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

Gabriela M. Baerlocher, MD[1], Monika Haubitz, PhD[1*], Oliver G. Ottmann, MD[2], Olatoyosi Odenike, MBBS[3], Alexander Roeth, MD[4], Michael A McDevitt, MD, PhD[5], Ted Shih[6*], Bart Burington[6*], Dianne Morfeld[6*], Neeru Batra, BS[6*], David Snyder, MD[7*] and Elisabeth Oppliger Leibundgut, PharmD[1]

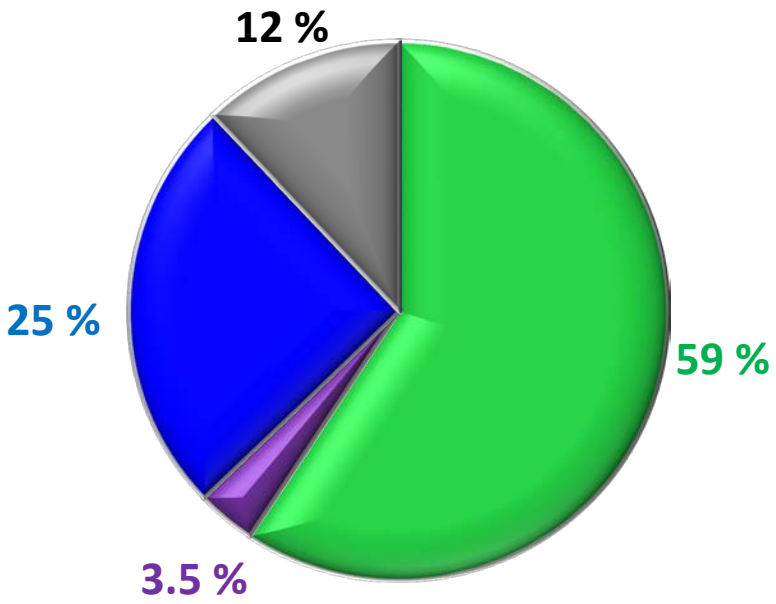
[1]Hematology, University Hospital and University of Bern, Bern, Switzerland;
[2]Department of Hematology/Oncology, Goethe-University Hospital, Frankfurt, Germany;
[3]The University of Chicago, Chicago, IL;
[4]Department of Hematology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany;
[5]Division of Hematological Malignancies, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD;
[6]Geron Corporation, Menlo Park, CA;
[7]City of Hope, Duarte

Disclosures

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

CALR Mutations in Patients with Essential Thrombocythemia (ET)

Distribution of Mutations in ET



- JAK2 V617F (59%)
- **CALR mutation (25%)**
- MPL mutation (3.5%)
- Non-mutated JAK2, MPL, CALR (12%)

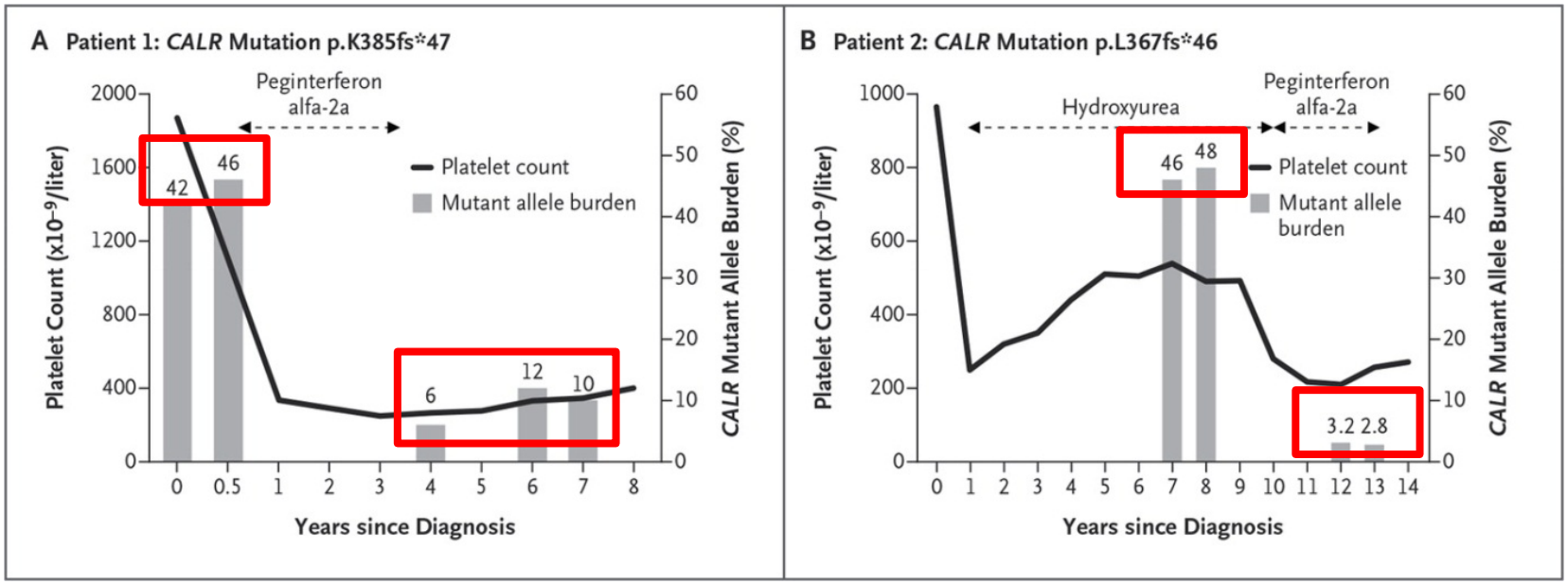
In ET, mutations in the calreticulin gene (CALR) are found in the majority of patients that are negative for mutations in the JAK2 and MPL genes.

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

N Engl J Med 2013;369:2379-2390

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.

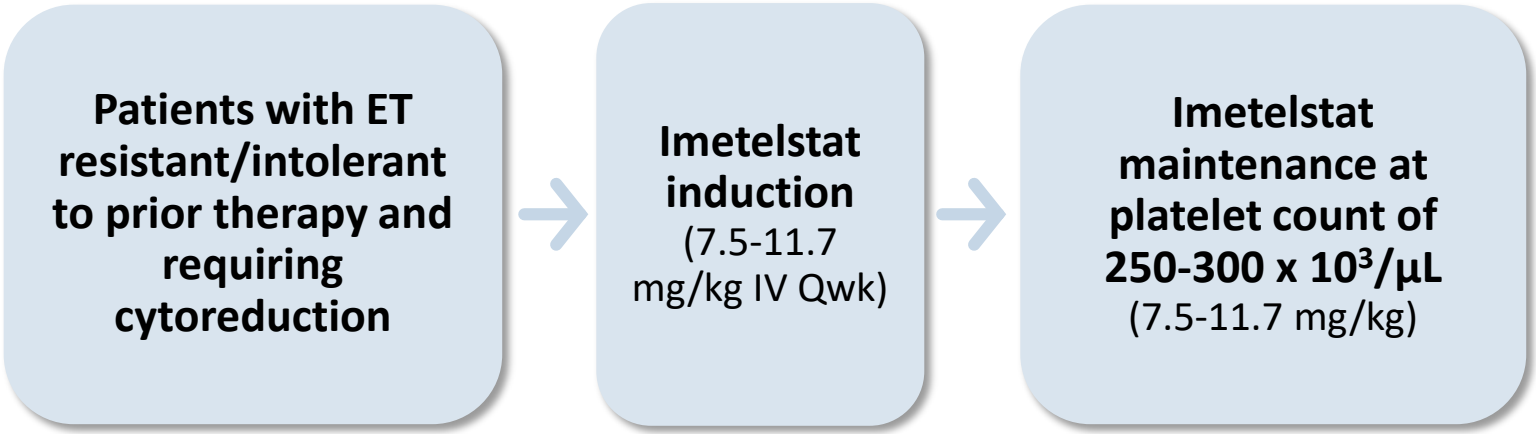
Cassinat B et al. N Engl J Med 2014;371:188-189.

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

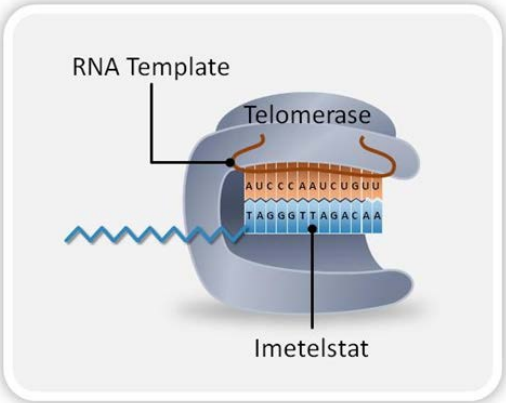
→

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

→

Imetelstat maintenance at platelet count of 250-300 x 10^3/µL
(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

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 x 10^3/µL** (7.5-11.7 mg/kg)

Endpoints of the Study

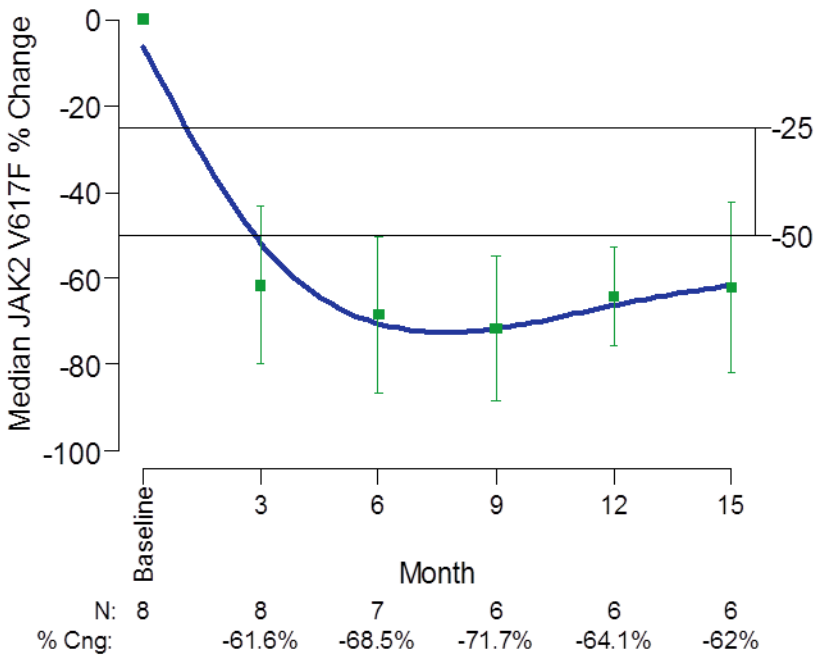
Endpoint	
Primary	• Best Overall Hematologic RR (CR + PR) within 1st yr of treatment
Secondary	• Clinicohematologic response within the 1st yr of therapy • Duration of hematologic response • Molecular response (JAK2 V617F /MPL W515^{mt}/CALR^{mt} patients) • Safety and tolerability
Exploratory	• CFU-Mega 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 $10^3/\mu L$)	788 (521-1359)
WBC Count (x $10^3/\mu L$)	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 CALR Mutation MPL $W515^{mt}$ None	8 (44%) 5 (28%) 2 (11%) 3 (17%)

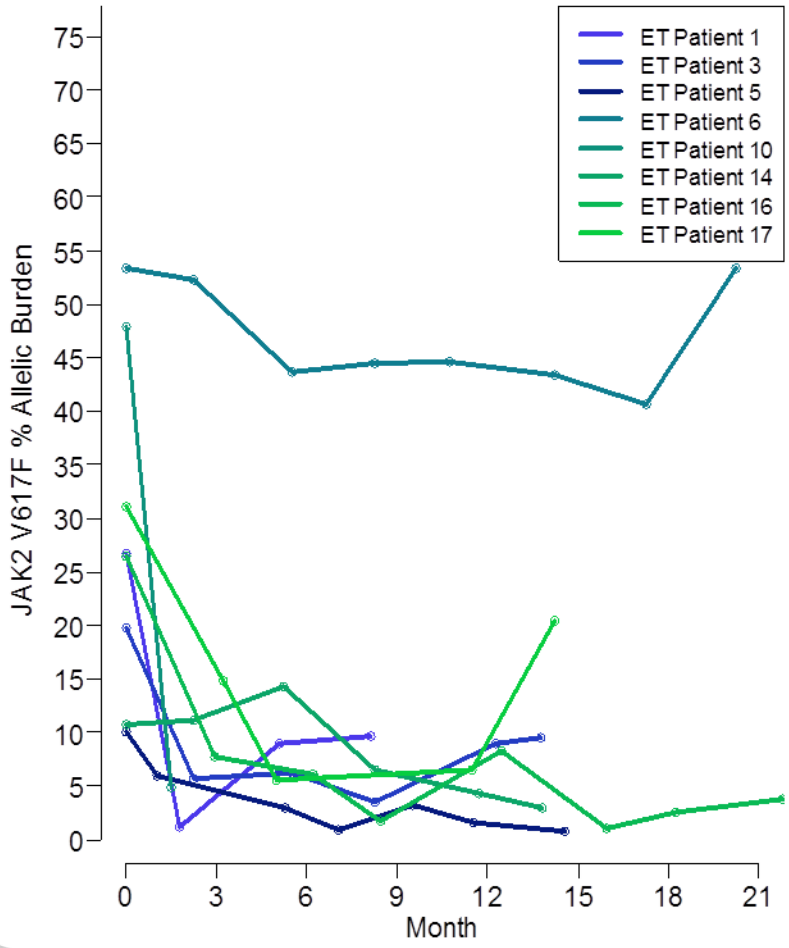
* 17 of 18 patients received prior hydroxyurea

Previously Reported: Secondary Endpoint--JAK2 V617F Allele Burden

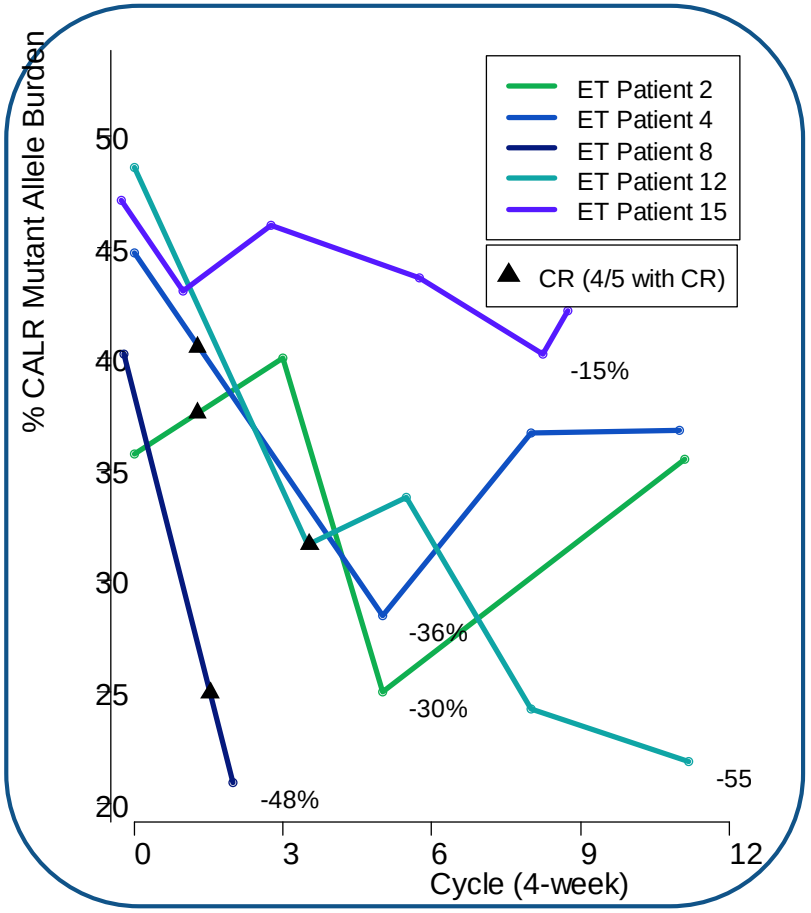


Median JAK2 V617F allelic burden is reduced more than 70% at month 9 and remains more than 60% reduced at month 15 even with less frequent maintenance dosing

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



Results: Decrease of CALR Mutant Allele Burden

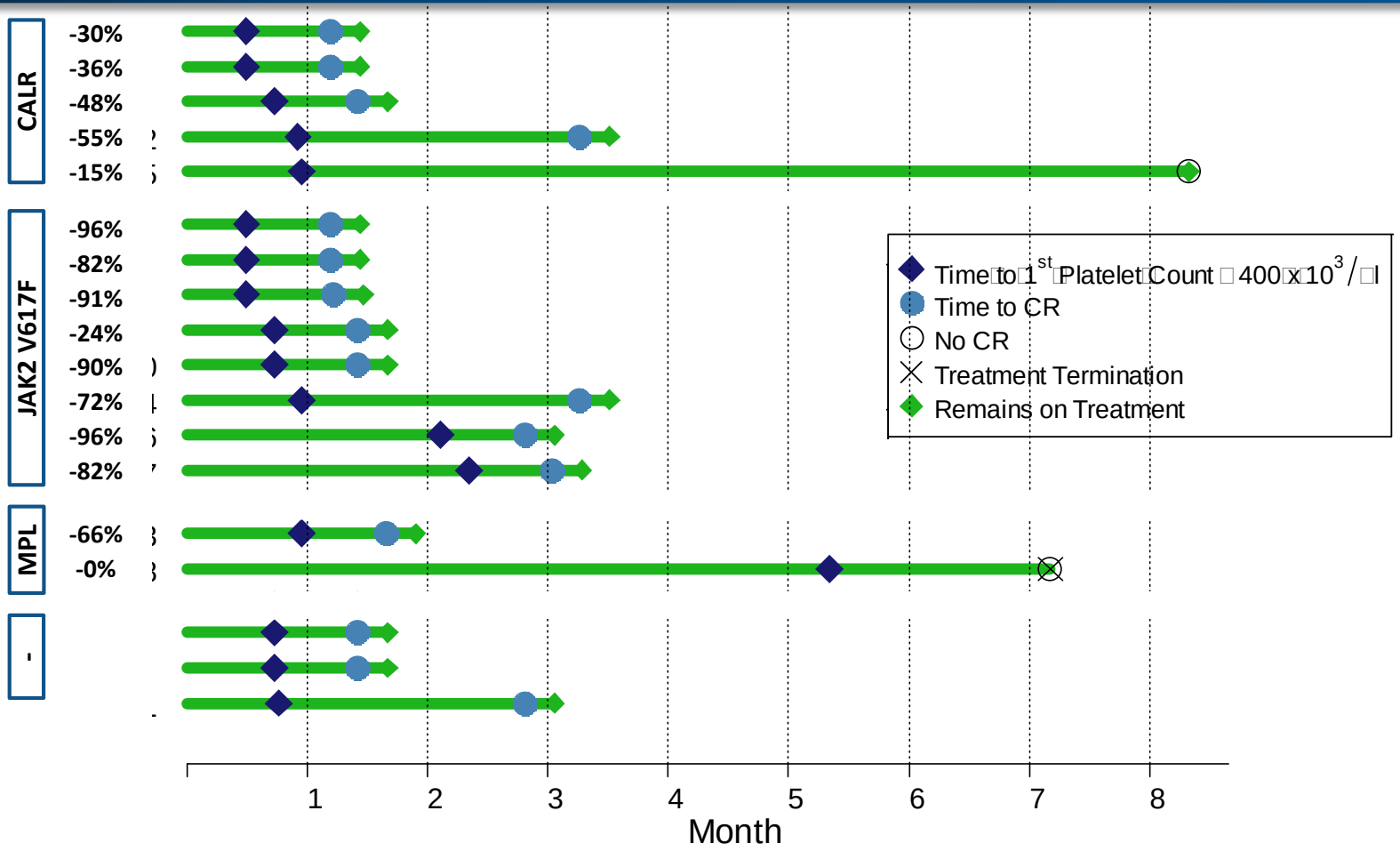


% change

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 ≥35% decreases, after 3-6 months of treatment
- Results confirm imetelstat's inhibition of neoplastic clonogenic cell growth in vivo

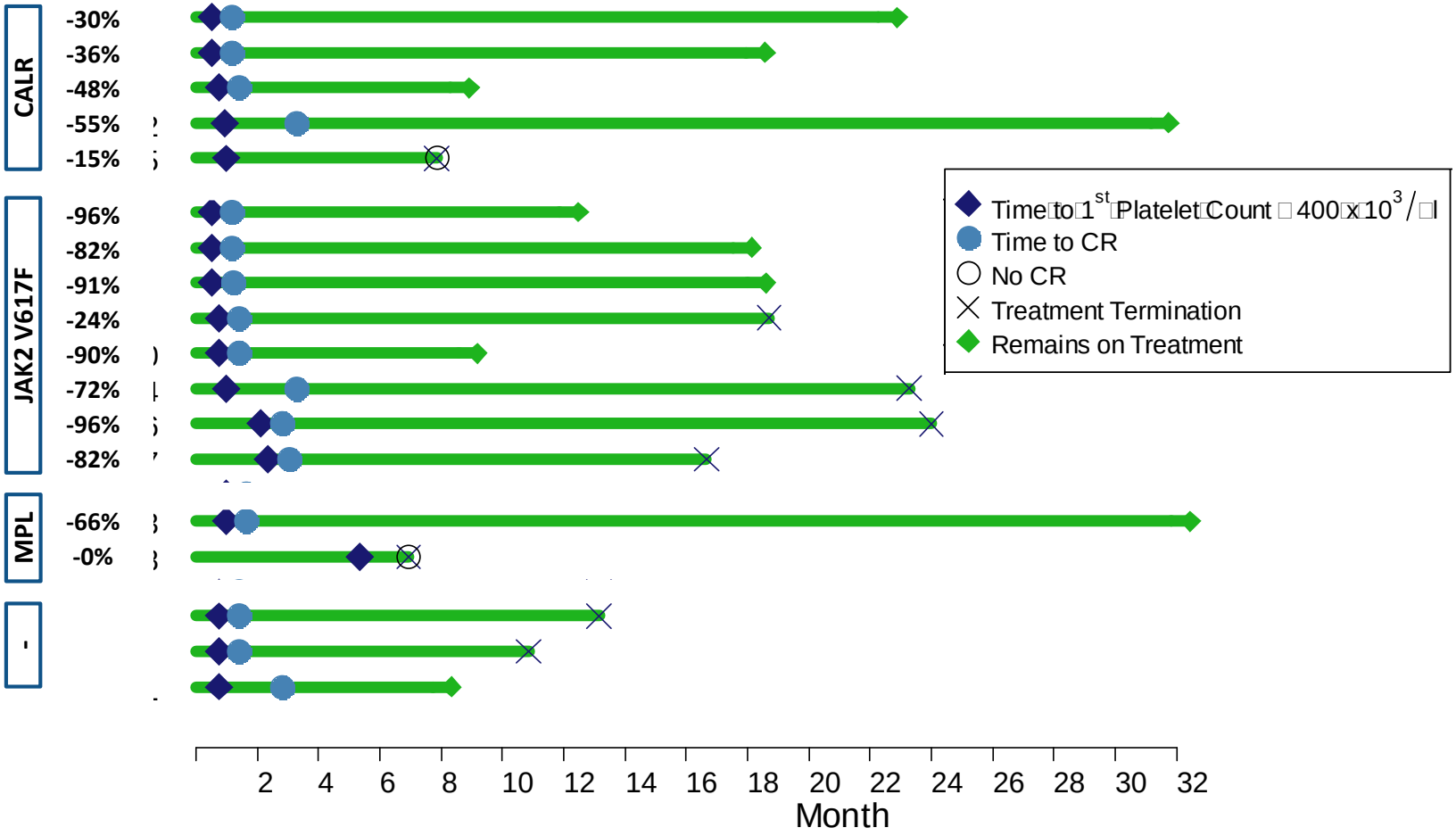
RESULTS: Hematologic Response by Baseline Mutation Status



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%)

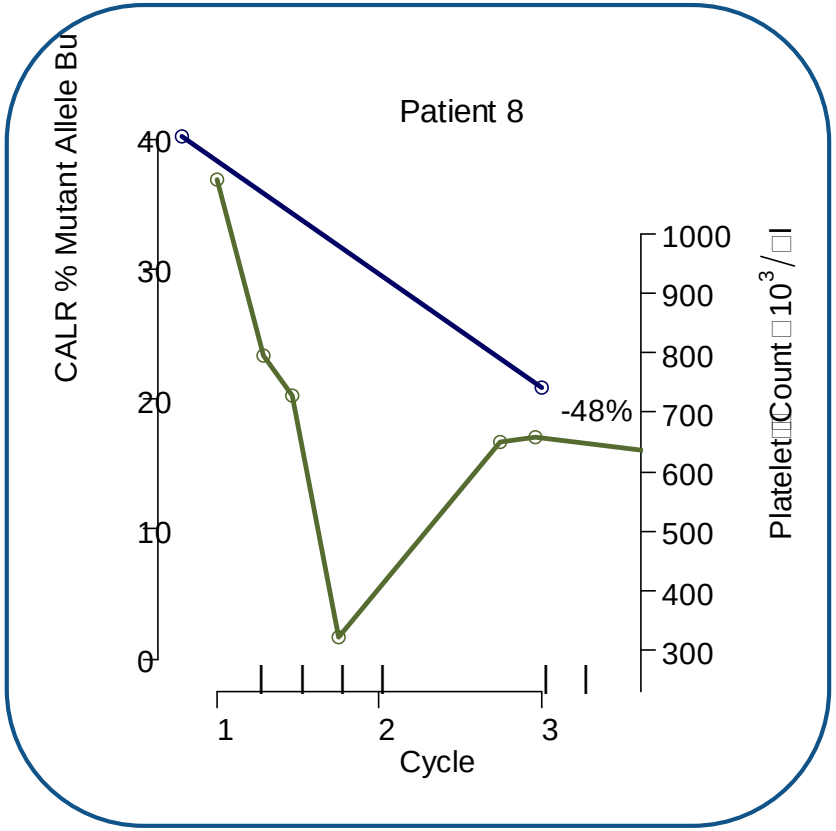
Baseline mutation status is not significantly associated with time to CR (P=0.45)

RESULTS: Durability of Hematologic Response by Mutation Status

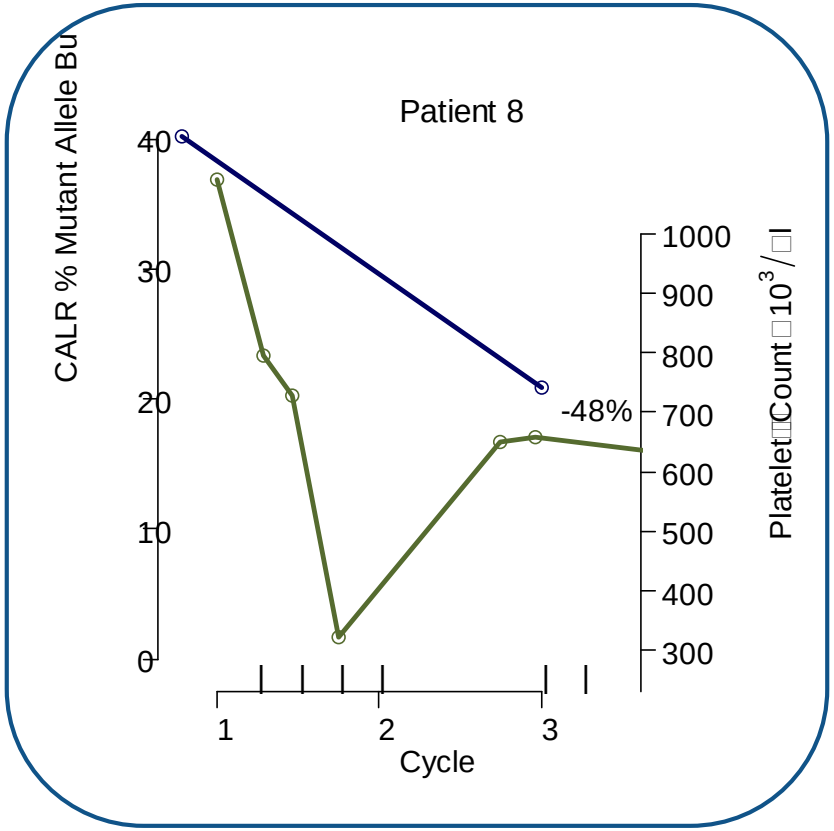


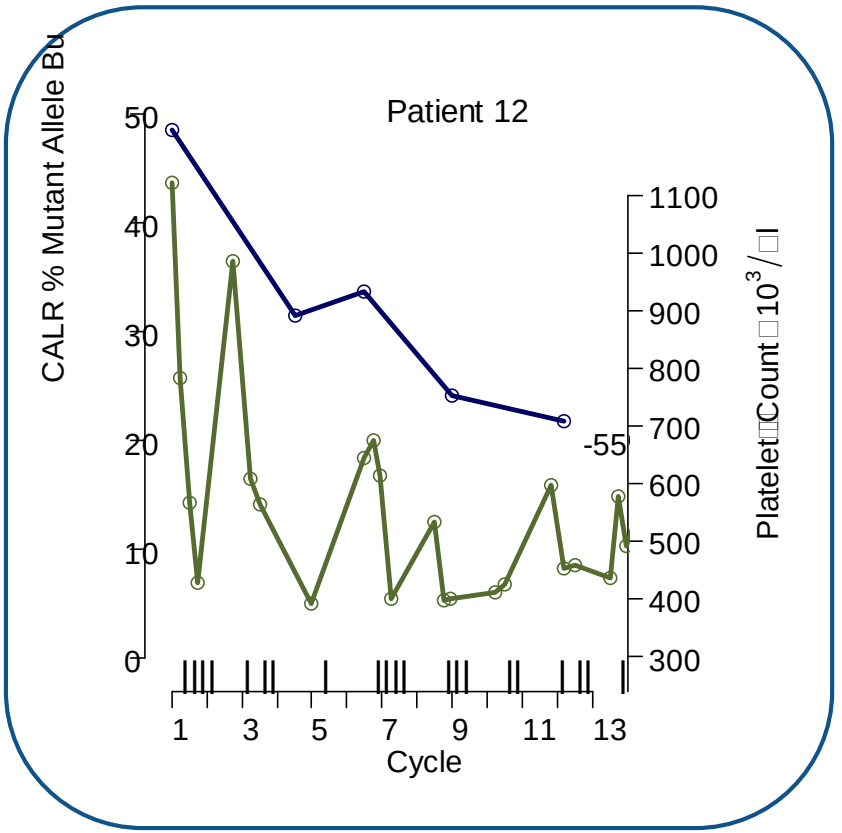
- Patients with CALR mutations are trending toward longer time on treatment (P=0.23)
- >= 35% reduction in allele burden ($CALR^{mt}$,JAK2 V617F,MPL^{mt}) is associated with longer time on treatment (P=0.03)

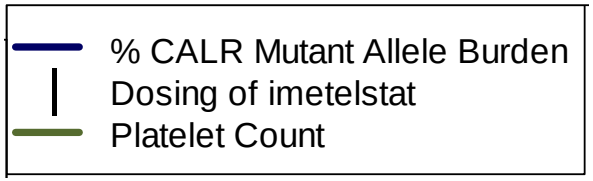
Individual Patient Responses



Individual Patient Responses







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

ACKNOWLEDGEMENTS

All of the patients, caregivers and staff who have participated in this study

and

City of Hope
Chona Gomez, Eunicia Reburiano

Johns Hopkins Medical Center
Lori Ann Tony, Kira Rashba

MD Anderson Cancer Center
Kurt Schroeder

University Hospital of Bern
Alexandre Theocharides, Michael Daskalakis

University of Chicago
Michael Daunov, Lisa Pape

University of Essen
Nicole Preising

University of Frankfurt
Lydia Wunderle, Caroline Zander

Upstate Oncology Associates
Hal Croswell, Amber Lewis, Kristina Stoeppler-Beige

and

Experimental Hematology, University of Bern
Monika Haubitz, Barbara Huegli, Ingrid Helsen