

# Allogeneic Hematopoietic Cell Transplantation for Relapsed/Refractory Hodgkin Lymphoma: A Multicenter Real-World Experience

## Relaps/Refrakter Hodgkin Lenfomada Allojenik Hematopoetik Hücre Nakli: Çok Merkezli Gerçek Yaşam Deneyimi

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### Abstract

**Objective:** Allogeneic hematopoietic cell transplantation (allo-HCT) remains a curative option for relapsed or refractory (R/R) Hodgkin lymphoma despite advances with novel therapeutic agents such as brentuximab vedotin (BV) and immune checkpoint inhibitors (CPIs). This study aimed to assess the benefit of prior exposure to novel therapeutic agents prior to allo-HCT in patients with R/R Hodgkin lymphoma.

**Materials and Methods:** This study's retrospective multicentric analysis involved 70 patients with R/R classical Hodgkin lymphoma who underwent allo-HCT.

**Results:** The analyzed patients were split into two main treatment cohorts: Era 1 (2004-2010) included 16 patients, while Era 2 (2011-2021) included 54 patients. Within the total patient cohort, 63 patients had previously received autologous stem cell transplantation. Forty patients were administered only BV (n=29) or BV preceding CPI (n=11) before allo-HCT. A median follow-up duration of 64 months (range: 40.7-87.3) revealed a 100-day non-relapse mortality (NRM) rate of 26%, with 3-year overall survival (OS) and progression-free survival (PFS) rates of 39% and 28%, respectively. Allo-HCT with haplotype-matched donors was linked to better OS and PFS. Post-transplant cyclophosphamide as a prophylactic approach for graft-versus-host disease significantly improved OS and PFS. A complete response during the post-transplant period significantly improved OS and PFS. Better OS, better PFS, and reduced NRM were observed both before and after allo-HCT in patients receiving BV and CPIs, although statistical significance was not reached. The OS and PFS curves and the NRM rates were similar between Era 1 and Era 2.

**Conclusion:** Allo-HCT is a potentially practical therapeutic approach for the treatment of patients with R/R Hodgkin lymphoma.

**Keywords:** Hodgkin lymphoma, Allogeneic stem cell transplantation, Brentuximab vedotin, Checkpoint inhibitors

### Öz

**Amaç:** Brentuksimab vedotin (BV) ve immün kontrol noktası inhibitörleri (CPI) ile sağlanan önemli terapötik ilerlemelere rağmen, nüks veya tedaviye dirençli (R/R) Hodgkin lenfoma olgularında allojenik hematopoetik kök hücre nakli (AKHN) küratif potansiyelini sürdürmektedir. Bu çalışma, R/R Hodgkin lenfoma hastalarında AKHN'nin klinik sonuçlarını değerlendirmeyi amaçlamaktadır.

**Gereç ve Yöntemler:** Retrospektif ve çok merkezli bu çalışmada, AKHN uygulanmış 70 R/R klasik Hodgkin lenfoma hastasının verileri analiz edilmiştir.

**Bulgular:** Hastalar tedavi dönemlerine göre iki gruba ayrıldı: dönem 1 (2004-2010, 16 hasta) ve dönem 2 (2011-2021, 54 hasta). Hastaların 63'ü daha önce olog kök hücre nakli geçirmişti. Kırk hastaya AKHN öncesinde BV (n=29) veya BV sonrası CPI (n=11) uygulanmıştı. Ortanca 64 aylık (40,7-87,3) takip süresinde 100 günlük nüks dışı mortalite (NDM) oranı %26; 3 yıllık genel sağkalım (GS) ve progresyonsuz sağkalım (PS) oranları sırasıyla %39 ve %28 olarak saptandı. Haploidentik donörlerle yapılan AKHN daha iyi GS ve PS ile ilişkiliydi. Graft-versus-host hastalığı profilaksisinde post-transplant siklofosamid kullanımı sağkalımı anlamlı biçimde iyileştirdi. Transplant sonrası tam yanıt elde edilmesi GS ve PS üzerinde belirgin avantaj sağladı. BV ve CPI alan hastalarda daha iyi GS, PS ve daha düşük NDM eğilimi gözlene de istatistiksel anlamlılık sağlanamadı. Tedavi dönemleri arasında GS, PS ve NDM açısından anlamlı fark izlenmedi.

**Sonuç:** Bulgularımız, AKHN'nin R/R Hodgkin lenfoma hastalarında uygulanabilir ve potansiyel olarak küratif bir tedavi seçeneği olmaya devam ettiğini göstermektedir.

**Anahtar Sözcükler:** Hodgkin lenfoma, Allojenik kök hücre nakli, Brentuksimab vedotin, Immün kontrol noktası inhibitörleri



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## Introduction

Hodgkin lymphoma generally has a high likelihood of cure. However, up to 20% of patients may experience relapsed or refractory (R/R) outcomes to initial treatments. High-dose salvage chemotherapy, accompanied by autologous stem cell rescue, has become an established therapeutic approach for patients with chemosensitive disease [1,2]. Autologous stem cell transplantation (ASCT) outcomes in cases of R/R Hodgkin lymphoma are generally unfavorable, with approximately 50% of these patients experiencing relapse [2,3]. Although emerging therapeutic agents such as immune checkpoint inhibitors (CPIs) like nivolumab or pembrolizumab and the anti-CD30 conjugate brentuximab vedotin (BV) have demonstrated substantial therapeutic potential, the risk of pending relapse in this patient population remains high [4,5,6]. Even with the advent of novel therapeutic agents, allogeneic hematopoietic stem cell transplantation (allo-HCT) has retained its curative potential, albeit with significant morbidity and mortality rates [3,7]. This study aimed to assess the benefit of prior exposure to novel therapeutic agents before allo-HCT in patients with R/R Hodgkin lymphoma.

## Materials and Methods

This study retrospectively assessed the outcomes of 70 patients with R/R classical Hodgkin lymphoma who underwent allo-HCT at three transplant centers from 2004 to 2021. Information on age, performance status, disease stage, prior lines of therapy, relapse rate, previous ASCT, duration and number of doses of BV and/or CPIs, clinical condition of the disease at the time of the transplant, conditioning regimen, donor origin, graft-versus-host disease (GVHD), and post-transplant outcomes were extracted from medical records. Conditioning intensity was classified as myeloablative (MAC), reduced-intensity (RIC), or non-myeloablative according to the consensus definitions of the European Society for Blood and Marrow Transplantation (EBMT) [8]. Patients were included from 2010 and earlier (Era 1) in one center and from 2011 onwards (Era 2) across all three centers. Therapeutic response was defined in accordance with the Lugano classification [9]. BV and CPIs were administered after transplantation only in cases of R/R disease. Computed tomography (CT) and/or positron emission tomography (PET)-CT were employed to assess disease condition before transplantation [9]. The post-transplant overall response rate (ORR) was the primary endpoint. Secondary endpoints included overall survival (OS), progression-free survival (PFS), non-relapse mortality (NRM), and response rates stratified by transplant years and pre- and post-transplant CPI and/or BV use. Neutrophil and platelet recovery were identified as at least three consecutive days of absolute neutrophil counts reaching at least  $0.5 \times 10^9/L$  and platelet counts reaching at least  $20 \times 10^9/L$  without transfusion [10]. Acute and chronic GVHD were evaluated based on standard grading criteria [11,12].

The Ankara University Human Research Ethics Committee approved the study (date: 22.04.2022; decision no: İ05-247-22). Despite limited statistical power due to sample size constraints, subgroup analyses were conducted to explore potential associations.

## Statistical Analysis

Demographic and patient characteristics were summarized and analyzed using descriptive methods. Two main eras were considered in the study. The primary analysis stratified patients into these two broad eras based on transplant year (Era 1: 2004-2010; Era 2: 2011-2021). In addition, to highlight the major shift in transplant practices after 2016, including the adoption of post-transplant cyclophosphamide, increased use of haploidentical donors, and wider availability of targeted agents (BV and CPIs), a secondary two-era comparison was performed (Era 4: 2004-2015; Era 5: 2016-2021). Analysis of a three-era structure reflects the transition from the period before the introduction of novel therapeutic agents (2004-2010) to an early targeted-therapy period before widespread post-transplant cyclophosphamide (2011-2015), and finally to the modern transplant era characterized by routine post-transplant cyclophosphamide use, expansion of haploidentical transplantation, and broad access to BV and CPIs (2016-2021), allowing the evaluation of long-term trends across clinically distinct periods.

Categorical variables were compared using Fisher's exact test or the chi-square test and continuous variables were analyzed using the t-test. Kaplan-Meier analysis was used to estimate survival and log-rank tests were used to analyze group differences. Statistical significance was accepted at  $p < 0.05$ . NRM was defined as death occurring prior to lymphoma progression or recurrence and was calculated as the duration of time from allo-HCT date to death. The cumulative incidence method was applied to estimate both relapse incidence and NRM. OS, PFS, NRM, and GVHD were analyzed using univariate and multivariate Cox proportional hazards models. To account for competing risks between relapse and NRM, we performed Fine-Gray subdistribution hazards modeling. Variables with significance of  $p < 0.05$  or strong clinical relevance were included in the multivariate models. All analyses were performed using IBM SPSS Statistics 20 (IBM Corp., Armonk, NY, USA).

## Results

Patient characteristics are detailed in Table 1. Among the 70 analyzed patients, 16 cases were from Era 1 (2004-2010) and 54 were from Era 2 (2011-2021). The median age of the participants was 35 years (range: 18-62) and 59% were male. A median of 4 treatment lines (range: 2-8) were administered before allo-HCT. Sixty-three patients (90%) had undergone a prior ASCT, and 4 patients (6%) had received a second ASCT. After 2013, 40 patients (57.1%) received only BV ( $n=29$ ) (median: 3 cycles, range: 1-14)

or BV followed by CPIs (nivolumab [n=10], pembrolizumab [n=1]), while 1 patient received only a CPI prior to allo-HCT. Among patients treated with BV alone, the responses included complete response (CR) (n=8), partial response (PR) (n=8), stable disease (SD) (n=12), and progressive disease (PD) (n=1). One patient receiving nivolumab alone had SD. Among 11 patients who received BV followed by a CPI, 3 achieved CR, 3 achieved PR, 3 had SD, and 2 had PD. Patients received a median of 6 CPI doses (range: 3-20), with a median interval from the last CPI dose to allo-HCT of 4.2 months (range: 1.6-7.9). No center-mandated wash-out period was implemented; the interval from CPI to allo-HCT represented routine clinical practice rather than predefined institutional policies. Nine patients (75%) transitioned directly to allo-HCT following CPI therapy, whereas 3 (25%) received single-line salvage therapy between CPI treatment and allo-HCT. The median Karnofsky Performance Status (KPS) score was 80 (range: 70-100) among all patients. By the time of allo-HCT, 11 patients (15.7%) had achieved CR, 18 patients (25.7%) had achieved PR, and 41 patients (58.6%) had SD or PD. Forty-seven patients received RIC (67.1%) and 46 received fludarabine-based conditioning. A significant proportion of patients in the fludarabine subset were administered a fludarabine/melphalan (Flu/Mel) regimen (n=35) or a Flu/Mel/total body irradiation (TBI) regimen (n=5) [13,14]. In the cohort of patients treated with MAC (32.9%), most patients received the busulfan/cyclophosphamide (Bu4/Cy120) (n=10) or Flu/TBI12 (n=8) regimen [15,16].

	Center 1	28	40.0%
Center	Center 2	27	38.6%
	Center 3	15	21.4%
Time of transplant	Era 1	16	22.9%
	Era 2	54	77.1%
Age, years, median		35 (18-62)	
Follow-up time, months, median		64.0 (40.7-87.3)	
Age, years	≤40	49	70.0%
	>40	21	30.0%
Sex	Male	41	58.6%
	Female	29	41.4%
KPS score before allo-HCT	≤70	25	35.7%
	>70	45	64.3%
Stage	Early	24	34.3%
	Advanced	46	65.7%
Treatment before allo-HCT	≤3 lines	26	37.1%
	>3 line	44	62.9%
RT use before allo-HCT	Yes	32	45.7%
	No	38	54.3%
BV use before allo-HCT	Yes	40	57.1%
	No	30	42.9%

CPI use before allo-HCT	Yes	12	17.1%
	No	58	82.9%
Disease status before allo-HCT	CR	11	15.7%
	PR	18	25.7%
	SD/PD	41	58.6%
Conditioning regimen	RIC	47	67.1%
	MAC	23	32.9%
Stem cell source	PB	62	88.6%
	BM	7	10.0%
	Umbilical cord	1	1.4%
ATG use	Yes	13	18.6%
	No	57	81.4%
Acute GVHD	Yes	29	41.4%
	No	40	57.1%
	N/A	1	1.4%
Chronic GVHD	Yes	17	24.3%
	No	52	74.3%
	N/A (deceased at D100)	1	1.4%
BV use after allo-HCT	Yes	11	15.7%
	No	59	84.3%
CPI use after allo-HCT	Yes	8	11.4%
	No	62	88.6%
Status at D100 after allo-HCT	CR	27	50.0%
	PR	13	24.1%
	SD/PD	14	25.9%
	N/A (deceased at D100)	16	
NRM	Yes	29	41.4%
	No	41	58.6%
Mortality at D100 after allo-HCT	Yes	18	25.7%
	No	52	74.3%

Allo-HCT: Allogeneic hematopoietic cell transplantation; ATG: antithymocyte globulin; BM: bone marrow, BV: brentuximab vedotin; CPI: immune checkpoint inhibitor; CR: complete response; D100: day 100 after allo-HCT; Era 1: 2004-2010; Era 2: 2011-2021; GVHD: graft-versus-host disease; KPS: Karnofsky Performance Status; MAC: myeloablative conditioning; N/A: not applicable; NRM: non-relapse mortality; PB: peripheral blood; PR: partial response; RIC: reduced-intensity conditioning; RT: radiotherapy; SD/PD: stable disease/progressive disease.

Transplants involved matched related donor (MRD; siblings) (n=39), matched unrelated donor (MUD) (n=16), haploidentical donor (n=11), and mismatched unrelated donor (MMUD) (n=4) origins. Sixty-two patients received peripheral blood transplants, 7 received bone marrow transplants, and 1 received an umbilical cord transplant. T-cell depletion in cases of unrelated and haploidentical donors consisted mainly of antithymocyte globulin (ATG) (n=13) or post-transplant cyclophosphamide (n=16). Patients undergoing MRD allo-HCT received conventional

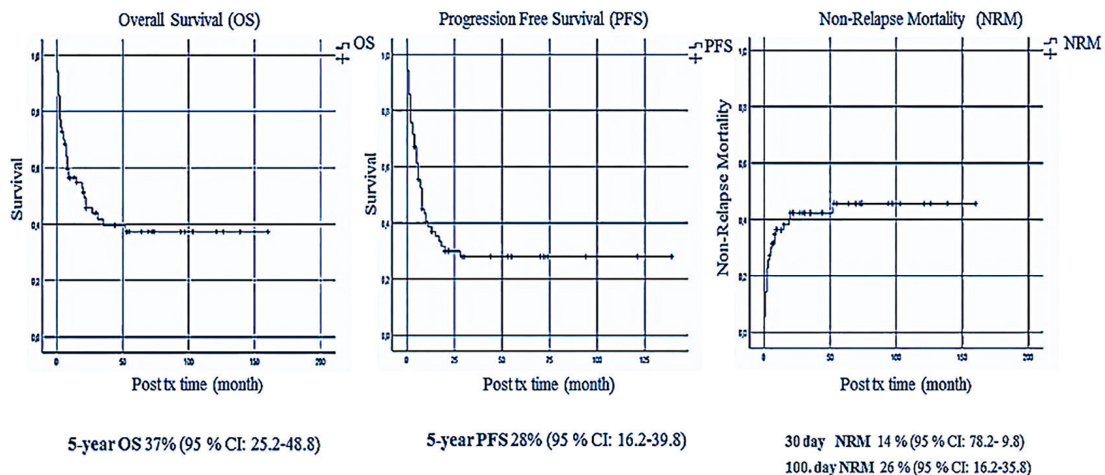
GVHD prophylaxis with calcineurin inhibitors. Cyclosporin combined with methotrexate was the most frequently administered GVHD prophylactic regimen, with cyclosporin and mycophenolate serving as the primary alternative. The infused CD34+ cell dose had a median value of  $5.6 \times 10^6/\text{kg}$  (range:  $0.6-14.7 \times 10^6/\text{kg}$ ).

Sixty-two patients (88.5%) were fully engrafted. Primary engraftment failure occurred in 8 patients (11.4%), 2 of whom had MRD transplants and 6 of whom had non-MRD transplants (haploidentical, MMUD, or MUD). Most transplants were performed before 2015. Similar findings have been reported in autologous transplant settings, where low CD34+ or total nucleated cell doses were associated with poor hematological recovery and increased early mortality [17]. Engraftment was seen after a median of 16 days (range: 13-28) for neutrophils and 13 days (range: 7-39) for platelets. Results of a chimerism assessment on day +100 were available for 48 patients (68.5%). Complete donor chimerism, defined as 95%-100% donor cells ( $n=44$ ), and mixed chimerism, defined as 75.5%-94% donor cells ( $n=34$ ), were observed in all but 1 patient. Fifteen patients died prior to chimerism assessment and 7 patients had no data. Twenty-nine patients (41.4%) experienced acute GVHD, and 15 of these patients (51.7%) had grade II-IV disease. Chronic GVHD was observed in 17 patients (24.3%), with moderate/severe involvement documented in 7 cases (41.2%). Invasive fungal infections were observed in 18 (25.7%) patients, with 4 cases being fatal. Causes of death were associated with bacterial ( $n=4$ ), viral ( $n=3$ ; cytomegalovirus colitis, cytomegalovirus pneumonia, tuberculosis), and sepsis-related ( $n=14$ ) complications, including cases with GVHD, relapse, or organ failure. In 5 cases, no specific pathogen was identified.

The median length of follow-up after allo-HCT was 64 months (range: 40.7-87.3). Following transplantation, 27 patients (50%)

achieved CR; disease relapse or progression was observed in 23 patients (33%), with a median time to relapse of 6.3 months (range: 1-24.5). Eleven patients (15.7%) and 8 patients (11.4%) who relapsed after allo-HCT received chemotherapy with BV and/or CPIs as salvage and/or maintenance therapy after the allo-HCT, respectively. Among these cases, 4 patients received BV exclusively as maintenance therapy, 1 patient received nivolumab monotherapy, and 7 patients received BV followed by CPI. After allo-HCT, the median course numbers of BV and CPI therapy were 4 (range: 2-18) and 3 (range: 1-51), respectively. Donor lymphocyte infusion (DLI) was provided for 10 patients to manage relapse or PD following allo-HCT: 2 patients received DLI for overt clinical relapse, while 8 patients were treated due to loss or decrease of donor chimerism. No patient received DLI prophylactically. Patients underwent a median of two DLIs (range: 1-3), with the first DLI occurring at a median of 8 months (range: 2-57). Six patients (60%) received DLI with salvage chemotherapy. ORRs (CR and PR) were 1/4 (25%) among patients receiving DLI alone and 4/6 (66%) for those patients receiving DLI and additional therapy. At the time of the analysis, 29 patients were alive (41%), including 23 with CR (79%), 4 with PR (14%), and 2 with SD (7%). The 3- and 5-year estimated OS rates were 39% (95% confidence interval [CI]: 27.2-50.8) and 37% (95% CI: 25.2-48.8), respectively. The 3- and 5-year PFS rate was 28% (95% CI: 16.2-39.8), while day +100 and 1-year NRM rates were 26% (95% CI: 16.2-35.8) and 37% (95% CI: 25.2-48.8), respectively (Figure 1).

Regarding donor type, pre-transplant CPI ( $p<0.05$ ), the inclusion of TBI in the conditioning regimen ( $p<0.001$ ), and post-transplant cyclophosphamide ( $p<0.001$ ) were more frequent in cases of haploidentical transplantation. ATG was more commonly used for MUD/MMUD transplants than for MRD ( $p<0.001$ ). A higher incidence of acute GVHD ( $p=0.09$ , not statistically significant) and a significantly higher rate of chronic GVHD ( $p=0.02$ ) were observed in patients receiving MRD transplants compared to



**Figure 1.** Overall survival, progression-free survival, and non-relapse mortality after allogeneic hematopoietic cell transplantation. CI: Confidence interval; NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; Post tx time: time since transplant.

those receiving MUD/MMUD or haploidentical transplants. Notably, the majority of cases of grade II-IV acute GVHD and moderate/severe chronic GVHD occurred in MRD recipients (9 and 6 patients, respectively).

The analysis revealed no significant differences between MRD, MUD/MMUD, and haploidentical transplants in terms of transplant centers (p=0.16), year of transplantation (p=0.41), or pre-transplant BV use (p=0.19) (Table 2). When OS and PFS

**Table 2. Patients' characteristics according to donor type.**

		MRD		MUD/MMUD		Haploidentical		p
Center	Center 1	16	41.0%	6	30.0%	6	54.6%	0.16
	Center 2	15	38.5%	11	55.0%	1	9.1%	
	Center 3	8	20.5%	3	15.0%	4	36.4%	
Time of transplant	Era 1	9	23.1%	6	30.0%	1	9.1%	0.41
	Era 2	11	28.2%	5	25.0%	3	27.3%	
	Era 3	19	48.7%	9	45.0%	7	63.6%	
Age, years	≤40	28	71.8%	11	55.0%	10	90.9%	0.11
	>40	11	28.2%	9	45.0%	1	9.1%	
Sex	Male	21	53.8%	13	65.0%	7	63.6%	0.67
	Female	18	46.2%	7	35.0%	4	36.4%	
KPS score before allo-HCT	≤70	13	33.3%	9	45.0%	3	27.3%	0.55
	>70	26	66.7%	11	55.0%	8	72.7%	
Disease stage	Early	16	41.0%	5	25.0%	3	27.3%	0.41
	Advanced	23	59.0%	15	75.0%	8	72.7%	
Treatment before allo-HCT	≤3 lines	17	43.6%	6	30.0%	3	27.3%	0.45
	>3 lines	22	56.4%	14	70.0%	8	72.7%	
RT before allo-HCT	No	23	59.0%	8	40.0%	7	63.6%	0.31
	Yes	16	41.0%	12	60.0%	4	36.4%	
BV before allo-HCT	No	18	46.2%	10	50.0%	2	18.2%	0.19
	Yes	21	53.8%	10	50.0%	9	81.8%	
CPI before allo-HCT	No	36	92.3%	15	75.0%	7	63.6%	<0.05
	Yes	3	7.7%	5	25.0%	4	36.4%	
TBI	No	34	89.5%	13	68.4%	2	18.2%	<0.001
	Yes	4	10.5%	6	31.6%	9	81.8%	
Conditioning regimen	MAC	11	28.2%	5	25.0%	7	63.6%	0.06
	RIC	28	71.8%	15	75.0%	4	36.4%	
Use of CY after allo-HCT	No	35	89.7%	17	85.0%	2	18.2%	<0.001
	Yes	4	10.3%	3	15.0%	9	81.8%	
ATG use	No	38	97.4%	8	40.0%	11	100%	<0.001
	Yes	1	2.6%	12	60.0%	0	0.0%	
Acute GVHD	No	20	51.3%	12	60.0%	8	80.0%	0.09
	Yes	19	48.7%	8	40.0%	2	20.0%	
II-IV acute GVHD	No	30	76.9%	14	70.0%	10	100%	
	Yes	9	23.1%	6	30.0%	0	0%	
Chronic GVHD	No	25	64.1%	18	90.0%	9	90.0%	0.02
	Yes	14	35.9%	2	10.0%	1	10.0%	
Severe chronic GVHD	No	33	84.6%	17	85.0%	10	100%	
	Yes	6	15.4%	3	15.0%	0	0%	

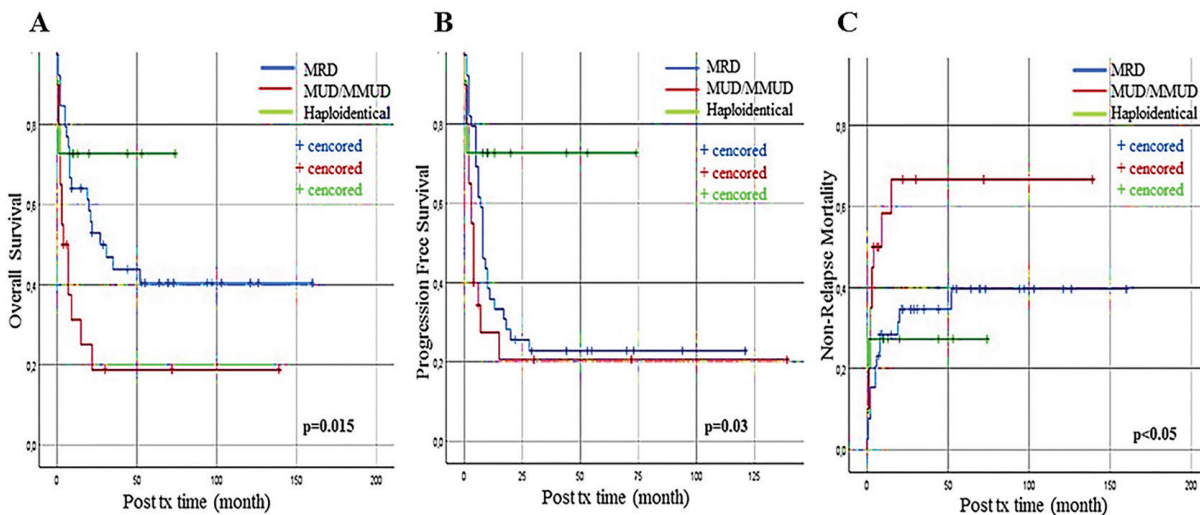
Allo-HCT: Allogeneic hematopoietic cell transplantation; ATG: antithymocyte globulin; BV: brentuximab vedotin; CPI: immune checkpoint inhibitor; Cy: cyclophosphamide; Era 1: 2004-2010; Era 2: 2011-2015; Era 3: 2016-2021; GVHD: graft-versus-host disease; KPS: Karnofsky Performance Status; MAC: myeloablative conditioning; MMUD: mismatched unrelated donor; MRD: matched sibling donor; MUD: matched unrelated donor; RIC: reduced-intensity conditioning; RT: radiotherapy; TBI: total body irradiation.

were analyzed by donor type, transplants from haploidentical donors were associated with significantly improved OS ( $p=0.015$ ) and PFS ( $p=0.03$ ) compared to those from MUD/MMUD and MRD origins. The MUD/MMUD group demonstrated significantly higher NRM in comparison to both haploidentical donor and MRD groups ( $p<0.05$ ) (Figure 2).

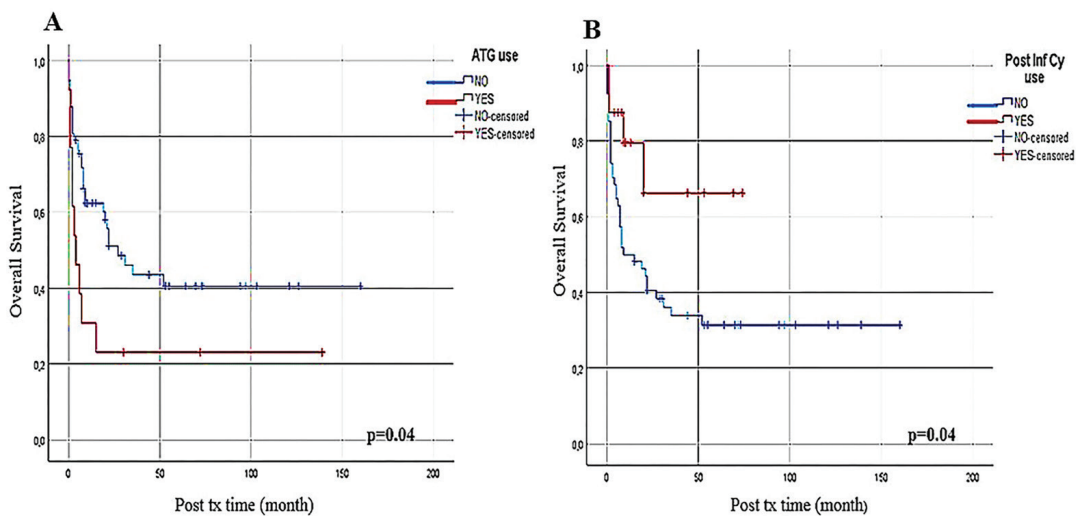
Regarding post-transplant cyclophosphamide versus ATG, patients who received post-transplant cyclophosphamide had significantly better OS ( $p=0.04$ ) and PFS ( $p=0.05$ ), but similar NRM ( $p=0.19$ ). Patients who received ATG exhibited a significant reduction in OS ( $p=0.04$ ) and an increase in NRM ( $p=0.01$ ); however, their PFS outcomes remained comparable to those in the other groups ( $p=0.28$ ). Upon stratifying the data by conditioning regimen (RIC vs. MAC), no statistically significant

differences were observed in OS ( $p=0.19$ ), PFS ( $p=0.38$ ), or NRM ( $p=0.41$ ) (Figure 3).

Among patients presenting with chemosensitive disease as defined by CR or PR, there was a significant trend for the increased use of BV before allo-HCT ( $p=0.03$ ), the selection of RIC ( $p=0.002$ ), and higher KPS scores ( $p=0.02$ ). In contrast, these patients demonstrated less ATG use ( $p=0.02$ ). OS, PFS, and NRM were also stratified by response status before and after allo-HCT (CR vs. all other outcomes, including PR and SD/PD). Achieving CR before allo-HCT was associated with better OS ( $p=0.28$ ), PFS ( $p=0.27$ ), and NRM ( $p=0.46$ ), although the impact was not statistically significant. Patients in CR after allo-HCT had a significant survival advantage compared to those who were not in CR (OS,  $p=0.02$ ; PFS,  $p<0.001$ ), but no difference was observed for NRM rates ( $p=0.13$ ) (Figure 4).



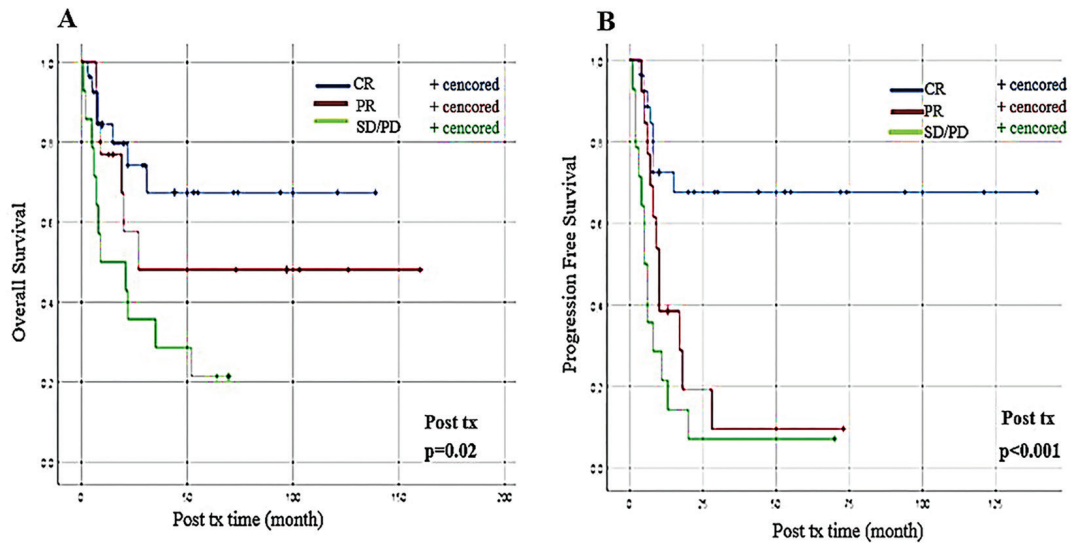
**Figure 2.** A) Overall survival, B) progression-free survival, and C) non-relapse mortality Kaplan-Meier curves based on donor type. MRD: Matched related donor; MUD/MMUD: matched unrelated donor/mismatched unrelated donor; Post tx time: time since transplant.



**Figure 3.** Overall survival according to the use of A) antithymocyte globulin and B) post-transplant cyclophosphamide. ATG: Antithymocyte globulin; Post Inf Cy: post-transplant cyclophosphamide; Post tx time: time since transplant.

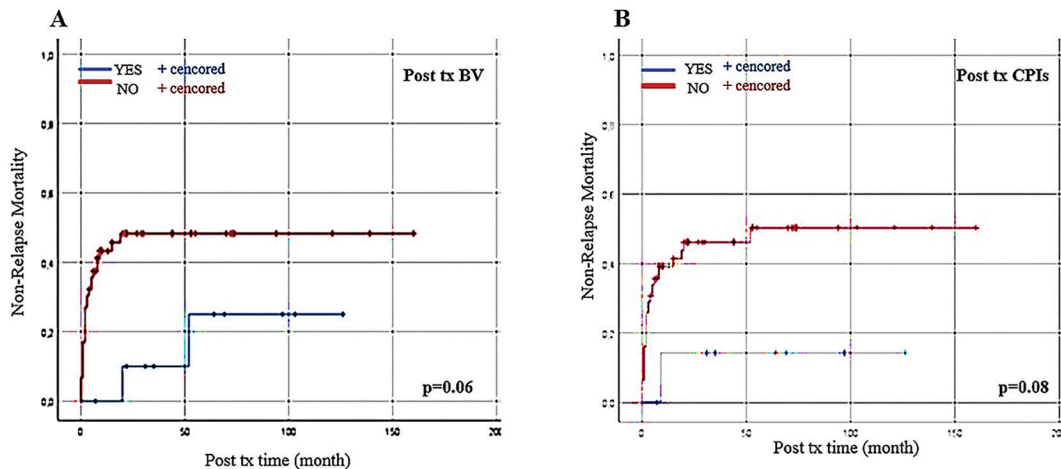
Patients who received BV at any point before (n=40) and/or after (n=11) allo-HCT showed a tendency of longer OS (before allo-HCT, p=0.5; after allo-HCT, p=0.2), longer PFS (before allo-HCT, p=0.17; after allo-HCT, p=0.23), and lower NRM (before allo-HCT, p=0.95; after allo-HCT, p=0.06). Among the patients who received CPIs at any point before (n=12) and/or after (n=8) allo-HCT, improved outcomes were observed, including OS (before allo-HCT, p=0.34; after allo-HCT, p=0.27), PFS (before allo-HCT, p=0.16; after allo-HCT, p=0.17), and NRM (before allo-HCT, p=0.34; after allo-HCT, p=0.08), but these findings did not approach the level of statistical significance (Figure 5).

Table 3 presents patient characteristics grouped by transplant era. No statistically significant difference in median age was observed between the two main eras (p=0.45). A greater percentage of patients in Era 1 received >3 lines of treatment prior to allo-HCT (81.3%) than in Era 2 (57.4%), but this difference was not statistically significant (p=0.08). In Era 2, 74.1% received BV before allo-HCT and 20.4% after allo-HCT, while 22.2% received CPIs before allo-HCT and 14.8% after allo-HCT. According to allo-HCT response, we did not notice any difference between the two eras (p=0.46), but CR rates after allo-HCT were significantly higher in Era 2 (p=0.01). RIC was the predominant conditioning regimen in both Era 1 (56.3%) and Era 2 (70.4%) (p=0.29).



**Figure 4.** A) Overall survival and B) progression-free survival according to response status following allogeneic hematopoietic cell transplantation.

CR: Complete response; Post tx time: time since transplant; PR: partial response: SD/PD: stable disease/progressive disease.



**Figure 5.** Non-relapse mortality according to the use of A) brentuximab vedotin and B) immune checkpoint inhibitors after allogeneic hematopoietic cell transplantation.

BV: Brentuximab vedotin; CPIs: immune checkpoint inhibitors; Post tx time: time since transplant.

The median follow-up duration was 53 months (range: 37.3-68.7) for Era 1 and 139 months (range: 26.6-251.4) for Era 2. There was a decline in the proportion of ATG administration in Era 2 (16.7%) compared to Era 1 (25%), but this difference did not reach statistical significance (p=0.45). Analysis of acute GVHD incidence showed a decrease from 50% in Era 1 to 38.9% in Era 2, although this difference did not reach statistical significance (p=0.11). Chronic GVHD occurred less frequently in Era 2 (22.2%) than in Era 1 (31.3%) without reaching statistical significance (p=0.12).

The analysis of survival following allo-HCT showed comparable OS (p=0.13) and PFS (p=0.14) between the two main eras. The prevalence of NRM was similar across the two eras (p=0.73). When data were stratified by three eras according to transplant year (Era 1: 2004-2010, Era 2: 2011-2015, Era 3: 2016-2021), OS (p=0.2) and PFS (p=0.1) were longer in Era 3, but the differences were not statistically significant. When patients were stratified into two different eras based on the date of the transplant (Era 4: 2004-2015, Era 5: 2016-2021), PFS demonstrated a statistically significant increase (p=0.03) (Figure 6).

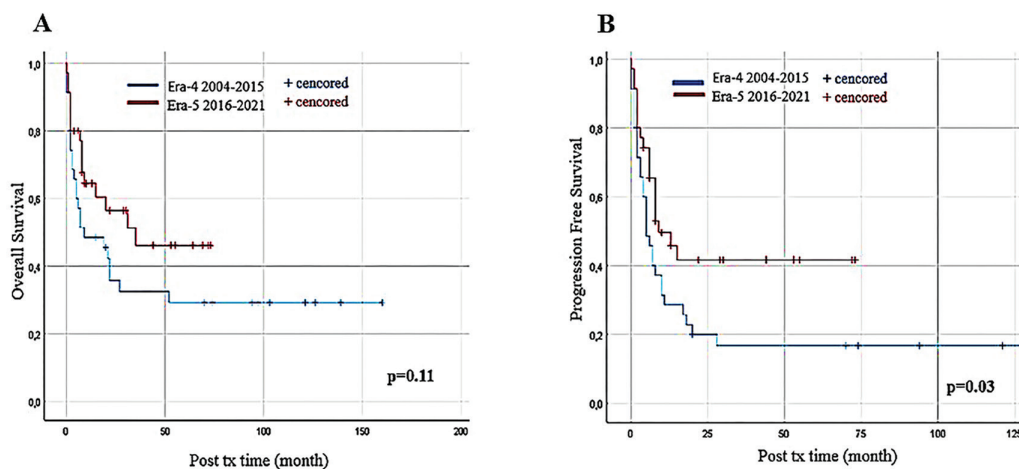
**Table 3. Patients' characteristics according to time of transplant.**

		Era 1 (2004-2010)		Era 2 (2011-2021)		p
Center	Center 1	0	0.0%	28	51.9%	<b>&lt;0.001</b>
	Center 2	16	100.0%	11	20.4%	
	Center 3	0	0.0%	15	27.8%	
Age, years, median		34 (18-16)		36 (21-62)		0.45
Follow-up time, months, median		53.0 (37.3-68.7)		139.0 (26.6-251.4)		<b>0.03</b>
Age, years	≤40	12	75.0%	37	68.5%	0.62
	>40	4	25.0%	17	31.5%	
Sex	Male	6	37.5%	35	64.8%	0.05
	Female	10	62.5%	19	35.2%	
KPS score before allo-HCT	≤70	7	43.8%	18	33.3%	0.45
	>70	9	56.3%	36	66.7%	
Stage	Early	6	37.5%	18	33.3%	0.76
	Advanced	10	62.5%	36	66.7%	
Treatment before allo-HCT	≤3 lines	3	18.8%	23	42.6%	0.08
	>3 lines	13	81.3%	31	57.4%	
RT before allo-HCT	No	6	37.5%	32	59.3%	0.13
	Yes	10	62.5%	22	40.7%	
BV before allo-HCT	No	16	100.0%	14	25.9%	<b>&lt;0.001</b>
	Yes	0	0.0%	40	74.1%	
CPI before allo-HCT	No	16	100.0%	42	77.8%	<b>0.04</b>
	Yes	0	0.0%	12	22.2%	
Disease status before allo-HCT	CR	1	6.3%	10	18.5%	0.46
	PR	4	25.0%	14	25.9%	
	SD/PD	11	68.8%	30	55.6%	
Conditioning regimen	MAC	7	43.8%	16	29.6%	0.29
	RIC	9	56.3%	38	70.4%	
Stem cell source	PB	12	75.0%	50	92.6%	0.07
	BM	3	18.8%	4	7.4%	
	Cord	1	6.3%	0	0.0%	
ATG use	No	12	75.0%	45	83.3%	0.45
	Yes	4	25.0%	9	16.7%	

**Table 3. Continued.**

		Era 1 (2004-2010)		Era 2 (2011-2021)		p
TBI	No	10	71.4%	39	72.2%	0.95
	Yes	4	27.6%	15	26.8%	
Acute GVHD	N/A	1	6.3%	0	0.0%	0.11
	Yes	8	50.0%	21	38.9%	
	No	7	43.8%	33	61.1%	
Chronic GVHD	N/A	1	6.3%	0	0.0%	0.12
	Yes	5	31.3%	12	22.2%	
	No	10	62.5%	42	77.8%	
BV after allo-HCT	Yes	0	0.0%	11	20.4%	<0.05
	No	16	100.0%	43	79.6%	
CPI after allo-HCT	Yes	0	0.0%	8	14.8%	0.10
	No	16	100.0%	46	85.2%	
Disease status at time of transplant	CR	2	15.4%	25	61.0%	0.01
	PR	6	46.2%	7	17.1%	
	SD/PD	5	38.5%	9	22.0%	
NRM	Yes	7	43.8%	22	40.7%	0.83
	No	9	56.3%	32	59.3%	
Mortality at day 100 after allo-HCT	Yes	5	31.3%	13	24.1%	0.56
	No	11	68.8%	41	75.9%	

Allo-HCT: Allogeneic hematopoietic cell transplantation; ATG: antithymocyte globulin; BM: bone marrow; BV: brentuximab vedotin; CPI: immune checkpoint inhibitor; CR: complete response; GVHD: graft-versus-host disease; KPS: Karnofsky Performance Status; MAC: myeloablative conditioning; N/A: not applicable; NRM: non-relapse mortality; PB: peripheral blood; PR: partial response; RIC: reduced-intensity conditioning; RT: radiotherapy; SD/PD: stable disease/progressive disease; TBI: total body irradiation.



**Figure 6.** A) Overall survival and B) progression-free survival according to the time of the transplant. Post tx time: Time since transplant.

Patients undergoing allo-HCT during Era 1 (2004-2010) were treated exclusively at a single center, whereas those treated in Era 2 (2011-2021) received treatment at all three centers. The survival outcomes, including OS (p=0.4), PFS (p=0.45), and NRM (p=0.14), did not show statistically significant differences across the two main eras.

**Univariate and Multivariate Outcomes**

**Graft-Versus-Host Disease**

Donor type significantly impacted the rate of chronic GVHD in univariate analysis (p=0.039), with MRD transplants having a higher incidence of chronic GVHD compared to those with MUD/

MMUD and haploidentical donors. In multivariate analysis, ATG administration was associated with a significantly reduced risk of chronic GVHD (hazard ratio [HR]: 0.13, 95% CI: 0-0.8, p=0.039).

**Survival**

Univariate analysis showed that haploidentical transplantation compared to MRD was associated with improved OS (HR: 3.3, 95% CI: 0.96-11.5, p=0.005), and CR/PR disease status after allo-HCT correlated with better OS (HR: 2.95, 95% CI: 1.32-6.61, p=0.008). ATG use (HR: 2.15, 95% CI: 1.04-4.42, p=0.037) and KPS score of ≤70 (HR: 0.18, 95% CI: 0.08-0.42, p=0.000) were associated with inferior OS. Multivariate analysis confirmed significant associations with OS for KPS score (HR: 0.1, 95% CI: 0.01-0.66,

p=0.01) and disease status after allo-HCT (CR/PR vs. SD/PD; HR: 4.24, 95% CI: 1.32-13.6, p=0.01).

**Progression-Free Survival**

Univariate analysis revealed that high KPS score (HR: 0.26, 95% CI: 0.11-0.57, p=0.01), haploidentical transplantation (HR: 3.9, 95% CI: 1.12-13.5, p=0.032), and CR/PR status after allo-HCT (HR: 3.8, 95% CI: 1.86-7.76, p=0.000) were significantly associated with improved PFS. Multivariate analysis showed that high KPS score (HR: 0.11, 95% CI: 0.01-0.68, p=0.01), CR/PR status before allo-HCT (HR: 3.51, 95% CI: 1.2-10.2, p=0.02), and CR/PR status after allo-HCT (HR: 2.76, 95% CI: 1.15-6.62, p=0.02) were independently associated with better PFS.

**Non-Relapse Mortality**

Univariate analysis showed increased NRM in the ATG cohort (HR: 2.77, 95% CI: 1.24-6.16, p=0.01). Multivariate analysis revealed that high KPS score (HR: 0.05, 95% CI: 0.04-0.96, p=0.047), pre-transplant BV (HR: 0.11, 95% CI: 0.0-0.72, p=0.035), and post-transplant CPI (HR: 0.0, 95% CI: 0.0-0.78, p=0.039) were significantly associated with reduced NRM. All univariate and multivariate analysis results, including non-significant findings, are presented in Tables 4 and 5 for complete transparency.

Fine-Gray analysis revealed that BV use before allo-HCT significantly reduced NRM (subdistribution HR: 0.60, 95% CI: 0.38-0.94, p=0.026), while acute GVHD was associated with increased NRM (subdistribution HR: 1.41, 95% CI: 1.01-1.97, p=0.043). Chronic GVHD showed a non-significant trend (Table 6).

**Table 4. Univariate analysis of graft-versus-host disease, overall survival, progression-free survival, and non-relapse mortality.**

Variable	Outcome	HR (95% CI)	p
Age (≤40 vs. >40)	OS	1.27 (0.65-2.46)	0.47
Treatment lines (≤3 vs. >3)	OS	1.38 (0.72-2.65)	0.32
Pre-transplant BV	OS	1.23 (0.66-2.28)	0.51
Pre-transplant CPI	OS	0.41 (0.12-1.35)	0.14
CPI cycles (1-9 vs. 10+)	OS	0.71 (0.31-1.64)	0.43
Interval from CPI to allo-HCT (days)	OS	0.85 (0.65-1.12)	0.26
Disease status before allo-HCT	OS	1.19 (0.62-2.26)	0.59
Conditioning (RIC vs. MAC)	OS	1.6 (0.78-3.27)	0.19
Post-transplant BV	OS	1.76 (0.73-4.24)	0.20
Post-transplant CPI	OS	1.8 (0.64-5.1)	0.26
Post-transplant CY	OS	0.36 (0.12-1.01)	0.053
Haplo vs. MRD	OS	3.3 (0.96-11.5)	<b>0.005</b>
CR/PR vs. SD/PD after allo-HCT	OS	2.95 (1.32-6.61)	<b>0.008</b>
ATG use	OS	2.15 (1.04-4.42)	<b>0.037</b>
KPS score of ≤70	OS	0.18 (0.08-0.42)	<b>0.000</b>
Pre-transplant CPI	PFS	0.39 (0.14-1.09)	0.073
Post-transplant CY	PFS	0.44 (0.18-1.04)	0.061
KPS score of ≤70	PFS	0.26 (0.11-0.57)	<b>0.01</b>
Haplo vs. MRD	PFS	3.9 (1.12-13.5)	<b>0.032</b>
CR/PR vs. SD/PD after allo-HCT	PFS	3.8 (1.86-7.76)	<b>0.000</b>
Post-transplant BV	PFS	0.68 (0.34-1.35)	0.27
Post-transplant CPI	PFS	0.61 (0.28-1.32)	0.20
Donor type	cGVHD	-	<b>0.039</b>
All variables above	aGVHD	-	>0.05
ATG use	NRM	2.77 (1.24-6.16)	<b>0.01</b>

aGVHD: Acute graft-versus-host disease; allo-HCT: allogeneic hematopoietic cell transplantation; ATG: antithymocyte globulin; BV: brentuximab vedotin; cGVHD: chronic graft-versus-host disease; CI: confidence interval; CPI: immune checkpoint inhibitor; CR/PR: complete response or partial response; CY: cyclophosphamide; GVHD: graft-versus-host disease; Haplo: haploidentical donor; HR: hazard ratio; KPS: Karnofsky Performance Status; MAC: myeloablative conditioning; MRD: matched related donor; NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; RIC: reduced-intensity conditioning; SD/PD: stable disease or progressive disease.

**Table 5. Multivariate analysis of overall survival, progression-free survival, non-relapse mortality, and chronic graft-versus-host disease.**

Variable	Outcome	HR (95% CI)	p
KPS score of ≤70	OS	0.1 (0.01-0.66)	<b>0.01</b>
CR/PR vs. SD/PD after allo-HCT	OS	4.24 (1.32-13.6)	<b>0.01</b>
KPS score of ≤70	PFS	0.11 (0.01-0.68)	<b>0.01</b>
CR/PR vs. SD/PD before allo-HCT	PFS	3.51 (1.2-10.2)	<b>0.02</b>
CR/PR vs. SD/PD after allo-HCT	PFS	2.76 (1.15-6.62)	<b>0.02</b>
Post-transplant CPI	PFS	0.28 (0.07-1.14)	0.07
KPS score of >70	NRM	0.05 (0.04-0.96)	<b>0.047</b>
Pre-transplant BV	NRM	0.11 (0.0-0.72)	<b>0.035</b>
Post-transplant CPI	NRM	0.0 (0.0-0.78)	<b>0.039</b>
ATG use	cGVHD	0.13 (0-0.8)	<b>0.039</b>

Allo-HCT: Allogeneic hematopoietic cell transplantation; ATG: antithymocyte globulin; BV: brentuximab vedotin; CI: confidence interval; CPI: immune checkpoint inhibitor; CR/PR: complete response/partial response; cGVHD: chronic graft-versus-host disease; HR: hazard ratio; KPS: Karnofsky Performance Status; NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; SD/PD: stable disease/progressive disease.

**Table 6. Fine-Gray subdistribution hazard ratios for non-relapse mortality.**

Variable	sHR (95% CI)	p
BV before allo-HCT	0.60 (0.38-0.94)	<b>0.026</b>
BV after allo-HCT	0.75 (0.47-1.20)	0.230
CPI before allo-HCT	1.21 (0.74-1.98)	0.440
CPI after allo-HCT	0.92 (0.58-1.46)	0.670
aGVHD	1.41 (1.01-1.97)	<b>0.043</b>
cGVHD	1.32 (0.91-1.91)	0.130
Haploidentical donor	0.84 (0.53-1.33)	0.460
KPS score of $\leq 70$	1.36 (0.92-2.01)	0.120
Disease: SD/PD	1.19 (0.78-1.82)	0.410

aGVHD: Acute graft-versus-host disease; allo-HCT: allogeneic hematopoietic cell transplantation; BV: brentuximab vedotin; cGVHD: chronic graft-versus-host disease; CI: confidence interval; CPI: immune checkpoint inhibitor; KPS: Karnofsky Performance Status; NRM: non-relapse mortality; SD/PD: stable disease/progressive disease; sHR: subdistribution hazard ratio.

## Discussion

This retrospective study analyzed the real-life allo-HCT outcomes of patients with R/R Hodgkin lymphoma. Despite its role after ASCT, the indications and timing of allo-HCT remain uncertain. In this study, patients were treated with a median of 4 prior regimens; 46% received radiation and 90% underwent ASCT. Despite heavy pretreatment, allo-HCT remained feasible and effective. Improved outcomes over time likely reflect advances in supportive care, transplant technologies, patient selection, and the integration of novel therapeutic agents such as BV and CPIs.

Our study showed a rise in allo-HCT frequency, BV/CPI use, and post-transplant chemosensitivity over time. In Era 2 (2011-2021), 40 of 54 patients received BV before allo-HCT, with 55% being chemosensitive at the time of the transplant, consistent with prior reports [18]. While some studies have suggested that pre-transplant BV may improve outcomes [19,20], others found no significant effect on OS, PFS, or NRM [21,22], other than improved PFS in chemorefractory patients [21]. BV exposure was associated with improved OS/PFS and lower NRM, though only multivariate analysis confirmed reduced NRM in the present study. This protective effect may reflect the immunomodulatory activity of BV and its lower peri-transplant toxicity [22].

Studies of BV administration for R/R Hodgkin lymphoma after allo-HCT are limited, though response rates of  $\geq 50\%$  have been reported [23,24,25]. In our cohort, BV yielded an ORR of 54.5% and CR rate of 18% among 11 relapsed patients; 2 of those patients received BV alone, while 9 received BV followed by DLI and/or CPIs. Six deaths occurred, mainly due to progression. The use of BV after allo-HCT did not significantly affect OS or PFS but was associated with reduced NRM, suggesting possible immunomodulatory effects [22]. The association of pre-transplant BV and post-transplant CPI use with better disease

control and lower systemic toxicity, together with the observed impact of high KPS score, which reflects superior baseline fitness, likely contributed to the reduced NRM rate. The 100-day NRM rate of 26% in our cohort was higher than rates reported in contemporary series, likely reflecting the combined impact of infectious complications, GVHD-related events, advanced disease at transplant, and variability in supportive care practices.

The success of CPI therapies has called into question the role of allo-HCT in Hodgkin lymphoma. In our cohort, CPI-exposed (n=12) and non-exposed patients (n=58) had comparable ages, prior therapies, KPS scores, stem cell sources, and GVHD rates, with no significant differences. Differences between these groups were limited to more prior lines of BV and greater TBI use in the CPI group.

This study indicates that CPI use, both before and after allo-HCT, was associated with improved survival without increasing immunological toxicities or NRM. In multivariate analysis, CPI use after allo-HCT showed a trend toward improved PFS, although this was not statistically significant. Consistent with the multicenter cohort reported by Perales et al. [26], our patients who used CPIs before allo-HCT (17.1%) demonstrated no OS or NRM benefit but had a favorable PFS trend. Relapse (8%) and GVHD rates (acute GVHD: 41.7%, chronic GVHD: 16.7%) were lower in our CPI-exposed patients, possibly reflecting differences in prophylaxis and patient selection. The updated joint CIBMTR/EBMT analysis reported by Perales et al. [26], which included more than 2000 allo-HCT recipients with Hodgkin lymphoma transplanted between 2008 and 2023, provided an important benchmark for contemporary outcomes. In that study, prior CPI exposure significantly reduced relapse and improved PFS without increasing NRM, while GVHD prophylaxis based on post-transplant cyclophosphamide led to superior OS and lower rates of acute and chronic GVHD. These findings closely parallel our observations, where BV/CPI exposure and post-transplant cyclophosphamide use were linked to reduced NRM and favorable disease control. The consistency between our real-world cohort and the large dataset reported by Perales et al. [26] reinforces the evolving role of targeted agents and post-transplant cyclophosphamide in reshaping allo-HCT outcomes in R/R Hodgkin lymphoma. However, these findings should be interpreted as associations rather than independent survival benefits, as neither CPI exposure nor post-transplant cyclophosphamide retained significance in multivariate analyses.

In our series, pre-transplant use of CPI was associated with an elevated risk of GVHD, as also seen in the literature [27,28]. Ijaz et al. [29] reported overall incidences of acute GVHD and chronic GVHD of 59% and 29%, respectively. In a larger cohort of 209 patients receiving pre-transplant CPIs, rates of acute GVHD, chronic GVHD, and NRM were 54%, 34%, and 14%, respectively, with 2-year PFS and OS of 47% and 69%, respectively [30]. The

same study further showed that intervals from CPI to allo-HCT of >80 days significantly reduced the rate of acute GVHD, while the administration of  $\geq 10$  CPI doses was significantly associated with lower chronic GVHD incidence [30].

Among our patients exposed to pre-transplant CPIs, 41.7% developed acute GVHD and 16.7% developed chronic GVHD. Neither the interval from CPI to allo-HCT ( $\leq 80$  vs.  $>80$  days) nor the number of CPI doses ( $<10$  vs.  $\geq 10$ ) influenced GVHD incidence (data not shown). These rates were lower than those reported in some earlier studies but consistent with those of De Philippis et al. [31], who observed acute GVHD and chronic GVHD incidences of 41% and 7% among 59 haploidentical donor transplants. Several factors may account for the lack of increased GVHD following CPI exposure in our cohort. Patients who underwent allo-HCT after CPI exposure likely constituted a more carefully selected group with more favorable clinical characteristics. Additionally, the interval between CPI administration and transplantation may have permitted partial immune stabilization, and the predominant use of post-transplant cyclophosphamide in our cohort could have attenuated CPI-related alloreactivity. Other CPI-associated transplant toxicities (e.g., sinusoidal obstruction syndrome/veno-occlusive disease, engraftment syndrome, immune-mediated organ toxicities) could not be evaluated, as these events were not systematically documented across the centers included in our retrospective dataset.

Although PFS was improved in the CPI group, OS, PFS, and NRM did not differ significantly between the groups and GVHD rates remained similar regardless of CPI exposure. These findings may reflect the protective role of post-transplant cyclophosphamide in immune reconstitution. Moreover, RIC regimens with acute GVHD have been linked to reduced relapse risk, supporting a graft-versus-tumor effect [32].

Our analysis included 4 patients who underwent stem cell transplantation from haploidentical donors with post-transplant cyclophosphamide prophylaxis, 2 with transplants from MMUDs, 3 with transplants from MUDs, and 3 with transplants from MRDs. Peripheral blood stem cells were used in all but one case. Pre-transplant CPI exposure was associated with a markedly lower relapse rate after allo-HCT (8%) compared to CPI-naïve patients (36.2%). Similar findings have been reported in other trials, supporting a graft-versus-lymphoma effect. For example, De Philippis et al. [31] documented a relapse rate of 8% in CPI-exposed patients (n=59) based on 2 years of follow-up. In comparison, Armand et al. [6] observed a 7% relapse rate within 5.5 months in a phase II study of 44 patients with classical Hodgkin lymphoma receiving pre-transplant CPI.

In our study, 8 patients with R/R disease after allo-HCT received CPIs (median of 3 cycles; range: 1-51), with a median interval of 60 months (range: 3.6-63). One patient had prior CPI exposure.

Chronic GVHD affecting the liver, eye, and oral mucosa occurred in 1 patient, and acute hepatic GVHD occurred in another (ORR: 50%; 2 CR, 2 PR). Although limited by sample size, multivariate analysis showed that CPI use after allo-HCT was significantly associated with reduced NRM. Prior studies similarly support CPI efficacy following transplantation, while shorter intervals from allo-HCT to CPI use, higher CPI doses, and prior GVHD have been linked to increased GVHD risk [27,29].

Several recent studies have reported favorable survival outcomes with haploidentical transplantation. For example, Rivas et al. [33] observed significantly better PFS and lower relapse rates with haploidentical donors compared to MRD or unmatched related donor transplantations. A large-scale analysis found equivalent OS and PFS rates across MRD, haploidentical, and MUD groups but noted a lower incidence of chronic GVHD with haploidentical donors [34].

In the present study, the haploidentical cohort showed a trend toward longer OS and PFS and lower NRM. Univariate analysis suggested superior survival with haploidentical donors, but multivariate analysis did not confirm the differences. Although haploidentical transplantation appeared to be associated with improved OS and PFS, this finding may have been influenced by the higher frequency of post-transplant cyclophosphamide use in this group. Because post-transplant cyclophosphamide was administered predominantly in cases of haploidentical transplants, the observed survival differences cannot be attributed solely to donor type. In multivariable analyses, donor type did not remain significant after adjustment for post-transplant cyclophosphamide, suggesting that these outcomes may reflect the effects of GVHD prophylaxis strategies and temporal changes in transplant practices rather than intrinsic donor characteristics. An international multicenter study demonstrated that GVHD prophylaxis with post-transplant cyclophosphamide improved PFS compared to its absence. However, no OS benefit was observed, while cyclophosphamide combined with ATG was associated with worse survival [30]. The apparent survival benefit observed among haploidentical recipients likely reflected post-transplant cyclophosphamide use and era-related advances rather than donor type alone. Although prior research demonstrated lower NRM with RIC regimens [35], we observed no survival advantage of RIC over MAC. Improved outcomes in recipients of post-transplant cyclophosphamide appear attributable to GVHD prophylaxis and era-related factors rather than conditioning intensity.

Overall, earlier studies of allo-HCT conducted before the incorporation of novel therapeutic agents showed much lower survival rates and higher NRM compared to more recent cohorts. Our Era 1 results align with these earlier findings, suggesting that later improvements are due to better transplant methods and the use of BV, CPIs, and post-transplant cyclophosphamide.

However, our era-based findings should be interpreted cautiously, as multiple concurrent shifts in transplant practice rather than novel agents alone contributed to differences between the eras; therefore, outcome interpretation primarily relies on direct BV/CPI-stratified analyses. When comparing outcomes across transplant eras, several factors may explain the absence of statistically significant survival differences despite increased BV and CPI use. Although exposure to BV and/or CPIs was higher in Era 2, survival did not differ significantly between eras. This likely reflects shorter follow-up durations and limited sample size, which may have attenuated any measurable survival advantage despite increased BV/CPI use. Notably, patients who received these agents after allo-HCT demonstrated improved OS, reduced NRM, and a significantly higher CR rate. The shorter median follow-up in Era 1 reflects higher early mortality, as follow-up information for patients of this early era was complete.

### Study Limitations

The limitations of this study include non-uniform era stratification, which reduced the clarity of temporal comparisons. Advances in care likely explain the improved PFS observed in 2016-2021. The retrospective design, varied patient populations, and small CPI cohorts limited the interpretation of GVHD. Different donor types and treatment regimens reduced the generalizability. Response assessments relied on the Lugano criteria, as PET/Deauville scoring results were not routinely available at the time. Outcomes with BV or CPIs together with allo-HCT should be interpreted cautiously given the small sample size and lack of statistical significance. In addition, the limited sample size, particularly regarding the BV and CPI subgroups, substantially reduced this study's statistical power. These subgroup findings should be interpreted as exploratory and hypothesis-generating rather than definitive, and non-significant trends should not be over-interpreted. Additionally, some HR estimates had wide CI values, reflecting the limited number of events and reduced model stability.

### Conclusion

Allo-HCT remains a viable option for R/R Hodgkin lymphoma. Donor type, GVHD prophylaxis, and integration of BV and CPIs influence survival rates. Haploidentical transplantation with post-transplant cyclophosphamide showed promising outcomes in this study and disease control and NRM improved with the use of novel agents, although the survival benefit was minimal. Larger prospective studies are needed to confirm these outcomes and clarify the role of allo-HCT in targeted therapy.

### Ethics

**Ethics Committee Approval:** The Ankara University Human Research Ethics Committee approved the study (date: 22.04.2022; decision no: İ05-247-22).

**Informed Consent:** Informed consent was waived due to the study's retrospective design.

### Footnotes

#### Authorship Contributions

Surgical and Medical Practices: D.K., U.Ş., G.C.S., D.G., A.G., S.C.B., S.K.T., M.K.Y., P.T., Ö.A., T.D., G.G., O.İ., M.B., M.A., M.Ö.; Concept: D.K., U.Ş., S.C.B., M.A., M.Ö.; Design: D.K., U.Ş., S.C.B., M.A., M.Ö.; Data Collection or Processing: D.K., U.Ş., G.C.S., D.G., A.G., S.C.B., S.K.T., M.K.Y., P.T., Ö.A., T.D., G.G., O.İ., M.B., M.A., M.Ö.; Analysis or Interpretation: D.K., U.Ş., G.C.S., D.G., A.G., S.C.B., S.K.T., M.K.Y., P.T., Ö.A., T.D., G.G., O.İ., M.B., M.A., M.Ö.; Literature Search: D.K., S.C.B., M.A., M.Ö.; Writing: D.K., U.Ş., G.C.S., D.G., A.G., S.C.B., S.K.T., M.K.Y., P.T., Ö.A., T.D., G.G., O.İ., M.B., M.A., M.Ö.

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