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Treatment approach and outcomes of patients with accelerated/blast-phase myeloproliferative neoplasms in the current era

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Abstract:
Progression of myeloproliferative neoplasms (MPNs) to accelerated or blast-phase is associated with poor survival outcomes. Since 2017 there have been several therapies approved for use in acute myeloid leukemia (AML); these therapies have been incorporated into the management of accelerated/blast-phase MPNs (MPN-AP/BP). We performed a multi-center analysis to investigate outcomes of patients diagnosed with MPN-AP/BP in 2017 or later. Two-hundred two patients were identified; median overall survival (OS) was 0.86 years. We also analyzed patients based on first-line treatment; the three most common approaches were intensive chemotherapy (IC) (n=65), DNA methyltransferase inhibitor (DNMTi)-based regimens (n=65), and DNMTi + venetoclax (VEN)-based regimens (n=54). Median OS was not significantly different by treatment type. In addition, we evaluated response by 2017 European LeukemiaNet (ELN) AML criteria and 2012 MPN-BP criteria in an effort to understand the association of response with survival outcomes. We also analyzed outcomes in 65 patients that received allogeneic hematopoietic stem cell transplant (allo-HCT); median OS was 2.30 years from time of allo-HCT. Our study demonstrates that survival amongst patients with MPN-AP/BP is limited in the absence of allo-HCT even in the current era of therapeutics and underscores the urgent need for new agents and approaches.-

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Treatment approach and outcomes of patients with accelerated/blast-phase myeloproliferative neoplasms in the current era

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Key Points:

1) Median OS in MPN-AP/BP is 0.86 years in a modern cohort without significant difference based on frontline treatment choice
2) Median OS in those that underwent allo-HCT is 2.3 years from time of allo-HCT; response prior to allo-HCT did not impact survival

Abstract

Progression of myeloproliferative neoplasms (MPNs) to accelerated or blast-phase is associated with poor survival outcomes. Since 2017 there have been several therapies approved for use in acute myeloid leukemia (AML); these therapies have been incorporated into the management of accelerated/blast-phase MPNs (MPN-AP/BP). We performed a multi-center analysis to investigate outcomes of patients diagnosed with MPN-AP/BP in 2017 or later. Two-hundred two patients were identified; median overall survival (OS) was 0.86 years. We also analyzed patients based on first-line treatment; the three most common approaches were intensive chemotherapy (IC) (n=65), DNA methyltransferase inhibitor (DNMTi)-based regimens (n=65), and DNMTi + venetoclax (VEN)-based regimens (n=54). Median OS was not significantly different by treatment type. In addition, we evaluated response by 2017 European LeukemiaNet (ELN) AML criteria and 2012 MPN-BP criteria in an effort to understand the association of response with survival outcomes. We also analyzed outcomes in 65 patients that received allogeneic hematopoietic stem cell transplant (allo-HCT); median OS was 2.30 years from time of allo-HCT. Our study demonstrates that survival amongst patients with MPN-AP/BP is limited in the absence of allo-HCT even in the current era of therapeutics and underscores the urgent need for new agents and approaches.

Introduction

Philadelphia-chromosome negative (Ph-neg) myeloproliferative neoplasms (MPNs) are a heterogeneous group of hematopoietic stem cell disorders characterized by proliferation of myeloid cells, activation of the JAK/STAT pathway, and a variable risk of progression to accelerated phase (AP) or blast phase (BP) that is influenced by disease phenotype and clinical, cytogenetic, and molecular features[1–3]. AP is defined as 10-19% blasts in the peripheral blood or bone marrow while BP requires ≥20% blasts[4]. While the median overall survival of patients with chronic-phase MPN is several years, development of an accelerated/blast-phase MPN (MPN-AP/BP) is associated with limited overall survival (OS) particularly in the absence of allogeneic hematopoietic stem cell transplant (allo-HCT). The median OS for patients with MPN-AP ranges from 12-18 months[5–7] while the median OS of those with MPN-BP is 3-5 months[8–11].

Since 2017 there have been several novel therapies approved for use in acute myeloid leukemia (AML) that have led to significant evolution in the treatment approach in this disease[12,13]. These treatment approaches are often applied to patients with MPN-AP/BP despite being molecularly and morphologically distinct from *de novo* AML[14–18]. There are limited prospective data for the utilization of these therapies in MPN-AP/BP and primarily real-world data has been analyzed to characterize their efficacy. There has been a particular focus on the outcomes of patients treated with venetoclax (VEN)-based therapies and isocitrate dehydrogenase (IDH) inhibitors. Median OS with VEN-based regimens ranges from 4-8 months[19–22] while utilization of IDH inhibition has demonstrated median OS ranging from 10-15 months[23–25]. In addition, prospective efforts have investigated the use of DNA methyltransferase inhibitors (DNMTi) in combination with the Janus Kinase (JAK) inhibitor ruxolitinib with reported median OS ranging from 7-9.5 months[26,27].

Given the limited prospective data for therapies in MPN-AP/BP, there is heterogeneity and lack of consensus regarding treatment approach in the current era of myeloid therapies. Therefore, we aimed to analyze outcomes in adult patients with MPN-AP/BP diagnosed in 2017 or later

utilizing a large multi-center retrospective cohort to better understand the impact of treatment approach. We also investigated assessment of response by both AML-specific and MPN-BP specific criteria in relation to survival outcomes. In addition, we analyzed outcomes in the patients that underwent allo-HCT for MPN-AP/BP.

Methods

All adult patients with MPN-AP/BP diagnosed in 2017 or later were identified at 9 participating academic centers. MPN-AP/BP was defined as the development of ≥10% blasts in the peripheral blood or bone marrow in patients with an underlying MPN. All participating centers obtained approval from their Institutional Review Board (IRB). Patient demographics were collected including age at diagnosis, gender, and self-reported race/ethnicity; one participating center was unable to contribute race/ethnicity data. Disease characteristics and treatment approaches for both chronic-phase MPN and MPN-AP/BP were collected. For patients with available cytogenetic/molecular data available at the time of MPN-AP/BP diagnosis a prognostic risk score was assigned using 2017 European LeukemiaNet (ELN) AML criteria[28]. Response to therapies administered for treatment of MPN-AP/BP were assessed using both 2017 ELN AML response criteria and 2012 MPN-BP response criteria[28,29]. Of note one participating center was only able to characterize response using 2017 ELN criteria. All analyses were performed using SAS software version 9.4 (Cary NC).

Each institution received approval from the IRB to conduct this retrospective project.

Results

Patient Demographics and Molecular Information

Two-hundred two patients with MPN-AP/BP diagnosed during the specified time period were identified. One-hundred forty patients had MPN-BP at time of progression while 62 had MPN-AP. The median age at time of MPN-AP/BP diagnosis was 68.6 years old (range 21-91 years old) and 39.6% were women. The most common chronic-phase MPN in patients was primary

myelofibrosis (PMF) which was noted in 33% of patients. When looking at underlying driver mutations at time of chronic-phase MPN, 61% of patients had *JAK2*-mutated disease, 16% had *CALR*-mutated disease, 9% had *MPL*-mutated disease, and 13% of patients had "triple-negative" disease. The most common therapies directed at chronic-phase MPN were hydroxyurea in 61% of patients and JAK inhibitor therapy in 36% of patients; six patients had previously undergone allo-HCT for their chronic-phase MPN. Additional characteristics are summarized in **Table 1.**

Median laboratory values at time of MPN-AP/BP diagnosis are characterized in **Table 1**. Of the 189 patients with available data needed for 2017 ELN AML risk stratification, 67% had high-risk disease. In addition, 166 patients had next generation sequencing (NGS) performed at time of MPN-AP/BP diagnosis. Mutations with an incidence of ≥10% included *ASXL* (31%), *TP53* (26%), *SRSF2* (23%), *TET2* (20%), *RUNX1* (17%), *IDH2* (14%), *DNMT3A* (11%), and *CBL* (10%). In addition, 7% and 4% of patients had disease with an *IDH1* mutation and *FLT3* mutation, respectively.

Survival Outcomes and Response to Therapy

The median OS for the entire 202 patient cohort was 0.86 years (**Figure 1A**); median OS for patients diagnosed with MPN-AP was 1.09 years while it was 0.67 years for those diagnosed with MPN-BP. Median follow-up time was 0.75 years; 51 patients were alive at time of data analysis. We also analyzed outcomes and responses based on the treatment approach for MPN-AP/BP. Of note, one patient proceeded directly to allo-HCT and seven patients received supportive care alone. Sixty-five patients (32%) received intensive chemotherapy (IC) as their initial therapy, 65 patients (32%) received DNA methyltransferase-inhibitor (DNMTi)-based therapy, 54 patients (27%) received DNMTi + VEN-based therapy, 4 patients received a targeted inhibitor as monotherapy, and 6 patients received other therapies. The specific therapies are summarized in **Supplemental Table 1**. Twenty-seven patients were treated in the context of a clinical trial. We analyzed differences in patient and disease characteristics

amongst those treated with IC, DNMTi-based therapy, and DNMTi + VEN-based therapy **(Table 2)**; patients treated with IC were significantly younger (p<0.0001) while patients treated with DNMTi-based therapy had significantly lower marrow and peripheral blood blasts (p=0.009; p=0.0006). Using Kaplan-Meier analysis, estimated OS based on treatment approach was also analyzed. Median OS for the IC group was 0.68 years, for the DNMTi + VEN-based group was 0.71 years, and 1.25 years for the DNMTi-based group (p=0.47) **(Figure 1B)**. Of note, the median OS of the DNMTi-based group was not significantly different when compared to those treated with IC or DNMTI + VEN (n=119) based approaches (median OS 0.72 years, p=0.80).

We also analyzed response to first-line treatment approach by both 2017 ELN and 2012 MPN-BP criteria, which is summarized in **Table 3**. The complete remission/complete remission with incomplete count recovery (CR/CRi) rate by 2017 ELN was 42% for the IC group, 41% for the DNMTi + VEN-based group, and 20% for the DNMTi-based group; when analyzing by 2012 MPN-BP response criteria the rate of acute leukemia response-complete (ALR-C) or better was 37% for the IC group, 39% for the DNMTi + VEN-based group, and 22% for the DNMTi-based group. Kaplan Meier analysis of survival by 2017 ELN criteria demonstrated a median OS of 1.37 years for those that achieved a CR/CRi compared to 1.05 years for those that achieved partial response (PR) or morphologic leukemia-free state (MLFS) and 0.59 years for those that achieved stable disease (SD) or treatment failure (TF) (p=0.0002) (**Figure 2A**). Analyzing OS by 2012 MPN-BP response demonstrated a median OS of 1.75 years for those that achieved ALR-C or better compared to 0.74 years for those that achieved acute leukemia response-partial (ALR-P) and 0.61 years for those that achieved SD or progressive disease (PD) (p=0.006) (**Figure 2B**).

A total of 115 therapies were utilized in the second-line and beyond (2L+) setting for MPN-AP/BP with only 18 administered in the context of a clinical trial. The specific therapies are summarized in **Supplemental Table 2** while the response to therapy is in **Table 4.**

In an effort to better understand factors impacting OS beyond treatment choice, we performed a univariate analysis of several clinical and molecular/cytogenetic factors at time of MPN-AP/BP diagnosis summarized in **Table 5A**. Stratification of age, hemoglobin, white blood count (WBC), and platelet count was derived from the Mutation-enhanced International Prognostic Score System (MIPSS)+ version 2.0 while stratification of blast percentage was derived from definitions of chronic-phase, accelerated-phase, and blast-phase MPN[4,30]. Stepwise Cox regression was performed to determine which factors from **Table 5A** were significant in a multivariate model (**Table 5B**), and included age > 65 (hazard ratio (HR) 1.87 (95% confidence interval (CI) 1.27-2.77)), WBC > 25 x 10^3/µL (HR 2.35 (95% CI 1.59-3.49)), hemoglobin > 10g/dL vs < 8g/dL (HR 0.44 (95% CI 0.27-0.72)), hemoglobin 8-10g/dL vs < 8g/dL (HR 0.63 (95% CI 0.43-0.93)), and *TP53* mutation (HR 2.15 (95% CI (1.46-3.15)). The stepwise Cox model included a p-value for entry of 0.50 and a p-value to remain of 0.15 for the potential factors.

Outcomes in patients that received allo-HCT

Sixty-five patients from our cohort went onto receive allo-HCT for MPN-AP/BP. Characteristics of patients that underwent allo-HCT are summarized in **Supplemental Table 3**. One patient proceeded directly to allo-HCT after MPN-AP/BP diagnosis, 44 patients proceeded after first-line therapy, and 20 patients proceeded to allo-HCT after 2L+ therapies. Fifty-one patients had NGS performed at time of MPN-AP/BP diagnosis; non-driver mutations with an incidence of ≥10% were *ASXL1* (29%), *RUNX1* (24%),*TP53* (20%), *SRSF2* (20%)*TET2* (18%), *IDH1* (10%), and *IDH2* (10%). To better understand how disease characteristics and treatment choices may have impacted receipt of allo-HCT, we performed univariate analysis of the variables summarized in **Supplemental Table 4A** at time of MPN-AP/BP diagnosis. Stepwise logistic regression using the predictors shown in **Supplemental Table 4A** resulted in the following statistically significant factors for receipt of allo-HCT: age ≥ 65 years, WBC > 25 x 10^3/µL, and hemoglobin > 10g/dL vs < 8g/dL (**Supplemental Table 4B)**. The stepwise logistic model included a p-value for entry of 0.50 and a p-value to remain of 0.15 for the potential factors.

Amongst the 65 patients that received allo-HCT, donor source was the following: 36 matched unrelated donors, 11 matched related donors, 11 haplo-identical donors, 6 mismatched unrelated donors, and 1 cord blood. Sixty patients received a reduced-intensity regimen while 15 patients received a myeloablative regimen. Twenty-five patients developed acute graft versus host disease (GVHD) while 16 developed chronic GVHD. We analyzed survival outcomes using the Kaplan-Meier method. Median OS from the time of MPN-AP/BP diagnosis was 3.1 years and was 2.30 years from the time of allo-HCT. **(Figures 3A and 3B)**. Thirty patients were alive at time of the data lock and amongst them 6 had relapsed MPN-AP/BP after allo-HCT. Amongst the 35 patients that died after allo-HCT, the cause of death was noted as transplant-related in 16, and relapse of MPN-AP/BP in 15. Four patients died of causes not related to allo-HCT or MPN-AP/BP. The 2-year rate of relapse after allo-HCT was 23% and 2-year non-relapse related mortality rate after allo-HCT was 25%.

We also analyzed several factors to try and identify what may correlate with improved OS in patients after allo-HCT. We performed Kaplan-Meier analysis of OS from time of allo-HCT based on 2017 ELN disease response going into allo-HCT; median OS was 2.85 years in patients with CR/CRi, 2.30 years for those with PR or MLFS, and 0.74 years for those with SD or TF (p=0.4994) **(Figure 3C)**. The median OS from time of allo-HCT was significantly longer in those that achieved CR/CRi/PR/MLFS compared to those that achieved SD/TF as best response prior to allo-HCT (1.37 years vs. 0.59 years, p<0.0001). We also performed univariate analysis of the variables at time of MPN-AP/BP diagnosis summarized in **Supplemental Table 5A** to identify potential factors associated with OS from time of allo-HCT. Multivariate analysis identified age ≥ 65, marrow blasts 10-19% vs <10%, serum creatinine (g/dL), and *TP53* mutation status as being significant factors **(Supplemental Table 5B)**. The stepwise logistic model included a p-value for entry of 0.50 and a p-value to remain of 0.15 for the potential factors.

Discussion

This series of 202 patients is, to our knowledge, the largest cohort of patients with MPN-AP/BP diagnosed and treated in the current era of myeloid therapies. Given the size of our cohort, heterogeneity in front-line treatment approaches, number of patients that proceeded to allo-HCT, and response assessment using both AML and MPN-BP specific criteria, we were able to report on survival across a variety of dimensions. In addition we were able to investigate the baseline factors that may influence front-line treatment choice and receipt of allo-HCT.

The median OS in the entire cohort was 0.86 years, which is consistent with the survival reported in historical cohorts[8,9,31]. There was no significant difference in OS based on front-line treatment approach. Patients that received IC were significantly younger while those that received DNMTi-based therapy had significantly lower marrow and peripheral blood blasts; these findings may help to elucidate some of the factors that underlie the selection of specific therapies. Interestingly, while CR rates were numerically higher with IC and DNMTi + VEN-based approaches, patients that received DNMTi-based approaches had numerically longer OS. While comprehensive adverse event data were not collected, this may speak to the ability of patients to stay on DNMTi-based therapy with disease control even if a CR is not achieved.

Amongst the patients that received allo-HCT in our cohort, the median OS was 2.3 years from time of allo-HCT. The significant variables impacting receipt of allo-HCT include age, WBC, hemoglobin, marrow blast percent, triple-negative disease status, and *TP53* mutation status. When looking at disease control prior to allo-HCT by 2017 ELN criteria, there was no significant association between response and OS after allo-HCT. Of note, median OS was longer for patients that achieved CR/CRi/PR/MLFS prior to allo-HCT compared to those that had SD/TF. This suggests that reduction in blast burden may be of some benefit but the necessity of achieving CR/CRi is not clear. The allo-HCT survival data reported in our cohort are consistent with previously reported data demonstrating that allo-HCT seems to offer durable OS in patients with MPN-AP/BP[32,33] but that the majority of patients do not receive allo-HCT[9]. Potential reasons

for a minority of patients with MPN-AP/BP receiving allo-HCT may be the relative lack of CRs achieved with current therapeutic options, age at diagnosis of disease, and defining pre-transplant disease control using AML-specific criteria.

There is also significant discussion in the literature about the best way to gauge response in patients with MPN-AP/BP. When comparing outcomes of MPN-BP in remission at time of allo-HCT compared to both de novo AML and AML arising from MDS, median OS is significantly shorter and the risk of relapse is significantly higher[34]. This serves to highlight that typical AML response criteria may not appropriately capture the depth of response to therapy amongst patietns with MPN-AP/BP. This observation may be due to the fact that even when therapies eradicate the AP/BP component of disease, features of the chronic phase MPN often persist, such as marrow fibrosis and circulating peripheral blasts. The 2012 MPN BP criteria[29] were designed with these limitations in mind, but use of these criteria has not been widely adopted in studies focused on MPN-AP/BP. Our analysis of 2017 ELN response criteria demonstrated that achievement of CR/CRi was associated with longer OS when compared to other responses; similar findings were seen in patients that achieved an ALR-C or better by MPN-BP 2012 criteria. Median OS was 1.37 years in patients that achieved CR/CRi by 2017 ELN criteria while median OS was 1.75 years in those who achieved ALR-C or better by 2012 MPN-BP criteria. These data suggest that utilization of 2012 MPN-BP criteria when assessing therapeutic response may be as useful, and perhaps more relevant in this population, as the 2017 ELN AML-specific criteria. It remains to be determined how to best characterize disease control prior to allo-HCT.

Lastly, our analysis sought to characterize the frequency of clinical trial enrollment in our cohort. Only 14% of patients in our cohort were treated in the context of a clinical trial for their front-line therapy; only 12% of 2L+ therapies were administered via clinical trial. Novel therapies are desperately needed for this patient group. An ongoing prospective trial investigating combined IDH2/JAK2 inhibition has noted promising preliminary results[35]. In addition, pre-clinical work has

identified other potential therapeutic targets including hypoxia-inducible factor (HIF) and DUSP6; in addition there may be role for BET inhibition, LSD1 inhibition, BCL-XL and CDK9 inhibition in MPN-AP/BP as well[36–41].

Our study has limitations given its retrospective nature. While this was a multi-center study, the centers included may not fully represent the breadth of patients with MPN-AP/BP. We were also unable to assess for both 2017 ELN response criteria and 2012 MPN-BP criteria in the entire cohort. In addition, there may be factors influencing treatment approach and receipt of allo-HCT that were not adequately captured.

In summary, our study demonstrates that even with new therapeutic approaches available for MPN-AP/BP, overall survival is quite limited. Only a minority of patients are treated in the context of a clinical trial, thus highlighting a significant need to not only for develop novel and effective therapies, but to also evaluate them in clinical trials inclusive of patients with MPN-AP/BP. Furthermore, prospective evaluation of both 2017 ELN and 2012 MPN-BP response criteria as well as other recently proposed MPN-AP/BP criteria is needed to ascertain the best method of response assessment[42].

Author Contributions

AAP designed the study plan, performed data analysis, wrote the manuscript. JJY offered input into study plan, collected data, and reviewed/revised the manuscript. JFC performed data analysis and reviewed/revised manuscript. OO designed the study plan and reviewed/revised the manuscript. All other authors collected data and reviewed/revised manuscript.

Conflict of Interests

AAP: Honoraria from AbbVie, Bristol Myers Squibb; Research Funding (institutional) from Pfizer, Kronos Bio
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Tables & Figure Legends

Table 1: Patient demographics and disease characteristics during chronic-phase MPN and at diagnosis of MPN-AP/BP

Demographics	**N=202**
Age at chronic-phase MPN diagnosis, median (range)	61.9 (21.9-91.0)
Female, n (%)	80 (39.6)
Race/Ethnicity, n (%)	**n=158**
White Race	142 (89.9)
Black Race	9 (5.7)
Asian Race	3 (1.9)
Other Race	4 (2.5)
Hispanic Ethnicity	11 (7.0)
Chronic-Phase MPN	**N=202**
Polycythemia Vera	40 (20%)
Essential Thrombocythemia	57 (28%)
Primary Myelofibrosis	67 (33%)
MPN-not otherwise specified/Other	38 (19%)
Driver Mutation	**N=202**
JAK2	124 (61%)
CALR	33 (16%)
MPL	18 (9%)
Triple Negative	27 (13%)
Therapies Received for chronic-phase MPN	**N=202**
Hydroxyurea	124 (61%)
JAK inhibitor	72 (36%)
Interferon	7 (4%)
DNMTi	11 (5%)
Other	39 (19%)
Allo-HCT	6 (3%)
MPN-AP/BP characteristics	**N=202**
Age at accelerated/blast phase MPN, median (range)	68.6 (22.7-94.0)
Latency period in years between chronic-phase MPN and MPN-AP/BP, median (range)	4.5 (0.0-44.2)
WBC (10^3/µL), median (range)	9.8 (0.6-144.6)
Hemoglobin (g/dL), median (range)	8.6 (5.1-16.5)
Platelets (10^3/µL), median (range)	99.0 (4.0-1839.0)
Peripheral Blast %, median (range)	13.0 (0.0-91.0)
Marrow Blast %, median (range)	22.0 (0.0-97.0)
Creatinine (g/dL), median (range)	0.95 (0.5-7.0)
Total Bilirubin (g/dL), median (range)	0.7 (0.2-3.4)
Palpable splenomegaly, n (%)	102 (52.0)
2017 ELN Risk at MPN-AP/BP Diagnosis	**n=189**

Favorable	5 (2.6)
Intermediate	58 (30.7)
High-Risk	126 (66.7)
Mutations at MPN-AP/BP Diagnosis	**n=166**
ASXL1	52 (31%)
TP53	43 (26%)
SRSF2	39 (23%)
IDH2	24 (14%)
EZH2	15 (9%)
U2AF1	12 7%)
IDH1	11 (7%)

MPN = myeloproliferative neoplasm; AP/BP = accelerated/blast phase; JAK = Janus kinase; DNMTi = DNA methyltransferase inhibitor; allo-HCT = allogeneic hematopoietic stem cell transplant; WBC = white blood count; ELN = European LeukemiaNet

Table 2: Characteristics of MPN-AP/BP patients treated with intensive chemotherapy, DNMTi-based therapy, and DNMTi + venetoclax-based therapy

Variable Mean (SD)	**IC (n=65)**	**DNMTi + VEN-based (n=54)**	**DNMTi-based (n=65)**	**p-value**
Age at diagnosis of MPN-AP/BP	62.9 (8.6)	71.2 (7.4)	69.7 (10.5)	<.0001**
WBC (10^3/µL)	17.6 (21.5)	23.5 (26.4)	21.8 (33.1)	0.48**
Platelet (10^3/µL)	188.7 (287.4)	184.4 (203.8)	235.5 (330.1)	0.54**
Hemoglobin (g/dL)	9.3 (2.2)	8.9 (1.9)	8.8 (1.6)	0.33**
% peripheral blasts	24.5 (22.9)	21.0 (22.9)	13.5 (14.4)	0.009**
% marrow blasts	36.8 (22.1)	34.6 (23.9)	21.9 (19.0)	0.0006**
Total bilirubin (g/dL)	0.8 (0.6)	0.8 (0.4)	0.9 (0.5)	0.70**
Creatinine (g/dL)	1.0 (0.3)	1.2 (0.5)	1.0 (0.9)	0.15**
Splenomegaly	30 (48.4)	21 (39.6)	39 (61.9)	0.052
Chronic-Phase MPN				
Polycythemia Vera	14 (21.5)	9 (16.7)	14 (21.5)	0.22
Essential Thrombocythemia	22 (33.9)	15 (27.8)	17 (26.2)	
Primary Myelofibrosis	13 (20.0)	18 (33.3)	26 (40.0)	
Other	16 (24.6)	12 (22.2)	8 (12.3)	
Driver Mutation				
JAK2	37 (56.9)	38 (70.4)	39 (60.0)	0.30
CALR	9 (13.9)	7 (13.0)	13 (20.0)	0.50
MPL	8 (12.3)	6 (11.1)	5 (7.7)	0.67
Triple Negative	13 (20.0)	4 (7.4)	10 (15.4)	0.15

Mutations				
ASXL1	13 (20.0)	16 (29.6)	16 (24.6)	0.48
EZH2	4 (6.2)	3 (5.6)	7 (10.8)	0.61*
SRSF2	7 (10.8)	19 (35.2)	8 (12.3)	0.0008
IDH1	3 (4.6)	3 (5.6)	4 (6.2)	1.00*
IDH2	7 (10.8)	6 (11.1)	6 (9.2)	0.94
U2AF1	4 (6.2)	5 (9.3)	3 (4.6)	0.66*
RUNX1	7 (10.8)	11 (20.4)	8 (12.3)	0.28
TP53	11 (15.9)	13 (24.1)	14 (21.5)	0.62

*Fisher's exact test, ** Analysis of variance F-test
MPN = myeloproliferative neoplasm; AP/BP = accelerated/blast phase; IC = intensive chemotherapy; DNMTi = DNA methyltransferase inhibitor; VEN = venetoclax; WBC = white blood count

Table 3: Response to First-Line Therapies for MPN-AP/BP

Therapy	2017 ELN Response	2012 MPN-BP Response
Intensive Chemotherapy (n=65) (n=65 evaluable for ELN) (n=51 evaluable for MPN-BP)	CR: 28% CRi: 14% MLFS: 2% PR: 11% TF: 45%	CCR: 8% ALR-C: 29% ALR-P: 20% SD: 10% PD: 17%
DNMTi + VEN-based (n=54) (n=54 evaluable for ELN) (n=42 evaluable for MPN-BP)	CR: 22% CRi: 19% MLFS: 6% PR: 4% SD: 17% TF: 32%	CCR: 2% ALR-C: 37% ALR-P: 20% SD: 15% PD: 27%
DNMTi-based (n=65) (n=65 evaluable for ELN) (n=49 evaluable for MPN-BP)	CR: 9% CRi: 11% MLFS: 2% PR: 9% SD: 32% TF: 37%	CMR: 6% CCR: 2% ALR-C: 14% ALR-P: 12% SD: 37% PD: 33%
Targeted monotherapy (n=4) (n=4 evaluable for ELN) (n=4 evaluable for MPN-BP)	CRi: 25% SD: 50% TF: 25%	ALR-P: 50% SD: 50%

Other therapies (n=6) (n=6 evaluable for ELN) (n=6 evaluable for MPN-BP)	CRi: 17% PR: 17% SD: 17% TF: 30%	ALR-C: 17% ALR-P: 17% SD: 33% PD: 33%

ELN = European LeukemiaNet; MPN = myeloproliferative neoplasm; BP = blast phase; ALR-C = acute leukemia response – complete; ALR-P = acute leukemia response – partial; CCR = complete cytogenetic response; CMR = complete molecular response; CR = complete remission; CRi = CR with incomplete hematologic recovery; DNMTi = DNA methyltransferase inhibitor; ELN = European LeukemiaNet; MPN-BP = myeloproliferative neoplasm-blast phase; MLFS = morphologic leukemia free state; PD = progressive disease; PR = partial remission; TF = treatment failure; SD = stable disease; VEN = venetoclax

Table 4: Response to Second-Line and Beyond Therapies for MPN-AP/BP

Therapy	2017 ELN Response	2012 MPN-BP Response
DNMTi + VEN-based (n=38) (n=38 evaluable for ELN) (n=36 evaluable for MPN-BP)	CR: 5% CRi: 5% MLFS: 16% PR: 5% SD: 13% TF: 55%	CCR: 3% ALR-C: 22% ALR-P: 14% SD: 22% PD: 39%
Intensive Chemo (n=37) (n= 37 evaluable for ELN) (n= 34 evaluable for MPN-BP)	CR: 16% CRi: 3% MLFS: 14% PR: 11% SD: 19% TF: 38%	CCR: 6% ALR-C: 15% ALR-P: 29% SD: 21% PD: 29%
DNMTi-based (n=16) (n=16 evaluable for ELN) (n=14 evaluable for MPN-BP)	CR: 6% MLFS: 6% PR: 6% SD: 25% TF: 56%	ALR-C: 14% ALR-P: 21% SD: 29% PD: 36%
Targeted monotherapy (n=11) (n=11 evaluable for ELN) (n=10 evaluable for MPN-BP)	CR: 9% CRi: 18% MLFS: 18% SD: 18% TF: 36%	CCR: 10% ALR-C: 30% ALR-P: 20% SD: 20% PD: 20%
Other therapies (n=13) (n=13 evaluable for ELN) (n= 13 evaluable for MPN-BP)	CR: 8% CRi: 8% PR: 23% SD: 38% TF: 23%	ALR-C: 15% ALR-P: 31% SD: 31% PD: 23%

ELN = European LeukemiaNet; MPN = myeloproliferative neoplasm; BP = blast phase; ALR-C = acute leukemia response – complete; ALR-P = acute leukemia response – partial; CCR = complete cytogenetic response; CMR = complete molecular response; CR = complete remission; CRi = CR with incomplete hematologic recovery; DNMTi = DNA methyltransferase inhibitor; ELN = European LeukemiaNet; MPN-BP = myeloproliferative neoplasm-blast phase; MLFS = morphologic leukemia free state; PD = progressive disease; PR = partial remission; TF = treatment failure; SD = stable disease; VEN = venetoclax

Table 5A: Univariate analysis of factors impacting overall survival in MPN-AP/BP

Variable	Hazard ratio (95% CI)	p-value
Age ≥ 65	1.840 (1.271, 2.667)	0.001
WBC > 25 x 10^3/µL	1.812 (1.267, 2.590)	0.001
Platelet > 100 x 10^3/µL	0.687 (0.497, 0.947)	0.022
Hemoglobin > 10g/dL vs < 8g/dL	0.380 (0.240, 0.603)	<.0001
Hemoglobin 8-10 g/dL vs < 8g/dL	0.626 (0.436, 0.899)	0.011
Peripheral blasts ≥ 20% vs < 10%	1.414 (0.956, 2.094)	0.08
Peripheral blasts 10-19% vs < 10%	1.242 (0.826, 1.867)	0.30
Marrow blasts ≥ 20% vs <10%	0.882 (0.456, 1.703)	0.71
Marrow blasts 10-19% vs <10%	0.805 (0.399, 1.626)	0.55
Total bilirubin	0.896 (0.647, 1.242)	0.51
Creatinine	1.164 (0.903, 1.502)	0.24
Splenomegaly	1.259 (0.908, 1.746)	0.17
Driver Mutation Status		
JAK2	0.970 (0.697, 1.351)	0.86
CALR	1.056 (0.690, 1.617)	0.80
MPL	1.848 (1.078, 3.166)	0.03
Triple negative	0.722 (0.436, 1.197)	0.21
2017 ELN risk		
High-risk vs intermediate / favorable	1.859 (1.282, 2.696)	0.001
Mutation Status		
TP53	2.085 (1.456, 2.996)	<.0001
IDH1	0.885 (0.433, 1.808)	0.74
IDH2	0.664 (0.389, 1.134)	0.13
ASXL1	0.897 (0.616, 1.307)	0.57
EZH2	1.076 (0.609, 1.901)	0.80
SRSF2	1.113 (0.742, 1.671)	0.60
RUNX1	0.774 (0.483, 1.241)	0.29
Chronic-phase MPN type		
ET vs other	1.134 (0.694, 1.853)	0.62

PMF vs other	1.194 (0.737, 1.935)	0.47
PV vs other	1.352 (0.803, 2.278)	0.26

Table 5B: Multivariate analysis of factors impacting overall survival in MPN-AP/BP

Variable	Hazard ratio (95% CI)	p-value
Age ≥ 65	1.870 (1.265, 2.765)	0.002
WBC > 25 x 10^9/L	2.354 (1.589, 3.488)	<.0001
Platelet > 100 x 10^9/L	0.443 (0.272, 0.723)	0.001
Hemoglobin > 10g/dL vs < 8g/dL	0.629 (0.425, 0.929)	0.02
TP53 mutation status	2.146 (1.460, 3.153)	0.0001
Splenomegaly	1.305 (0.925, 1.842)	0.13

MPN = myeloproliferative neoplasm; AP/BP = accelerated/blast phase; WBC = white blood count; ELN = European LeukemiaNet; ET = essential thrombocythemia; PMF = primary myelofibrosis; PV = polycythemia vera

Figure Titles/Legends

Figure 1A: Overall survival of patients diagnosed with MPN-AP/BP from 2017 onwards

Figure 1B: Overall survival of patients with MPN-AP/BP by frontline treatment approach

Legend: DNMTi = DNA methyltransferase inhibitor; VEN = venetoclax; IC = intensive chemotherapy

Figure 2A: Overall survival of patients with MPN-AP/BP by 2017 ELN response criteria

Figure 2B: Overall survival of patients with MPN-AP/BP by 2012 MPN-BP criteria

Legend: ALR-C = acute leukemia response – complete; ALR-P = acute leukemia response – partial; CCR = complete cytogenetic response; CMR = complete molecular response; CR = complete remission; CRi = CR with incomplete hematologic recovery; ELN = European LeukemiaNet; MPN-BP = myeloproliferative neoplasm-blast phase; MLFS = morphologic leukemia free state; PD = progressive disease; PR = partial remission; TF = treatment failure; SD = stable disease

Figure 3A: Overall survival of patients with MPN-AP/BP that underwent allo-HCT from time of diagnosis

Figure 3B: Overall survival from time of allo-HCT in patients with MPN-AP/BP

Figure 3C: Overall survival from time of allo-HCT in patients with MPN-AP/BP stratified by 2017 ELN response prior to allo-HCT

Legend: ELN = European LeukemiaNet; CR = complete remission; CRi = CR with incomplete hematologic recovery; MPN-BP = myeloproliferative neoplasm-blast phase; MLFS = morphologic leukemia free state; PD = progressive disease; PR = partial remission; TF = treatment failure; SD = stable disease

Figure 1

Figure 1

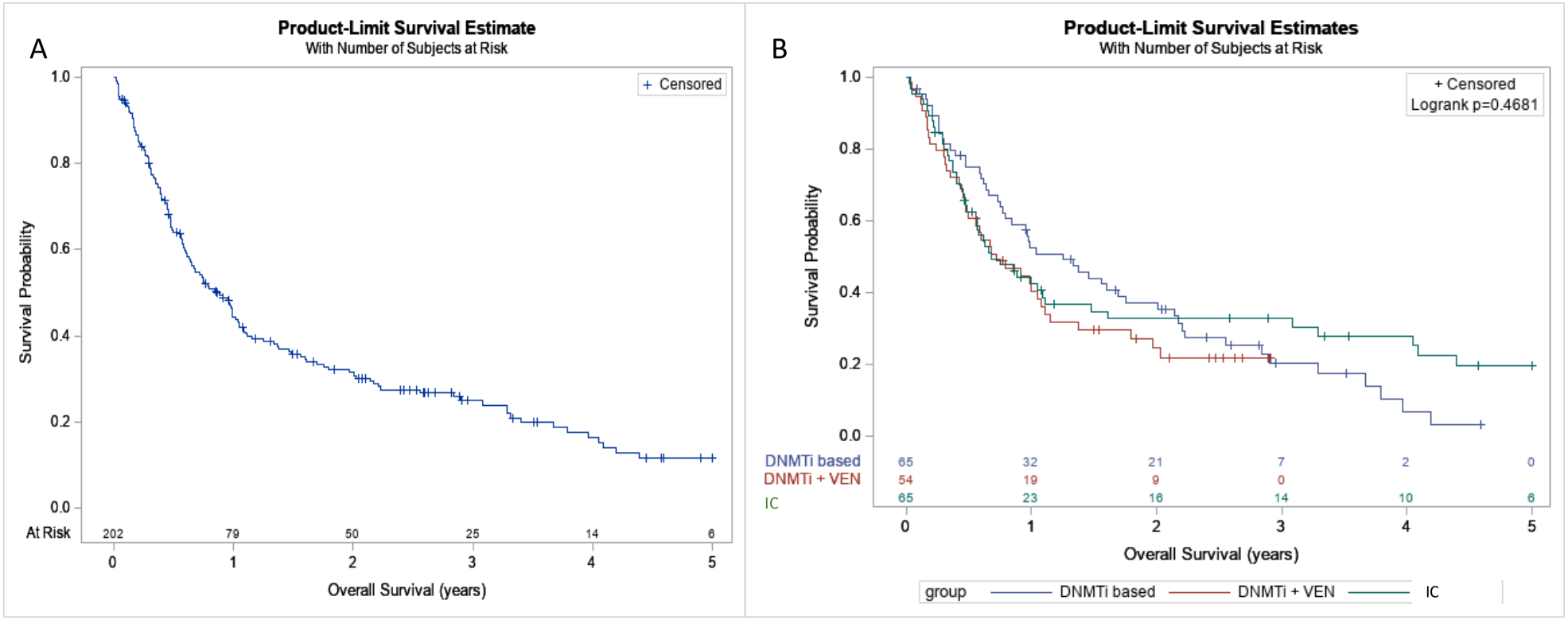

Figure 2

Figure 2

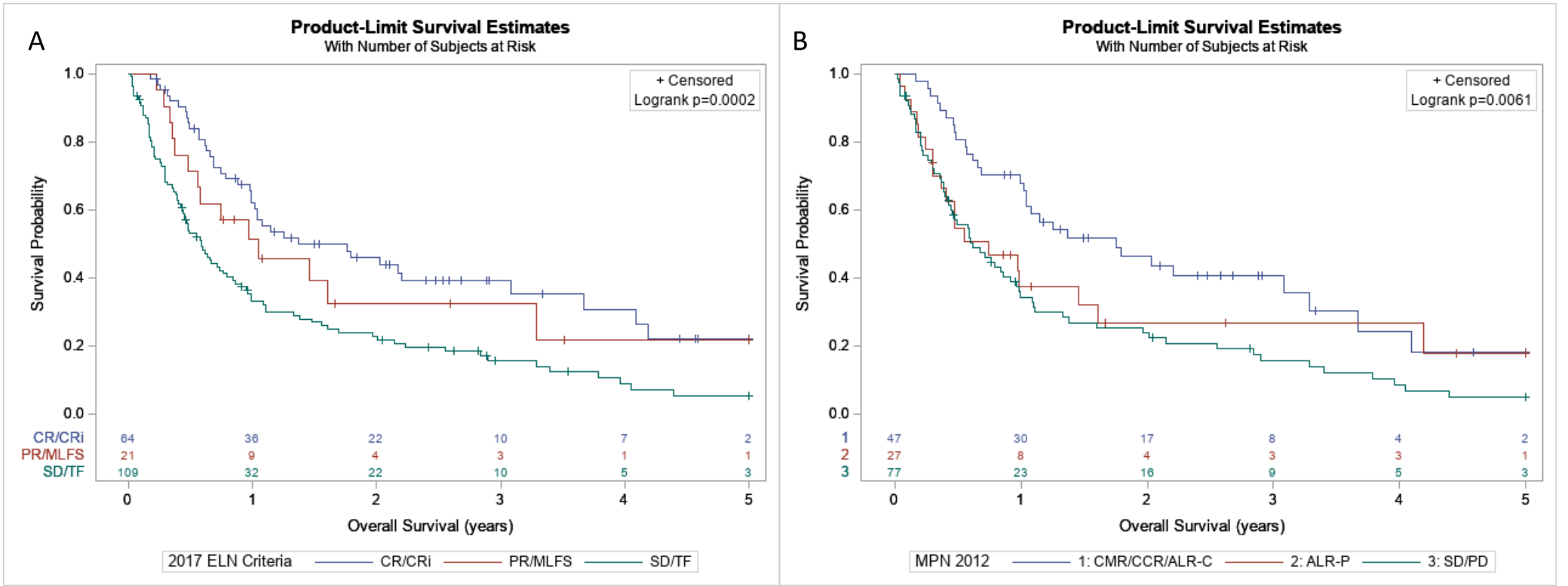

Figure 3

Figure 3