

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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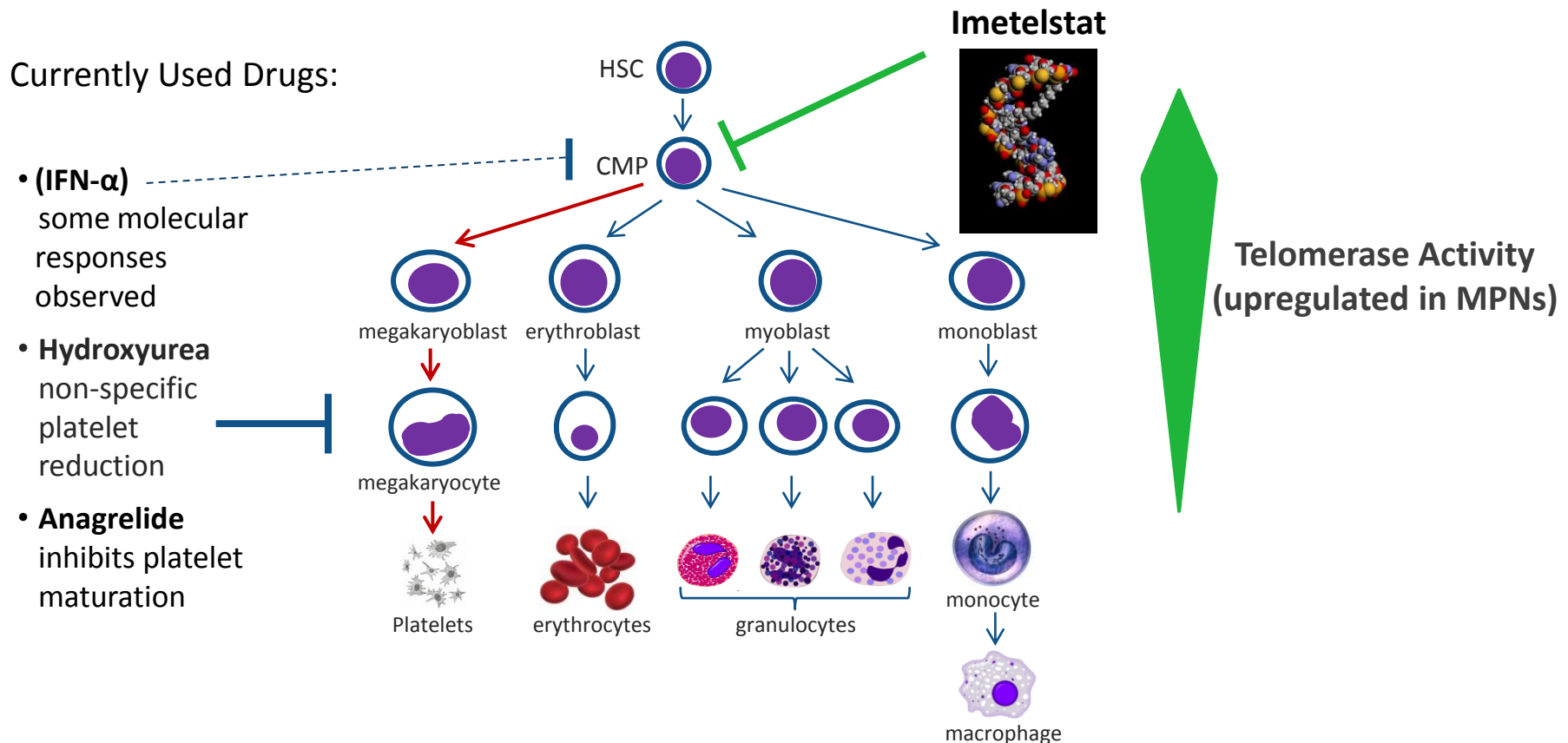
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Rationale for Treating ET Patients with Imetelstat

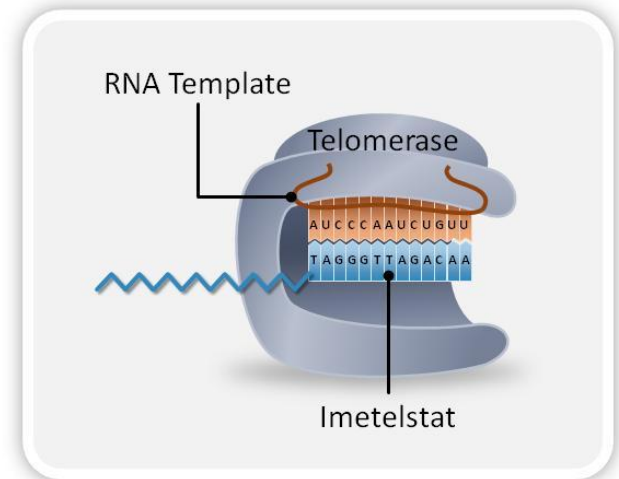
- Novel mechanism of action which targets a driver of the malignancy
 - Upregulated telomerase may be centrally involved with proliferation and immortality of neoplastic progenitor cells*
 - Imetelstat may selectively inhibit proliferation of neoplastic progenitors



Imetelstat: First-in-class Telomerase Inhibitor

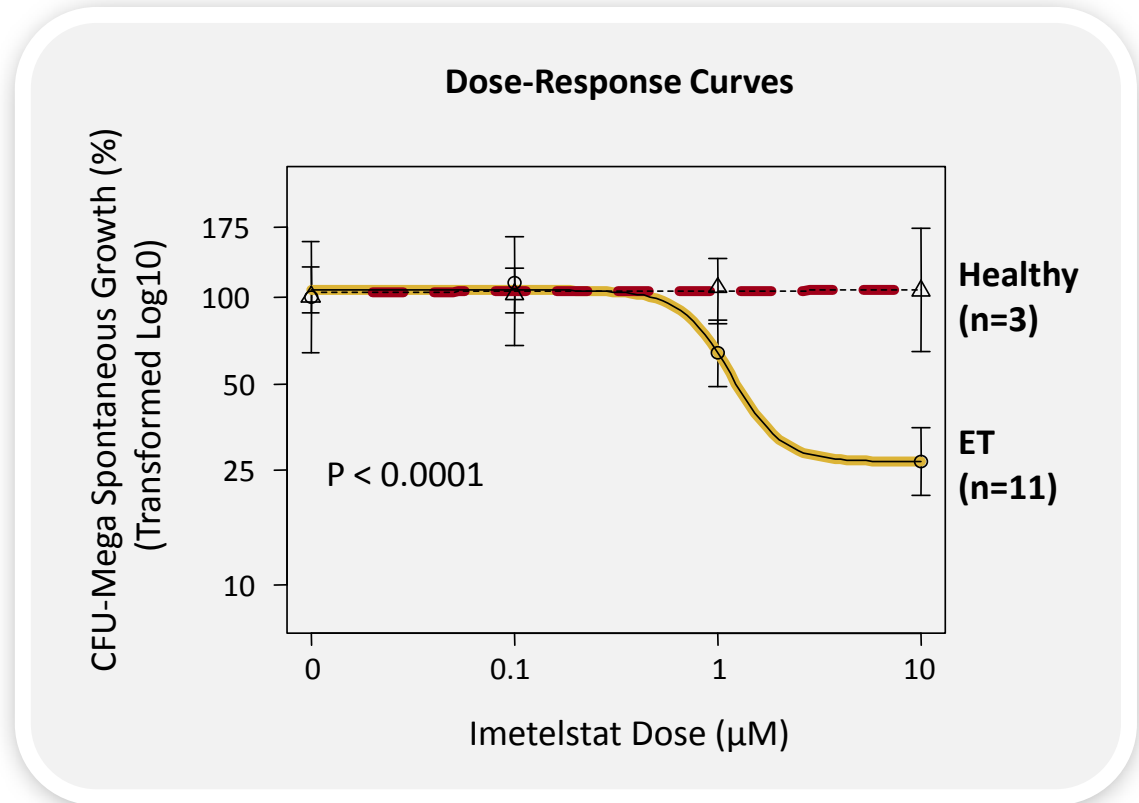
Imetelstat

- 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)
 - $IC_{50} = 0.15-1.77$ μ M (cell-based)
- Long half-life in bone marrow, spleen and liver
 - Tissue $t_{1/2} = 50-90$ hr in rodents
 - Predicted human $t_{1/2} = 41$ hr with doses 7.5-11.7 mg/kg

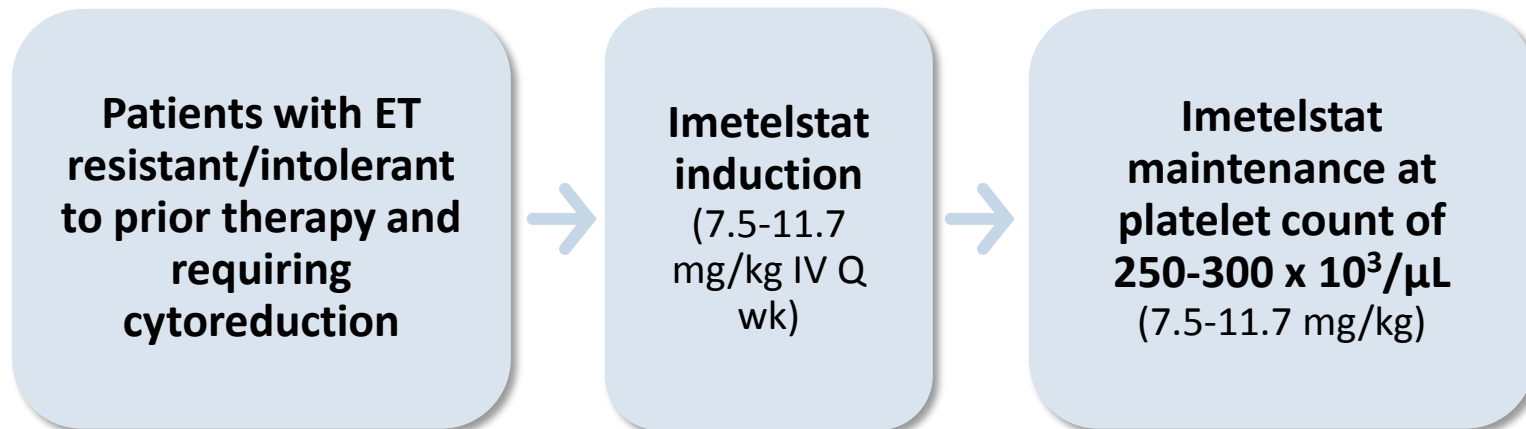


Imetelstat Reduces Neoplastic Progenitor Proliferation

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



METHODS: Study Design



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

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} patients)• Safety and tolerability
Exploratory	<ul style="list-style-type: none">• 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 ($\leq 400 \times 10^3/\mu\text{L}$) maintained for at least 4 consecutive weeks , in the absence of thromboembolic events	1) Platelet count $\leq 400 \times 10^3 \mu\text{L}$, AND 2) No disease related symptoms, AND 3) Normal spleen size, AND 4) WBC $\leq 10 \times 10^3/\mu\text{L}$	Reduction of any specific molecular abnormality to undetectable levels
PR	Platelets $\leq 600 \times 10^3/\mu\text{L}$ or a 50% reduction in platelets maintained for at least 4 consecutive weeks , in the absence of thromboembolic events	Platelet count $\leq 600 \times 10^3/\mu\text{L}$ or decrease > 50% from baseline	1) A reduction of $\geq 50\%$ from baseline value in patients with < 50% mutant allele burden at baseline OR 2) A reduction of $\geq 25\%$ 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 /μL)	788 (521-1359)
WBC Count (x 10 ³ /μL)	7.8 (3-14.6)
Splenomegaly	1 (6%)
JAK2 V617F	8 (44%)
MPL W515 ^{mt}	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%)

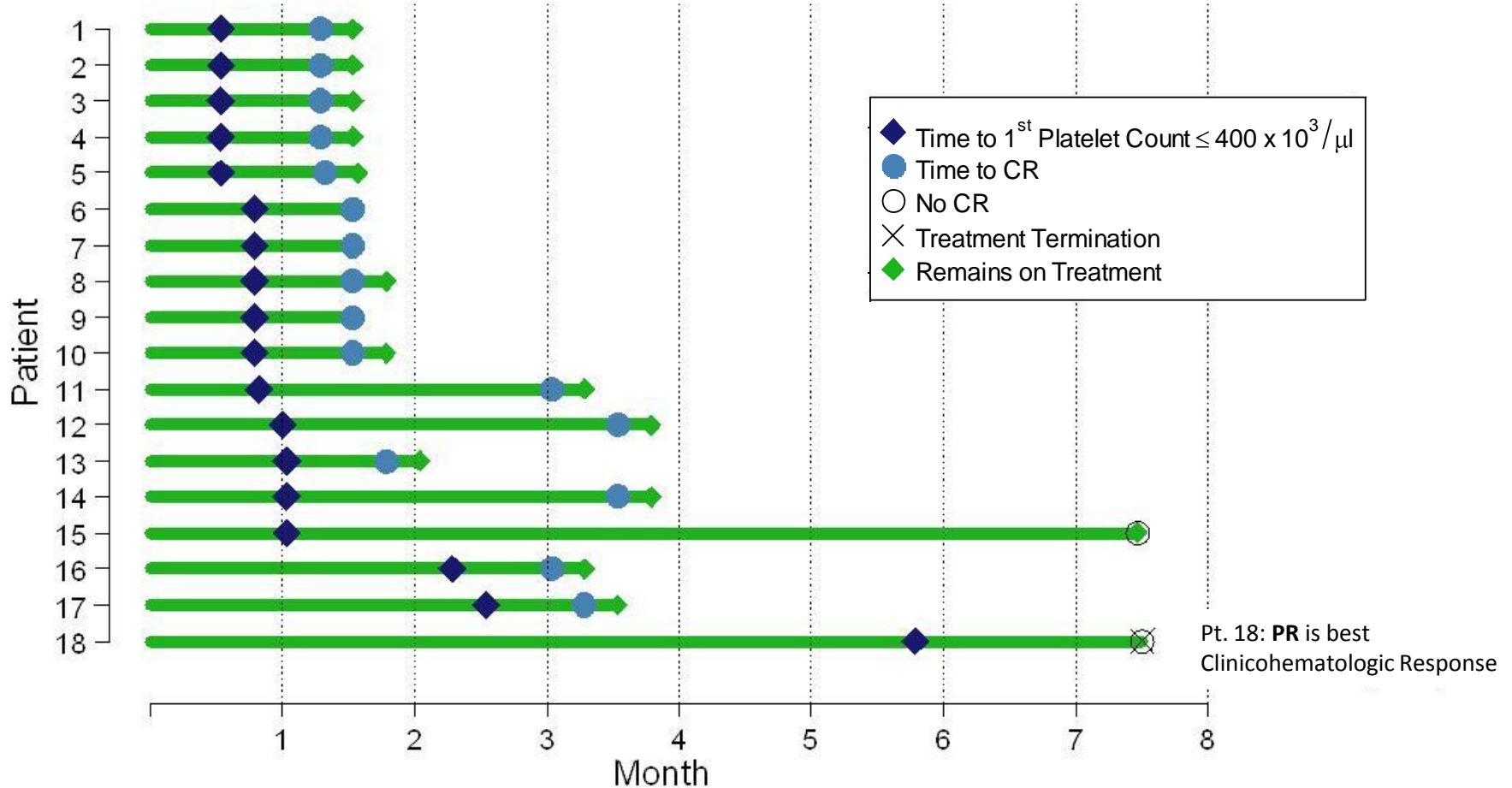
* 17 of 18 patients received prior hydroxyurea

RESULTS: Primary Endpoint--Hematologic Response

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

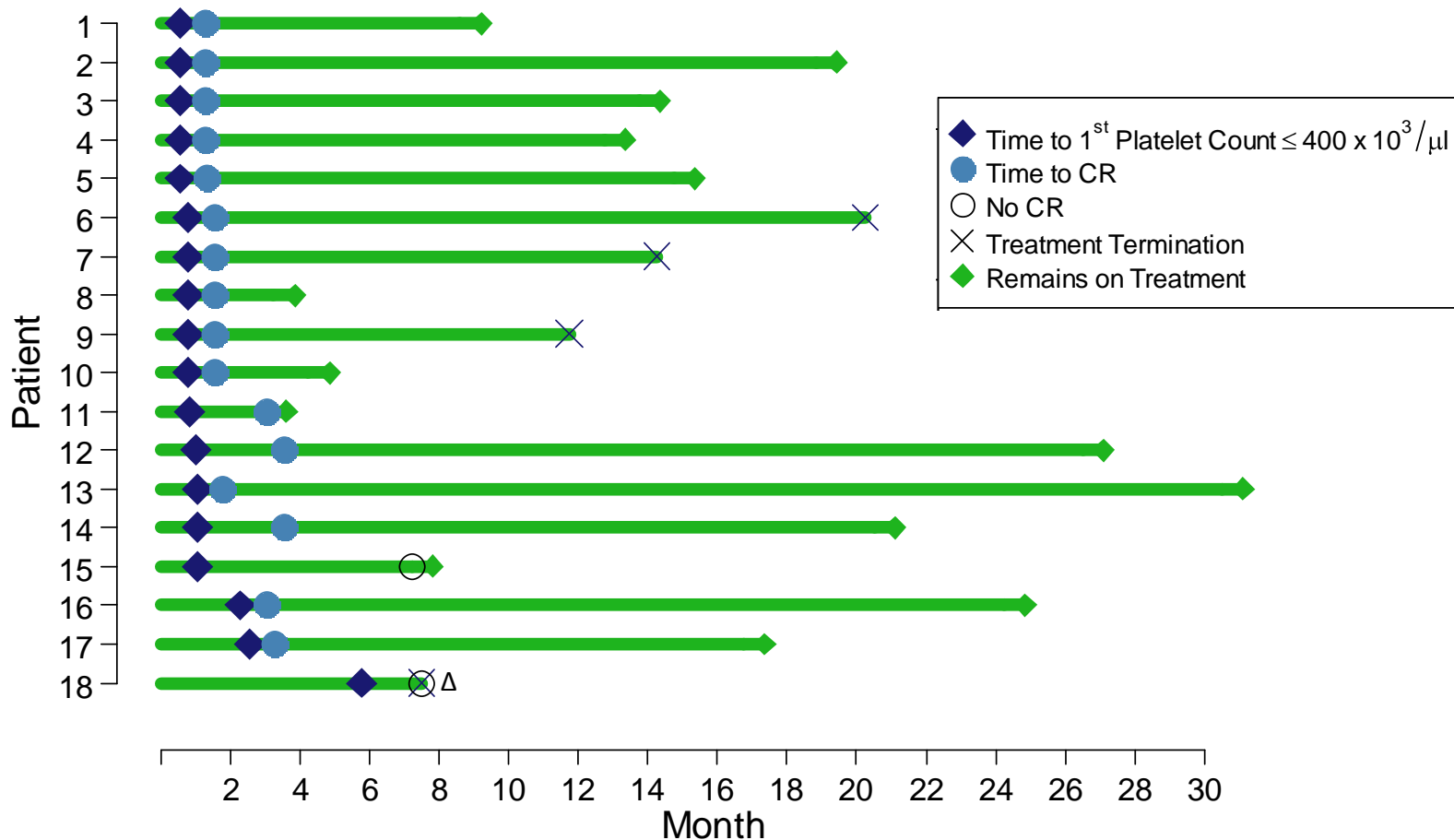
- Complete response (CR) in 16 of 18 (88.9%) patients
- Partial response (PR) in 2 of 18 (11.1%) patients

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



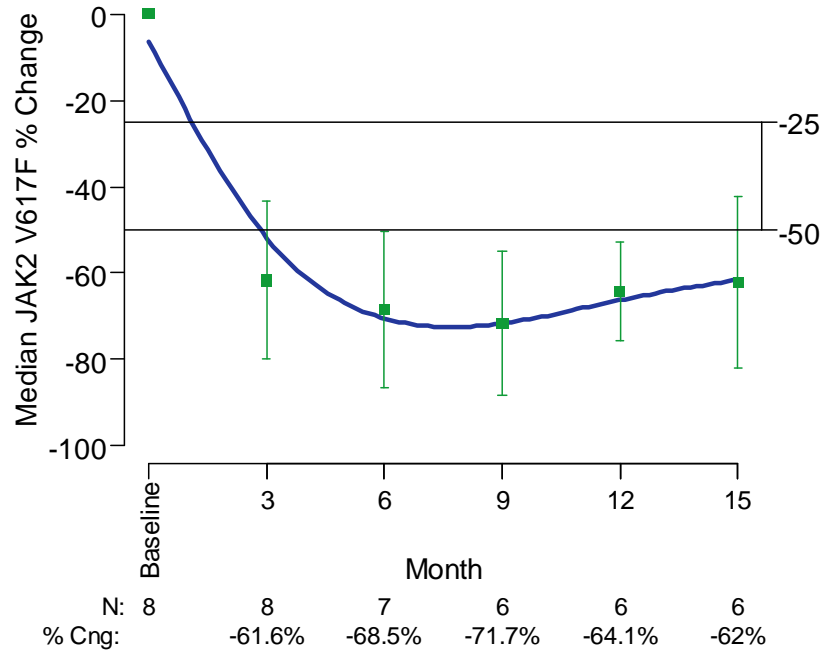
Δ Pt. 18: No PD but treatment termination related to near-weekly dosing required to maintain PR

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

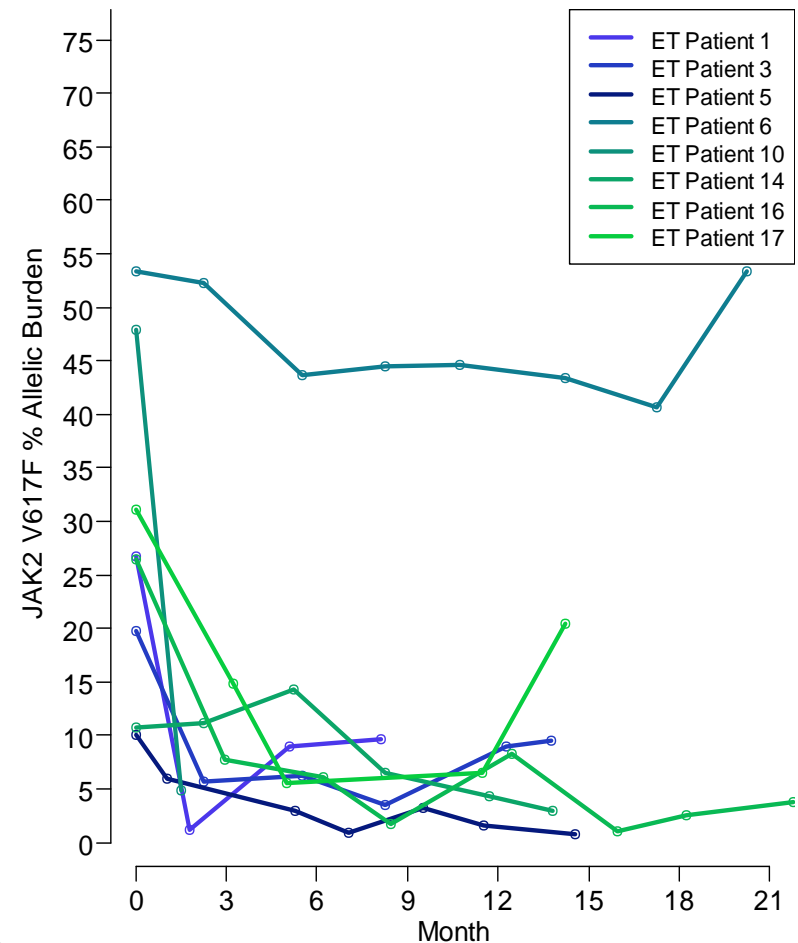
Frequency of Imetelstat Maintenance Therapy After CR	N=15
Weekly	0
Every 2 weeks	3 (20%)
Every 3 weeks	2 (13%)
≥ Every 4 weeks	10 (67%)

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

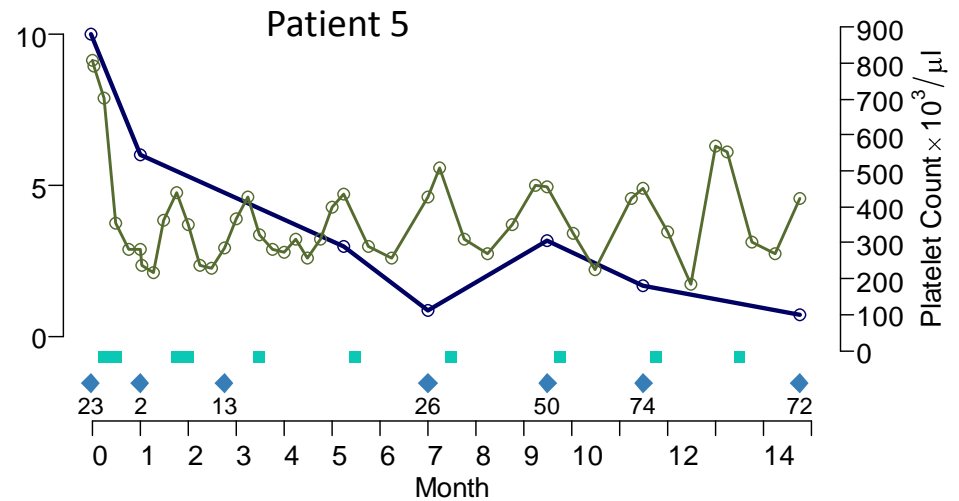
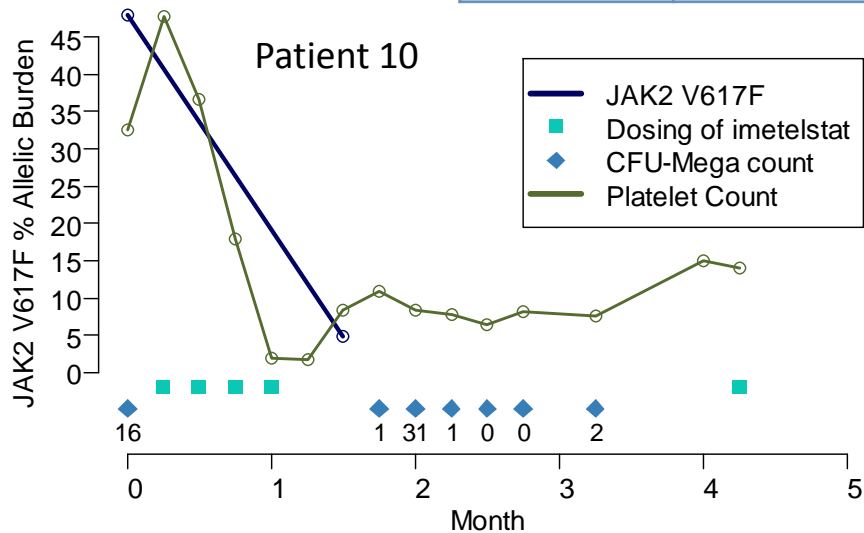
PR observed in 7/8 (88%) and maintained for 6/7 (86%) patients



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 / <u>Related</u>	Grade 3 / <u>Related</u>	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

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