# 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

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 progression-free survival (PFS) at 14.7 months. Thus, PD1 blockade are commonly used as a bridge to allogeneic stem cell transplantation (allo-SCT).[2] In fact, studies highlighted higher frequency of severe graft-*versus*-host disease (GVHD) after allo-SCT in patients with pretransplant PD1 blockade exposure. A meta-analysis reported high rate of acute GVHD (aGVHD) (56%), and hyperacute GVHD (7%) with mortality attributed to GVHD of 11%.[3] However, no studies compared the occurrence of GVHD between patients who received PD1 blockade or not before allo-SCT, 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 an extended accessible program, patients who received allo-SCT 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 European Society for Blood and Marrow Transplantation (EBMT) registry. All patients who received allo-SCT signed an informed consent form, authorizing the collection and use for research purposes of their laboratory and clinical data regarding SCT. 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 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-SCT were collected. Because PD1 blockade half-life is 27 days,[6,7] time between last PD1 blockade infusion and allo-SCT was ultimately cut in 30-day periods.

The primary endpoint was the cumulative incidence of aGVHD and cGVHD from allo-SCT. 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 hematopoietic stem cell (HST) infusion to death from any cause from allo-SCT. We censored patients who either died or were lost to follow-up. PFS was determined as survival from allo-SCT without progression. NRM was defined as the time from stem cell 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 of <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 pretransplant 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-SCT (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-SCT was 50 (interquartile range [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 onset of aGVHD was similar in both groups, with median time at 31.5 days (IQR, 22-53) in PD1 group and 35.0 days in no PD1 group (IQR, 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;

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

| | Overall N=149 | PD1 blockade exposure N=50 | No PD1 exposure N=99 | *P* |
|---|---|---|---|---|
| Male sex, N (%) | 97 (65.1) | 35 (70.0) | 62 (62.6) | 0.48 |
| Mean age at diagnosis in years (range) | 30.61 (9.4-63.4) | 28.81 (14.1-61.6) | 31.52 (9.4-63.4) | 0.18 |
| Stage at diagnosis, N (%) | | | | 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, N (%) | | | | 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 allo-SCT (SD) | 3.34 (2.0) | 3.79 (2.2) | 3.04 (1.9) | 0.046* |
| Previous auto-SCT, N (%) | 112 (93.3) | 31 (86.1) | 81 (96.4) | 0.09 |
| Disease status at allo-SCT, N (%) | | | | 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 in years at allo-SCT (range) | 35.14 (18.3-65.1) | 33.57 (19.2-65.1) | 35.93 (18.3-65.1) | 0.27 |
| RIC, N (%) | 134 (90.5) | 46 (92.0) | 88 (89.8) | 0.89 |
| TBI, N (%) | 62 (41.6) | 24 (48.0) | 38 (38.4) | 0.43 |
| Mean dose (Gy) | 2.16 | 2.42 | 2 | 0.21 |
| HLA matching, N (%) | | | | 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, N (%) | | | | 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, N (%) | | | | 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) | |

NA: not available; NOS: not otherwise specified; auto/allo SCT: autologous/allogeneic stem cell transplantation; CR: complete response; PR: partial response; min: minimum; max: maximum; RIC: reduced intensity conditioning; TBI: total body irradiation; HLA: human leukocyte 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: cyclosporin; MMF: mycophenolate mofetil; ATG: anti thymoglobuline; PTCy: post-transplant cyclophosphamide; MTX: methotrexate; SD: standard deviation. *Significant.

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 aGVHD and cGVHD 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 (*Online Supplementary Table S1*).

Using Cox analysis, the unique factor associated with aGVHD was the delay between last PD1 blockade injection and allo-SCT (*Online Supplementary Table S2*).

We then compared the impact of time from last PD1 injection on aGVHD and cGVHD occurrence separated in four categories: <30 days, 30-60 days, >60 days, no PD1 blockade. We did neither identify any difference regarding initial diagnostic characteristics of Hodgkin lymphoma, nor those of allo-SCT (*Online Supplementary Table S3*). 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 (Figure 2A; *P*=0.0045) and severe aGVHD (Figure 2B; *P*=0.0044) if it

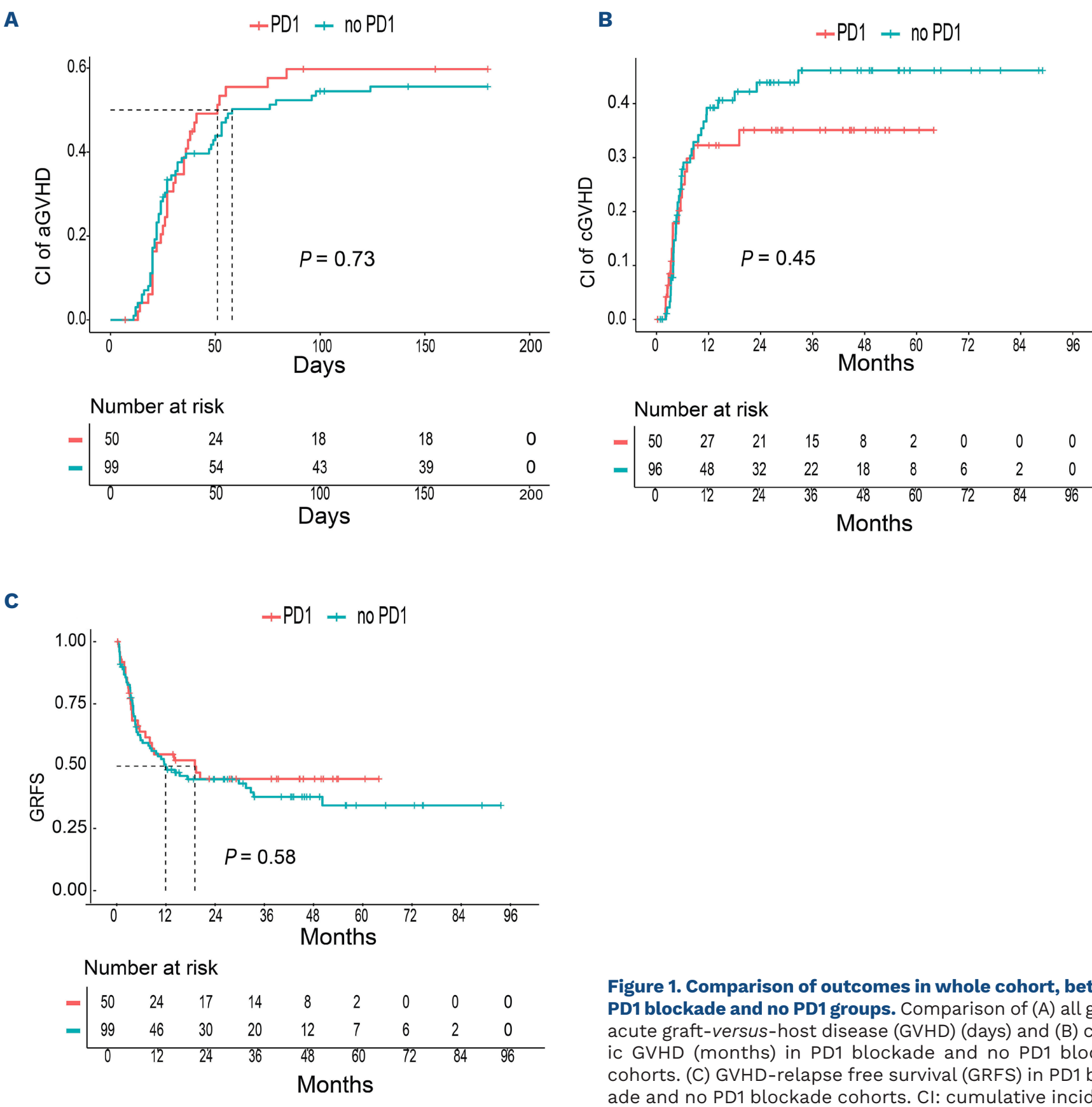


**Figure 1. Comparison of outcomes in whole cohort, between PD1 blockade and no PD1 groups.** Comparison of (A) all grades acute graft-*versus*-host disease (GVHD) (days) and (B) chronic GVHD (months) in PD1 blockade and no PD1 blockade cohorts. (C) GVHD-relapse free survival (GRFS) in PD1 blockade and no PD1 blockade cohorts. CI: cumulative incidence.

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 cGVHD (Figure 2C; *P*=0.057), lower GRFS (Figure 2D; *P*=0.055), but significant higher NRM (*data 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% (95% confidence interval [CI]: 68.3-82.7), 73.2% (95% CI: 65.6-81.6) and 44.6% (95% CI: 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

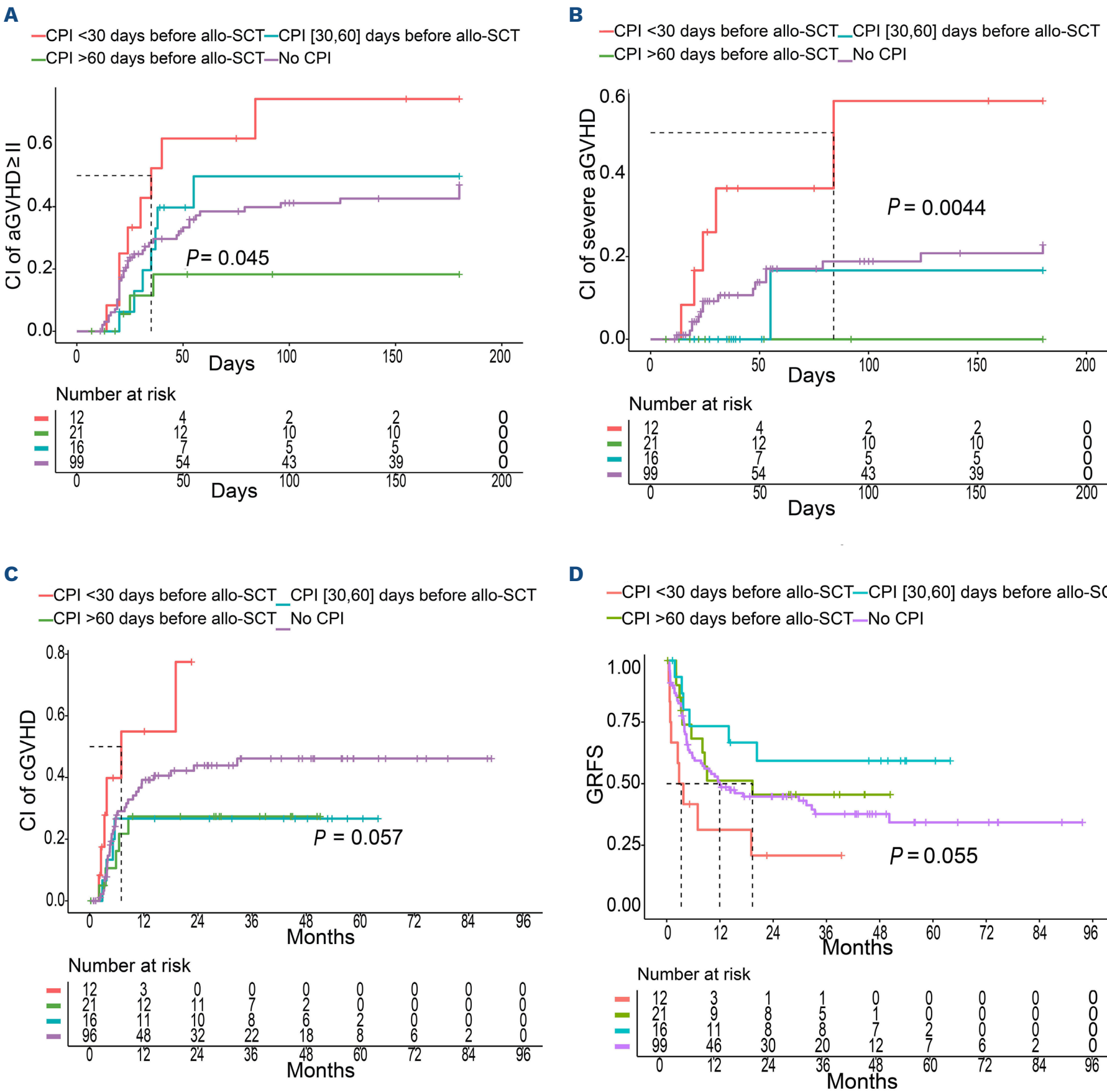


**Figure 2. Comparison of outcomes depending on delay from last PD1 blockade injection to allogeneic stem cell transplantation.** Cumulative incidence (CI) of (A) acute graft-*versus*-host disease (aGVHD) grade ≥II, (B) severe aGVHD (grades III and IV) depending on delay (days), (C) chronic GVHD (cGVHD) (months) and (D) GVHD relapse-free survival (GRFS) (months) from last PD1 blockade injection to allogeneic stem cell transplantation (allo-SCT). CPI: checkpoint inhibitor.

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-SCT ranging between 28 and 62 days.[3] Merryman *et 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% *vs*. 8%; *P*=0.02) without correlation with time of last injection.[11]

The US 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-SCT, 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-SCT on aGVHD or treatment-related mortality.[13] Implication of PD1 axis appears differential between secondary lymphoid organs 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 lymphotoxins, 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-SCT. The results highlight the significance of the timing between PD1 blockade exposure and allo-SCT 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-SCT and extend these findings.

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**Disclosures**

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**Contributions**

Study conception and design by AV and EK. Data collection by EK. Statistical analysis and generation of figures by FB. Interpretation of results by EK, AV, NV and DM. Draft manuscript writing by EK. All authors reviewed the results and approved the final version of the manuscript.

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**Data-sharing statement**

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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