

Monitoring of Calr Allele Burden in Patients with Essential Thrombocythemia Treated with Imetelstat, a Telomerase Inhibitor, Reveals Rapid and Substantial Molecular Responses

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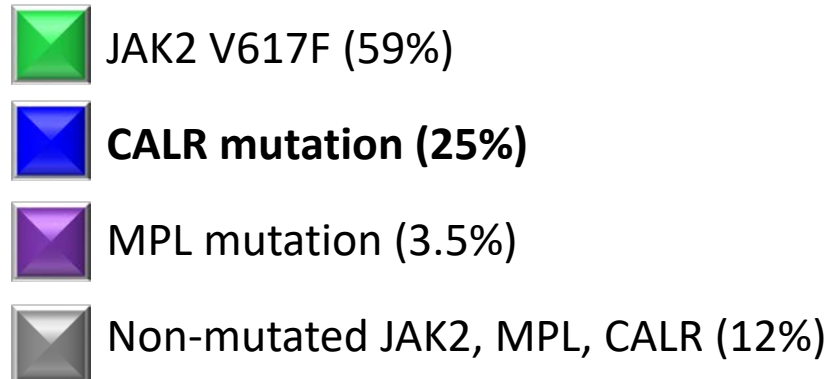
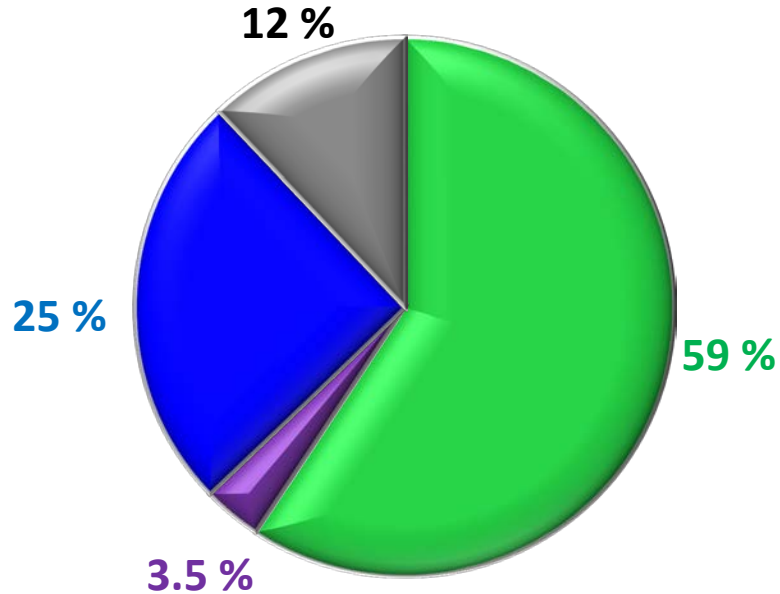
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Disclosures

- **Baerlocher, G. – Geron Corporation (Research funding)**

CALR Mutations in Patients with Essential Thrombocythemia (ET)

Distribution of Mutations in ET

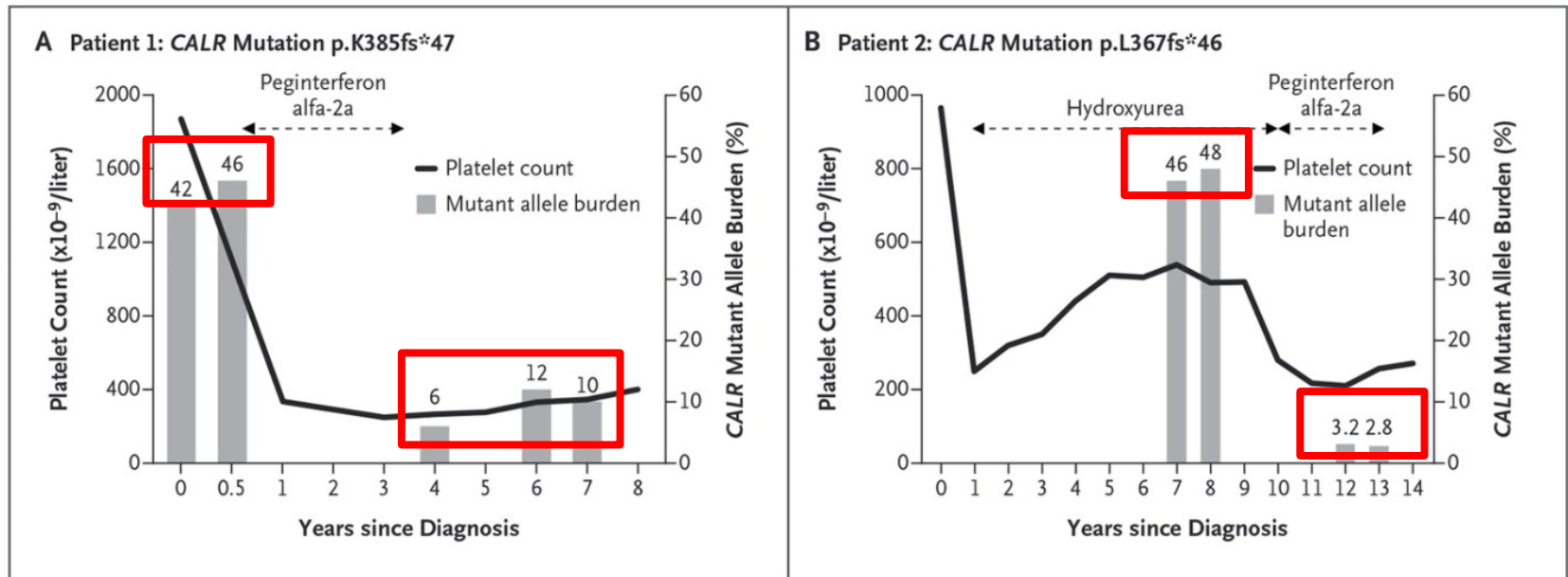


In ET, mutations in the calreticulin gene (CALR) are found in the majority of patients that are negative for mutations in the JAK2 and MPL genes.

Patients with mutated CALR have a better prognosis and a lower risk of thrombosis than those with mutated JAK2.

Evolution of Platelet Count and CALR Mutation Burden with INF- α

Two Patients with ET



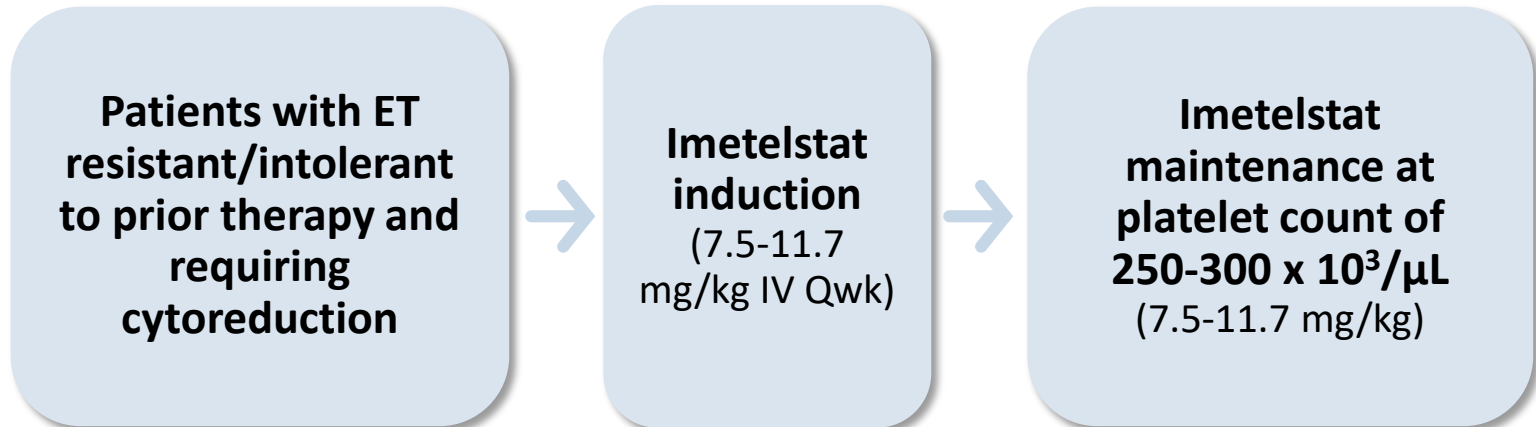
Recently, decreases in the CALR mutant allele burden have been observed with interferon alpha (IFN- α) after long-term treatment of two- and four-years, respectively.

Aim

We aimed to assess molecular response to imetelstat therapy in ET patients with CALR mutations by serial measurements of CALR mutant allele burden.

Clinical Phase II ET Study with Imetelstat (IT)

Study Design



Clinical Phase II ET Study with Imetelstat (IT)

Study Design

Patients with ET resistant/intolerant to prior therapy and requiring cytoreduction

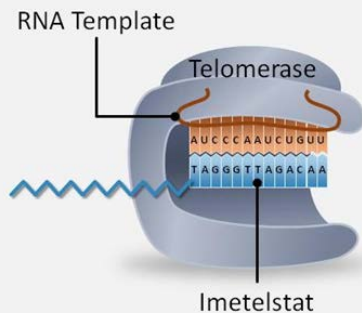


Imetelstat induction
(7.5-11.7 mg/kg IV Qwk)



Imetelstat maintenance at platelet count of $250-300 \times 10^3/\mu\text{L}$
(7.5-11.7 mg/kg)

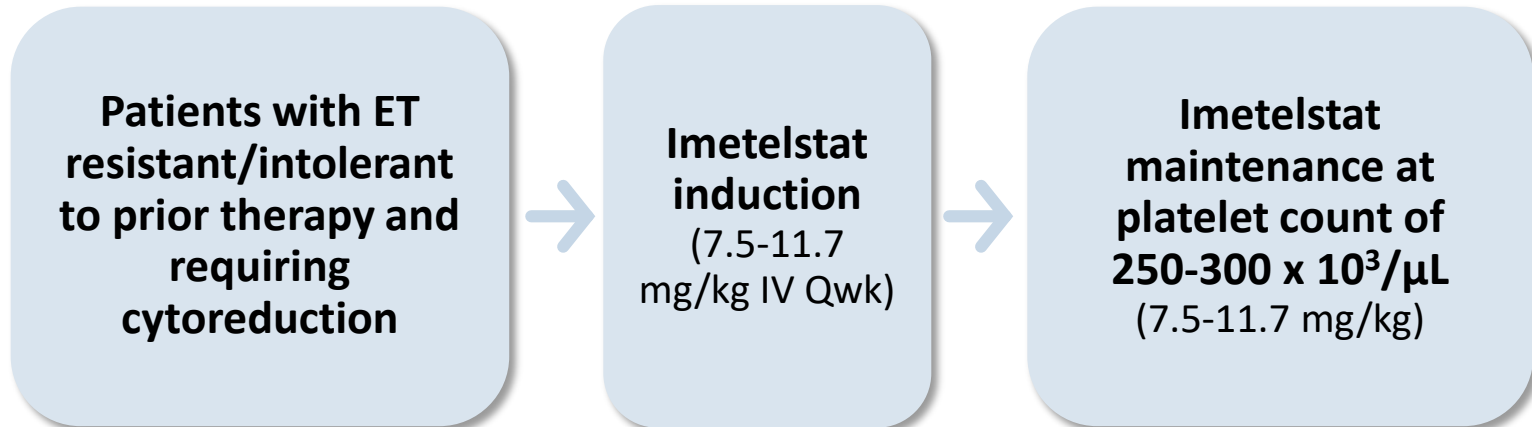
Imetelstat



- First telomerase inhibitor in clinical development
- 13-mer modified oligonucleotide with palmitoyl lipid tail
- Competitively binds to RNA template of telomerase

Clinical Phase II ET Study with Imetelstat (IT)

Trial has completed enrollment with a total of 18 ET patients



Endpoints of the Study

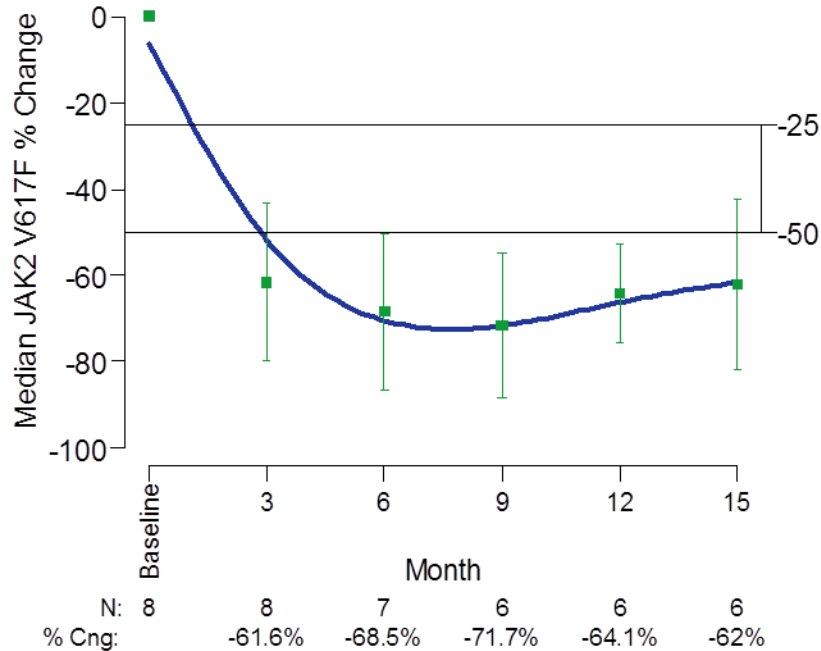
Endpoint	
Primary	<ul style="list-style-type: none">• Best Overall Hematologic RR (CR + PR) within 1st yr of treatment
Secondary	<ul style="list-style-type: none">• Clinicohematologic response within the 1st yr of therapy• Duration of hematologic response• Molecular response (JAK2 V617F /MPL W515^{mt}/CALR^{mt} patients)• Safety and tolerability
Exploratory	<ul style="list-style-type: none">• CFU-Mega spontaneous growth (selected sites)

ET Patient Baseline Characteristics

	N=18 Median (Range) or N (%)
Age (years)	59.5 (21-83)
Years Since Initial Diagnosis	7.2 (0.3-24.9)
Platelet Count (x 10 ³ /μL)	788 (521-1359)
WBC Count (x 10 ³ /μL)	7.8 (3-14.6)
Splenomegaly	1 (6%)
More than one prior therapy (anagrelide +/- IFN)*	13 (72%)
Resistant to at least one prior therapy	8 (44%)
Intolerant of or refused at least one prior therapy	14 (78%)
Mutation Status	
JAK2 V617F	8 (44%)
CALR Mutation	5 (28%)
MPL W515 ^{mt}	2 (11%)
None	3 (17%)

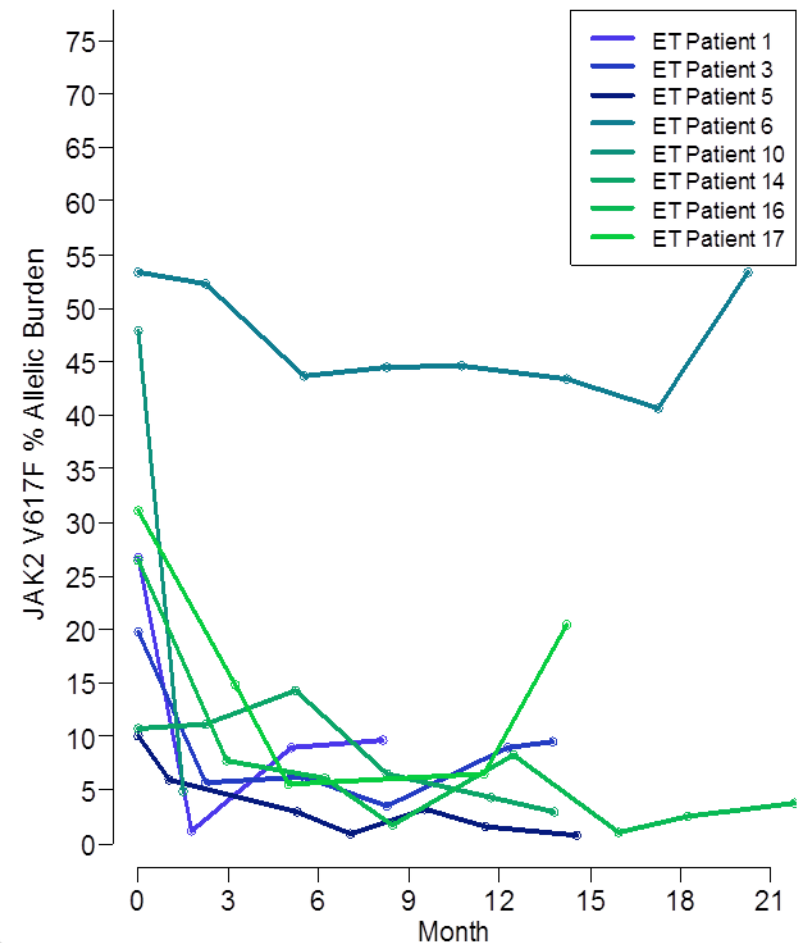
* 17 of 18 patients received prior hydroxyurea

Previously Reported: Secondary Endpoint--JAK2 V617F Allele Burden

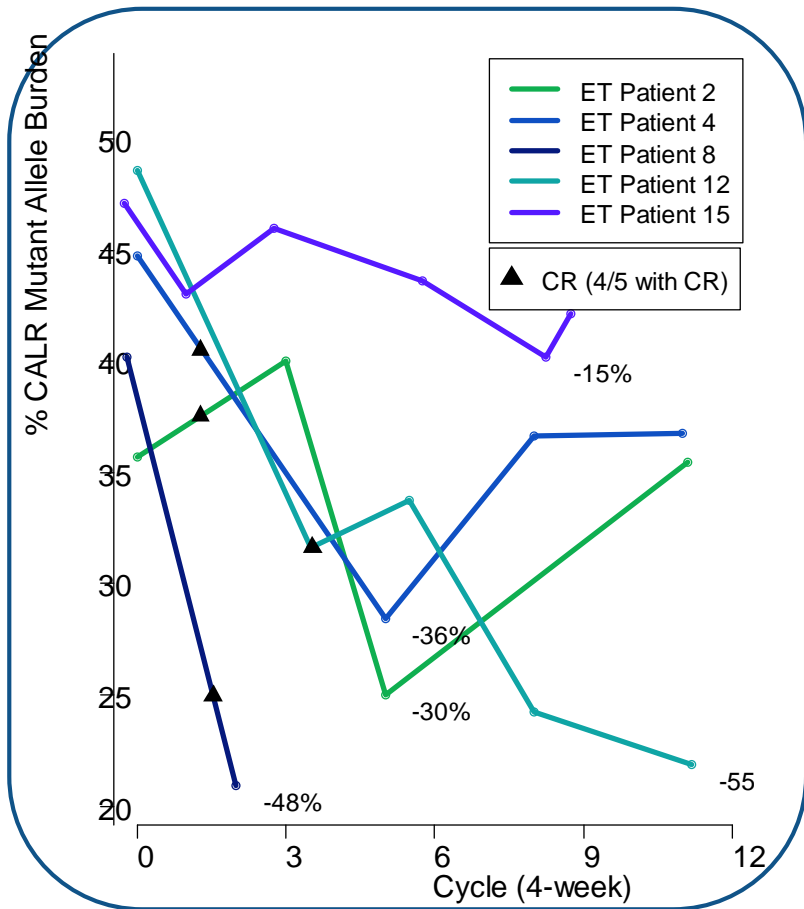


Median JAK2 V617F allelic burden is reduced more than 70% at month 9 and remains more than 60% reduced at month 15 even with less frequent maintenance dosing

PR observed in 7/8 (88%) and maintained for 6/7 (86%) patients



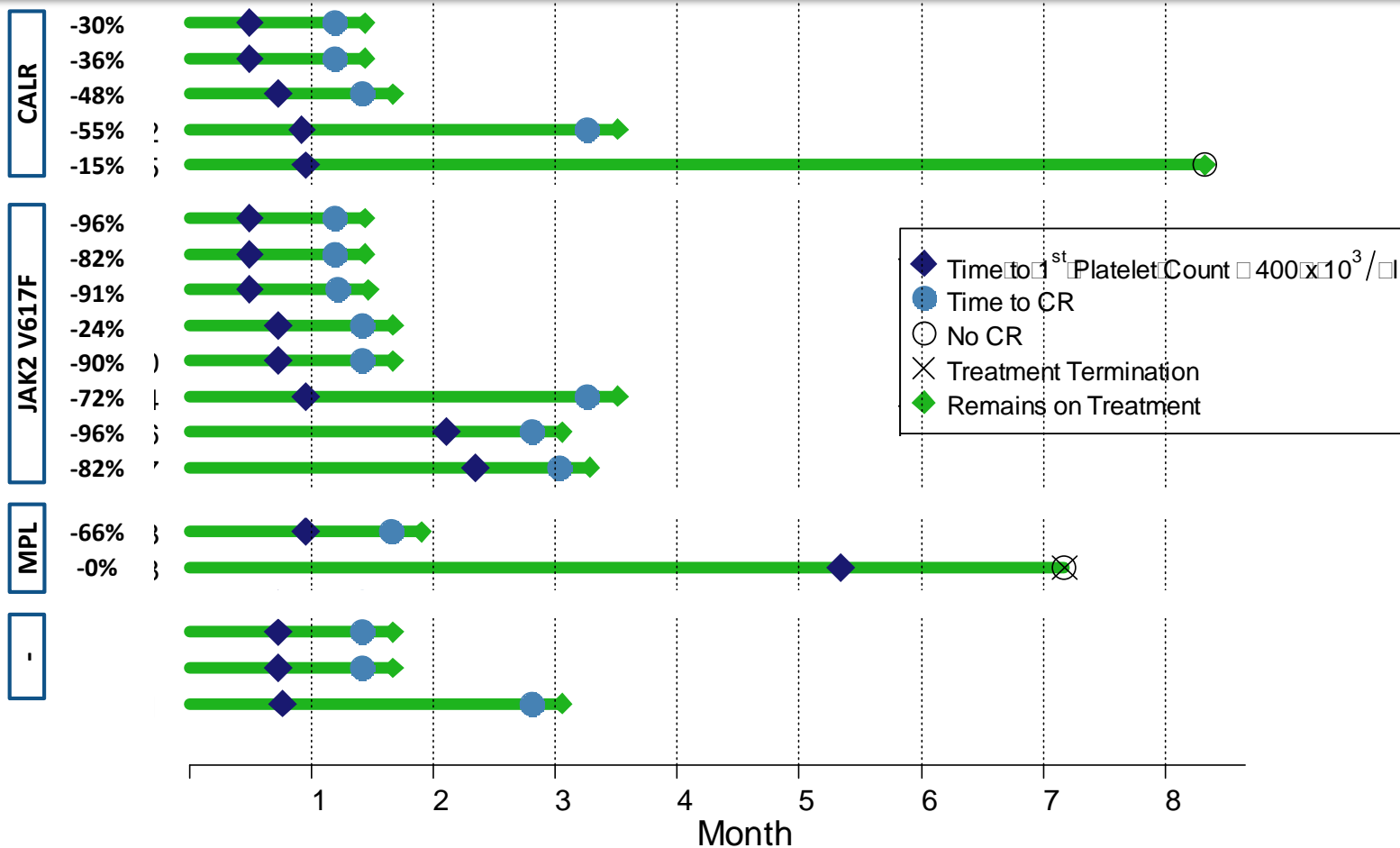
Results: Decrease of CALR Mutant Allele Burden



Cycle	Pt 2	Pt 4	Pt 8	Pt 12	Pt 15
Baseline	35.7	44.7	40.2	48.6	47
3	+12	--	-48	-35	-2
6	-30	-36	--	-31	-6
9	--	-18	--	-50	-15,-11
12	-1	-18	--	-55	--
Best % Reduction	-30	-36	-48	-55	-15
Best Hematologic Response	CR	CR	CR	CR	PR

- All 5 patients with CALR mutations demonstrated reduction of allele burden (median 36%), including 3/5 patients who achieved $\geq 35\%$ decreases, after 3-6 months of treatment
- Results confirm imetelstat's inhibition of neoplastic clonogenic cell growth in vivo

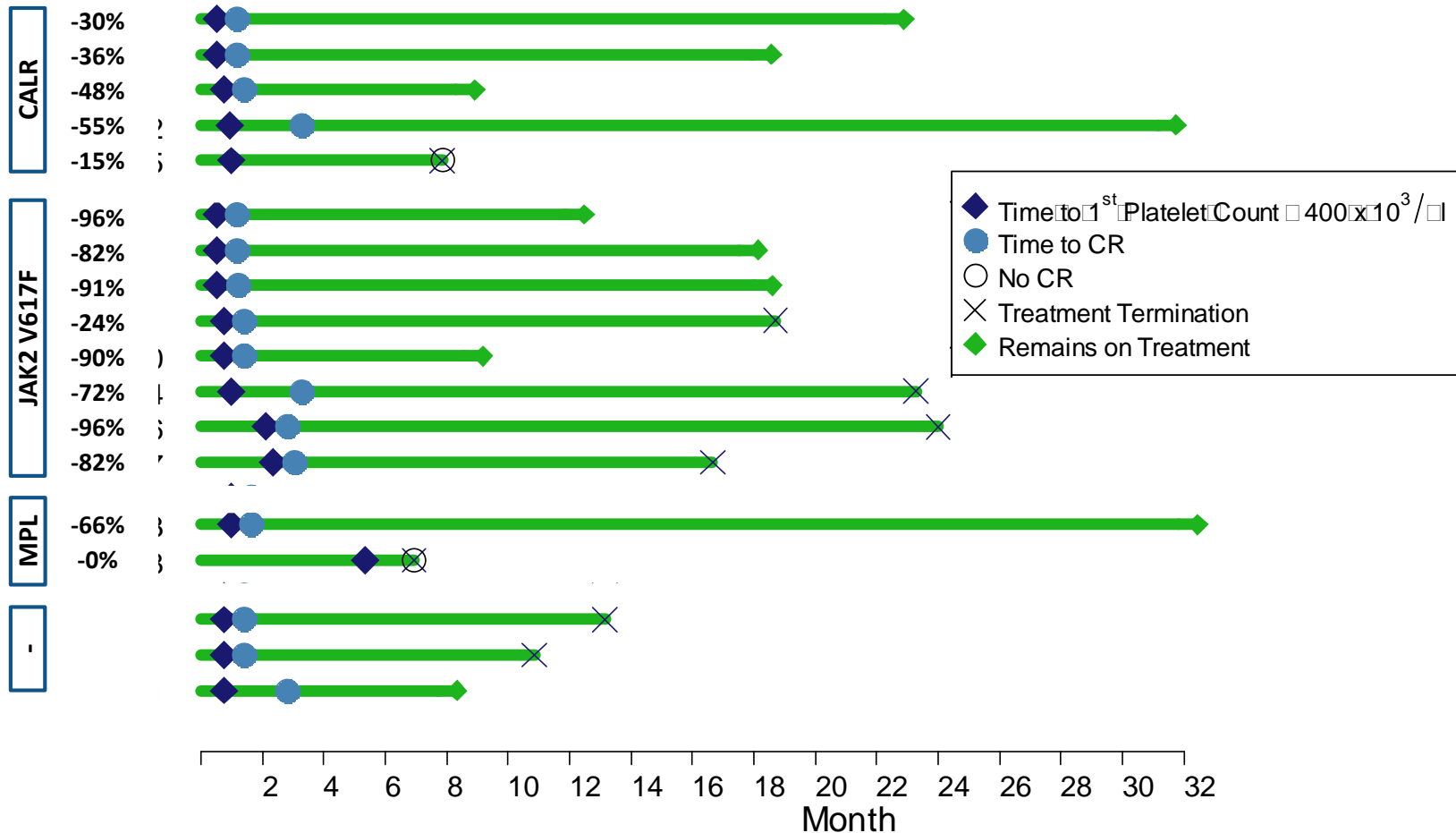
RESULTS: Hematologic Response by Baseline Mutation Status



N=18	Mut. CALR	JAK2 V617F	Mut. MPL	None	Total
CR	4 (80%)	8 (100%)	1 (50%)	3 (100%)	16 (89%)
PR	1 (20%)	0	1 (50%)	0	2 (11%)

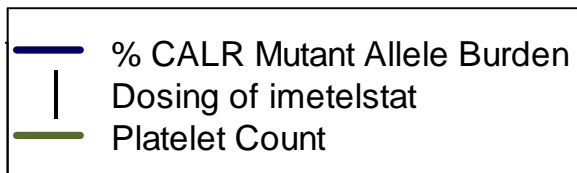
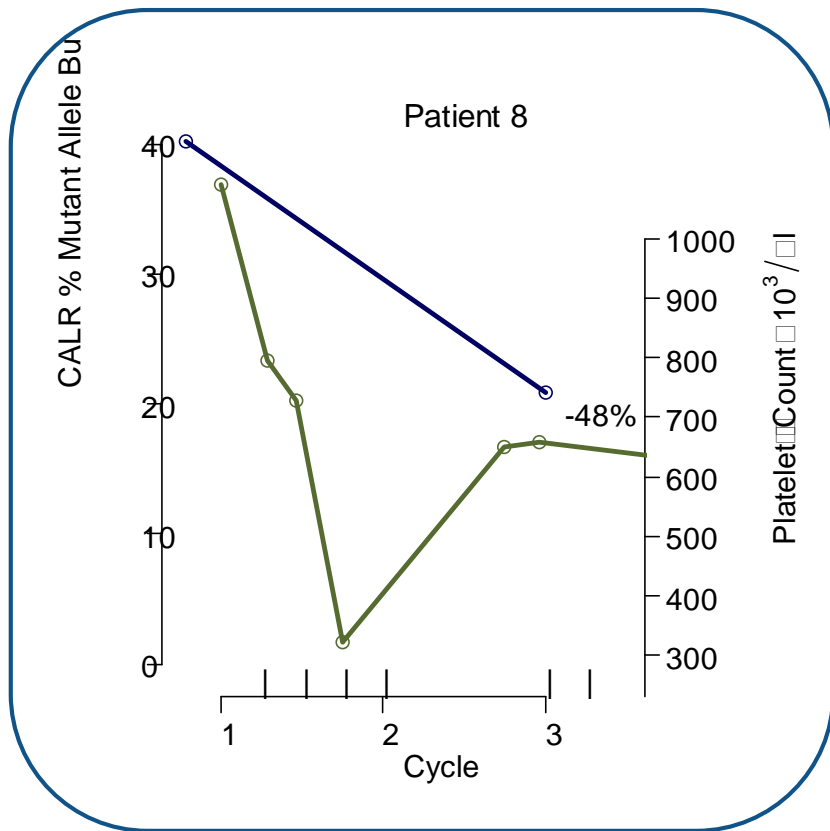
Baseline mutation status is not significantly associated with time to CR (P=0.45)

RESULTS: Durability of Hematologic Response by Mutation Status



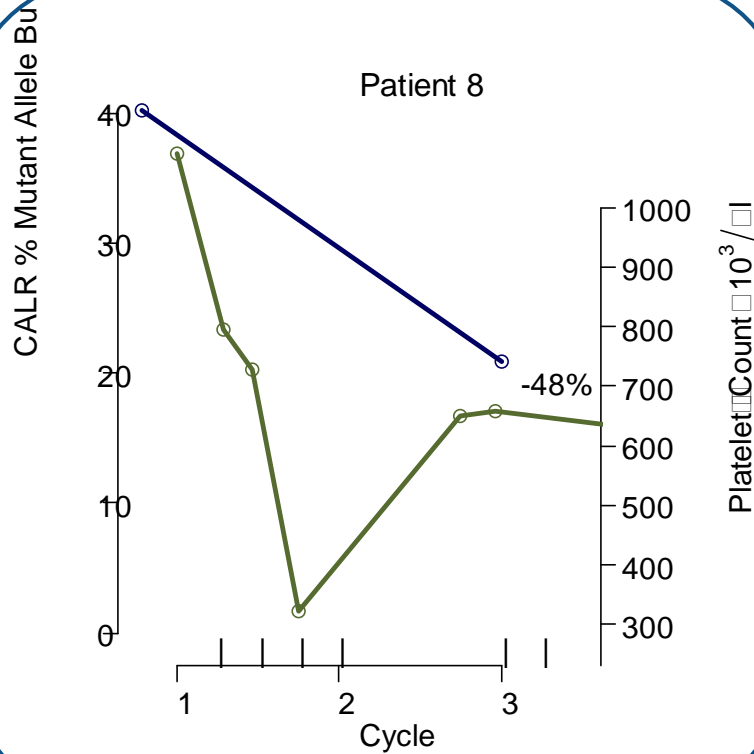
- Patients with CALR mutations are trending toward longer time on treatment (P=0.23)
- $\geq 35\%$ reduction in allele burden (CALR^{mt}, JAK2 V617F, MPL^{mt}) is associated with longer time on treatment (P=0.03)

Individual Patient Responses

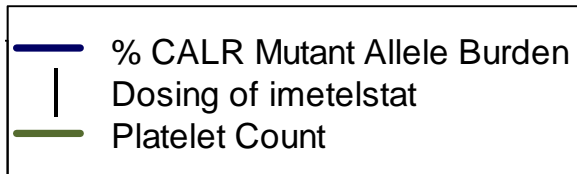
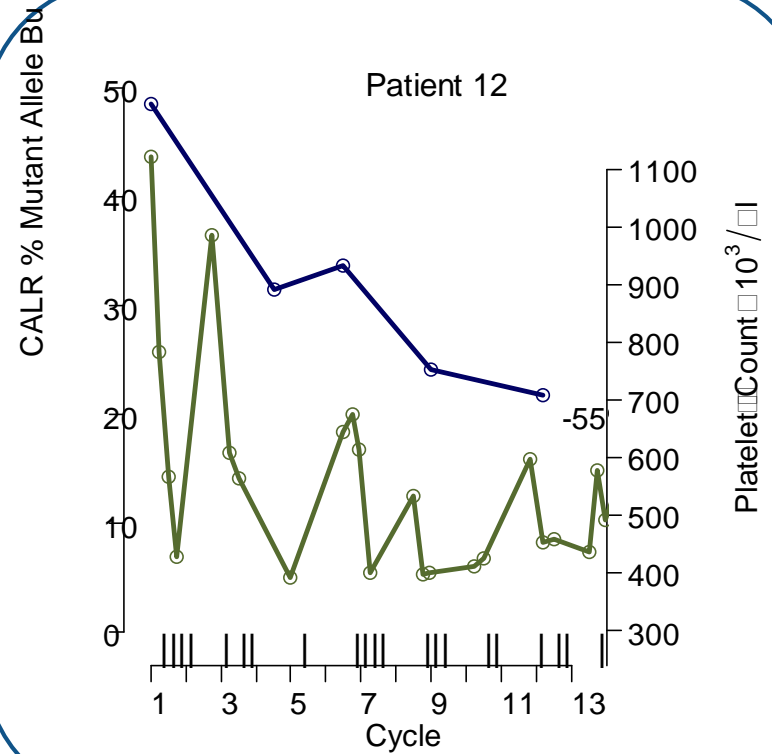


Individual Patient Responses

Patient 8



Patient 12



CONCLUSIONS

Imetelstat reduces Mutated CALR and JAK2V617F Allele Burden

- In 4 of 5 patients with CALR-mutated ET, imetelstat induced a rapid hematologic CR and in 3 patients this response was associated with a substantial decrease in the allele burden of 35-50% after 3-6 cycles of treatment
- JAK2V617F molecular responses were reached in 7 / 8 patients (as previously reported)
- Overall 9/13 patients with JAK2 or CALR mutations reached a >35% decrease of the mutant clone within 3-6 cycles of treatment
- Mutation status at baseline is not significantly associated with hematologic response

This additional evidence of reduction in the clonal allele burden supports imetelstat's potential to modify the biology of MPNs long-term

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