Supplemental Tables and Figures:

Table S1: Risk factors of patients enrolled on trial lacking high risk features of age >60 years and/or history of thrombosis

Table S2: Baseline symptom burden and Quality of Life by Treatment Arm

Table S3: Loss or Gain of Cytogenetic Abnormalities During Study Period

Table S4: Reasons for Discontinuation by Treatment Arm

Figure S1: Baseline moderate (score $\geq$ 3) symptoms by Disease type

Figure S2: Individual items of the Response criteria met (%) at 12 months for A) PV and B) ET

Figure S3: Average weekly dose by complete response (CR) versus non-CR for A) HU and B) PEG

Figure S4: Maximum percent change (%) from baseline in spleen by imaging for A) PV and B) ET. 58 PV (HU: 27, PEG: 31) and 51 ET (HU: 24, PEG: 27) patients had at least 1 post-baseline imaging assessment and were evaluable for spleen response.

Figure S5: Bone marrow response at 12 months and best response. Bone marrow response evaluation criteria adapted from ELN-IWG [Barosi et al. Blood. 2013 6;121(23):4778-81].

Figure S6: Average weekly dose by histopathology response for A) HU and B) PEG

Figure S7: A) *JAK2V617F* allele burden at baseline, 12 and 24 months for ET and PV by arm.

Figure S8: A) *CALR* allele burden at baseline, 12 and 24 months by arm B) *TET2* allele burden at baseline, 12 and 24 months by arm C) *JAK2*V617F allele burden at baseline by complete response for PV D) *JAK2*V617F allele burden at baseline by complete response for ET E) association of baseline mutational status with complete response

Table S1:

Number of Essential thrombocythemia and polycythemia vera patients enrolled with "high-risk" features other than age >60 years or history of thrombosis						
	CV risk factors[1]	Erythromelalgia	Migraines	Splenomegaly[2]	Extreme Thrombocytosis[3]	Hemorrhage
ET (n=20)	7 (35%)	4 (20%)	8 (40%)	NA	3 (15%)	5 (25%)
PV (n=16)	8 (50%)	3 (19%)	5 (31%)	4 (25%)	2 (13%)	NA

[1] hypertension and/or diabetes requiring therapeutic intervention

[2] As defined by (> 5 cm below the left costal margin on palpitation) or symptomatic splenomegaly (splenic infarcts or requiring analgesia)

[3] defined as > 1000 x 10^9/L in PV and 1500 x 10^9/L for ET

Table S2:

	HU (n=82)	PEG (n=82)	Total (n=164)	P value*
MPN-SAF TSS (0-100)	**14.6 (11.4)**	**17.0 (13.6)**	**15.8 (12.6)**	**0.22**
Worst fatigue (0-10)	3.9 (2.9)	4.5 (2.8)	4.2 (2.9)	
Early satiety (0-10)	1.6 (2.2)	1.7 (2.6)	1.6 (2.4)	
Abdominal pain (0-10)	0.9 (1.7)	0.9 (1.8)	0.9 (1.8)	
Abdominal discomfort	1.2 (2.0)	1.2 (2.1)	1.2 (2.0)	
Inactivity (0-10)	1.0 (1.8)	1.8 (2.5)	1.4 (2.2)	
Headache (0-10)	1.7 (2.4)	1.7 (2.7)	1.7 (2.6)	
Concentration problems (0-10)	1.3 (1.8)	1.6 (2.4)	1.5 (2.1)	
Dizziness (0-10)	1.6 (2.0)	1.7 (2.3)	1.7 (2.2)	
Numbness (0-10)	1.8 (2.2)	1.9 (2.5)	1.8 (2.4)	
Insomnia (0-10)	2.1 (2.4)	2.7 (3.2)	2.4 (2.8)	
Sad mood (0-10)	1.2 (1.8)	1.8 (2.5)	1.5 (2.2)	
Sexuality (0-10)	1.5 (2.5)	1.5 (2.6)	1.5 (2.6)	
Cough (0-10)	1.0 (1.7)	0.8 (1.5)	0.9 (1.6)	
Night sweats (0-10)	1.4 (2.0)	1.4 (2.2)	1.4 (2.1)	
Itching (0-10)	1.6 (2.6)	2.5 (3.0)	2.1 (2.8)	
Bone pain (0-10)	1.2 (2.1)	1.4 (2.4)	1.3 (2.3)	
Fever (0-10)	0.2 (0.5)	0.1 (0.3)	0.1 (0.4)	
Weight loss (0-10)	1.0 (1.9)	0.9 (2.0)	0.9 (2.0)	
Overall QoL (0-10)	3.0 (2.6)	3.1 (2.9)	3.0 (2.8)	
EORTC QLQ-C30 GHS/QoL (0-100)	73.8 (18.8)	67.9 (24.3)	70.8 (22.0)	0.09

Mean (SD) values presented for each item

*independent samples t-test comparison

Table S3

Diagnosis	Treatment	Abnormality at Baseline Lost at Follow Up	No. of cells	Total cells Analyzed	Time point lost
PV	PEG	+9‘ +9,+22	[8] [1]	20	24 months
PV	HU	t(14;21)(q24;q22) t(14;21)(q24;q22),del(20)(q13.1q13.2)	[9] [11]	20	24 months
PV	HU	del(20)(q13.2)	[21]	21	24 months
PV	PEG	+8	No data	No data	12 months
PV	HU	+9	[5]	20	24 months
ET	PEG	‘-Y	[4]	20	9 months*
Diagnosis	**Treatment**	Abnormality at Baseline Gained at Follow Up	No. of cells	Total cells Analyzed	Time point Gained
PV	HU	del(20)(q11.2q13.3)	[5]	20	36 months
PV	PEG	del(16)(q22) ‘-Y	[2] [3]	20	24 months
PV	HU	del(20)(q11.2)	[2]	20	24 months
PV	HU	‘-Y	[19]	20	24 months*

*End of study

Table S4:

	HU (n=86)	PEG (n=82)	Total (N=168)
Study closure by sponsor	49 (57%)	45 (55%)	94 (56%)
Adverse event	9 (11%)	12 (15%)	21 (13%)
Patient refusal / withdrawal	10 (12%)	9 (11%)	19 (11%)
Completed protocol treatment	6 (7%)	10 (12%)	16 (10%)
Treatment never started	6 (7%)	0	6 (4%)
Lack of efficacy	1 (1%)	3 (4%)	4 (2%)
Lost to follow-up	2 (2%)	2 (2%)	4 (2%)
Physician decision	0	1 (1%)	1 (1%)
Patient developed other disease	1 (1%)*	0	1 (1%)
Transfer to another study	1 (1%)**	0	1 (1%)
Death	1 (1%)	0	1 (1%)

*patient developed mastocytosis

**patient transferred to MPN-111 trial which was designed to evaluate PEG in patients refractory and intolerant to HU.

Figure S1:

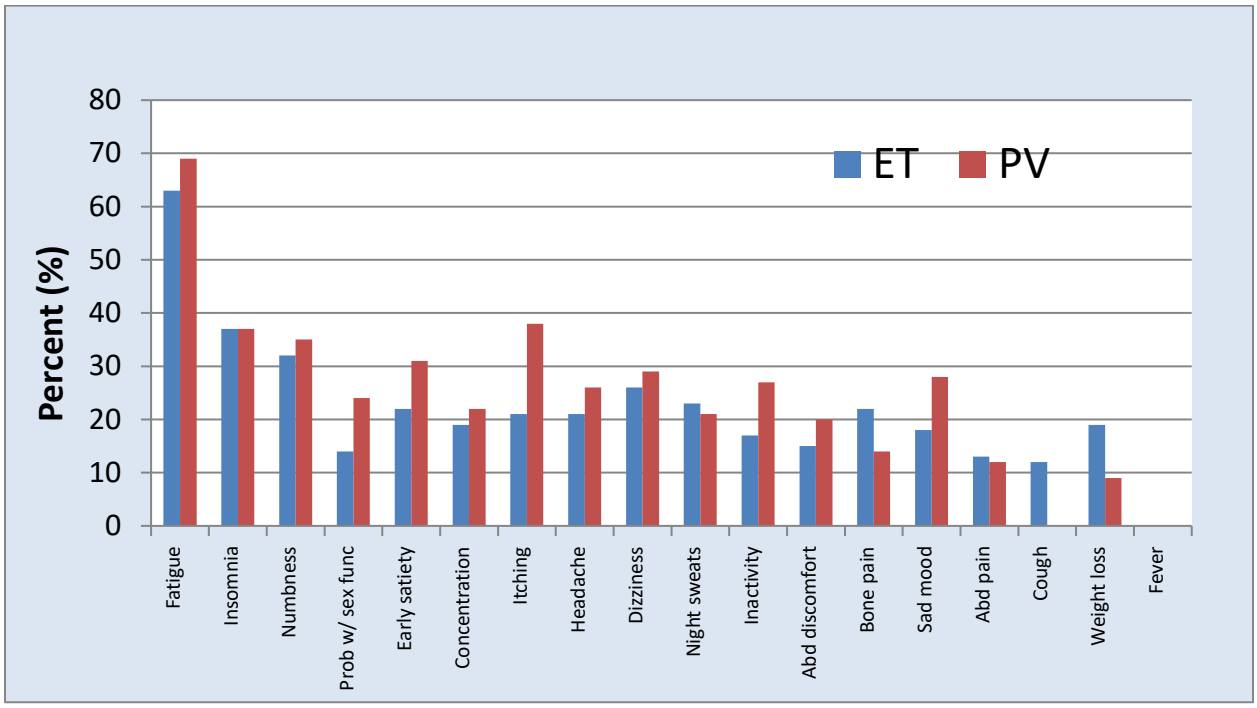
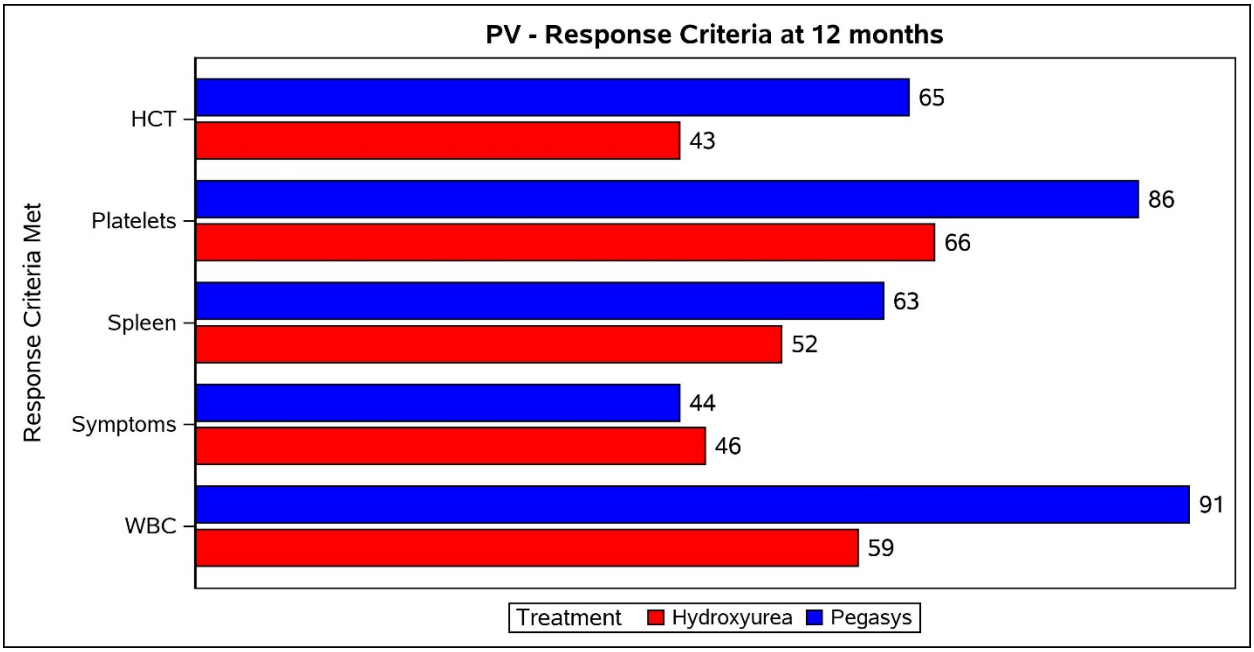

80
70
60
50
40
30
20
10
0
Percent (%)
ET
PV
Fatigue
Insomnia
Numbness
Prob w/ sex func
Early satiety
Concentration
Itching
Headache
Dizziness
Night sweats
Inactivity
Abd discomfort
Bone pain
Sad mood
Abd pain
Cough
Weight loss
Fever

Figure S2:


PV - Response Criteria at 12 months
Response Criteria Met
HCT
Platelets
Spleen
Symptoms
WBC
65
43
86
66
63
52
44
46
91
59
Treatment
Hydroxyurea
Pegasys

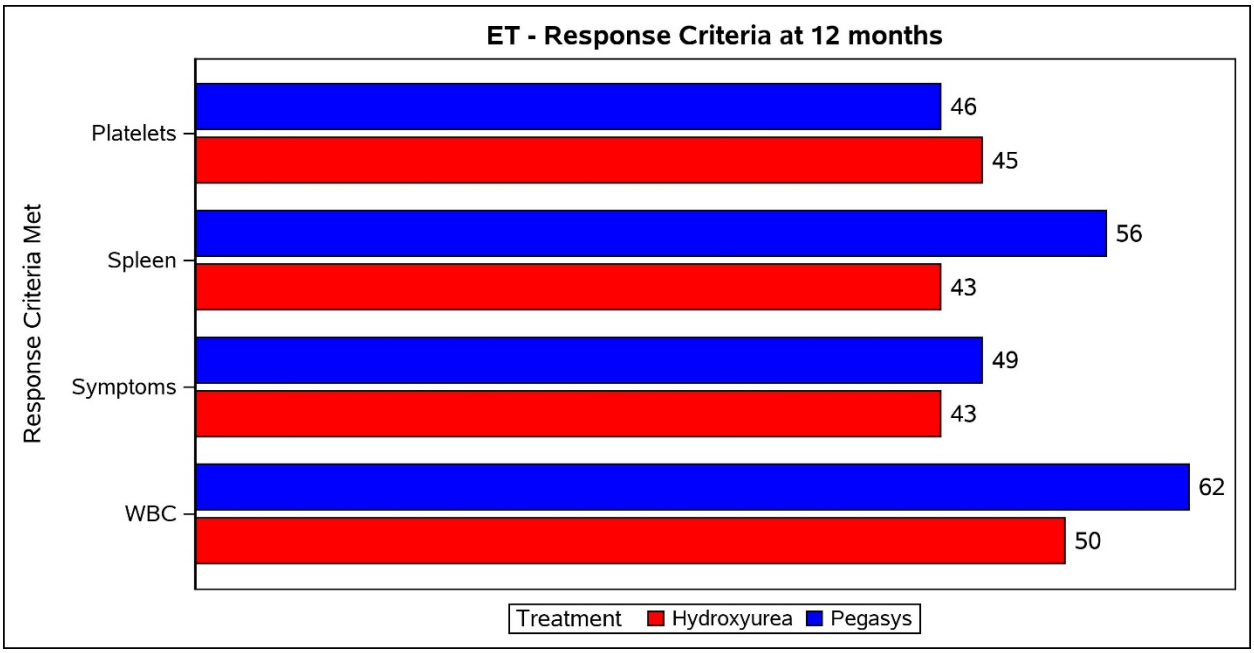
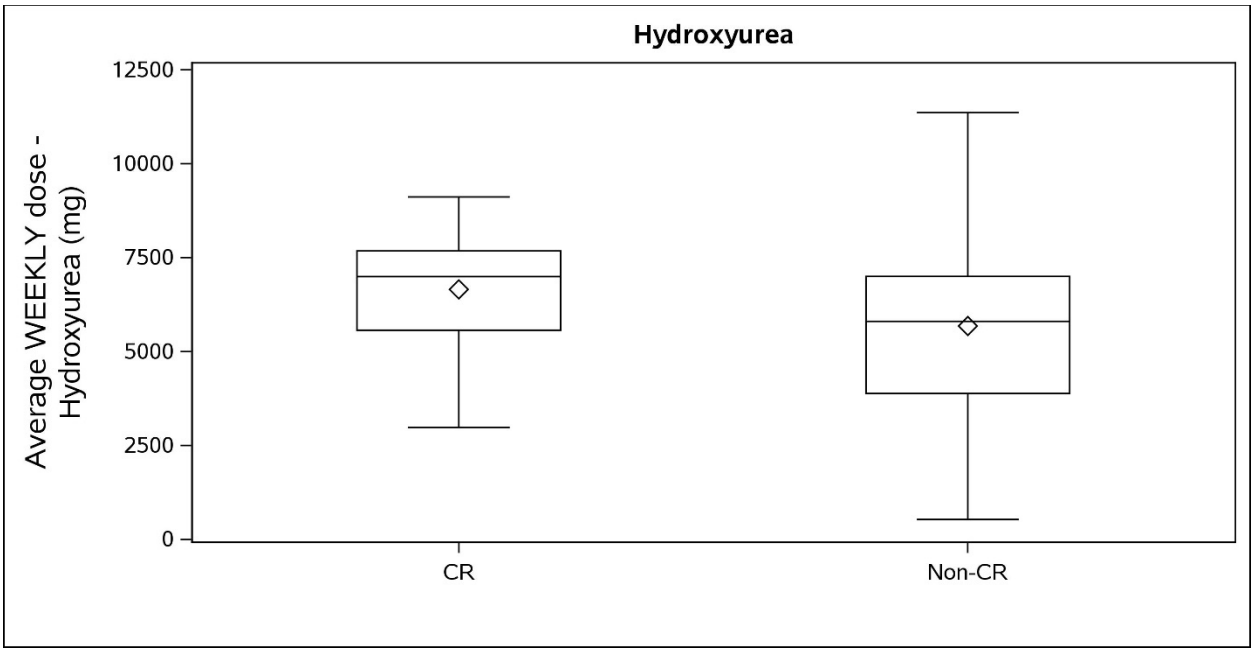

ET - Response Criteria at 12 months
Response Criteria Met
Platelets
Spleen
Symptoms
WBC
46
45
56
43
49
43
62
50
Treatment
Hydroxyurea
Pegasys

Figure S3:


Hydroxyurea
Average WEEKLY dose - Hydroxyurea (mg)
12500
10000
7500
5000
2500
0
CR
Non-CR

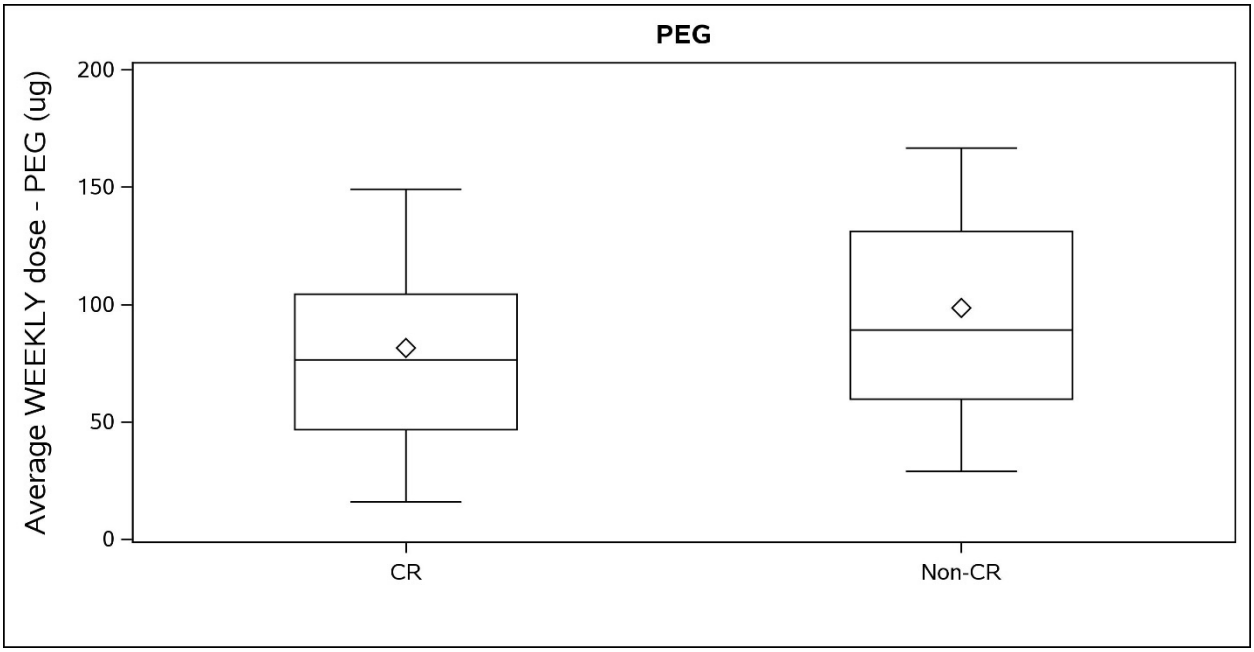
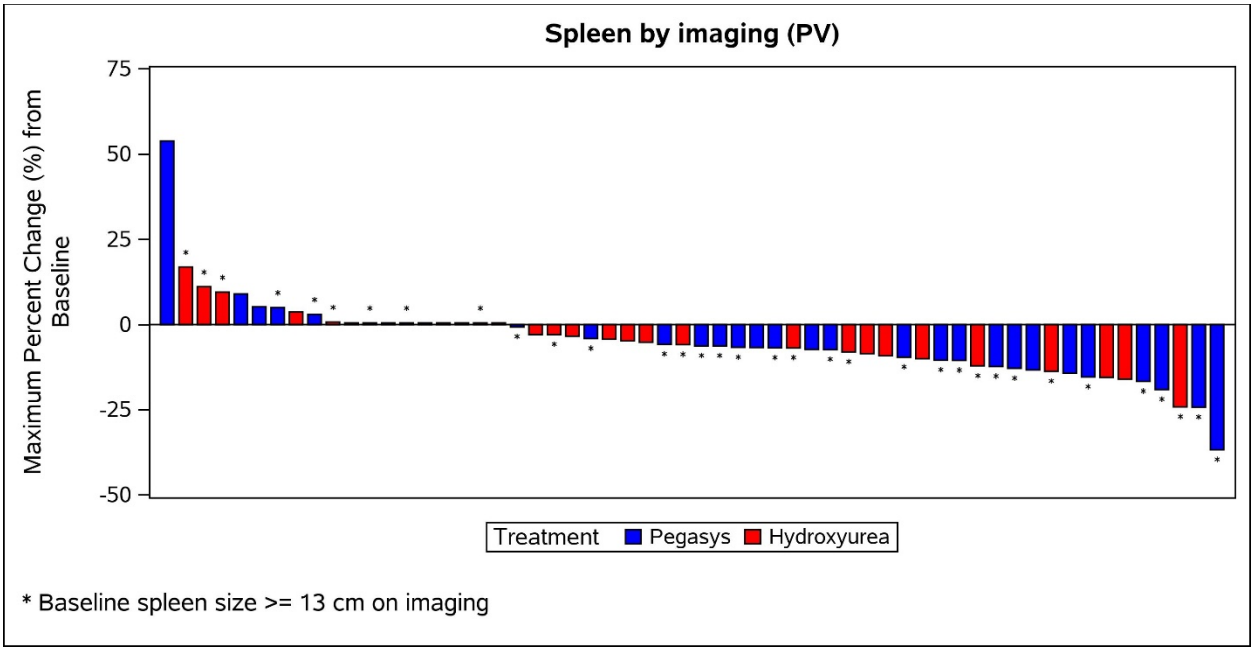

PEG
Average WEEKLY dose - PEG (ug)
200
150
100
50
0
CR
Non-CR

Figure S4:


Spleen by imaging (PV)
Maximum Percent Change (%) from Baseline
75
50
25
0
-25
-50
Treatment
Pegasys
Hydroxyurea
* Baseline spleen size >= 13 cm on imaging

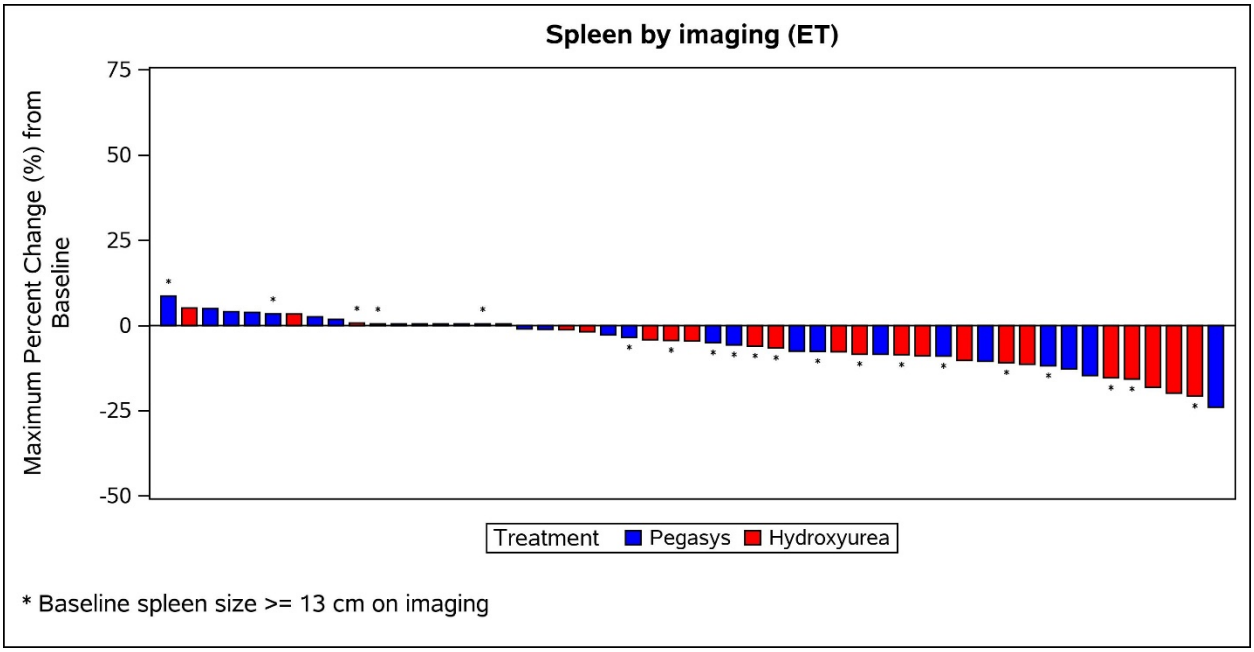
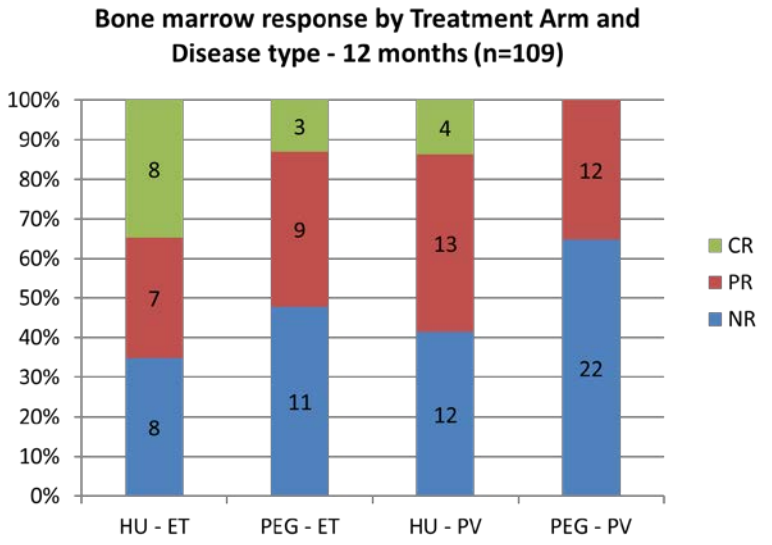

Spleen by imaging (ET)
Maximum Percent Change (%) from Baseline
75
50
25
0
-25
-50
Treatment
Pegasys
Hydroxyurea
* Baseline spleen size >= 13 cm on imaging

Figure S5:

Complete histo-pathology remission
- ET- disappearance of megakaryocyte hyperplasia
- PV- presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia

Partial histo-pathology remission
- ET- megakaryocyte hyperplasia reduced
- PV- marrow cellularity and trilineage hyperplasia reduced
- Reduction of MK and marrow cellularity by 30% but doesn't meet CR

No histo-pathology response
- ET / PV- Does not satisfy partial histo-pathology remission



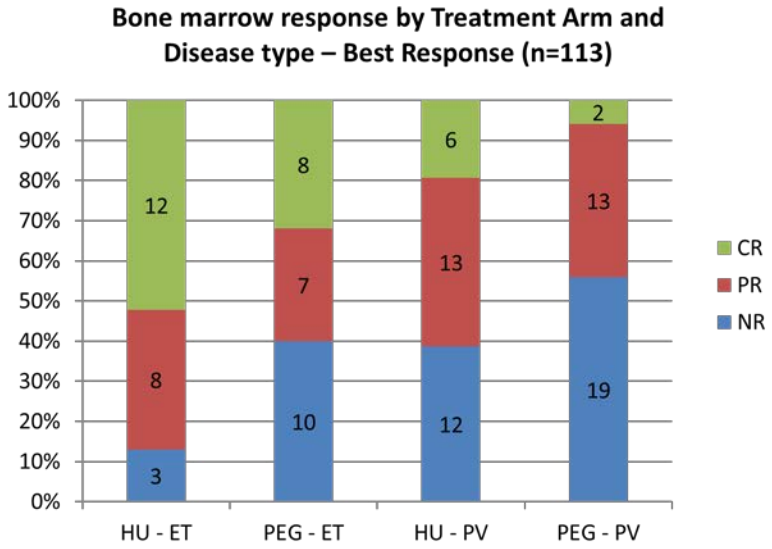
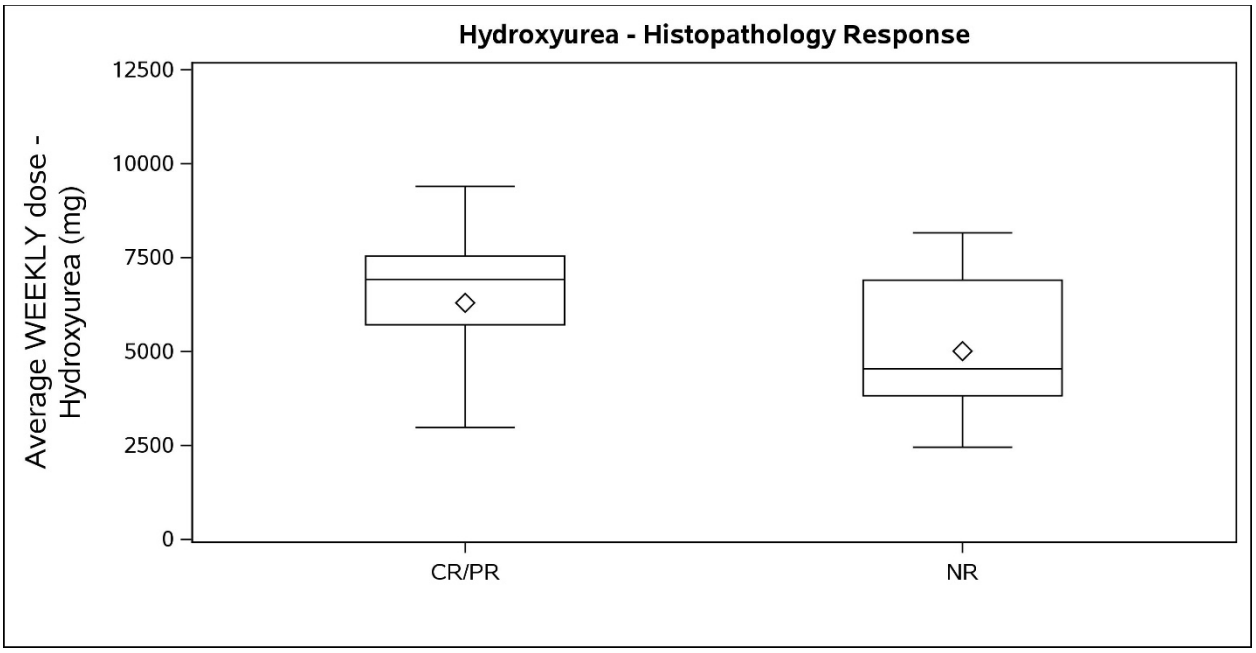


Figure S6

A.


Hydroxyurea - Histopathology Response
Average WEEKLY dose - Hydroxyurea (mg)
12500
10000
7500
5000
2500
0
CR/PR
NR

B.

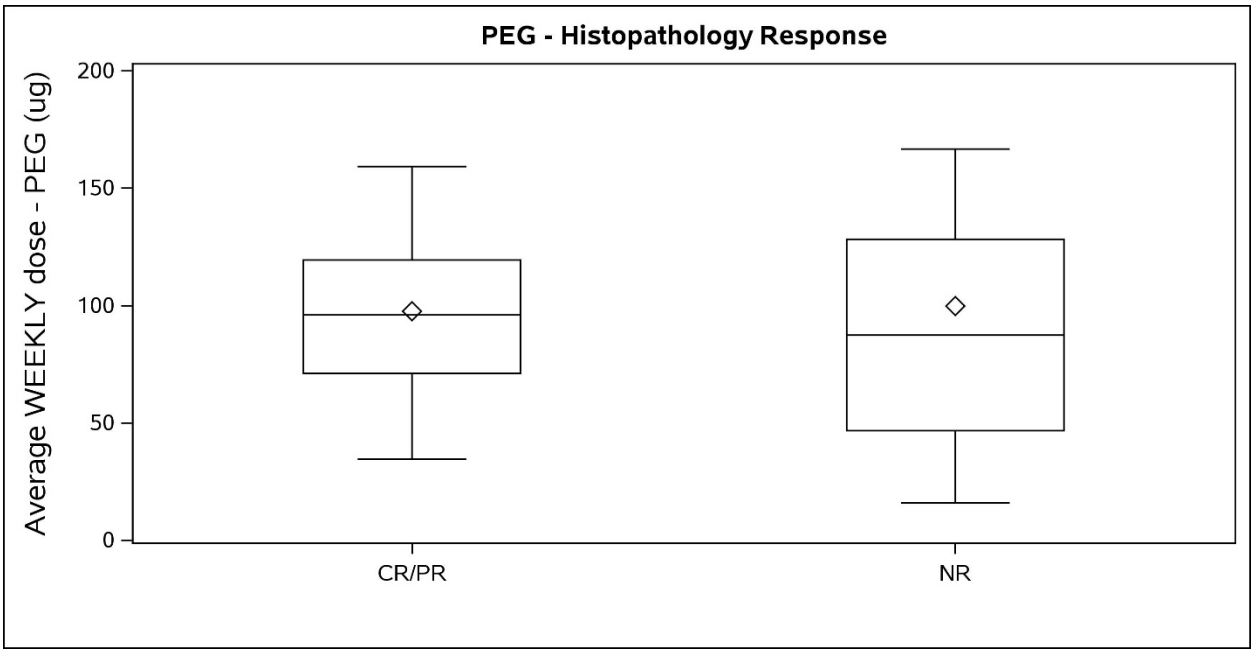

PEG - Histopathology Response
Average WEEKLY dose - PEG (ug)
200
150
100
50
0
CR/PR
NR

Figure S7

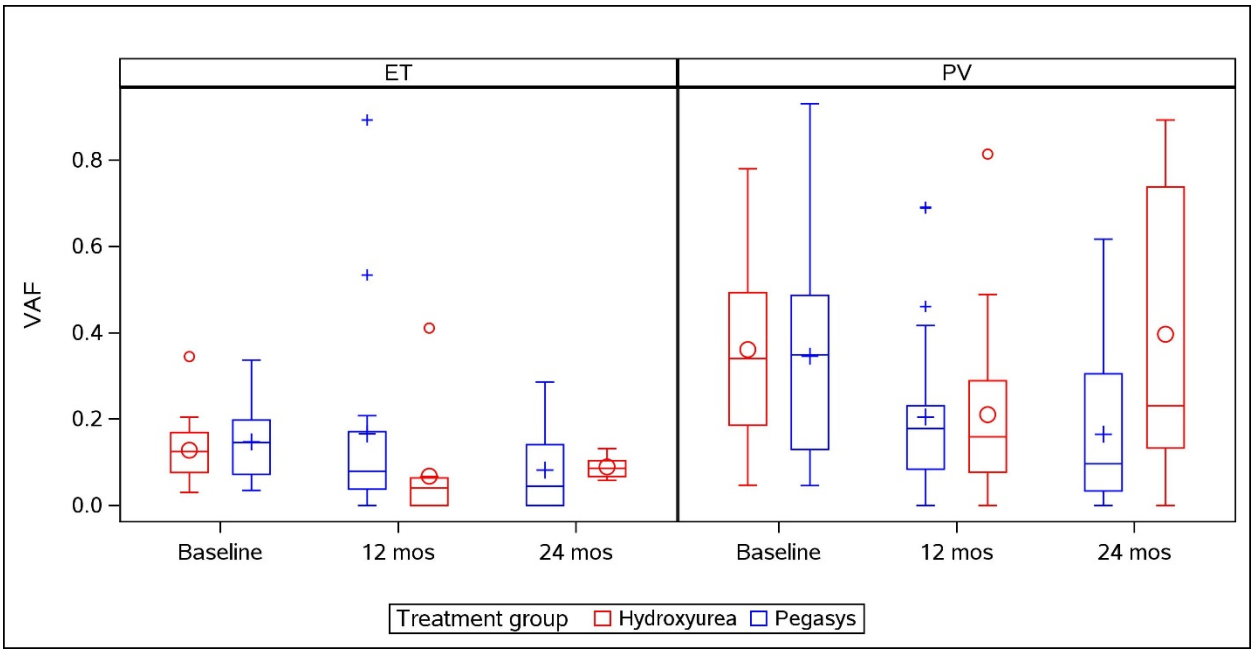
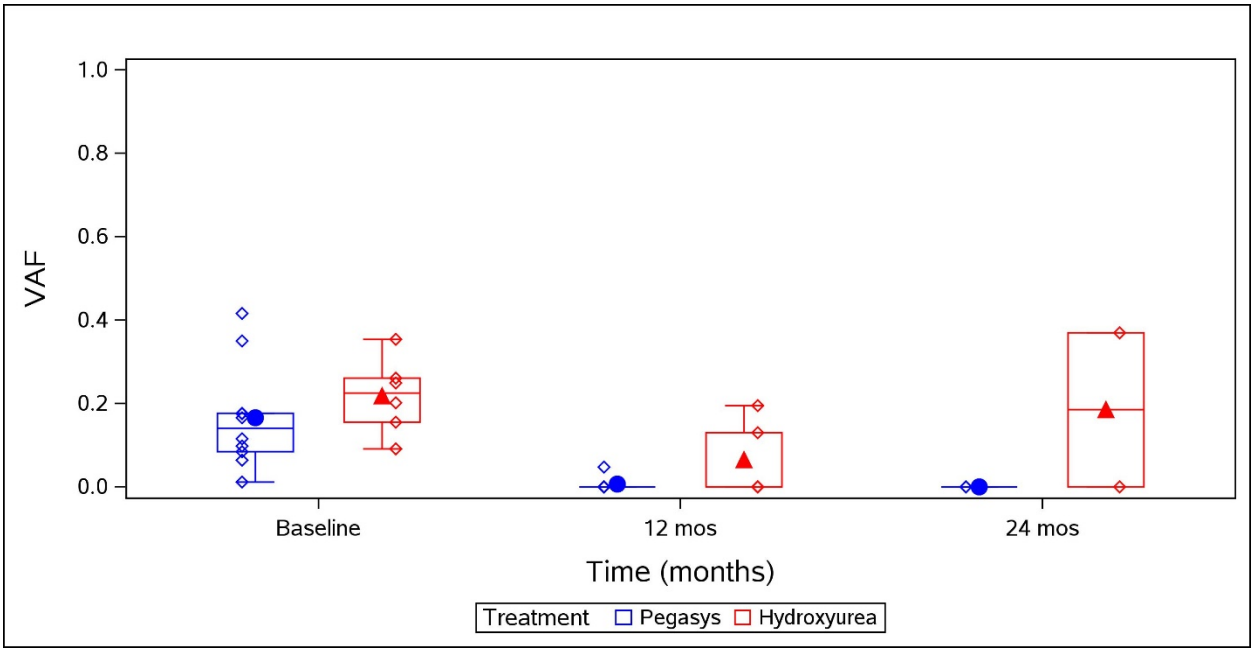
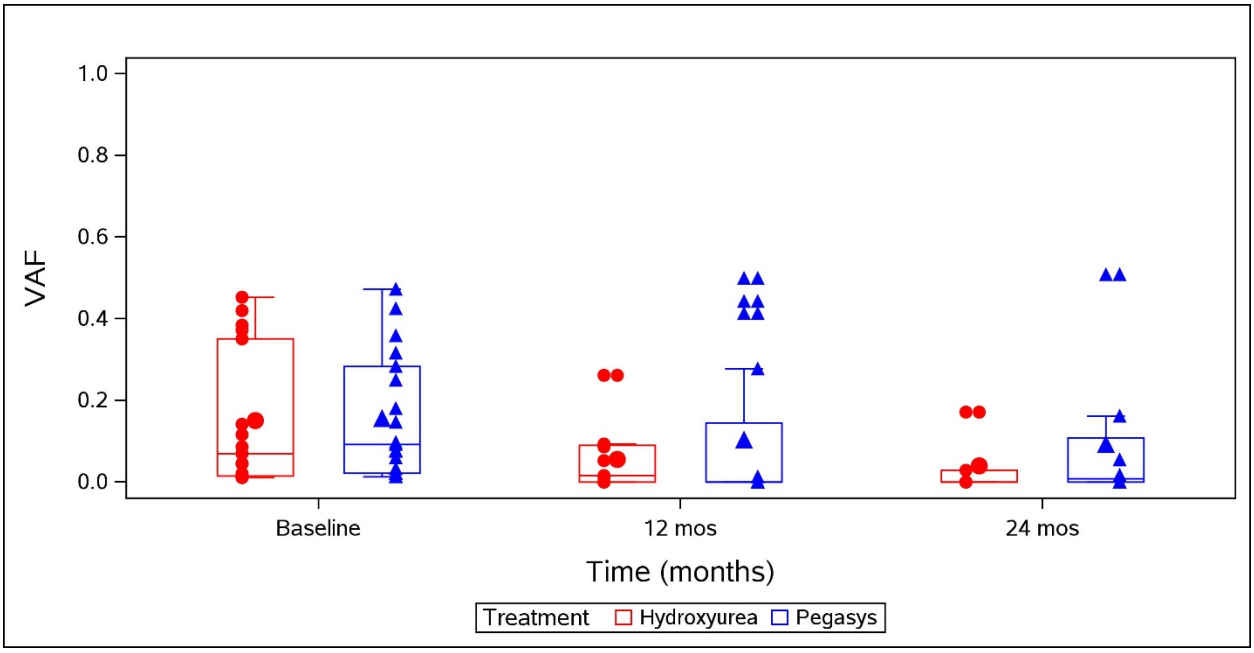

ET
PV
VAF
0.0
0.2
0.4
0.6
0.8
Baseline
12 mos
24 mos
Baseline
12 mos
24 mos
Treatment group
Hydroxyurea
Pegasys

Figure S8

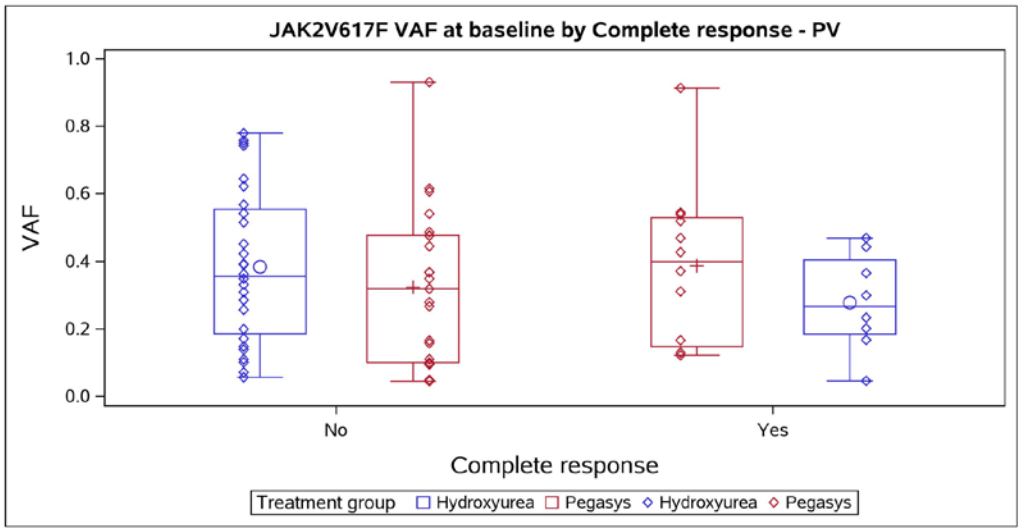
A


1.0
0.8
0.6
0.4
0.2
0.0
VAF
Baseline
12 mos
24 mos
Time (months)
Treatment
Pegasys
Hydroxyurea

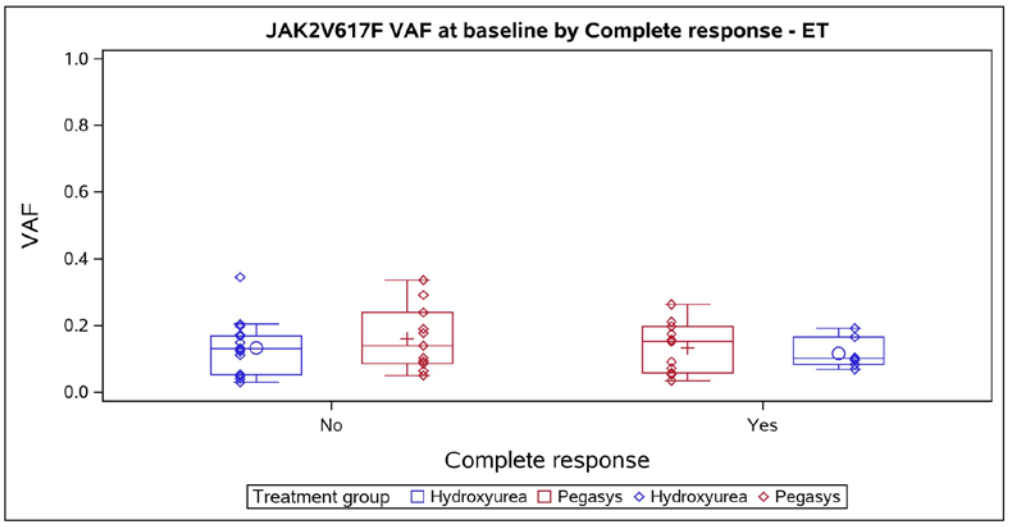
B


1.0
0.8
0.6
0.4
0.2
0.0
VAF
Baseline
12 mos
24 mos
Time (months)
Treatment
Hydroxyurea
Pegasys

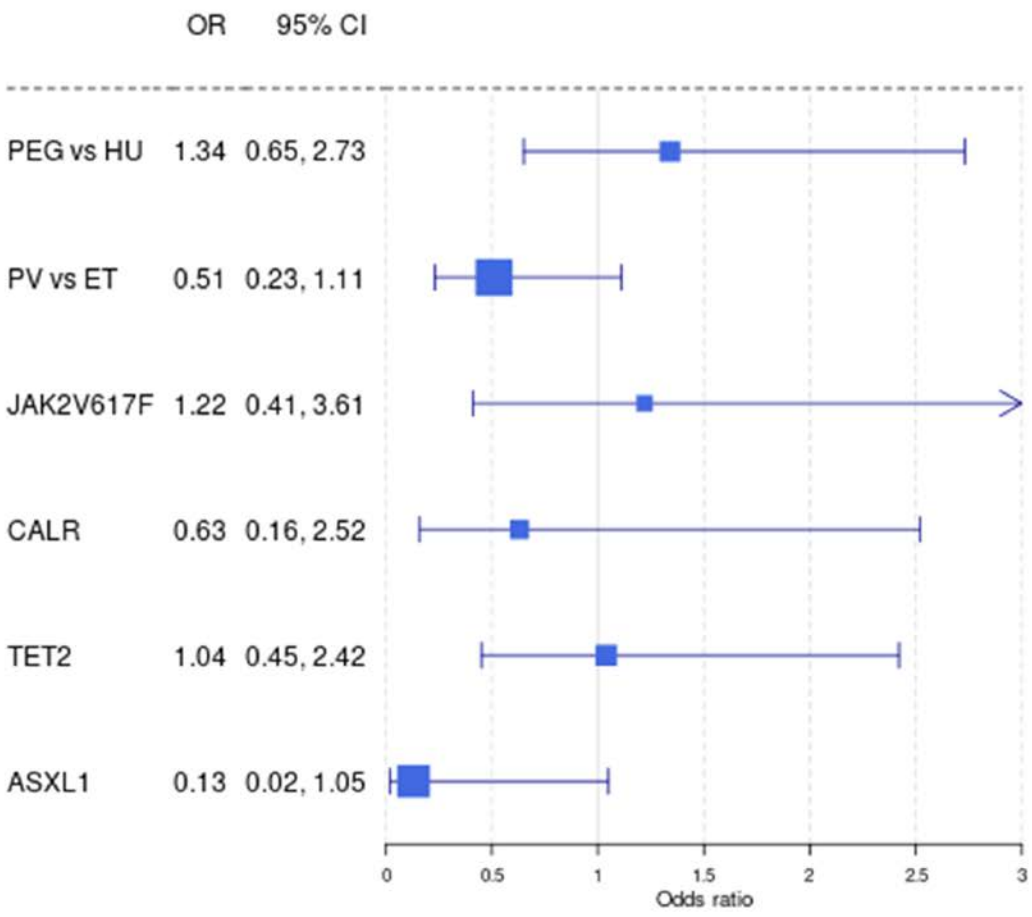
C


JAK2V617F VAF at baseline by Complete response - PV
VAF
1.0
0.8
0.6
0.4
0.2
0.0
No
Yes
Complete response
Treatment group Hydroxyurea Pegasys Hydroxyurea Pegasys

D


JAK2V617F VAF at baseline by Complete response - ET
VAF
1.0
0.8
0.6
0.4
0.2
0.0
No
Yes
Complete response
Treatment group Hydroxyurea Pegasys Hydroxyurea Pegasys

E


OR
95% CI
PEG vs HU 1.34 0.65, 2.73
PV vs ET 0.51 0.23, 1.11
JAK2V617F 1.22 0.41, 3.61
CALR 0.63 0.16, 2.52
TET2 1.04 0.45, 2.42
ASXL1 0.13 0.02, 1.05
0
0.5
1
1.5
2
2.5
3
Odds ratio