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RESEARCH ARTICLE

# Outcomes after allogeneic hematopoietic cell transplant in patients diagnosed with blast phase of myeloproliferative neoplasms: A retrospective study from the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation

Guillermo Ortí[1] | Luuk Gras[2] | Nienke Zinger[3] | Maria Chiara Finazzi[4] | Katja Sockel[5] | Marie Robin[6] | Edouard Forcade[7] | Daniele Avenoso[8] | Nicolaus Kröger[9] | Jürgen Finke[10] | Aleksandar Radujkovic[11] | Mathilde Hunault-Berger[12] | Wilfried Schroyens[13] | Tsila Zuckerman[14] | Jean Henri Bourhis[15] | Yves Chalandon[16] | Adrian Bloor[17] | Rik Schots[18] | Liesbeth C. de Wreede[19] | Joana Drozd-Sokolowska[20] | Kavita Raj[21] | Nicola Polverelli[22] | Tomasz Czerw[23] | Juan Carlos Hernández-Boluda[24] | Donal McLornan[25] | Ibrahim Yakoub-Agha[26]

**Correspondence**
Guillermo Ortí, Department of Hematology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain.
Email: gorti@vhio.net

## Abstract

Allogeneic hematopoietic cell transplant (allo-HCT) provides the only potential route to long-term remission in patients diagnosed with blast phase transformation of myeloproliferative neoplasm (BP-MPN). We report on a large, retrospective European Society for Blood and Marrow Transplantation registry-based study of BP-MPN patients undergoing allo-HCT. BP-MPN patients undergoing first allo-HCT between 2005 and 2019 were included. A total of 663 patients were included. With a median follow-up of 62 months, the estimated 3-year overall survival (OS) was 36% (95% confidence interval [CI], 32–36). Factors associated with lower OS were Karnofsky Performance Score (KPS) <90 (hazard ratio [HR] 1.65, $p < .001$) and active disease at allo-HCT (HR 1.45, $p < .001$), whereas patients undergoing allo-HCT more recently associated with a higher OS (HR 0.96, $p = .008$). In a selected patient's population, the 3-year OS of patients undergoing allo-HCT in complete response (CR) and with a KPS ≥90 was 60%. KPS < 90 (HR 1.4, $p = .001$) and active disease (HR 1.44, $p = .0004$) were associated with a lower progression-free survival (PFS). Conversely, most recent allo-HCT associated with a higher PFS (HR 0.96, $p = .008$). Active disease at allo-HCT (HR 1.34, $p = .03$) was associated with a higher cumulative incidence of relapse (RI) and allo-HCT in earlier calendar years (HR 0.96, $p = .02$) associated with a lower RI. Last, KPS < 90 (HR 1.91, $p < .001$), active disease (HR 1.74, $p = .003$) and allo-HCT from mismatched related donors were associated

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with a higher non-relapse mortality (HR 2.66, $p = .003$). In this large series of BP-MPN patients, about one third were alive at 3 years after transplantation. Patients undergoing allo-HCT in the more recent era, with a KPS ≥90 and in CR at transplant had a better prognosis.

## 1 | INTRODUCTION

Blast phase (BP) transformation of myeloproliferative neoplasms (BP-MPN) is a dreaded "final stage event" in MPN and frequently associated with a dismal prognosis.[1] BP-MPN is defined as ≥20% blast cells in either BM or peripheral blood (PB).[2–5] Constitutive activation of the JAK2 signaling and related pathways, a highly proliferative MPN stem cell compartment, presence of a "chronically inflamed" bone marrow (BM) niche and acquisition of additional clonal events are mechanisms associated with MPN transformation to BP.[6] Both the prognosis and the genomic landscape of BP-MPN differ from de novo acute myeloid leukemia (AML) and post-myelodysplastic syndrome AML,[7,8] suggesting a distinct pathophysiology of BP-MPN.[9,10]

Overall, the prognosis of BP-MPN patients is poor, with a median overall survival (OS) of only 3–5 months in many series.[11,12,13] The standard therapeutic approach for fit patients is intensive chemotherapy.[14] However, promising results have been published recently regarding the role of hypomethylating agents (HMA) and target-directed agents.[15,16] Randomized studies on the treatment of BP-MPN are lacking, and available data are frequently derived from retrospective cohorts and small prospective studies. In treatment-eligible patients, the overall response rate ranges from 20% to 50%.[13–16] Intensive chemotherapy (IC) or HMA seem to provide similar survival,[12] despite the fact that complete responses (CR) are more often achieved with the former. Importantly, achievement of CR has been associated with improved survival in several series.[11,12,17]

Despite an increasingly number of therapeutic approaches being investigated in BP-MPN,[14] allogeneic hematopoietic cell transplant (allo-HCT) offers the only potential of long-term disease-free survival.[11,18] Unfortunately, allo-HCT remains an option for a minority, reserved for "transplant eligible" patients with an available donor.[11,12] Donor T-cell-driven graft-versus-leukemia effect[19] represents the main advantage of allo-HCT compared to non-cellular therapy-based approaches. Controversial reports have been published previously regarding the impact of disease status at transplant, with recent data from the Center for International Blood and Marrow Transplant Research (CIBMTR) suggesting no survival advantage post-allo-HCT in patients in CR[20] compared to patients undergoing allo-HCT with active disease, whereas in other studies improved long-term survival was found in patients transplanted in CR.[16,21,22]

Recent evidence suggests that the mutational landscape of BP-MPN and accelerated phase MPN (AP-MPN) impacts the long-term outcomes of these patients.[20,23] In this respect, the mutational status of a number of genes, such as *TP53*, has been shown to impact on post allo-HCT outcomes.[20] In contrast, the prognostic impact of other mutations, including those affecting the so-called MPN driver genes, remains unclear.

We hereby report a retrospective European Society for Blood and Marrow Transplantation (EBMT) registry-based study analyzing prognostic factors and outcomes of 663 patients with BP-MPN undergoing allo-HCT.

## 2 | METHODOLOGY

This was a retrospective, multicenter, registry-based analysis approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a non-profit scientific society representing more than 600 transplant centers mainly in Europe. Data are entered, managed, and maintained in a central database with Internet access. EBMT centers commit to obtain informed consent according to the local regulations applicable at the time in order to report pseudonymized data to the EBMT.

### 2.1 | Patient selection and definitions

Patient selection was performed by identifying patients ≥18 years at allo-HCT, diagnosed with either primary myelofibrosis (PMF), essential thrombocythemia (ET), polycythemia vera (PV) or secondary myelofibrosis of unknown MPN subtype who had transformed to BP-MPN and for this indication, underwent a first allo-HCT was between 2005 and 2019.

BP-MPN was defined as progression of MPN to acute leukemia by the detection of ≥20% blasts in PB (assessed by blood smear) or BM (assessed by BM aspirate or trephine). Response was assessed according to international consensus criteria.[3,5,24] Disease status at allo-HCT was defined as follows: patients with <5% of BM blasts were considered in complete remission and patients with ≥5% BM blasts were considered as having active disease. Likewise, response after allo-HCT was assessed according to the number of blasts in BM and PB. In this respect, CR was defined a < 5% blasts in BM and the absence of blasts in PB.

Primary graft failure was defined as failing to reach neutrophil $>0.5 \times 10^9$/L within the first 28 days after stem cell infusion or documentation of autologous reconstitution by chimerism analysis in the absence of relapse.

### 2.2 | Outcomes

The primary endpoint of the study was OS after allo-HCT. Secondary endpoints were as follows: progression-free survival (PFS), non-

relapse mortality (NRM), relapse incidence (RI), cumulative incidence (CIN) of limited or extensive chronic graft-versus-host-disease (cGvHD) and GvHD relapse-free survival (GRFS) after allo-HCT, and the CIN of Grade II, III, or IV acute GvHD (aGvHD) during the first 100 days after allo-HCT. Different criteria were used to assess both aGvHD and cGvHD. aGvHD was graded according to two different criteria depending on the year of GvHD diagnosis[25,26]; likewise cGvHD, which was assessed according to two different National Institute of Health criteria.[27,28] GRFS was defined as the time from the date of allo-HCT to the first date of the following events: aGvHD (Grade III or IV), extensive cGvHD, relapse or death, whichever occurred first.

### 2.3 | Statistical analysis

Clinical, demographical and transplantation related characteristics at baseline were tabulated and expressed as median and interquartile range (IQR) for continuous variables and frequencies for categorical variables. Baseline was defined as the day of the stem cell infusion. Median follow-up after baseline and 95% confidence intervals (CI) were calculated using the reverse Kaplan–Meier (KM) method. The primary endpoint (OS) and secondary endpoints PFS and GRFS were analyzed using the KM method and the log-rank test. Multivariable Cox proportional hazards models were fitted to assess the impact of several risk factors simultaneously. NRM together with RI were analyzed in a competing risk framework and Gray's test was used to compare differences between groups. Cause-specific hazard ratios for NRM and relapse were studied in separate multivariable Cox proportional hazard models. For patients with continuous progression recorded after allo-HCT a relapse date 3 weeks after allo-HCT was assumed. All multivariable analyses (MVA) were performed on the basis of compete cases. As a sensitivity analysis for the primary endpoint, the substantive model compatible fully conditional specification imputation of covariates (SMCFCS) approach was used to impute multiple values (50 times) for all covariates included in the analysis of OS that had missing values. The resulting 50 datasets were each separately analyzed and results were combined using Rubin's rules.[29] The incidence of aGvHD was studied together with death before aGvHD as a competing event. The incidence of cGvHD was studied together with death before cGvHD as a competing event. Assessment of hematologic recovery was performed in a competing risk framework with death a competing event. The association of the following potential prognostic factors and outcomes were assessed: patient age, donor age, number of treatment lines before allo-HCT, type of treatment before allo-HCT (intensive chemotherapy, hypomethylating agents, ruxolitinib, and other non-intensive therapies), initial disease diagnosis (PMF, PV, ET, sMF unknown MPN type) patient and donor sex, graft source, type of conditioning, type of GvHD prophylaxis, total body irradiation (TBI), T-cell depletion, *JAK2* mutation at diagnosis, Karnofsky Performance Score (KPS), disease stage at allo-HCT, HCT specific-comorbidity index (HCT-CI), donor type, year of allo-HCT, the interval between diagnosis and AML transformation and the time interval from diagnosis to allo-HCT.

Outcomes in the analysis for aGvHD/death before aGvHD were artificially censored at 100 days. All statistical tests were two-sided, and significance was determined when $p < .05$. All analyses were performed in R version 4.2.2[30] using "survival," "cmprsk," "prodlim," and "smcfcs" packages.

## 3 | RESULTS

A total of 663 BP-MPN patients who underwent allo-HCT in 169 EBMT registered institutions were selected from the registry. BP had evolved from PMF in 269 patients (41%), ET in 221 patients (33%) and PV in 169 patients (25%), and from secondary myelofibrosis of unknown MPN subtype in 4 patients (1%). Table 1 shows patient- and transplant-specific characteristics of the cohort. Furthermore, Tables S1 and S2 demonstrate patient- and transplant-specific characteristics according to the allo-HCT period and type of donor, respectively. Median age was 60 years (IQR, 54–64) and 61% were male. Reduced intensity conditioning (RIC) allo-HCT was performed in 427 patients (65%) and T-cell depletion in 447 patients (69%). Median time from MPN diagnosis to allo-HCT was 5.5 years (IQR, 1.8–13.1) and median time from diagnosis to leukemic transformation was 5.2 years (IQR, 1.4–12.6). The median time from diagnosis of BP-MPN to allo-HCT was 4.4 months (IQR, 2.9–6.2). Median follow-up after allo-HCT for the entire cohort was 5.2 years (IQR, 2.5–7.9).

### 3.1 | Engraftment and early response

Graft failure was reported in 36 patients (5.5%). Median time to neutrophil engraftment (>0.5 $\times$ $10^9$/L) after allo-HCT was 18 days (IQR, 14–23) whereas median time to platelet engraftment >20 $\times$ $10^9$/L was 20 days (IQR, 14–43) and to >50 $\times$ $10^9$/L was 23 days (IQR, 16–44). Data regarding response after allo-HCT within the first 100 days after allo-HCT was available in 528 patients (80%). CR was reported in 399 patients (76%, 95% CI 72%–79%), whereas 46 patients (9%, 95% CI 6%–11%) had relapse or progressive disease and 83 (16%, 95% CI 13%–19%) were never in CR.

### 3.2 | Overall survival

The estimated 3- and 5-year OS was 36% (95% CI, 32–39) and 32% (95% CI, 28%–36%), respectively (Figure 1A) and the median OS was 13.9 months (95% CI, 10.8–16.3). Table S3 highlights that the 5-year OS was 32% (95% CI, 25–40), 25% (95% CI, 9–41), 24% (95% CI, 16–31), and 37% (95% CI, 30–44) in allo-HCT for matched sibling donors (MSD), mismatched related donors (MMRD), mismatched unrelated donors (MMUD), and matched unrelated donors (MUD), respectively (log-rank test $p = .06$). Furthermore, OS improved over time; for patients undergoing allo-HCT between 2005–2010, 2010–2014, and

**TABLE 1** Patient, disease, and transplantation characteristics.

| | | N (%) |
|---|---|---|
| Total | | 663 (100) |
| Patient sex | Male | 405 (61) |
| | Female | 258 (39) |
| Initial diagnosis | PMF | 269 (41) |
| | ET | 221 (33) |
| | PV | 169 (25) |
| | sMF, unknown initial diagnosis. | 4 (1) |
| Age at allo-HCT, median (IQR) | Years | 60 (54–64) |
| Number of treatment lines pre allo-HCT (n missing = 285, 43%) | ≤1 line | 196 (52) |
| | ≥2 lines | 182 (48) |
| Median time to AL transformation | Months (IQR) | 63 (17–152) |
| Type of last treatment before allo-HCT (n missing = 285, 43%) | Intensive chemotherapy (IC) | 184 (49) |
| | HMA | 22 (6) |
| | Ruxolitinib | 13 (3) |
| | Other, non-intensive | 126 (33) |
| JAK2 mutation at diagnosis (n missing = 305, 46%) | Present | 223 (62) |
| | Absent | 135 (38) |
| Year of allo-HCT | 2005–2009 | 132 (20) |
| | 2010–2014 | 292 (44) |
| | 2014–2019 | 239 (36) |
| Type of GvHD prophylaxis (*n* missing = 21, 3%) | CNI based | 559 (87) |
| | PTCy | 63 (10) |
| | Other | 20 (3) |
| Chromosomal abnormalities (*n* missing = 415, 63%) | Normal | 134 (54) |
| | Abnormal | 114 (46) |
| Conditioning (*n* missing = 9, 1%) | MAC | 227 (35) |
| | RIC | 427 (65) |
| T-cell depletion (*n* missing = 15, 2%) | Yes | 447 (69) |
| | No | 201 (31) |
| Graft source | PB | 592 (89) |
| | BM | 58 (9) |
| | CB | 13 (2) |
| HCT-CI (*n* missing = 191, 29%) | 0 (low risk) | 210 (44) |
| | 1–2 (intermediate risk) | 126 (27) |
| | ≥3 (high risk) | 136 (29) |
| TBI | Yes | 109 (16) |
| | No | 554 (84) |
| HLA matching | HLA fully matched donors | 285 (65) |
| Type of donor | MSD | 187 (28) |
| | MUD | 231 (35) |
| | MMUD | 121 (18) |
| | MMRD | 58 (9) |
| | Unknown UD mismatch | 65 (10) |
| Karnofsky Performance Score | <90 | 240 (40) |
| | ≥90 | 367 (60) |

(Continues)

**TABLE 1** (Continued)

| | | N (%) |
|---|---|---|
| Disease stage | Complete remission | 291 (45) |
| | Active disease | 372 (55) |
| CMV status (*n* missing = 20, 3%) | Recipient-neg/donor-neg | 164 (25) |
| | Other | 479 (75) |

Abbreviations: AL, acute leukemia; BM, bone marrow; CB, cord blood; CMV, cytomegalovirus; CNI, calcineurin inhibitors; ET, essential thrombocythemia; GvHD, graft-versus-disease prophylaxis; HCT, hematopoietic cell transplant; HCT-CI, hematopoietic cell transplant comorbidity index; HLA, human leukocyte antigen; HMA, hypomethylating agents; IQR, interquartile range; JAK, janus kinase; MF, myelofibrosis; MMRD, mismatch related donor; MMUD, mismatch unrelated donor; MSD, matched sibling donor; MUD, matched unrelated donor; PB, peripheral blood; PMF, primary myelofibrosis; PTCy, post-transplant cyclophosphamide; PV, polycythemia vera; RIC, reduced intensity conditioning; Rux, ruxolitinib; sMF: secondary myelofibrosis.

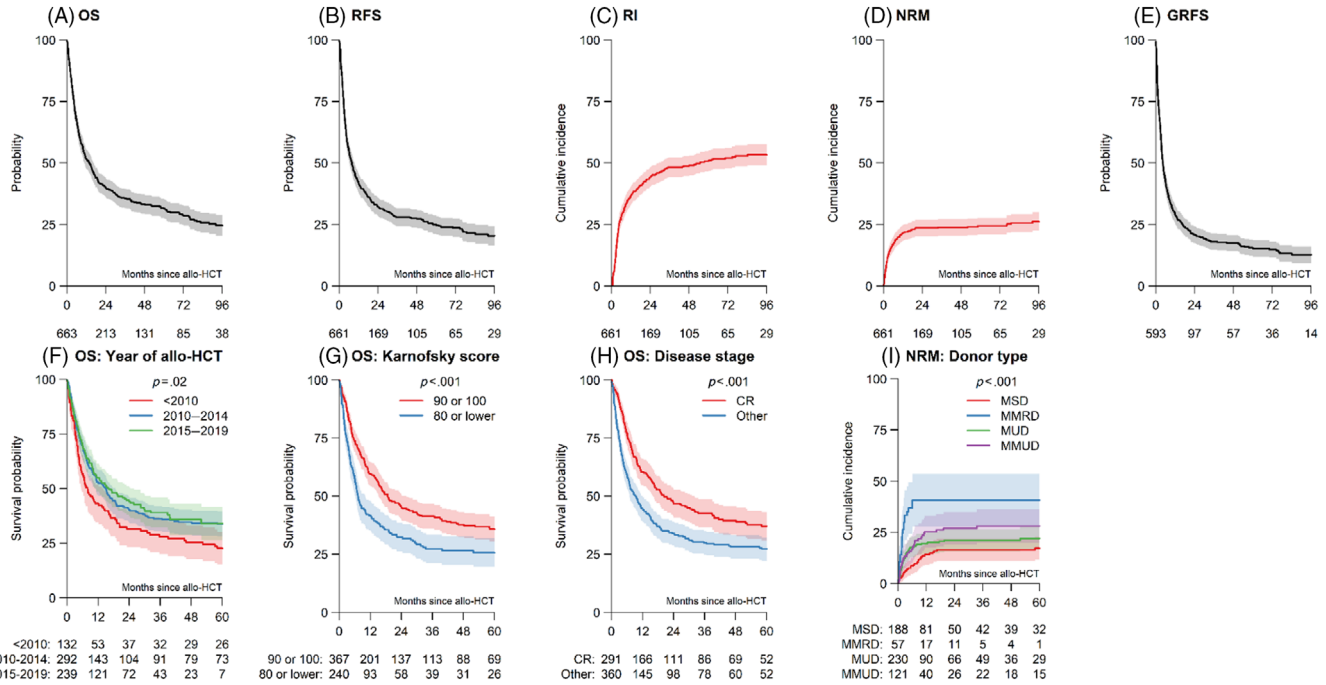


**FIGURE 1** Outcome after allo-HCT in patients diagnosed with blast phase transformation of myeloproliferative neoplasm: probability of (A) OS, (B) RFS, (C) cumulative RI, (D) NRM, (E) GRFS, and probability of OS according to (F) KPS, (G) year of allo-HCT, (H) disease stage at allo-HCT, and (I) cumulative incidence of NRM by donor type. The 95% confidence intervals are shown as a shaded area. Numbers below the graphs show the number of patients at risk. Relapse status was unknown for two patients, hence curves of RFS, RI, and NRM include data from 661 patients. Likewise, the acute and/or chronic GvHD status was unknown for 70 patients, hence the GRFS curve included data from 593 patients. allo-HCT, allogeneic hematopoietic cell transplant; CR, complete response; GRFS, graft-versus-host-disease relapse-free survival; GvHD, graft-versus-host-disease; KPS, Karnofsky Prognostic Score; MMRD, mismatch related donor; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; NRM, non-relapse mortality; OS, overall survival; RFS, relapse-free survival; RI, relapse incidence [Color figure can be viewed at wileyonlinelibrary.com]

2015–2019, 3-year OS was 23% (95% CI, 15–30), 34% (95% CI, 28–39), and 34% (95% CI, 26–42), respectively (Figure 1F, $p = .02$). The 5-year OS was 36% (95% CI, 30%–41%) and 26% (95% CI, 19%–32%) in patients with a KPS ≥90 and KPS <90, respectively (Figure 1G, log-rank $p = .001$). Lastly, the 5-year OS was 37% (95% CI, 31–43) in patients undergoing allo-HCT in CR compared to 27% (95% CI, 22–32) in patients undergoing allo-HCT with active disease (Figure 1H, log-rank $p < .001$).

MVA for OS included a total of 585 patients with complete data (Table 2). KPS <90 was associated with a higher risk of death (hazard ratio [HR] compared to ≥90 1.58, 95% CI 1.28–1.95, $p < .001$), active disease at time of allo-HCT (HR compared to in CR 1.43, 95% CI 1.16–1.76, $p < .001$), while undergoing an allo-HCT in a more recent years associated with a lower risk of death (HR per year later 0.96, 95% CI 0.93–0.99, $p = .004$). We also observed a trend toward better OS in female patients undergoing allo-HCT ($p = .11$).

By way of sensitivity analysis, the MVA analysis was also performed using multiple imputations of the missing data. Results were similar to and supported those obtained in the complete case analysis but confidence intervals were somewhat smaller (Table S4).

We then tested whether the association between OS and prognostic factors was different in patients with or without active

**TABLE 2** Hazard ratio's (HR) for overall survival (OS) and progression free survival (PFS), cause specific hazard ratios for relapse and non-relapse mortality (NRM) and 95% confidence intervals (CI) obtained with multivariable Cox proportional hazard models.

| | OS | | PFS | | Relapse | | NRM | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | (Overall) p | HR (95% CI) | (Overall) p | HR (95% CI) | (Overall) p | HR (95% CI) | (Overall) p |
| Age at allo-HCT (per 10 year increase) | 1.10 (0.97–1.25) | 0.14 | 1.03 (0.91–1.16) | 0.63 | 1.02 (0.89–1.18) | 0.76 | 1.04 (0.85–1.28) | .70 |
| Sex | | | | | | | | |
| Male | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Female | 0.84 (0.68–1.04) | 0.11 | 0.96 (0.78–1.17) | 0.66 | 0.98 (0.77–1.26) | 0.89 | 0.92 (0.65–1.30) | .62 |
| Karnofsky prognostic score | | | | | | | | |
| ≥90 | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| <90 | 1.58 (1.28–1.95) | <0.0001 | 1.35 (1.10–1.66) | 0.003 | 1.11 (0.86–1.43) | 0.42 | 1.93 (1.37–2.74) | .0002 |
| Year of allo-HCT (per year later) | 0.96 (0.93–0.99) | 0.004 | 0.96 (0.93–0.99) | 0.006 | 0.95 (0.92–0.99) | 0.008 | 0.97 (0.92–1.02) | .28 |
| Donor type | | (0.09) | | (0.18) | | (0.92) | | (.01) |
| MSD | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| MMRD | 1.43 (0.94–2.17) | 0.09 | 1.42 (0.96–2.11) | 0.08 | 0.97 (0.56–1.67) | 0.9 | 2.45 (1.32–4.56) | .005 |
| MMUD | 1.29 (0.96–1.72) | 0.09 | 1.21 (0.91–1.61) | 0.18 | 1.06 (0.75–1.49) | 0.73 | 1.65 (0.99–2.74) | .05 |
| MUD | 0.93 (0.71–1.21) | 0.58 | 0.95 (0.74–1.23) | 0.7 | 0.93 (0.69–1.25) | 0.62 | 1.03 (0.64–1.69) | .89 |
| Interval diagnosis—AML (per year later) | 1.00 (0.99–1.02) | 0.81 | 1.00 (0.99–1.02) | 0.74 | 1.00 (0.99–1.02) | 0.62 | 1.00 (0.98–1.02) | .9 |
| Disease stage at allo-HCT | | | | | | | | |
| CR | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Active disease | 1.43 (1.16–1.76) | 0.0007 | 1.42 (1.17–1.74) | 0.0005 | 1.32 (1.04–1.68) | 0.02 | 1.67 (1.18–2.37) | .004 |
| Stem cell source | | | | | | | | |
| PB | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Other | 1.15 (0.81–1.62) | 0.43 | 1.01 (0.73–1.41) | 0.94 | 0.80 (0.50–1.26) | 0.33 | 1.36 (0.82–2.25) | .23 |

Abbreviations: AL, acute leukemia; Allo-HCT, allogeneic hematopoietic cell transplant; CI, confidence interval; CR, complete response; HR, hazard ratio; MMRD, mismatch related donor; MMUD, mismatched unrelated donor; MSD, matched sibling donor; MUD, matched unrelated donor; NRM, non-relapse mortality; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; RI, relapse incidence.

disease at time of allo-HCT by including interaction terms. There was significant interaction between stage of disease at allo-HCT and sex ($p = .01$) and stage of disease and KPS ($p = .007$) as Table S5 shows. In patients in CR at time of allo-HCT the risk of death in male and female patients was not significantly different while the risk of death in patients not in CR was significantly higher in male than female patients. The risk of death was only significantly different between patients with KPS <90 and KPS ≥90 in patients not in CR but not in patients in CR at time of allo-HCT.

## 3.3 | Cause of death

A total of 436 patients died during the follow up and for 421 of these the cause of death was available. Overall, 190 (45%) died due to disease relapse or progression, 124 patients (30%) due to infection, 57 patients (14%) due to GvHD, 23 patients (5%) due to organ damage or organ failure, 6 patients (1%) died due to secondary malignancy, 13 patients (3%) due to other transplant-related causes and 8 patients (2%) died due to other causes. Regarding cause of death according to type of donor, disease relapse or progression was the most frequent cause of death in allo-HCT from MSD, MUD, and MMUD (50%, 44% and 47%, respectively); whereas infection was the most frequent cause of death in patients undergoing allo-HCT from MMRD (60%).

## 3.4 | Non-relapse mortality

Estimated 3- and 5-year NRM was 24% (95% CI, 20–27) and 24% (95% CI, 21%–28%), respectively (Figure 1B). The 5-year NRM was higher in patients undergoing allo-HCT from a MMRD (41%; 95% CI, 28–54) compared to MSD (17%; 95% CI, 12–23), MUD (22%; 95% CI, 16–28) and MMUD (28%; 95% CI, 20–36; Gray's test $p < .001$). Furthermore, the 5-year NRM was higher in patients receiving post-transplant cyclophosphamide (PTCy) 38% (95% CI, 25–50) compared to patients receiving calcineurin inhibitors (CNI)-based prophylaxis (22%; 95% CI, 18–25) or any other form of GvHD prophylaxis (31%; 95% CI, 10–53; Gray's test $p = .01$). The estimated 5-year NRM was 189 (95% CI, 15–23) and 33% (95% CI, 27–39) in patients with a KPS

≥90 and KPS <90, respectively (Figure 1I; Gray's test $p < .001$). Furthermore, the 5-year NRM was 19% (95% CI, 14–24) in patients undergoing allo-HCT in CR compared to 29% (95% CI, 24–34) in patients with active disease (Gray's test $p < .001$). Regarding graft source, PB was associated with a lower 5-year NRM 23% (95% CI, 20–27) compared to other graft sources 34% (95% CI, 22–45) (Gray's test $p = .04$). We observed a trend on NRM according to the HCT-CI, in this respect the 5-year NRM was 18% (95% CI, 13–23), 29% (95% CI, 20–37), and 29% (95% CI, 21–37) in patients with an HCT-CI of 0, 1–2, and ≥3, respectively (Gray's test $p = .06$). NRM did not significantly differ according to type of conditioning ($p = .72$), type of treatment prior to allo-HCT ($p = .46$) or cytomegalovirus (CMV) status of recipient/donor ($p = .35$).

The NRM MVA showed that KPS <90 (HR compared to ≥90 1.93, 95% CI 1.37–2.74, $p = .0002$) and not being in CR at allo-HCT (HR compared to CR 1.67, 95% CI 1.18–2.37, $p = .004$) associated with a higher risk of NRM. Furthermore, the type of donor associated with the risk of NRM. A higher risk of NRM was observed in patients undergoing allo-HCT from a MMRD (HR 2.45, 95% CI 1.32–4.56, $p = .005$) and MMUD (HR 1.65, 95% CI 0.99–2.74, $p = .05$) compared to MSD (Table 2).

## 3.5 | Relapse incidence

The cumulative 3- and 5-year RI was 48% (95% CI, 44–52) and 51% (95% CI, 47%–55%), respectively (Figure 1C). The 5-year RI was 53% (95% CI 48–57) and 38% (95% CI, 24–51) in patients receiving a CNI-based GvHD prophylaxis and PTCy, respectively (Gray's test $p = .04$). There was a trend toward a higher cumulative RI in patients undergoing allo-HCT from MSD 57% (95% CI, 50–65), compared to MMRD 38% (95% CI, 23–53), MMUD 52% (95% CI, 43–61), and MUD 48% (95% CI, 41–55) (Gray's test $p = .10$). Surprisingly, we did not find any significant differences in cumulative RI according to disease status at allo-HCT ($p = .67$), nor with the type of conditioning regimen ($p = .27$) or the use of T-cell depletion ($p = .66$).

RI MVA showed that a more recent allo-HCT was associated with a lower risk of relapse (HR per year later 0.95, 95% CI 0.92–0.99, $p = .008$) and patients with active disease at allo-HCT associated with a higher relapse risk compared to those in CR (HR 1.32, 95% CI 1.04–1.68, $p = .02$).

## 3.6 | Progression-free survival

The estimated 3- and 5-year PFS was 28% (95% CI, 24–32) and 25% (95% CI, 21%–29%), respectively (Figure 1C), and the median PFS was 7.8 months (95% CI, 6.2–9.5). The 5-year PFS was 16% (95% CI, 9–22), 27% (95% CI, 22–32), and 29% (95% CI, 21–36) in patients undergoing allo-HCT between 2005–2010, 2010–2014, and 2015–2019, respectively (log-rank $p = .01$). The 5-year PFS was 27% (95% CI, 22–32) and 22% (95% CI, 16–28) in patients with a KPS ≥90 and KPS <90, respectively (log-rank $p = .01$). Last, the estimated 5-year PFS was 29% (95% CI, 23–35) in patients undergoing allo-HCT in CR compared to 22% (95% CI, 18–27) in patients with active disease (log-rank $p < .001$). PFS MVA showed that KPS <90 (HR compared to ≥90 1.35, 95% CI 1.10–1.66, $p = .003$), not being in CR at allo-HCT (HR compared to CR 1.42, 95% CI 1.17–1.74, $p = .0005$) were associated with a higher risk of progression/death while a more recent allo-HCT (HR per year later 0.96, 95% CI 0.93–0.99, $p = .006$) was associated with a lower risk of progression/death. We found similar interaction effects as in the OS MVA between disease stage at allo-HCT and sex and disease stage and KPS (Table S5).

Using the results from the OS and PFS MVA including interaction terms we next calculated predicted OS and PFS curves for four reference patients; (1) being in CR and KPS ≥90 at allo-HCT, (2) in CR and KPS <90, (3) not in CR and KPS ≥90, and (4) not in CR and KPS <90. The reference patients were further assumed to be male, 60 years of age at allo-HCT, with 5.25 years between diagnosis and AML transformation, having had an allo-HCT in 2018 from a matched unrelated donor with PB as graft source. The predicted 5-year OS and PFS was low for patients not in CR and KPS <90 and higher for patients in CR or with a KPS ≥90 (Figure 2).

## 3.7 | GvHD and GvHD relapse-free survival (GRFS)

The 100-day CIN of Grade II–IV and III–IV aGvHD was 29% (95% CI, 25–32) and 13% (95% CI, 10–15), respectively. The 100-day CIN of aGvHD in patients with TBI-based conditioning was 38% (95% CI, 29–47), higher than in those with non-TBI-based conditioning (27%; 95% CI, 23–31; Gray's test $p = .02$). In MVA for aGVHD, use of a MMRD associated with a higher risk of aGvHD compared to MSD (HR 3.25, 95% CI 1.56–6.78, $p = .002$) and TBI-based conditioning also associated with a higher risk of aGvHD (HR compared to conditioning without TBI 1.70, 95% CI 1.14–2.53, $p = .007$).

The 1- and 3-year CIN of cGvHD was 30% (95% CI, 27–34) and 35% (95% CI, 31–38), respectively. The 1- and 3-year GRFS was 29% (95% CI, 25–33) and 18% (95% CI, 15–21), respectively. A higher 3-year CIN of cGvHD was observed in patients with PB as source of the graft (36%, 95% CI, 32–40) compared to patients with other graft sources (21%, 95% CI, 11–31, Gray's test $p = .02$). There was a trend toward a lower 3-year CIN of cGvHD in patients that underwent allo-HCT from MMRD 21% (95% CI, 9–32) compared to MSD 34% (95% CI, 27–41), MUD 41% (95% CI, 34–48) and MMUD 32% (95% CI, 23–41) (Gray's test $p = .11$). In MVA of cGVHD (results not shown), having active disease at time of allo-HCT associated with a higher risk of cGvHD (HR compared to CR 1.47, 95% CI 1.09–1.99, $p = .01$).

## 3.8 | Post-transplant treatment

Data on post allo-HCT treatment were available in 285 patients (43%). Of those, 178 patients (62%) received disease-related treatment. Of the 285 patients with available data, 56 patients (20%) received a donor lymphocyte infusion (DLI) after allo-HCT. The

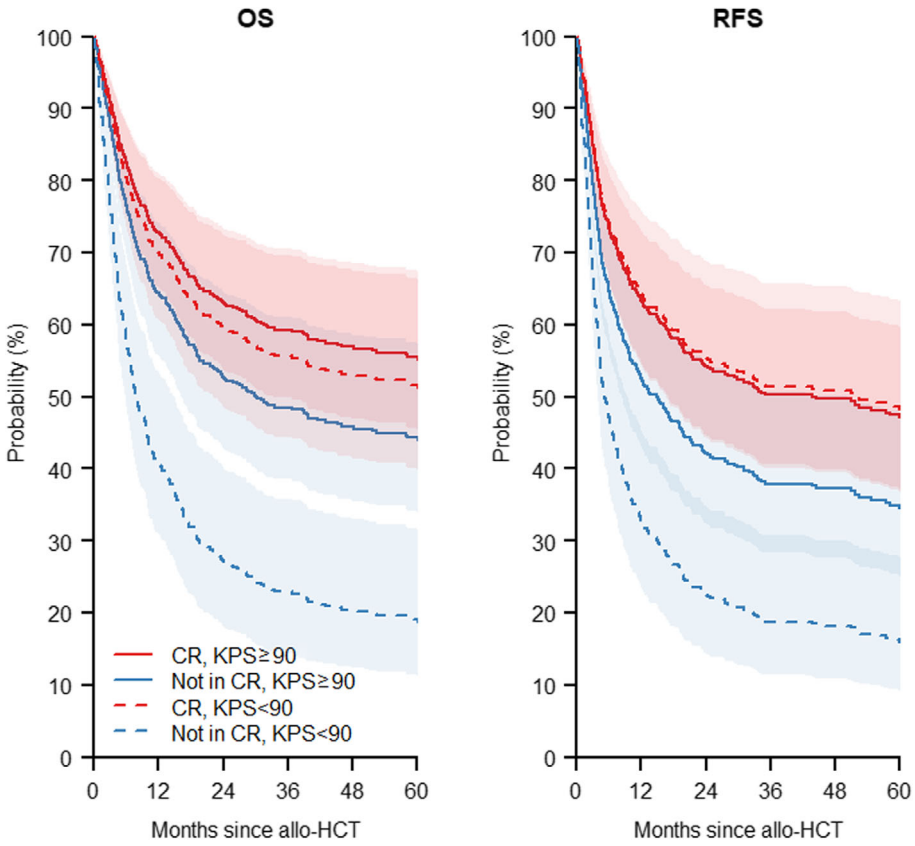


**FIGURE 2** Predicted probability of OS and PFS after allo-HCT in four reference patients diagnosed with blast phase transformation of myeloproliferative neoplasm in CR and KPS ≥90 at time of allo-HCT, in CR and KPS <90, not in CR and KPS ≥90 and not in CR and KPS <90. Reference patients were further assumed to be male, 60 years of age at allo-HCT, with 5.25 years between diagnosis and leukemic transformation, having had an allo-HCT in 2018 from a matched unrelated donor with peripheral blood as graft source. The 95% confidence intervals are shown as a shaded area. The 5-year probability of OS was 56% (95% CI 46–68) for the patient in CR and KPS ≥90, 49% (95% CI 37–64) when in CR and KPS <90, 44% (95% CI 34–57) when not in CR and KPS ≥90, and 19% (95% CI 11–32) when not in CR and KPS <90. For PFS, these figures were 47% (95% CI 38–60%), 49% (95% CI 37–64%), 35% (95% CI 25–48%), and 16% (95% CI 9–28%), respectively. allo-HCT, allogeneic hematopoietic cell transplant; CI, confidence intervals; CR, complete response; KPS, Karnofsky Prognostic Score; OS, overall survival; PFS, progression-free survival [Color figure can be viewed at wileyonlinelibrary.com]

median number of DLI per patient was 3 (range, 1–8). The main reason for DLI was: disease-related 51%, mixed chimerism 30%, planned 2% and "other" 17%. Additional data on post allo-HCT treatment were lacking.

## 4 | DISCUSSION

This study represents the largest cohort of BP-MPN patients undergoing allo-HCT reported to date. Overall, the estimated 3- and 5-year OS was 36% and 32%, respectively. Main reason for treatment failure was disease relapse, with an estimated 3-year incidence of 48%. We identified a number of risk factors associated with the main complications following allo-HCT and determine the subgroup of patients demonstrating improved survival.

First, as demonstrated by others, we observed that the overall prognosis of BP-MPN patients undergoing allo-HCT has improved over more recent years, particularly in BP-MPN patients undergoing allo-HCT from 2010 onwards. This is most likely due to improvements in patient selection and supportive care alongside better pre- and post-transplant disease control strategies. Our data suggest that improvement in disease control before and after transplant have been translated in longer OS, at least in this cohort. Better supportive care in allo-HCT reduces the NRM rate, and retrospective data suggests such improvement from 2010.[31] However, in our study we did not find such improvement in NRM, NRM was similar between transplant periods in univariable and multivariable analyses, as others have also recently observed.[32] Regarding the NRM observed in this study, notably, patients undergoing allo-HCT in more recent transplant periods were older (data not shown). Unfortunately, there were no data available on post-transplant maintenance strategies with agents such as *JAK2* inhibitors, hypomethylating agents, or other therapeutic approaches, which potentially impact on disease control. Despite improvements in OS and PFS in most recent years, it seems that there is no plateau in respective curves, which suggests that patients might continue to relapse over time.

Disease status at transplant has been shown to be a highly relevant prognostic factor in both de novo and relapsed AML patients

undergoing allo-HCT.[33,34] Retrospective analyses regarding disease status in BP-MPN allo-HCT has demonstrated contrasting results. The CIBMTR reported data on a cohort of 177 BP-MPN patients undergoing allo-HCT, highlighting that the number of blasts was not a prognostic factor for survival,[20] whereas in contrast, in other allo-HCT retrospective studies there was a clear association regarding disease status at time of allo-HCT and long-term survival.[11,17,21] Interestingly, a recent study suggested that the number of blasts at time of all-HCT was not relevant in MPN-CP and MPN-AP patients undergoing allo-HCT.[35] In our analysis, however, pre transplant CR was a favorable prognostic factor for the endpoints of OS, PFS, RI and NRM. Of note, data regarding measurable residual disease (MRD) was unavailable in our study and in our opinion the role of MRD following BP-MPN allo-HCT requires systematic prospective evaluation.

More recently, the use of PTCy has facilitated the incorporation of MMRD in allo-HCT donor selection algorithms. In this context, data suggest that outcomes after allo-HCT from MMRD with PTCy might be comparable to MSD.[36] In our cohort, choice of GvHD prophylaxis and the type of donor did not associate with OS in MVA. Interestingly, we observed that in this study most patients receiving PTCy as GvHD prophylaxis underwent allo-HCT from MMRD (Table S2); furthermore, we also observed that MMRD associated with a higher NRM when compared to other donors, with infection being the cause of death in 60% of patients undergoing allo-HCT from MMRD. Historically, the use of MMRD has been linked to a higher NRM due to higher GvHD, but with the advent of PTCy, NRM rates have remarkably improved.[37] A univariate analysis of the transplant era performed only on patients undergoing allo-HCT from MMRD showed those who underwent allo-HCT more recently (particularly those undergoing allo-HCT after 2015) associated with higher survival. Lastly, KPS was a strong prognostic factor for NRM, PFS and OS. KPS has been previously identified an independent prognostic factor for survival across a number of studies in different disease diagnosis.[37,38] Our findings further corroborate previously reported data, specifically describing the pre allo-HCT clinical status of BP-MPN patients. Of note, median age was 60 years and KPS was ≥90% in 60% of patients. Taking altogether, our results seem to suggest a better ability of MMRD transplant in longer-term control of disease, at cost of increased infectious risk and NRM. In this context, fit patients at higher risk (e.g., active disease, etc.) might benefit of such approach with careful infectious surveillance, while other choices could be preferred in patients in CR or with impaired performance status.

Limitations of our study include the retrospective, registry-based nature and incomplete data in some areas. Of note, centers were approached to complete missing data where possible. Furthermore, this cohort is likely to be a selected population as a significant proportion BP-MPN patients do not undergo transplant. We acknowledge that it would have been of pivotal interest to analyze the role of gene mutations such as *CALR*, *TP53*, *ASXL1*, among others in determining post allo-HCT outcomes; however, missing data for these variables precluded robust analysis. Interestingly, the mutational landscape of BP-MPN has been previously reported to impact on patient outcomes post allo-HCT.[18,21] In this regard, we analyzed the role of *JAK2* mutation at diagnosis and we found no impact on either survival or RI. Many groups are collectively focused on harmonization of both response and diagnostic criteria.[3–5,24,39] Forward thinking strategies to prospectively incorporate these criteria into BP-MPN allo-HCT trials are required.

In conclusion, this is the largest study on BP-MPN patients undergoing allo-HCT reported to date. These results demonstrate that BP-MPN allo-HCT patients have poor outcomes overall; however, survival improvements in more recent years are evident. Overall, the optimal therapeutic approach for BP-MPN represents an unmet medical need which requires further exploration. Allo-HCT remains the only therapy with curative potential in this setting; with patients in CR at time of transplant, with a higher KPS and undergoing allo-HCT in the more recent era associating with an improved prognosis. Strategies to improve these outcomes are much needed.

## AUTHOR CONTRIBUTIONS

Concept and design were undertaken by Donal McLornan, Guillermo Ortí, and Luuk Gras, and approved by all authors. Data analysis was performed by Luuk Gras. Collection and assembly of data were performed by all authors. All authors contributed to manuscript writing and final approval.

## AFFILIATIONS

[1]Department of Hematology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain
[2]EBMT Statistical Unit, Leiden, The Netherlands
[3]EBMT Leiden Study Unit, Leiden, The Netherlands
[4]Department of Oncology and Hematology, University of Milan and Papa Giovanni XXIII, Bergamo, Italy
[5]Medical Clinic I, University Hospital Dresden, TU Dresden, Germany
[6]Hopital Saint Louis, APHP, Université de Paris Cité, Paris, France
[7]Service d'Hématologie Clinique et Thérapie Cellulaire, Bordeaux, France
[8]Kings College Hospital, London, UK
[9]University Hospital Eppendorf, Hamburg, Germany
[10]University of Freiburg, Freiburg, Germany
[11]University of Heidelberg, Heidelberg, Germany
[12]CHRU, Angers, France
[13]Antwerp University Hospital (UZA), Antwerp, Edegem, Belgium
[14]Rambam Medical Center, Haifa, Israel
[15]Gustave Roussy Cancer Campus, Villejuif, France
[16]Hôpitaux Universitaire Genève, Département d'Oncologie, Service d'Hématologie, Faculty of Medicine, University of Geneva, Geneva, Switzerland
[17]Christie NHS Trust Hospital, Manchester, UK
[18]Universitair Ziekenhuis Brussel, Brussels, Belgium
[19]Leiden University Medical Center, Leiden, The Netherlands
[20]University Clinical Centre, Medical University of Warsaw, Warsaw, Poland
[21]University College London Hospital, London, UK
[22]USD Trapianti di Midollo, Adulti, Brescia, Italy
[23]Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice, Poland

[24]Department of Hematology, Hospital Clínico Universitario, Valencia, Spain

[25]Department of Stem Cell Transplantation, University College London Hospital, London, UK

[26]CHU de Lille, Univ. Lille, INSERM U1286, Lille, France

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## CONFLICT OF INTEREST

Guillermo Ortí declares having received honoraria from BMS, Incyte, Jazz, Novartis and Pfizer. Yves Chalandon declares consulting fees from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, Astra-Zeneca, Servier; Travel support from MSD, Roche, Gilead, Amgen, Incyte, Abbvie, Janssen, Astra-Zeneca, Jazz. There are no other conflicts of interest to disclose.

## DATA AVAILABILITY STATEMENT

The final analysis dataset will be available upon specific request to the Working Party Chair.

## ORCID

*Guillermo Ortí* https://orcid.org/0000-0002-7889-5807
*Marie Robin* https://orcid.org/0000-0003-1388-9876
*Daniele Avenoso* https://orcid.org/0000-0003-4218-4170
*Aleksandar Radujkovic* https://orcid.org/0000-0002-8543-5016
*Tsila Zuckerman* https://orcid.org/0000-0002-6204-977X
*Yves Chalandon* https://orcid.org/0000-0001-9341-8104
*Joana Drozd-Sokolowska* https://orcid.org/0000-0002-4562-6264
*Nicola Polverelli* https://orcid.org/0000-0001-6297-9697
*Tomasz Czerw* https://orcid.org/0000-0003-3108-4035
*Juan Carlos Hernández-Boluda* https://orcid.org/0000-0002-4289-3113

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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