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# Updated Durability of Response and Safety in MANIFEST Arm 3: Pelabresib (CPI-0610) Combined With Ruxolitinib for JAK Inhibitor Treatment-Naïve Patients With Myelofibrosis


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## OBJECTIVE

**To report updated efficacy, safety, and biomarker results from Arm 3 (pelabresib + ruxolitinib in JAKi-naïve patients with myelofibrosis) of the MANIFEST study**

## SUMMARY


**In Arm 3 of the Phase 2 MANIFEST study, the combination of pelabresib and ruxolitinib in JAKi-naïve patients with myelofibrosis resulted in durable and deepening splenic and symptom responses beyond Week 24.**

**A clinically meaningful anemia improvement and reduced transfusion burden was observed.**

**No new safety signals were observed with a longer follow-up of 11 additional months. The most common treatment-emergent adverse events were low grade.**



**References:** 1. Mascarenhas J, et al. *Cancer* 2022;128:2717–2727; 2. Mascarenhas J, et al. *J Clin Oncol* 2023:JCO2201972; 3. Harrison CN, et al. *Future Oncol* 2022;18:27:2987–2997; 4. Kleppe M, et al. *Cancer Cell* 2018;33:29–43.e7; 5. Clinicaltrials.gov. NCT02158858. Available at: https://clinicaltrials.gov/ct2/show/NCT02158858. Accessed May 24, 2023; 6. Clinicaltrials.gov. NCT04603495. Available at: https://clinicaltrials.gov/ct2/show/NCT04603495. Accessed May 24, 2023.



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**Abbreviations:** BET, bromodomain and extraterminal domain; BMF, bone marrow fibrosis; CHR, complete hematologic response; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Hgb, hemoglobin; HMR, high-molecular risk; HU, hydroxyurea; Int, intermediate; IPSS, International Prognostic Scoring System; JAK, Janus kinase; JAKi, JAK inhibitor; MF, myelofibrosis; MOF, multiorgan failure; PV, polycythemia vera; RBC, red blood cell; SVR35, 35% reduction in spleen volume at Week 24; TD, transfusion dependent; TI, transfusion independent; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score at baseline; VAF, variant allele frequency.



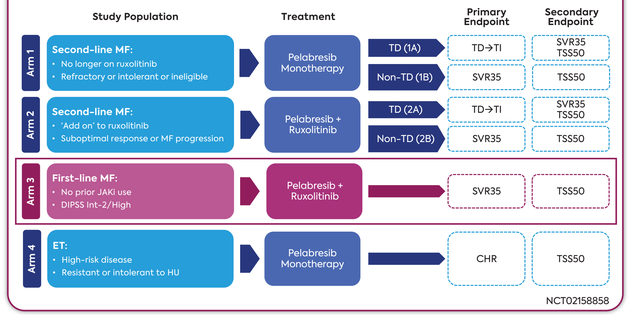
**Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority**

## INTRODUCTION

- An unmet need persists with JAKi monotherapy because a substantial proportion of patients discontinue treatment due to progressive disease and treatment-emergent adverse events, such as anemia and thrombocytopenia, and have a poor prognosis[1–3]
- Preclinical data indicated overlapping effects of BET and JAK inhibition in MF[4]
- Pelabresib, a BET inhibitor, downregulates the expression of genes that contribute to the heterogeneous pathology of MF[2]
- The combination of BET and JAK inhibition in patients with MF may represent a potential therapeutic approach to address disease pathology which requires further investigation[2–4]

## STUDY DESIGN[5]

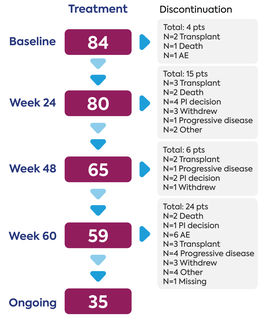
**Figure 1. MANIFEST: Ongoing, global, open-label Phase 2 study investigating pelabresib in myelofibrosis and essential thrombocythemia**




## RESULTS

**Table 1. Patient disposition**

| | Arm 3 |
|---|---|
| **Enrolled (n)** | 84 |
| Ongoing treatment [n (%)] | 35 (42) |
| Discontinued treatment [n (%)] | 49 (58) |
| **Primary reason for treatment discontinuation [n (%)]** | |
| Progressive disease | 6 (7) |
| AE* or lab abnormality | 7 (8) |
| Withdrew consent | 7 (8) |
| PI decision | 7 (8) |
| Death | 5 (6) |
| Stem cell transplant | 10 (12) |
| Other | 6 (7) |
| Missing[‡] | 1 (1) |
| **Pelabresib dose (median, range)** | 125 mg QD (50, 225) |
| **Ruxolitinib dose (median, range)** | 10 mg BID (5, 25) |




- Median treatment duration[‡]: Median: 26.7 months (95% CI 19.1–30.8)

*Two patients were initially discontinued due to AEs that later resulted in death. [†]Pending data entry. [‡]Kaplan–Meier estimate.

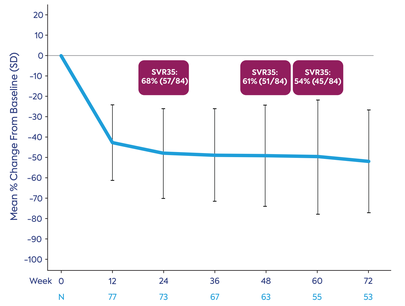
**Table 2. Patient demographics and baseline characteristics**

| | | N=84 |
|---|---|---|
| **Age (years)** | Mean (SD) | 67 (10) |
| **Gender** | Male, n (%) | 59 (70) |
| **DIPSS** | Int-1, n (%) | 19 (23) |
| | Int-2, n (%) | 52 (62) |
| | High, n (%) | 13 (16) |
| **IPSS** | Int-1, n (%) | 10 (12) |
| | Int-2, n (%) | 29 (35) |
| | High, n (%) | 45 (54) |
| **MF subtype** | Primary MF, n (%) | 46 (55) |
| | Post-PV MF, n (%) | 9 (11) |
| | Post-ET MF, n (%) | 27 (32) |
| | Missing*, n (%) | 2 (2) |
| **Hemoglobin (g/dL)** | Median (min, max) | 9 (7, 17) |
| | <10, n (%) | 55 (66) |
| **Platelet (× $10^9$/L)** | Median (min, max) | 294 (100, 1849) |
| **Spleen volume (cc)** | Median (min, max) | 1698 (458, 4782) |
| **TSS** | Median (min, max) | 16 (0, 38) |
| **Mutations** | HMR[†], n (%) | 47 (56) |
| | *ASXL1*, n (%) | 37 (44) |
| | *JAK2 V617F*[‡], n (%) | 59 (70) |
| | *CALR*[‡], n (%) | 17 (20) |
| | *MPL*, n (%) | 6 (7) |
| | Triple negative, n (%) | 3 (4) |

*Pending data entry; [†]HMR mutations: *ASXL1, EZH2, IDH1/2, SRSF2, U2AF1*; [‡]One patient had both *JAK2 V617F* and *CALR* mutations.

Data cutoff 29 July 2022

**Figure 2. Spleen volume mean percentage change over time**

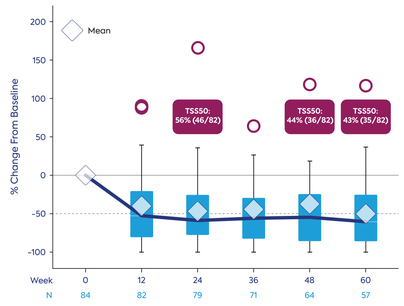



| N=84 | |
|---|---|
| **Median time to SVR35 response** | 12 wks (range 10–51) |
| **Median follow-up* for SVR35 response** | 84 wks (95% CI 66–90) |
| **Response maintained at data cutoff** | 70% (47/67) |

*Median has not been reached; reverse Kaplan–Meier estimate of median duration of follow-up for SVR35 response. Spleen volume per local radiology review. Spleen volume mean percentage change: patients with an available spleen volume assessment for the corresponding time points.

**SVR35 response was observed in 68% (57/84) of patients at Week 24, 61% (51/84) at Week 48 and 54% (45/84) at Week 60**

**Figure 3. TSS mean percentage change over time**

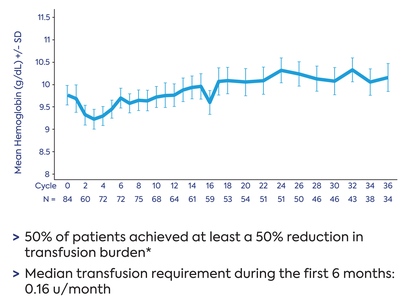



| TSS50 | |
|---|---|
| **At any time** | 83% (68/82*) |

*Two ongoing patients were nonevaluable for TSS50; n=1 due to missing baseline, n=1 due to baseline TSS=0.

**TSS50 occurred in 56% (46/82) of patients at Week 24, 44% (36/82) at Week 48 and 43% (35/82) at Week 60**

**Figure 4. Hemoglobin improvement over time**



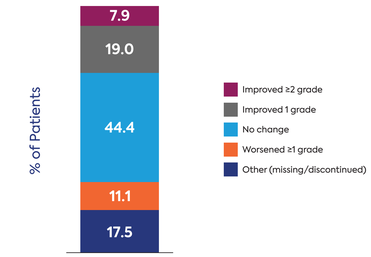

- 50% of patients achieved at least a 50% reduction in transfusion burden*
- Median transfusion requirement during the first 6 months: 0.16 u/month

| Non-TD | Hemoglobin Response[†] |
|---|---|
| **Response Rate** | 27% (21/79) |
| **Median time to response** | 60 wks (range 2–174) |
| **Median duration of response** | 28 wks (range 12–135) |

*Defined as a reduction of ≥50% from baseline in the number of units of RBC transfusion during any 12-wk period post baseline. Patients are evaluable if receiving ≥4 RBC transfusion units at baseline. [†]Hemoglobin response is defined as the proportion of patients who enrolled as non-TD and achieved ≥1.5 g/dL Hgb increase from baseline over any consecutive 12-wk period in the absence of RBC transfusions.

**Hemoglobin response was observed in 27% (21/79) of non-TD patients**

**Figure 5. Change in bone marrow fibrosis grade at Week 24 by central pathology review**

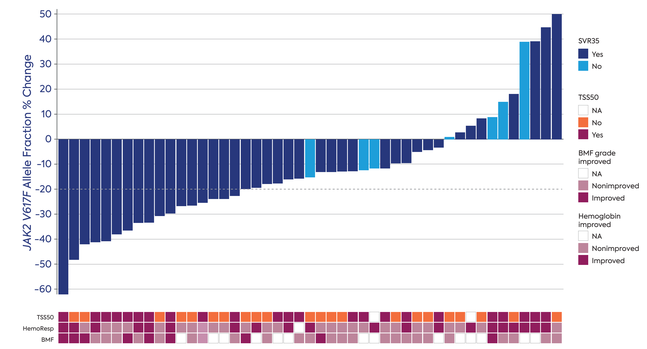



- 27% (17/63) of patients showed ≥1 grade improvement in BMF at Week 24
  - This improvement was maintained in 59% (10/17) of patients at the next available assessment or longer
- 40% (25/63) of patients had ≥1 grade improvement at any time
- 59% (16/27) of patients had a ≥15% increase in distance between nuclei of CD61+ cells* in the bone marrow

*Marker of megakaryocytes; an increased distance between CD61+ nuclei cells is indicative of megakaryocyte declustering in the bone marrow. Patients were evaluable if nonmissing baseline or discontinued without a Week 24 bone marrow assessment; bone marrow fibrosis grade was assessed by three independent and blinded pathologists per central pathology review, maturing data with central review ongoing.

**27% of patients had ≥ 1 grade improvements in bone marrow fibrosis at Week 24**

**Figure 6. Overlapping clinical responses associated with *JAK2 V617F* VAF reduction at Week 24**




- 18/47 (38%) patients reached a ≥20% reduction in *JAK2 V617F* VAF
  - Median (min, max) reduction was –14% (–62%, 50%)
  - An association of *JAK2 V617F* VAF reductions and bone marrow fibrosis was observed with SVR35 (8 pts), TSS50 (5 pts) and Hgb responses (5 pts)*

*Hgb assessment within 2 weeks after RBC transfusion was excluded from the analysis; any level of increase from baseline (range: 0.1–3.8 g/dL).

**Clinical responses were associated with *JAK2 V617F* VAF reduction at Week 24**

**Table 3. Treatment-emergent adverse events**

| TEAEs of all grades that occurred in ≥20% of patients | | All Grade N=84* n (%) | Grade 3 N=84* n (%) | Grade 4 N=84* n (%) |
|---|---|---|---|---|
| **Hematologic Events** | Anemia | 36 (43%) | 29 (35%) | 1 (1%) |
| | Thrombocytopenia[†] | 46 (55%) | 14 (17%) | 3 (4%) |
| **Nonhematologic Events** | **Gastrointestinal events** | | | |
| | Diarrhea | 36 (43%) | 2 (2%) | 0 |
| | Constipation | 25 (30%) | 0 | 0 |
| | Nausea | 24 (29%) | 0 | 0 |
| | Abdominal pain[‡] | 22 (26%) | 0 | 0 |
| | **Other nonhematologic events** | | | |
| | Respiratory tract infection[§] | 34 (41%) | 8 (10%) | 2 (2%) |
| | Asthenic conditions[¶] | 32 (38%) | 1 (1%) | 1 (1%) |
| | Musculoskeletal pain** | 27 (32%) | 0 | 0 |
| | Dizziness[††] | 23 (27%) | 0 | 0 |
| | Cough | 20 (24%) | 0 | 0 |
| | Dysgeusia | 20 (24%) | 0 | 0 |
| | Dyspnea | 19 (23%) | 4 (5%) | 0 |
| | Headache | 18 (21%) | 0 | 0 |
| | Muscle spasms | 17 (20%) | 0 | 0 |

*Safety-evaluable population: received at least one dose of study drug at the time of the data cut; [†]Includes TEAE platelet count decrease; [‡]Includes TEAE abdominal pain upper; [§]Includes TEAEs of upper respiratory tract infection, viral upper respiratory tract infection, bronchitis, sinusitis, rhinitis, nasopharyngitis, pneumonia, COVID-19, COVID-19 pneumonia and influenza; [¶]Include TEAEs of asthenia, fatigue, lethargy and malaise; **Includes TEAEs of arthralgia and myalgia; [††]Includes TEAEs of balance disorder and vertigo. MOF, multiorgan failure.

- Serious adverse events reported in ≥2 pts were anemia, pyrexia and COVID-19 (3 pts each), gastrointestinal hemorrhage, multiple organ dysfunction syndrome, pneumonia, respiratory tract infection, urinary tract infection, fall and respiratory failure (2 pts each)
- Twelve pts (14%) reported TEAEs that led to pelabresib discontinuation
- Eight Grade 5 TEAEs were reported in 7 pts
  - Acute respiratory distress syndrome due to ruxolitinib withdrawal (2 pts each), MOF due to COVID (reported as two separate TEAEs in the same pt), MOF due to sepsis secondary to pneumonia, respiratory failure due to COVID-19, bacterial endocarditis and urinary tract infection
  - All were assessed by the PI as not related to pelabresib, except MOF due to sepsis secondary to pneumonia