



## Combination of azacitidine, venetoclax and ruxolitinib in blast phase myeloproliferative neoplasms

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## SHORT REPORT

# Combination of azacitidine, venetoclax and ruxolitinib in blast phase myeloproliferative neoplasms

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## Summary

Myeloproliferative neoplasms in blastic phase (MPN-BP) have a dreadful prognosis. We report the characteristics and outcomes of five MPN-BP patients treated with a never-before-described combination of azacytidine and venetoclax (to control BP transformation), added to ruxolitinib (needed to control constitutional symptoms). Median age was 76 years (range 72–84), and worst performance status was 2. The overall response rate was 80%, and the complete remission rate was 40%. With median follow-up of 10.0 months (range 4.2–13.4), median overall survival was 13.4 months (95% CI 4.2–13.4). We did not detect any unexpected treatment-related toxicity, and quality of life was improved.

## KEYWORDS

azacitidine, blast phase myeloproliferative neoplasms, ruxolitinib, venetoclax

## INTRODUCTION

Philadelphia-negative myeloproliferative neoplasms in blastic phase (MPN-BP) have a dreadful prognosis with median survival of fewer than 6 months. For non-transplant candidates, there is still no standard treatment.<sup>1</sup> The combination of azacitidine (AZA, hypomethylating agents [HMA]) and venetoclax (VEN) has become the new standard of care for de-novo acute myeloid leukaemia (AML),<sup>2</sup> particularly for non-transplant candidates. To note, post-MPN AML was excluded from the registering trial. The combination of HMA and ruxolitinib (RUX) has been reported to achieve prolonged overall survival (OS) for MPN in accelerated and blast phase in a phase 2 study.<sup>3</sup> However, none of these treatments have become the standard of care for MPN-BP. The AZA-VEN combination seems the most attractive therapy for leukaemic transformation, and the addition to RUX appears of interest as a way of keeping the constitutional symptoms and/or splenomegaly of myelofibrosis under control. To the best of our knowledge, no data have evaluated the safety and effectiveness of the combination of AZA, VEN

and RUX in this setting. In the present work, we report the characteristics and outcomes of five patients with MPN-BP treated with this combination.

## METHODS

## Study design and patients

We reported data from five patients with MPN-BP who received AZA, VEN and RUX in our institution. MPN-BP was defined by  $\geq 20\%$  blasts in the peripheral blood or bone marrow, with a documented prior diagnosis of essential thrombocythemia (ET), polycythemia vera (PV) or myelofibrosis (MF).<sup>4</sup> This study was conducted in accordance with 'good clinical practice' (GCP) and applicable regulatory requirements, including the 2008 version of the Declaration of Helsinki. This study complies with the reference methodology MR-004 concerning research reusing data already collected. Patients have the right to access, rectify, oppose and delete their data or to limit their processing.

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## Treatments

RUX was administered at a dose  $\geq 10$  mg twice daily to control constitutional symptoms and/or splenomegaly of myelofibrosis. AZA-VEN was added to treatment after the leukaemic transformation: VEN was administered orally at a daily dose of 200–400 mg on days 1 through 14 at 28 based on expected and observed cytopenia; AZA at a dose of 50 or 75 mg/m<sup>2</sup> (dose changed to manage haematological toxicity), subcutaneously on days 1 through 7 every 28-day cycle. None of the patients were eligible for allogeneic SCT.

## Response and safety

We used modified Cheson criteria for response assessment: complete remission (CR) is defined by no peripheral blood blasts, bone marrow blasts  $< 5\%$ ; absence of blasts with Auer rods; absence of extramedullary disease; leukocytes  $\geq 4 \times 10^9/L$ , haemoglobin  $\geq 10$  g/L and platelets  $\geq 100 \times 10^9/L$ ; incomplete remission CRi is defined by no peripheral blood blasts with incomplete count recovery; partial remission (PR) is defined as  $\geq 50\%$  decrease in peripheral blood blasts irrespective of blood counts.<sup>5</sup> As patients were cytopenic at leukaemic transformation, we retained haematological grade  $\geq 3$  adverse events that appeared only after the initiation of treatment.

## Statistical analysis

OS was estimated using the Kaplan–Meier method and compared between groups by the log-rank test. OS was defined as the time from initiation of treatment to death from any cause. Patients alive at the data cut-off date (February 1, 2023) were censored. The main results are given with their 95% confidence interval (95% CI). Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc.).

## RESULTS

### Patient characteristics

At the time of leukaemic transformation, the five patients had myelofibrosis: four secondary MF (two post-PV, one post-ET and one JAK2V617F negative postmyelodysplastic/myeloproliferative neoplasm unclassifiable) and one primary myelofibrosis. The median age was 76 years (range 72–84), and the worse performance status was 2. RUX was administered to control constitutional symptoms for four patients and splenomegaly for two patients. Four patients had RUX before leukaemic transformation. For the first patient, RUX was discontinued at AZA-VEN initiation and resumed after two cycles due to disabling constitutional symptoms. For the next three patients, RUX was continued because the

**TABLE 1** Patient characteristics at time of leukaemic transformation.

	All patients (N=5)
Age (range), years	76 [72–84]
Sex ratio (male/female)	4/1
Prior MPN, n (%)	
PV	2 (40)
ET	1 (20)
MF	5 (100)
Prior ruxolitinib, n (%)	4 (80)
Clinical status at diagnosis	
Performance status = 2, n (%)	4 (80)
Constitutional symptoms, n (%)	4 (80)
Splenomegaly, n (%)	2 (40)
Full blood count at diagnosis	
WBC (range), $\times 10^9/L$	9.8 (1.2–131.9)
Peripheral blood blasts (range), %	18 (13–27)
Haemoglobin (range), g/dL	7.9 (4.8–8.5)
Platelets (range), $\times 10^9/L$	40 (19–220)
Mutations, n (%)	
JAK2 V617F	4 (80)
Additional mutated genes $> 2$ patients <sup>a</sup>	
NRAS	2 (50)
RUNX1	2 (50)
TET2	2 (50)

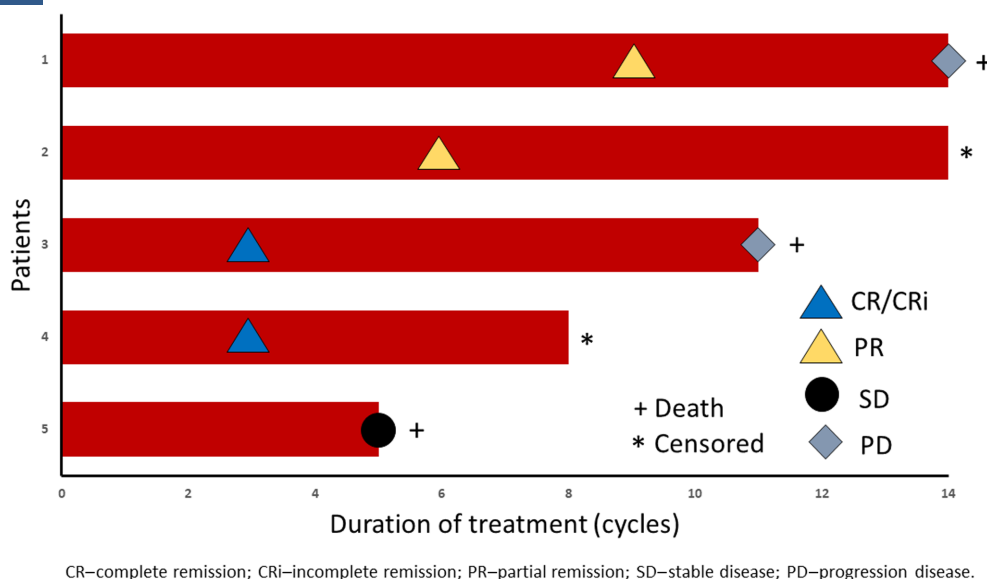
Abbreviations: ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; WBC, white blood count.

<sup>a</sup>NGS analysis available on 4/5 patients.

combination appeared safe and effective for the first. Patient characteristics are summarized in [Table 1](#).

## Response

Patients completed a median of 11 cycles (range 5–14). The best response obtained was 80%, with two CR/CRi and two PR remissions. Median time to best response was four cycles (range, 3–9). Duration and response to treatment are detailed in [Figure 1](#). Quality of Life Assessment Form was not filled out. However, we observed constitutional symptom control, clinical spleen reduction  $\geq 50\%$ , and all patients could accomplish daily living activities at home. ». Median platelet count was  $150 \times 10^9/L$  (range 60–380) at best response with a median improvement of  $125 \times 10^9/L$  (range, 5–200). Median haemoglobin level was 10.6 g/dL (range, 9.0–13.8) at best response with a median gain of 2.7 g/dL (range 1.5–7.6). With median follow-up of 10.0 months (range 4.2–13.4), three patients died of progression to AML, including one at 11 cycles in CR, one at 14 cycles in PR and one at 5 cycles in SD. All patients were alive at 3 months. Median OS was 13.4 months (95% CI 4.2–13.4).



**FIGURE 1** Duration and response to treatment. Patients have completed a median of 11 cycles (range 5–14). The overall response rate was 80%, with two CR/CRi and two PR remissions. With median follow-up of 10.0 months (range 4.2–13.4), three patients died of progression and two are still alive.

## Safety

The reason for treatment discontinuation was always related to relapse and not toxicity. Three patients (60%) were treated as outpatients only, with no reported treatment-related deaths. The main adverse events observed were prolonged cytopenia grade  $\geq 3$ : neutropenia ( $n = 4$ , 80%), anaemia ( $n = 2$ , 40%) and thrombocytopenia ( $n = 1$ , 20%). Two patients experienced febrile neutropenia during the initial cycle but none in subsequent cycles. One interstitial pneumonia of undetermined aetiology requiring intensive care hospitalization was reported without recurrence, despite continued treatment for 4 months. The median duration of each cycle was 29 days (range 27–38). The main reason for postponing a cycle was neutropenia grade 4. To date, cycle is resumed when neutrophils  $\geq 0.5 \times 10^9/L$ , and VEN is administered 200 mg 21d/28, AZA 75 mg/m<sup>2</sup> 7d/28 and RUX  $\geq 10$  mg twice daily (adapted to MF symptoms). Other notable adverse events are outlined in Supplemental Table S1.

## DISCUSSION

We report for the first time a cohort of patients with MPN-BP treated with a triple-based combination of ruxolitinib (continued to avoid bound effect for MF symptoms) along with the nowadays standard treatment for AML: azacitidine and venetoclax. We observed encouraging haematological responses, which were prolonged for some patients. In addition, the combination appeared manageable, without unexpected adverse events.

MPN-BP patients have a poor prognosis with the current treatment options and standards of care unless they are offered allo-SCT.<sup>1</sup> Unfortunately, there is a lack of treatment

guidelines for the management of allo-SCT-ineligible MPN-BP patients.<sup>4</sup> Retrospective studies show that HMA can offer survival similar to intensive chemotherapy (IC) with less toxicity.<sup>6,7</sup> These clinical data are based on the finding that hypermethylation of *p15 INK4b* and *p16 INK4a* suppressor genes has been associated with MPN-BP, suggesting that MPN-derived cells with aberrant DNA methylation respond to HMA therapy.<sup>8</sup>

Recently, studies have demonstrated that adding venetoclax to azacytidine results in rapid response and improved survival (median OS of 14.7 months) for untreated AML patients ineligible for IC.<sup>2</sup> The biological basis is that AZA may synergistically inhibit the pro-survival MCL1- and BCL-XL-based pathways, thereby increasing the dependence of leukaemia cells on BCL-2.<sup>9,10</sup> Of note, patients with MPN-BP were excluded from the registration trial. Two retrospective studies have described the combination of VEN with HMA for MPN-BP with a more favourable response rate but without significant improvement in OS.<sup>11,12</sup>

Adding ruxolitinib to azacytidine appears to be safely feasible in MPN-BP. Preclinical studies of murine and primary MPN-BP cells have demonstrated synergistic anti-clonal activity of the hypomethylating agent decitabine, combined with the selective *JAK1/2* inhibitor, ruxolitinib.<sup>13</sup> A phase 2 study showed median favourable OS of 9.5 months for MPN-AP/BP treated with HMA-RUX, compared with historical controls.<sup>3</sup> A phase 1b study has confirmed the safety and tolerability of AZA-RUX in advanced MPN.<sup>14</sup>

The safety and efficacy of a combination of ruxolitinib and venetoclax were evaluated in a phase I multicentre study.<sup>15</sup> Twenty heavily pretreated patients with relapsed/refractory AML were treated without dose-limiting toxicity. The highest doses were VEN 400 mg daily and RUX 30 mg

twice daily. JAK1/2 inhibitor ruxolitinib restored sensitivity to the BCL-2 inhibitor venetoclax in AML patient cells *ex vivo* in different model systems and *in vivo* in an AML xenograft mouse model.<sup>16</sup> These findings highlight the potential of JAK inhibitors to counteract stroma-induced resistance to BCL-2 inhibitors in AML.

Because MPN-BP develops from a pre-existing MPN malignancy, we hypothesized that it could be of interest to continue the treatment of the underlying MPN in parallel to the treatment of blastic phase development. Indeed, there is no reason to believe that BP development parallels the loss of activity when treating the underlying MPN malignancy. In addition, it is possible that a combination of the three different mechanisms of action might prolong the duration of the control of the BP phase development. We hypothesize that the activity of this combination might be based on greater sensitivity to venetoclax by increasing the dependence of leukaemic cells on BCL-2 by azacytidine and by restoring BCL-2 sensitivity by ruxolitinib.

In our small cohort, the combination of AZA, VEN and RUX appears safe and effective for treating MPN-BP patients. Further studies are needed to confirm these promising results.

#### AUTHOR CONTRIBUTIONS

TS, EC and JT involved in conception and design. TS, JCC, PGH, NM, DD, NM, AB, MV, HG, EC and JT involved in the collection and assembly of data. TS involved in data analysis and interpretation. TS, JCC, EC and JT involved in manuscript writing.

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#### FUNDING INFORMATION

None.

#### CONFLICT OF INTEREST STATEMENT

JT is on a board for Novartis; EC is on a board and a consultant for Novartis; the remaining authors declare no conflict of interest.

#### DATA AVAILABILITY STATEMENT

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

#### PATIENT CONSENT STATEMENT

Patients were informed orally, completely and honestly during a consultation in understandable terms. A written document was given to them specifying the research objectives and their rights.

#### PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

#### CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

Not applicable.

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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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