2013 Congress of the European Hematology Association
Abstract 4398

IMETELSTAT: A NOVEL APPROACH WITH ROBUST HEMATOLOGIC AND MOLECULAR RESPONSES IN A PHASE 2 STUDY IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA (ET) WHO ARE REFRACTORY OR INTOLERANT TO PRIOR THERAPY

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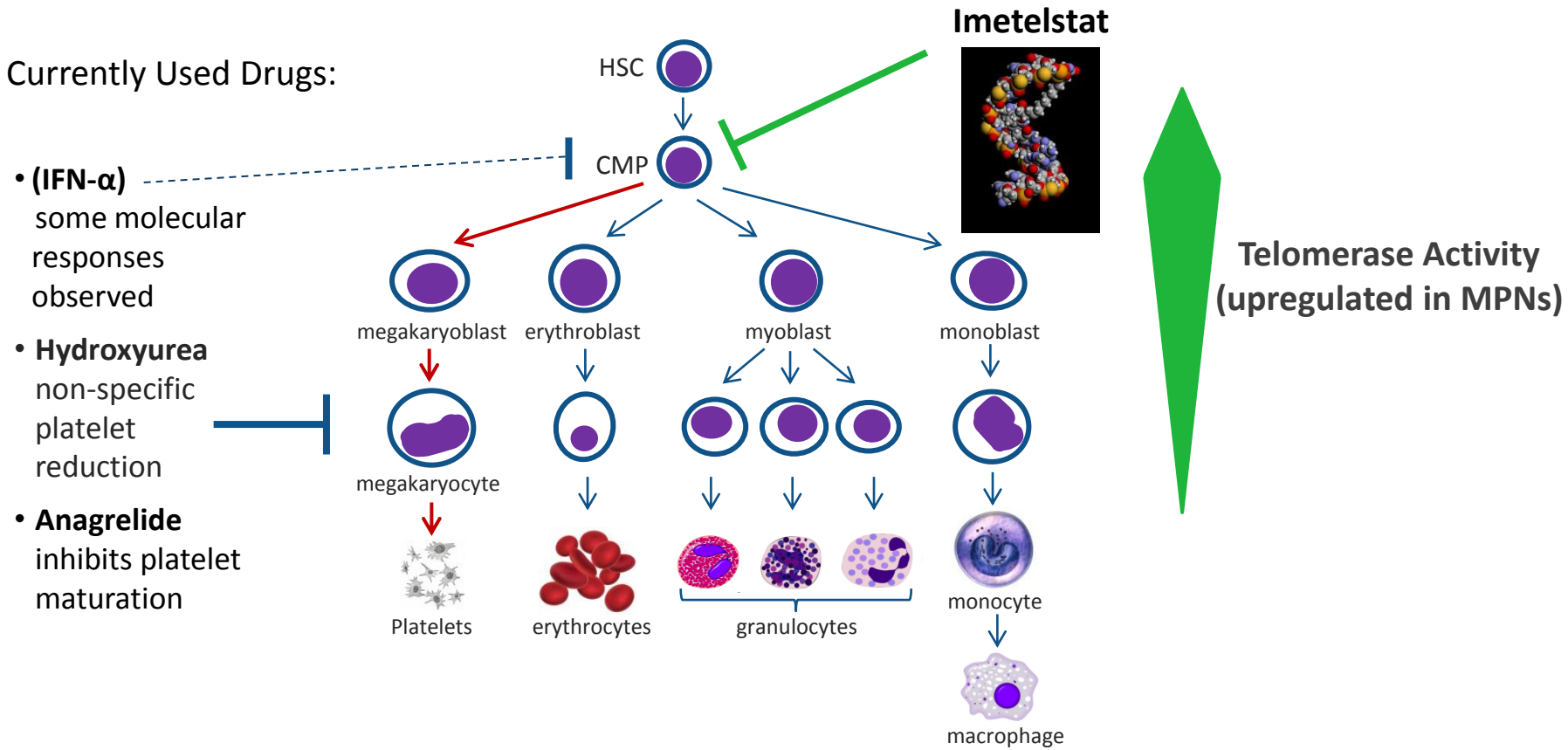
Disclosures

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

Rationale for Treating ET Patients with Imetelstat

- Novel mechanism of action which targets a driver of the malignancy
  - Upregulated telomerase may be centrally involved with proliferation and immortality of neoplastic progenitor cells*
  - Imetelstat may selectively inhibit proliferation of neoplastic progenitors

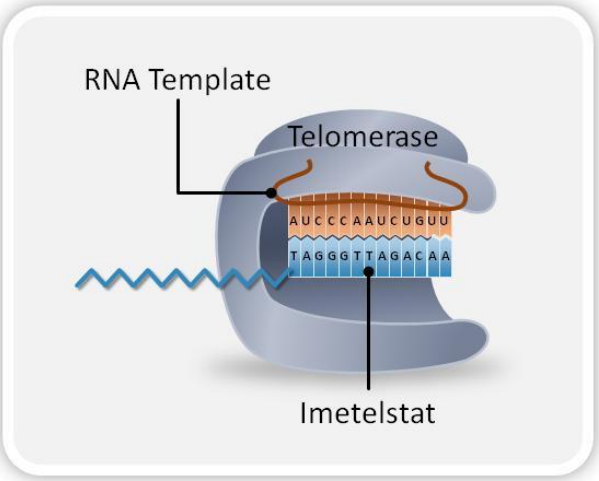


*"The Hallmarks of Cancer: The Next Generation", Hanahan & Weinberg, Cell 2011; Spanoudakis et al, Leukemia Research 2011

Imetelstat: First-in-class Telomerase Inhibitor

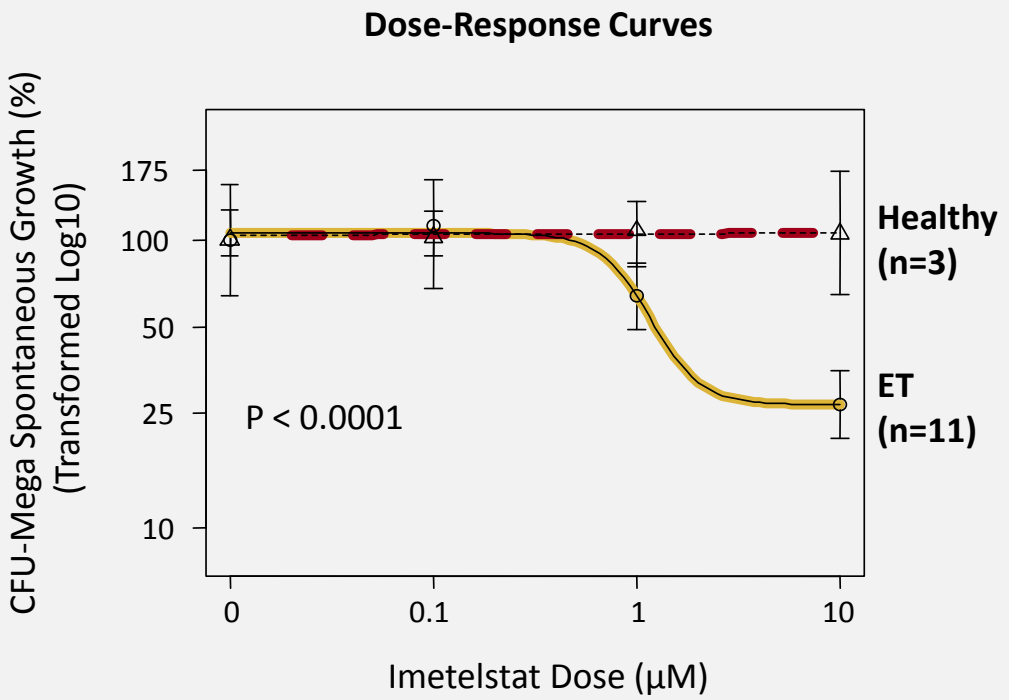
Imetelstat

- First telomerase inhibitor in clinical development
- 13-mer modified oligonucleotide with palmitoyl lipid tail
- Competitively binds to RNA template of telomerase
- Potent inhibitor of telomerase enzyme activity
  - IC_{50} = 0.5-10 nM (cell-free)
  - IC_{50} = 0.15-1.77 µM (cell-based)
- Long half-life in bone marrow, spleen and liver
  - Tissue $t_{½}$ = 50-90 hr in rodents
  - Predicted human $t_{½}$ = 41 hr with doses 7.5-11.7 mg/kg



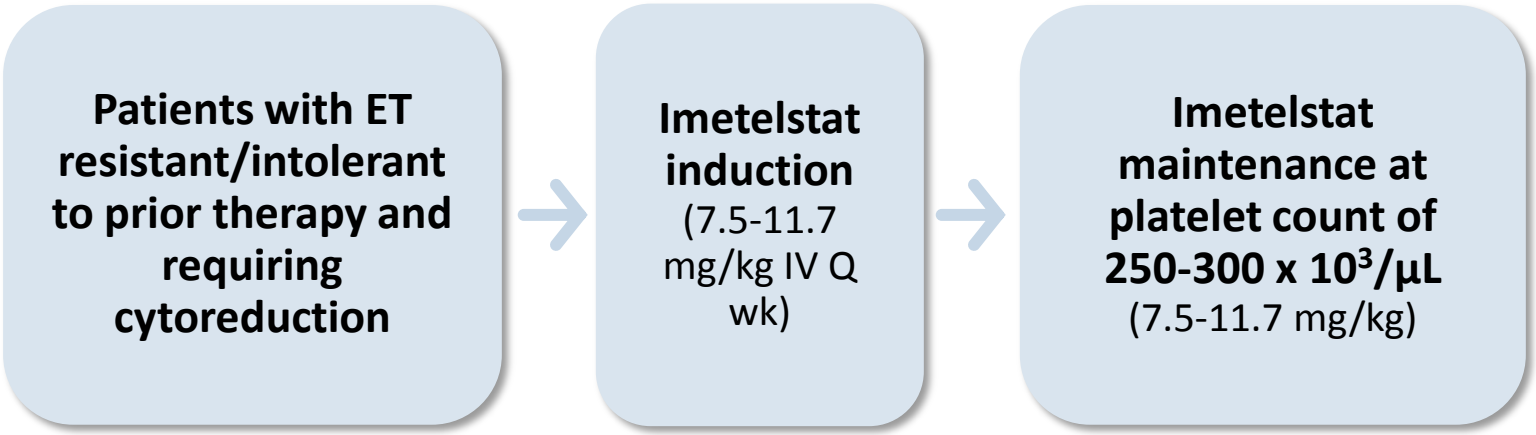
Imetelstat Reduces Neoplastic Progenitor Proliferation

- Clonal granulocytes in ET and other MPNs have short telomeres and telomerase activity
- Imetelstat exhibits selective dose-dependent growth inhibition of CFU-Mega



Presented at the 2011 ASH Annual Meeting Abstract 3843 (C Brunold et al)

METHODS: Study Design



- **Trial has completed enrollment with a total of 18 ET patients**

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 W515mt patients) • Safety and tolerability
Exploratory	• CFU-Mega spontaneous growth (selected sites)

METHODS: Primary and Secondary Endpoints / Response Definitions

	Primary Endpoint	Secondary Endpoints	
	Hematologic Response Grade*	**Clinicohematologic Response Grade****	**Molecular Response Grade****
CR	Normalization of platelets **(≤400 x 10^3/µL)** maintained for **at least 4 consecutive weeks**, in the absence of thromboembolic events	1) Platelet count **≤ 400 x 10^3 µL**, AND 2) No disease related symptoms, AND 3) Normal spleen size, AND 4) WBC **≤ 10 x 10^3/µL**	Reduction of any specific molecular abnormality to undetectable levels
PR	Platelets **≤600 x 10^3/µL or a 50% reduction** in platelets maintained for **at least 4 consecutive weeks**, in the absence of thromboembolic events	Platelet count **≤ 600 x 10^3/µL or decrease > 50%** from baseline	1) A **reduction of ≥ 50%** from baseline value in patients with **< 50%** mutant allele burden at baseline OR 2) A reduction of ≥ **25%** from baseline value in patients with **> 50%** mutant allele burden at baseline

*Assessed by weekly blood counts during induction and less frequently during maintenance

** Definition (**European LeukemiaNet, Barosi et al., Blood 2009**); assessed approx. every 12 weeks

RESULTS: 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%)
JAK2 V617F MPL $W515^{mt}$	8 (44%) 2 (11%)
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%)

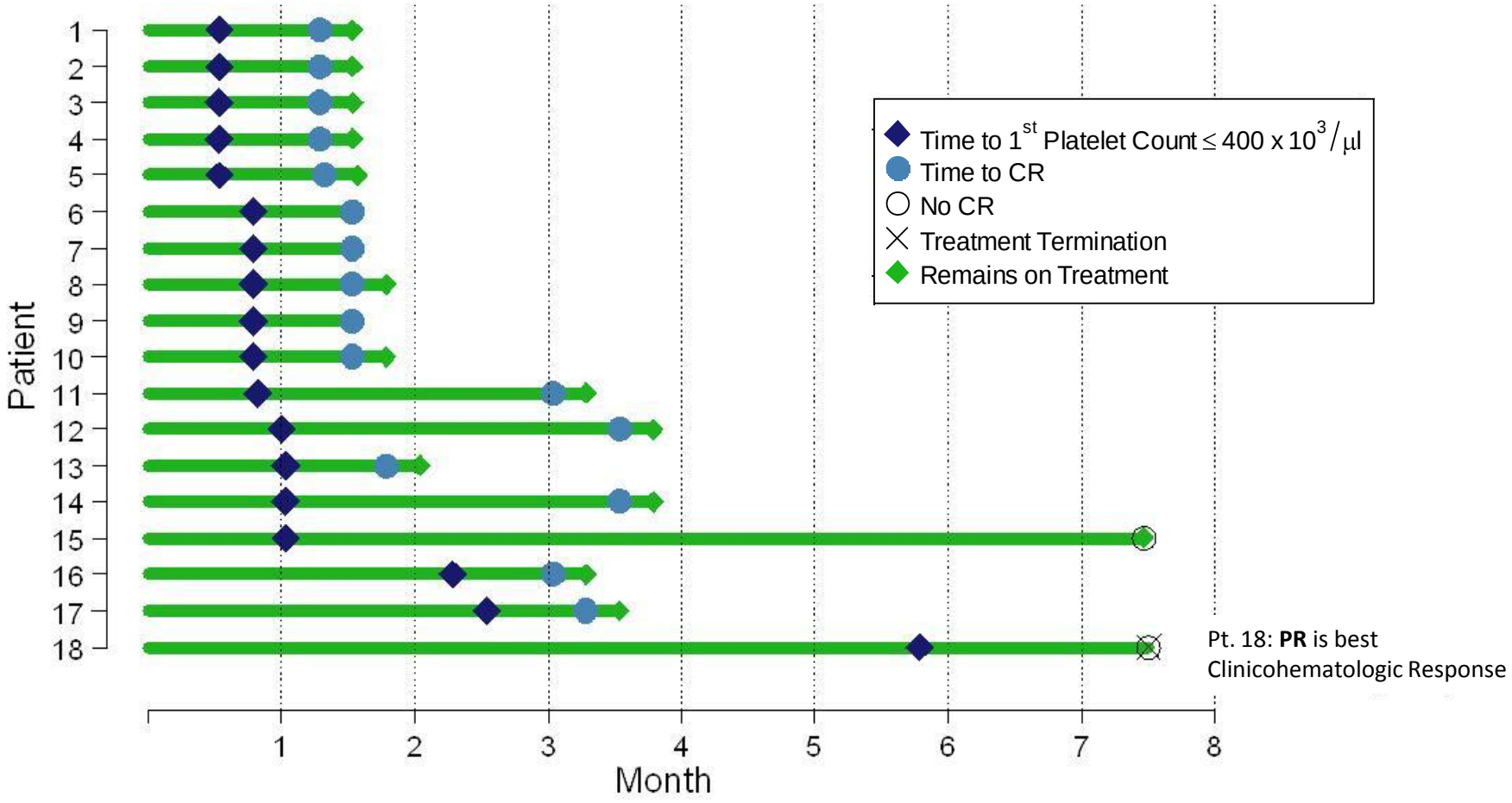
* 17 of 18 patients received prior hydroxyurea

RESULTS: Primary Endpoint--Hematologic Response

Overall hematologic response in 100% of patients (n = 18)

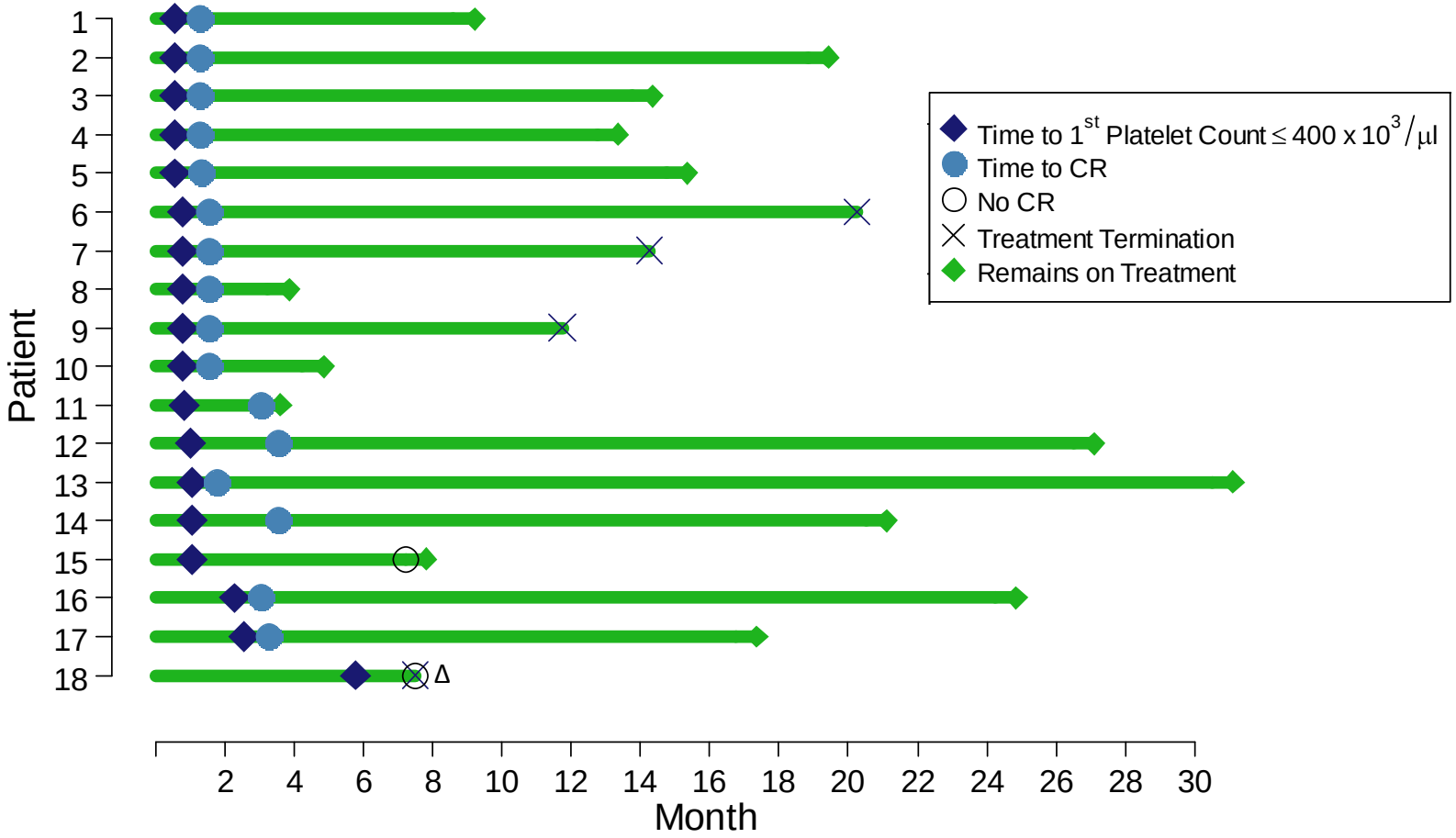
- Complete response (CR) in 16 of 18 (88.9%) patients
- Partial response (PR) in 2 of 18 (11.1%) patients

Clinicohematologic CR in 17 of 18 (94.4%) patients



RESULTS: Durability of Hematologic Response

- Patients have been treated with imetelstat for a median of 14 months (range 3mn – 2.5yr)
- 13 of the 16 patients (81.3%) with a hematologic CR remain on treatment
- 1 of 2 patients with a hematologic PR remains on treatment
- The median duration of response has not been reached



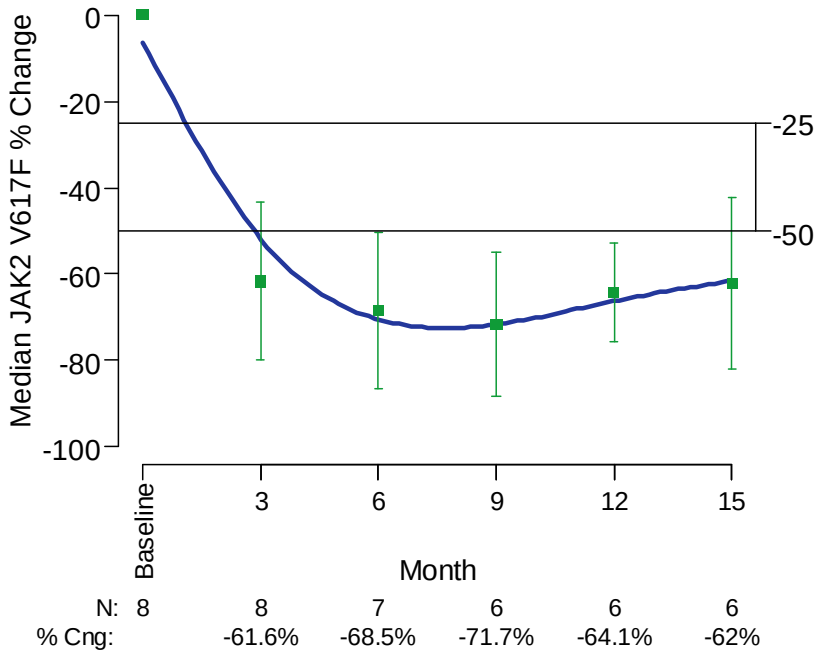
Δ Pt. 18: No PD but treatment termination related to near-weekly dosing required to maintain PR

RESULTS: Imetelstat Dosing Frequency During Maintenance Phase

- 15 / 16 patients with a hematologic CR have maintenance therapy (1 just achieved CR)
- Maintenance dosing frequency generally decreased with time (range weekly to Q7 weeks) with all patients who achieved CR receiving imetelstat every 2 weeks or less frequently

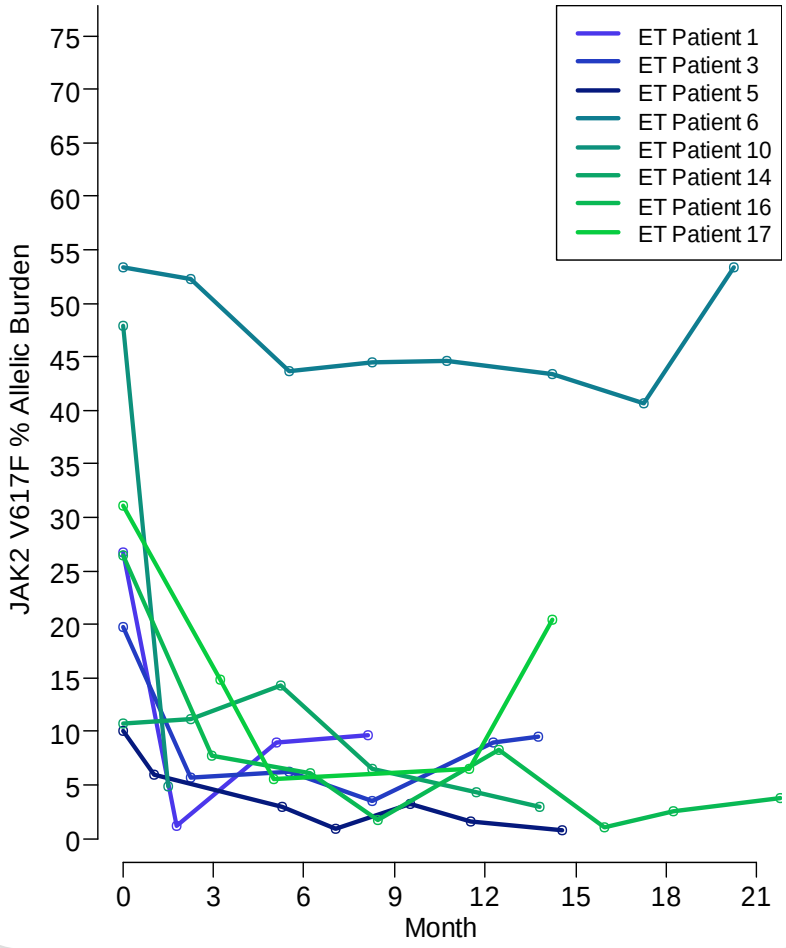
Frequency of Imetelstat Maintenance Therapy After CR	N=15
Weekly	0
Every 2 weeks	3 (20%)
Every 3 weeks	2 (13%)
≥ Every 4 weeks	10 (67%)

RESULTS: Secondary Endpoint--JAK2 V617F Allelic 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

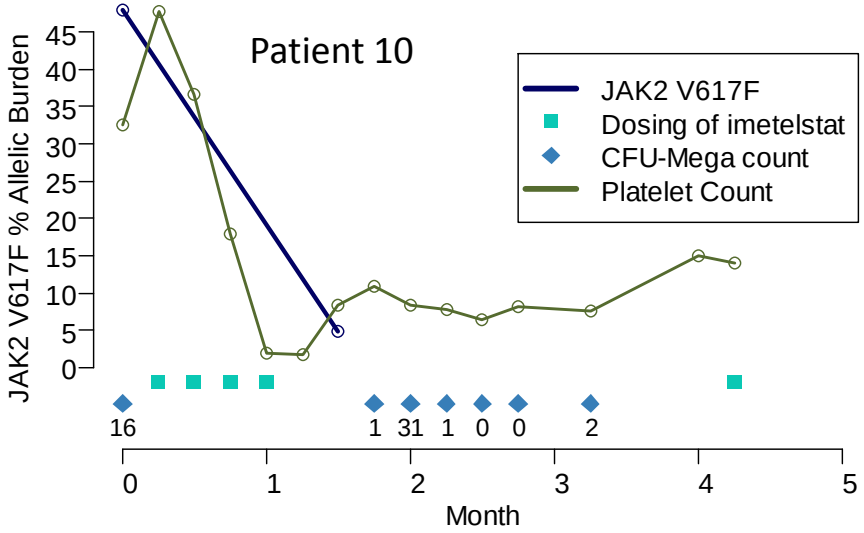
PR observed in 7/8 (88%) and maintained for 6/7 (86%) patients

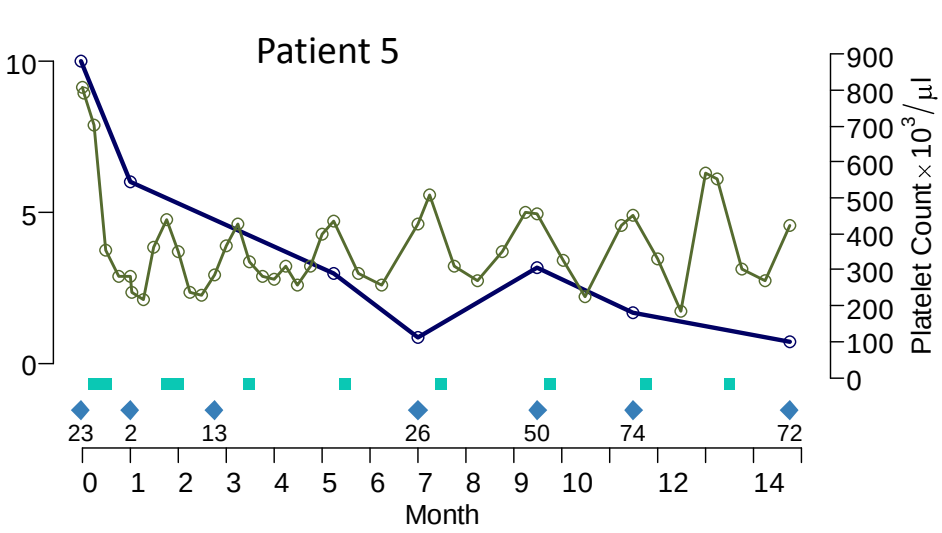


RESULTS: Exploratory Endpoint--CFU-Mega

A median 93% decrease in spontaneous growth of **CFU-Mega** was observed in all 5 pts from selected sites

Patient #	Baseline Count	1-2 month Count
5	22.7	1.7
9	8.0	0.3
10	16.3	1
11	73.7	5.3
15	>50	7.7





- Simultaneous reduction of plts, JAK2 V617F and CFU-Mega
- CFU-Mega reduction persists with infrequent maintenance dosing

Some higher CFU-Mega values follow lengthened intervals between maintenance doses

Non-Laboratory Adverse Events

Adverse Event Frequency (N=20) 18 ET + 2 PV	All Grades / Related	Grade 3 / Related	All Grades / All Events	Grade 3 / All Events
GI Events (Nausea/Diarrhea/Constipation/Vomiting)	18 (90%)	0	18 (90%)	0
Fatigue	16 (80%)	2 (10%)	17 (85%)	2 (10%)
Headache	10 (50%)	1 (5%)	12 (60%)	2 (10%)
Decreased Appetite	8 (40%)	0	9 (45%)	0
Musculoskeletal Disorders (Pain)	8 (40%)	0	15 (75%)	1 (5%)
Bleeding Events	7 (35%)	0	12 (60%)	2* (10%)
Infusion Reactions	7 (35%)	1**(5%)	7 (35%)	1** (5%)
Pyrexia	5 (25%)	0	9 (45%)	0
Chills	5 (25%)	0	8 (40%)	0
Infections	5 (25%)	1*** (5%)	19 (95%)	3 (15%)
Dizziness	4 (20%)	0	11 (55%)	0
Cough	2 (10%)	0	9 (45%)	0

* Grade 3 post-operative hemorrhagic anemia/ epistaxis
**Grade 3 syncope; patient remains on treatment
***Influenza

- No thromboembolic events
- Two Grade 4 AEs unrelated to imetelstat
- No Grade 5 AEs

Laboratory Abnormalities

Laboratory Parameter* (N=20)	All Grades	Grade 3	Grade 4
ALT	18 (90%)	2 (10%)	0
AST	18 (90%)	1 (5%)	0
Alkaline phosphatase (ALP)	13 (65%)	0	0
Bilirubin, total	6 (30%)	0	0
Neutropenia	15 (75%)	8 (40.0%)	3 (15%)
Anemia	17 (85%)	3 (15%)	0
Thrombocytopenia	11 (55%)	1 (5%)	0

*shift from baseline

- Hepatic enzyme abnormality patterns observed
  - Majority were Grade 1 elevations in ALT/AST; 2 pts Grade 3 increases in ALT/AST were reversible on dose reduction
  - Serial Grade 1 ALP increase with primarily unconjugated Grade 1 hyperbilirubinemia observed
  - No liver injury symptoms reported; no patients discontinued study treatment due to enzyme elevations
  - Investigation and monitoring of these safety signals are ongoing
- No cases of febrile neutropenia were reported

CONCLUSIONS

Imetelstat appears to be a promising treatment for ET

- Treatment in 18 ET patients who had previously failed or were intolerant to conventional therapies resulted in 100% hematologic responses (88.9% CR)
- All 16 patients with a hematologic CR were able to subsequently reduce their frequency of imetelstat administration and 13 remain on treatment (median 14 months, range 3 mn – 2.5 yrs)
- Molecular responses (PR) were reached in 7 / 8 patients (88%) and were maintained in 6 patients
- A median 93% reduction of neoplastic clonogenic growth in patients after 1-2 months of treatment was demonstrated in the 5 patients tested, confirming prior *ex vivo* data
- Imetelstat was generally well tolerated; no patients have discontinued due to an adverse event

These data suggest that imetelstat has a relatively selective inhibitory effect on the growth of the neoplastic clone(s) which drive ET, and thus has the potential to modify the underlying biology of the disease

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
Meike Dahlhaus, Monika Haubitz, Barbara Huegli