| **RIC (%)** | 134 (90.5) | 46 (92.0) | 88 (89.8) | 0.89 |
| **TBI (%)** | 62 (41.6) | 24 (48.0) | 38 (38.4) | 0.43 |
| **Mean dose (Gy)** | 2.16 | 2.42 | 2 | 0.21 |
| **HLA matching (%):** | | | | 0.81 |
| **Siblings** | 42 (28.4) | 13 (26.0) | 29 (29.6) | |
| **MUD** | 36 (24.3) | 11 (22.0) | 25 (25.5) | |
| **MMUD** | 4 ( 2.7) | 1 ( 2.0) | 3 ( 3.1) | |
| **Haploidentical** | 66 (44.6) | 25 (50.0) | 41 (41.8) | |
| **Stem Cells Source (%):** | | | | 0.75 |
| **BM** | 34 (23.0) | 10 (20.0) | 24 (24.5) | |
| **PBSC** | 113 (75.8) | 39 (78.0) | 74 (74.7) | |
| **CB** | 2 (1.4) | 1 (2.0) | 1 (1.0) | |

| | | | | |
|---|---|---|---|---|
| **Immunosuppressive therapy (%):** | | | | 0.78 |
| **Calcineurin Inhibitors+MMF** | 30 (20.1) | 9 (18.0) | 21 (21.2) | |
| **Calcineurin Inhibitors+MMF+ATG** | 41 (27.5) | 13 (26.0) | 28 (28.3) | |
| **CSA+MMF+PTCy** | 60 (40.3) | 23 (46.0) | 37 (37.4) | |
| **CSA+MTX** | 16 (10.7) | 5 (10.0) | 11 (11.1) | |
| **Others** | 2 (1.3) | 0 (0.0) | 2 (2.0) | |

**Table 1. Characteristics at initial Hodgkin diagnosis, in whole cohort and comparison between PD1 Blockade and no PD1 Blockade groups.**

NA : Not Available, Auto/Allo SCT : Autologous/Allogenic Stem Cell Transplantation, CR : Complete Response, PR : Partial Response, min : minimum, max : maximum, RIC: Reduced Intensity Conditioning, TBI: Total Body Irradiation, HLA: Human Leucocyte Antigen, MUD: Matched Unrelated Donor, MMUD: Mismatched Unrelated Donor, BM: Bone marrow, PBSC: Peripheral Blood Stem Cell, CB: Cord Blood, CMV: Cytomegalovirus, D/R: Donor/Recipient, CSA: Ciclosporin, MMF: Mycophenolate Mofetil, ATG: Anti Thymoglobuline, PTCy: Post-transplant Cyclophosphamide, MTX: Methotrexate, SD: Standard Deviation.

**Figure 1. Comparison of outcomes in whole cohort, between PD1 blockade and no PD1 groups.** Comparison of all grades acute GVHD (days, A) and chronic GVHD (months, B) in PD1 Blockade and no PD1 Blockade cohorts. Graft versus Host Disease Relapse Free Survival (GRFS) in PD1 Blockade and no PD1 Blockade cohorts (C).

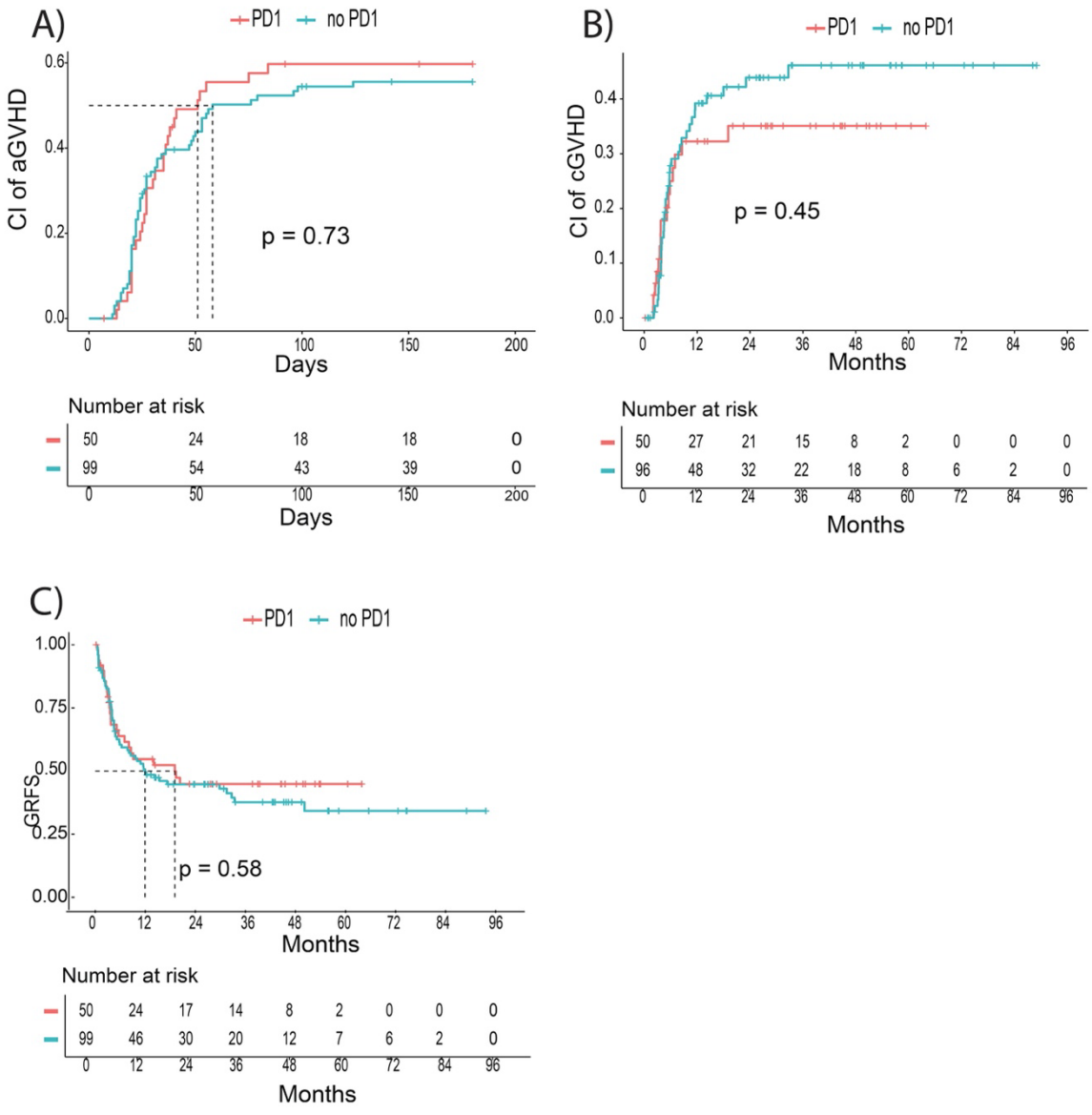
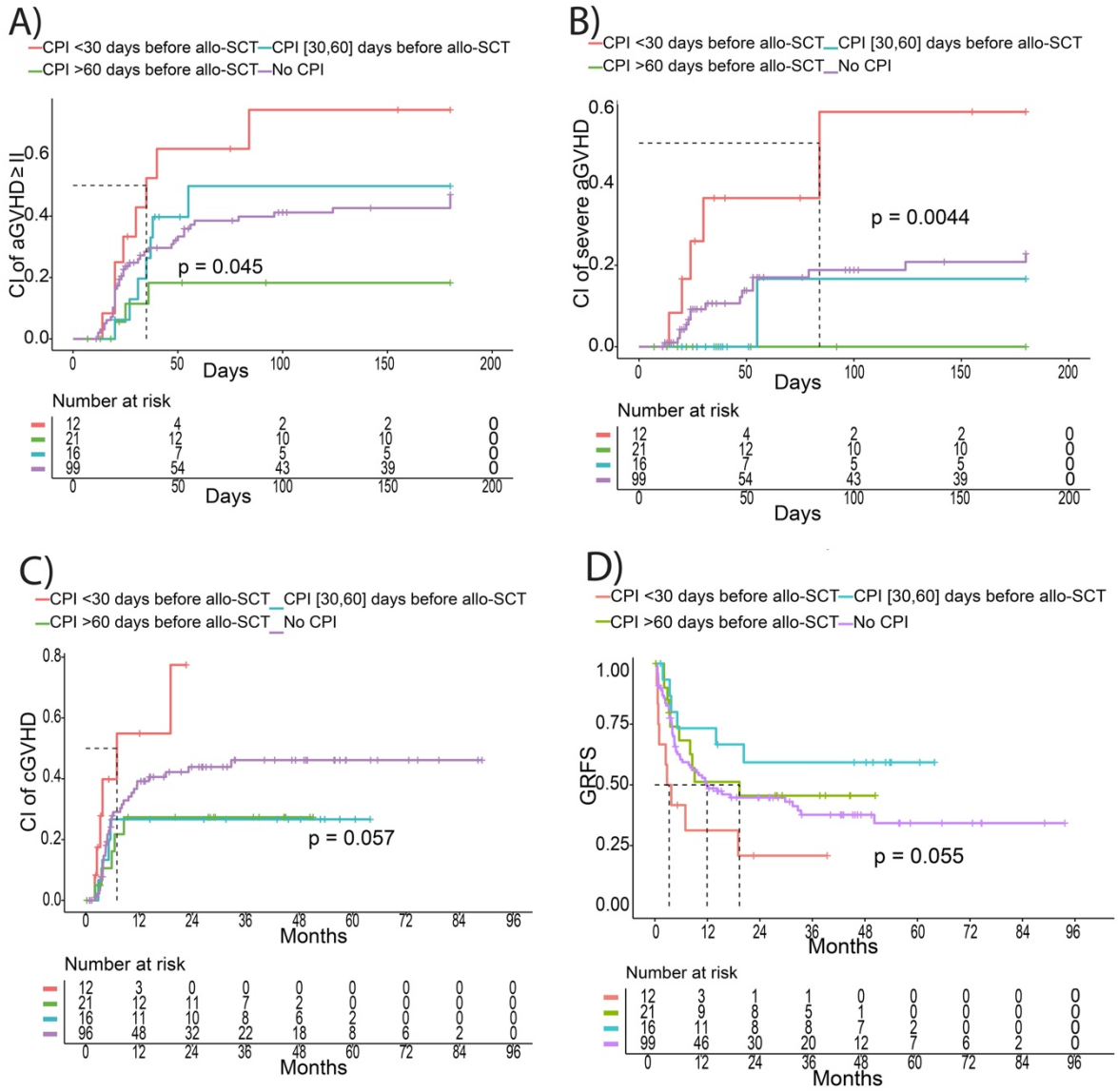


**Figure 2: Comparison of outcomes depending on delay from last PD1 blockade injection to allo-SCT .** Cumulative incidence (CI) of acute GVHD ≥ grade II (A), severe acute GVHD (grades III and IV, B) depending on delay (days), chronic GVHD (cGVHD, months, C) and Graft Versus Host Disease Relapse Free Survival (GRFS, months, D) from last PD1 Blockade injection to allo-SCT.



| | Overall N=149 | PD1 blockade N=50 | No PD1 N=99 | p.value |
|---|---|---|---|---|
| **Acute GVHD** | 86 (57.7) | 29 (58.0) | 57 (57.6) | 1.00 |
| **Acute GVHD ≥II (%)** | 59 (39.6) | 18 (36.0) | 41 (41.4) | 0.65 |
| **Severe grade GVHD (III-IV) (%)** | 22 (14.8) | 6 (12.0) | 16 (16.2) | 0.67 |
| **Stage skin aGVHD (%):** | | | | 0.37 |
| **1** | 26 (17.4) | 9 (18.0) | 17 (17.2) | |
| **2** | 26 (17.4) | 8 (16.0) | 18 (18.2) | |
| **3** | 22 (14.8) | 8 (16.0) | 14 (14.1) | |
| **4** | 2 (1.3) | 2 (4.0) | 0 (0.0) | |
| **Stage gut aGVHD (%):** | | | | 0.62 |
| **1** | 7 (4.7) | 2 (4.0) | 5 (5.1) | |
| **2** | 6 (4.0) | 3 (6.0) | 3 (3.0) | |
| **3** | 2 (1.3) | 1 (2.0) | 1 (1.0) | |
| **4** | 12 (8.1) | 2 (4.0) | 10 (10.1) | |
| **Stage aGVHD liver (%):** | | | | 0.30 |
| **1** | 6 (4.0) | 4 (8.0) | 2 (2.0) | |
| **2** | 1 (0.7) | 0 (0.0) | 1 (1.0) | |
| **3** | 4 (2.7) | 1 (2.0) | 3 (3.0) | |
| **4** | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| **Best response first line (%):** | | | | 0.61 |
| **CR** | 101 (67.8) | 35 (70.0) | 66 (66.7) | |
| **PR** | 9 (6.0) | 2 (4.0) | 7 (7.1) | |
| **Stable** | 1 (0.7) | 1 (2.0) | 0 (0.0) | |
| **Progression** | 14 (9.4) | 4 (8.0) | 10 (10.1) | |
| **NA** | 24 (16.1) | 8 (16.0) | 16 (16.2) | |
| **Chronic GVHD and NIH score (%):** | 47 (31.5) | 13 (26.0) | 34 (34.3) | 0.24 |
| **Mild** | 12 (25.5) | 3 (23.1) | 9 (26.5) | 0.70 |
| **Moderate** | 17 (36.2) | 4 (30.8) | 13 (38.2) | |
| **Severe** | 11 (23.4) | 4 (30.8) | 7 (20.1) | |
| **NA** | 7 (14.8) | 2 (15.4) | 5 (14.7) | |

**Supplementary Table 1: Characteristics of acute and chronic graft versus host disease, in whole cohort and comparison between PD1 blockade and no PD1 groups**

NA: Not Available, GVHD: Graft Versus Host Disease, CR: Complete Response, PR: Partial Response, PD1: Programmed cell Death protein 1

| Characteristics | OR[1] | 95% CI[1] | p-value |
|---|---|---|---|
| Number cycles CPI | 1.04 | 0.91, 1.20 | 0.6 |
| Time from last PD1 blockade infusion (30 days periods) | 0.39 | 0.15, 0.75 | 0.022* |
| RIC Conditioning | 24,5 | 0.00, NA | >0.9 |
| Stem Cell Source PSC | 2.34 | 0.35, 17.3 | 0.4 |
| Age at allo-SCT >50Y | 2.12 | 0.27, 18.5 | 0.5 |
| PTCy | 0.68 | 0.15, 2.96 | 0.6 |

[1]OR = Odds Ratio, CI = Confidence Interval, PTCy: Post-Transplant Cyclophosphamide, PD1: Programmed cell Death protein 1, RIC: Reduced Intensity Conditioning, PSC: Peripheral Stem Cell, allo-SCT: allogeneic stem cell transplantation

**Supplementary Table 2**: **Multivariate analysis of risk factors of acute Graft Versus Host Disease**

| | <30 days N=12 | [30-60] N=16 | >60 days N=21 | No PD1 N=99 | p.value |
|---|---|---|---|---|---|
| **Male sex (%)** | 10 ( 83.3) | 12 (75.0) | 12 (57.1) | 62 (62.6) | 0.81 |
| **Age at diagnosis, mean (SD)** | 27.6 (9.4) | 28.4 (11.9) | 30.1 (12.9) | 31.5 (11.6) | 0.52 |
| **Disease status at allo-HSCT:** | | | | | 0.051 |
| **CR** | 5 (41.7) | 5 (1.2) | 16 (76.2) | 66 (66.7) | |
| **PR** | 5 ( 1.7) | 10 (62.5) | 3 (14.3) | 24 (24.2) | |
| **Stable** | 2 (16.7) | 0 (0.0) | 2 (9.5) | 4 (4.0) | |
| **Progression** | 0 (0.0) | 0 0.0) | 0 (0.0) | 2 (2.0) | |
| **NA** | 0 (0.0) | 1 (6.2) | 0 (0.0) | 3 (3.0) | |
| **Number of lines before Allo-HSCT (SD)** | 3.5 (2.6) | 3.80 (2.6) | 4.10 (1.5) | 3.04 (1.9) | 0.15 |
| **Previous (%):** | | | | | 0.04* |
| **Allo-HSCT** | 2 (16.7) | 2 (12.5) | 0 (0.0) | 3 (3.0) | |
| **Auto-HSCT** | 8 (66.7) | 9 (56.2) | 14 (66.7) | 81 (81.8) | |
| **NA** | 2 (16.7) | 5 (31.2) | 7 (33.3) | 15 (15.2) | |
| **Mean Age at HSCT (SD)** | 32.3 (10.3) | 34.3 (14.3) | 34.0 (13.1) | 35.9 (12.0) | 0.74 |
| **TBI (%)** | 4 (33.3) | 6 (37.5) | 13 (61.9) | 38 (38.4) | 0.56 |
| **RIC conditioning (%)** | 10 (83.3) | 16 (100.0) | 19 (90.5) | 88 (88.9) | 0.81 |
| **PTCy (%)** | 4 (33.3) | 9 (56.2) | 9 (42.9) | 37 (37.4) | 0.43 |
| **ATG (%)** | 8 (66.7) | 5 (31.2) | 4 (19.0) | 37 (37.4) | 0.12 |
| **HLA matching (%):** | | | | | 0.97 |
| **Siblings** | 4 (33.3) | 4 (25.0) | 5 (23.8) | 29 (29.3) | |
| **MUD** | 4 (33.3) | 0 (0.0) | 3 (14.3) | 25 (25.3) | |
| **Haploidentical** | 4 (33.3) | 8 (50.0) | 12 (57.1) | 41 (41.4) | |
| **MMUD** | 0 (0.0) | 0 (0.0) | 1 (4.8) | 3 (3.0) | |
| **NA** | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.0) | |
| **Stem cell source (%):** | | | | | 0.79 |
| **BM** | 4 (33.3) | 4 (25.0) | 2 (9.5) | 24 (24.2) | |
| **CSP** | 8 (66.7) | 12 (75.0) | 18 (85.7) | 73 (73.7) | |
| **USP** | 0 (0.0) | 0 (0.0) | 1 (4.8) | 1 (1.0) | |
| **NA** | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.0) | |

**Supplementary Table 3: Characteristics at initial Hodgkin diagnosis and HSCT, depending on delay of last PD1 blockade injection and comparison with no PD1 group.**

NA: Not Available, Auto/Allo-HSCT: Autologous/Allogenic Hematological Stem Cell Transplantation, CR: Complete Response, PR: Partial Response, RIC: Reduced Intensity Conditioning, TBI: Total Body Irradiation, HLA: Human Leucocyte Antigen, MUD: Matched Unrelated Donor, MMUD: Mismatched Unrelated Donor, BM: Bone marrow, PBSC: Peripheral Blood Stem Cell, CB: Cord Blood, ATG: Anti Thymoglobulin, PTCy: Post-Transplant Cyclophosphamide, GVHD: Graft Versus Host Disease, CR: Complete Response, PR: Partial Response, PD1: Programmed cell Death protein 1