Ruxolitinib-Induced Complete Molecular Remission in Polycythemia Vera

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BACKGROUND

Polycythemia Vera (PV):

- *BCR-ABL1-negative* myeloproliferative neoplasm (MPN), along with essential thrombocythemia (ET) and primary myelofibrosis (PMF)
- Characterized by **bone marrow hypercellularity and erythroid predominance and elevated red cell mass**
- Increased risk for **thrombotic and hemorrhagic complications** (**Figure 1**).
- Often associated with **inflammatory-driven symptoms** (**Figure 1**).

JAK2^{V617F} mutation:

- Acquired mutation in hematopoietic stem cells (HSCs) → results in **constitutive activation of the JAK/STAT pathway** with associated **attendant risks and clinical features of disease.**

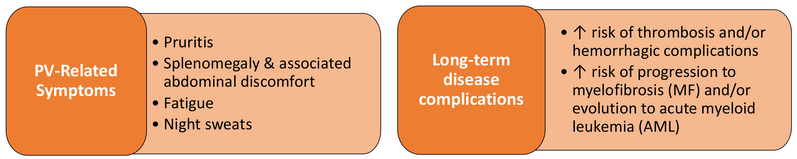

Figure 1. Symptoms and long-term complications of polycythemia vera (PV).

STUDY OBJECTIVES + DESIGN

Objective

Characterize the clinical and molecular features of PV patients that achieve a CMR in order to:

1) identify potential predictors of molecular response, &

2) assess patients' clinical outcomes.

Framework/Context

A. Case analysis of a RUX-treated PV patient who achieved CMR

B. Literature review of existing prospective and retrospective studies, with specific attention to reduction in allele burden and clinical outcomes with RUX treatment (Table 1).

Study Design

Study Feasibility

Feasibility study for a multi-center retrospective analysis of PV patients achieving CMR with RUX therapy is in-process; total number of participating sites to be determined.

Outcome Measures

Outcomes measures include histomorphological response, overall survival, progression-free survival, and event-free survival, among others.

Figure 2. Overview of PV/RUX CMR objectives and study design.

RESULTS: CASE PRESENTATION

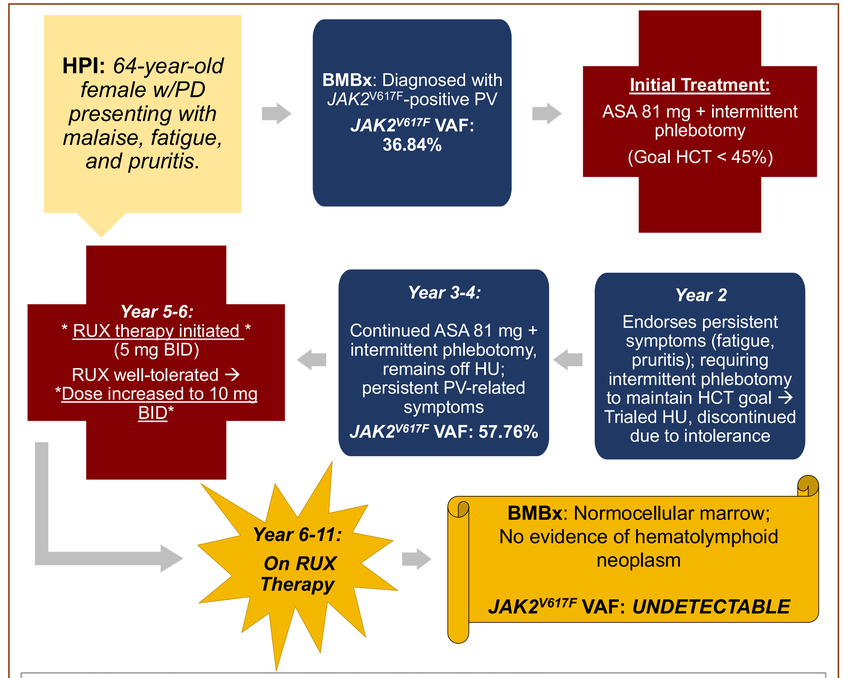

Figure 3. Schematic of treatment timeline of PV patient achieving CMR with RUX therapy.

PV: Polycythemia Vera, BMBx: bone marrow biopsy, PD: Parkinsons Disease, VAF: variant allele frequency, ASA: Aspirin, HCT: Hematocrit, HU: Hydroxyurea, RUX: Ruxolitinib

RESULTS: LITERATURE REVIEW

Table 1. Review of molecular response and clinical outcomes reported from clinical trials of RUX versus BAT.

TRIAL	REPORTED REDUCTION IN *JAK2^{V617F}* ALLELE BURDEN	BEST CLINICAL OUTCOME REPORTED
RESPONSE	**RUX-Treatment Group** ***Mean change from baseline:*** –12.2% at week 32 ***Maximum change from baseline:*** –34.7% at week 112; ~ –40% at >5 years of follow-up **BAT Group** ***- No reduction at week 32***	**SURVIVAL OUTCOMES** *EFS, PFS, and OS not reported* **≥50% TSS IMPROVEMENT (14-item MPN-SAF)** **RUX:** 49% at week 32 **BAT:** 5% (n=4) at week 32
RESPONSE-2	**RUX-Treatment Group** ***Median change from baseline:*** –15% at end of treatment (week 260) **BAT Group** ***Median change from baseline:*** +2%* at end of treatment (week 260) **Interpretation limited by the number of patients remaining on BAT.*	**SURVIVAL OUTCOMES** *EFS, PFS, and OS not reported* **≥50% TSS IMPROVEMENT (14-item MPN-SAF)** **RUX:** 45% at week 28 (n=29); 45% at week 260 (n=28) **BAT:** 23% at week 28 (n=5); 16% at week 260 (n=10)
MAJIC-PV	**> 25% VAF REDUCTION AT 12 MONTHS** **RUX:** 46% (n=40) **BAT:** 26% (n=23) **> 50% VAF REDUCTION AT 12 MONTHS** **RUX:** 14% (n=9) **BAT:** 18% (n=9)	**SURVIVAL OUTCOMES** **Molecular responders** (with > 50% reduction *JAK2^{V617F}* documented at last timepoint) had **significantly improved PFS, EFS, and OS** (*p=.001, p=.001, and p=.01, respectively*). **≥50% TSS IMPROVEMENT AT ≥1 TIMEPOINT** **RUX:** 61% **BAT:** 30%

CLINICAL RELEVANCE & CONCLUSIONS

Potential for CMR

JAKi therapy may have the potential to induce CMR in certain PV patients.

However, it is still unproven whether malignant HSC eradication is necessary to achieve cure.

Predictors of RUX Response?

The genotypic or phenotypic factors that may predict molecular response to RUX in PV patients remains an area of interest for future studies.

The dose and duration of RUX therapy needed to attain a CMR is not known.

Future Directions

Future research is indicated to elucidate mechanistic understanding of JAKi-targeted clearance of PV HSCs.

Whether continued RUX treatment is required to maintain CMR is yet to be determined.

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