Somatic mutations/chromosomal aberrations

Nil | JAK2/CALR/MPL +1 | +2 | +3 or more

FIGURE 2

Higher odds for CP | Higher odds for MF

NRAS | ZRSR2 | 7q | U2AF1 | SRSF2 | EZH2 | ASXL1 | CBL | 1p | JAK2 clone >50% | 9p
Age >60 | Male sex | rs11104870 (T) | rs13219787 (A)

Odds ratio for Myelofibrosis

Least likely | Most likely

MPL | CALR | SH2B3 | SF3B1 | CUX1 | DNMT3A | V617F | U2AF1 | IDH1 | SRSF2 | TET2 | RUNX1 | EZH2 | ASXL1 | NF1 | TP53 | CBL | PPM1D | NFE2 | KRAS | NRAS | PTNP11

log odds of occurring 2nd in gene pair

Odds ratio for Polycythemia vera

Higher odds for ET | Higher odds for PV

9pUPD | JAK2 clone >50% | NFE2 | rs12340895 (G) | Age >60 | Male Sex | rs10758658 (A) | rs11042125 (T) | rs409801 (C) | rs2236496 (C)

(9p. Reduced MCH) | (11p. Reduced Hb) | (9p. Increased Plt) | (9p. Reduced MCV)

9p | V617F | U2AF1 | SRSF2 | TET2 | RUNX1 | EZH2 | ASXL1 | NF1 | TP53 | CBL | PPM1D | NFE2 | KRAS | NRAS | PTNP11

-3 | 0 | 3

rs13219787 (A) | 0.008 (12q. Reduced Plt)

(6p. Increased MCH)
**FIGURE 3**

- **Genomic classification**
- **Distribution of MPN subtypes**
- **Outcomes in PV/ET**
- **Outcomes in myelofibrosis**

**Start**
- **TP53, 17p LOH 5-/5q-**
  - Yes
  - **MPN with TP53 disruption/aneuploidy**
  - Proportion of subtypes: ET, PV, MF, Other
  - Median EFS: 13.8y
  - Overall survival: 2.4y**

- No
  - **1 or more of 18 genetic aberrations**
    - Yes
    - **MPN with chromatin/spliceosome mutation**
    - Proportion of patients: ET, PV, MF, Other
    - EFS: 12.1y***
    - Overall survival: 3.5y

  - No
    - **CALR or 20q-**
      - Yes
      - **MPN with CALR mutation**
      - Proportion of subtypes: ET, PV, MF, Other
      - EFS: 18.1y
      - Overall survival: 18.9y

    - No
      - **JAK2, CALR, MPL or 20q-**
        - Yes
        - **MPN with MPL mutation**
        - Proportion of subtypes: ET, PV, MF, Other
        - EFS: 15.2y*
        - Overall survival: 11.5y

      - No
        - **JAK2, 9p LOH or NFE2**
          - Yes
          - **MPN with homozygous JAK2 or NFE2 mutation**
          - Proportion of subtypes: ET, PV, MF, Other
          - EFS: 18.6y
          - Overall survival: 13.6y

        - No
          - **Other clonal driver**
            - Yes
            - **Myeloproliferation with other driver mutation**
            - Proportion of subtypes: ET, PV, MF, Other
            - EFS: 17.4y
            - Overall survival: 7.5y

            - No
              - **Myeloproliferation with no known driver mutation**
                - Proportion of subtypes: ET, PV, MF, Other
                - EFS: >25y**
                - Overall survival: >25y

---

^EZH2, IDH1/2, ASXL1, PHF6, CUX1, ZRSR2, SRSF2, U2AF1, KRAS, NRAS, GNAT, CBL, T7/9q LOH, 4q LOH, RUNX1, STAG2, BCOR

**AML transformation**

**MF transformation**

**Overall survival**

*p<0.05, **p<0.01, ***p<0.001 for outcome difference compared with MPN with heterozygous JAK2 mutation**
FIGURE 4

A

Cohort

Age

Male

Other genetic

MPN Subtype*

ASXL1

RUNX1

NRAS

IDH2

SRSF2

TET2

ASXL1

Cytogenetic

TP53

DNMT3A

U2AF1

Other clinical

JAK2

EZH2

NFE2

IDH2

MPL

ASXL1

Other genetic

Hb ↓

WCC ↑

Plt ↓

Age

CHRONIC PHASE

MYELOFIBROSIS

MF transformation

AML transformation

Death

Death

(n=403)

(n=1599)

(n=31)

(n=121)

(n=325, 47% genomic data)

(n=276)

B

Chronic phase

Training cohort cross-validation (n=1599)

External validation (n=325, 47% genomic data)

Myelofibrosis

Training cohort cross-validation (n=276)

External validation (n=190, 58% genomic data)