Imetelstat Rapidly Induces and Maintains Substantial Hematologic and Molecular Responses in Patients with Essential Thrombocythemia (ET) Who Are Refractory or Intolerant to Prior Therapy: Preliminary Phase II Results

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The Rationale for Novel Therapies for Patients with ET

Current therapies for ET primarily aim at prevention of thrombotic/hemorrhagic occurrence

- Non-specific platelet reduction
- Some molecular responses seen

New therapies are needed to address underlying disease

- Novel mechanism of action to target neoplastic progenitor cells driving malignancy

Upregulated telomerase may be centrally involved with proliferation and replicative immortality of neoplastic progenitor cells*

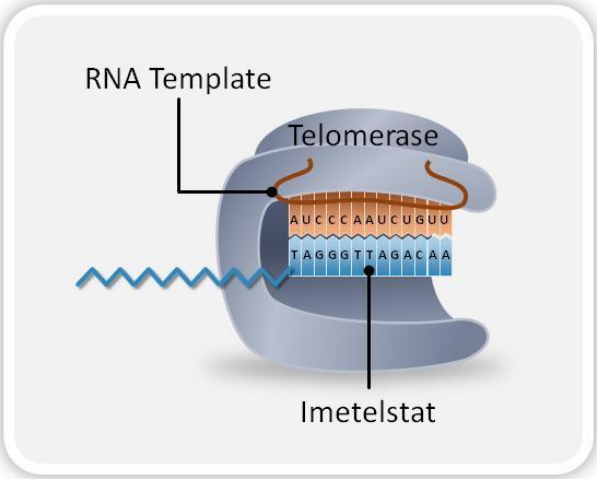
Inhibiting telomerase, therefore, seems to be an attractive approach for treating patients with ET

*"The Hallmarks of Cancer: The Next Generation", Hanahan & Weinberg, Cell 2011

Imetelstat: First-in-class Telomerase Inhibitor

Imetelstat

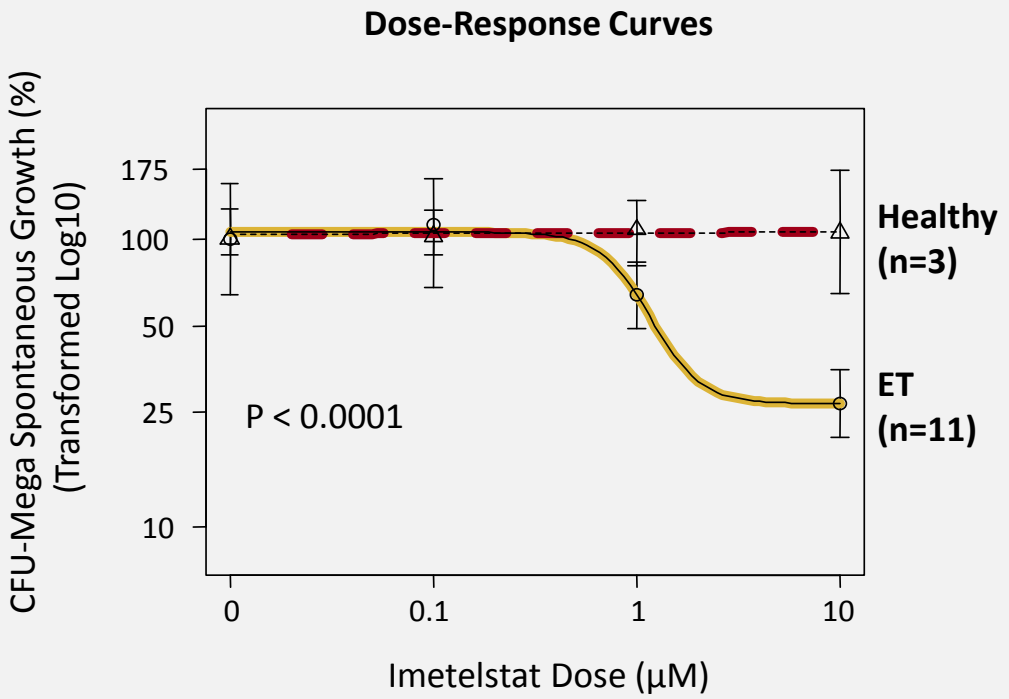
- First telomerase inhibitor in clinical development
- 13-mer modified oligonucleotide with palmitoyl lipid tail
- Competitively binds to RNA template of telomerase
- Potent inhibitor of telomerase enzyme activity
  - IC_{50} = 0.5-10 nM (cell-free)
  - IC_{50} = 0.15-1.77 µM (cell-based)
- Long half-life 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

Imetelstat's effect on CFU-Mega from peripheral blood:

- Inhibits neoplastic (spontaneous) megakaryocyte growth from patients with ET
- Does not inhibit normal (cytokine-dependent) megakaryocyte growth from healthy individuals



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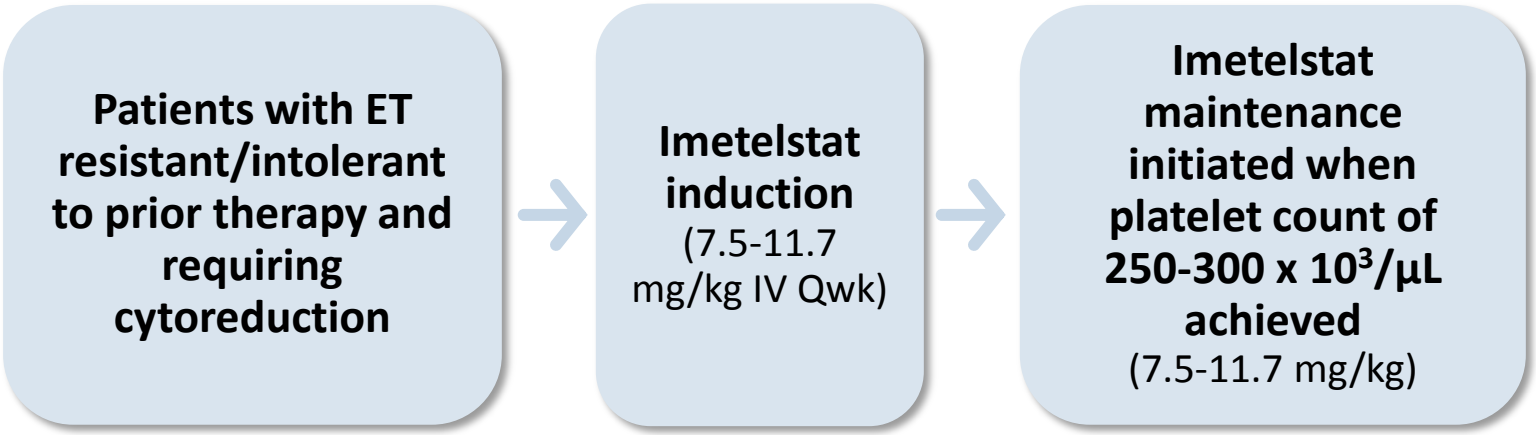
METHODS: Phase II Study Design



Endpoint	
Primary	• Best Overall Hematologic RR (CR + PR) within 1st yr of treatment
Secondary	• Duration of hematologic response • Molecular Response (JAK2 V617F /MPL W515^{mt} patients) • Safety and tolerability
Exploratory	• CFU-Mega spontaneous growth (selected sites only)

METHODS: Response Definitions

European LeukemiaNet Response Criteria Adapted from Barosi et al., Blood 2009

Hematologic Response Grade	Definition
Complete Response (CR)	Normalization of platelets **(≤400 x 10^3/µL)** maintained for **at least 4 consecutive weeks**, in the absence of thromboembolic events
Partial Response (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

Molecular Response Grade	Definition
Complete Response (CR)	Reduction of any specific molecular abnormality to **undetectable** levels
Partial Response* (PR)	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
No Response (NR)	Any response that does not satisfy complete or partial response

* Applies only to patients with a baseline value of mutant allele burden ≥ 10%

RESULTS: Patient Demographics

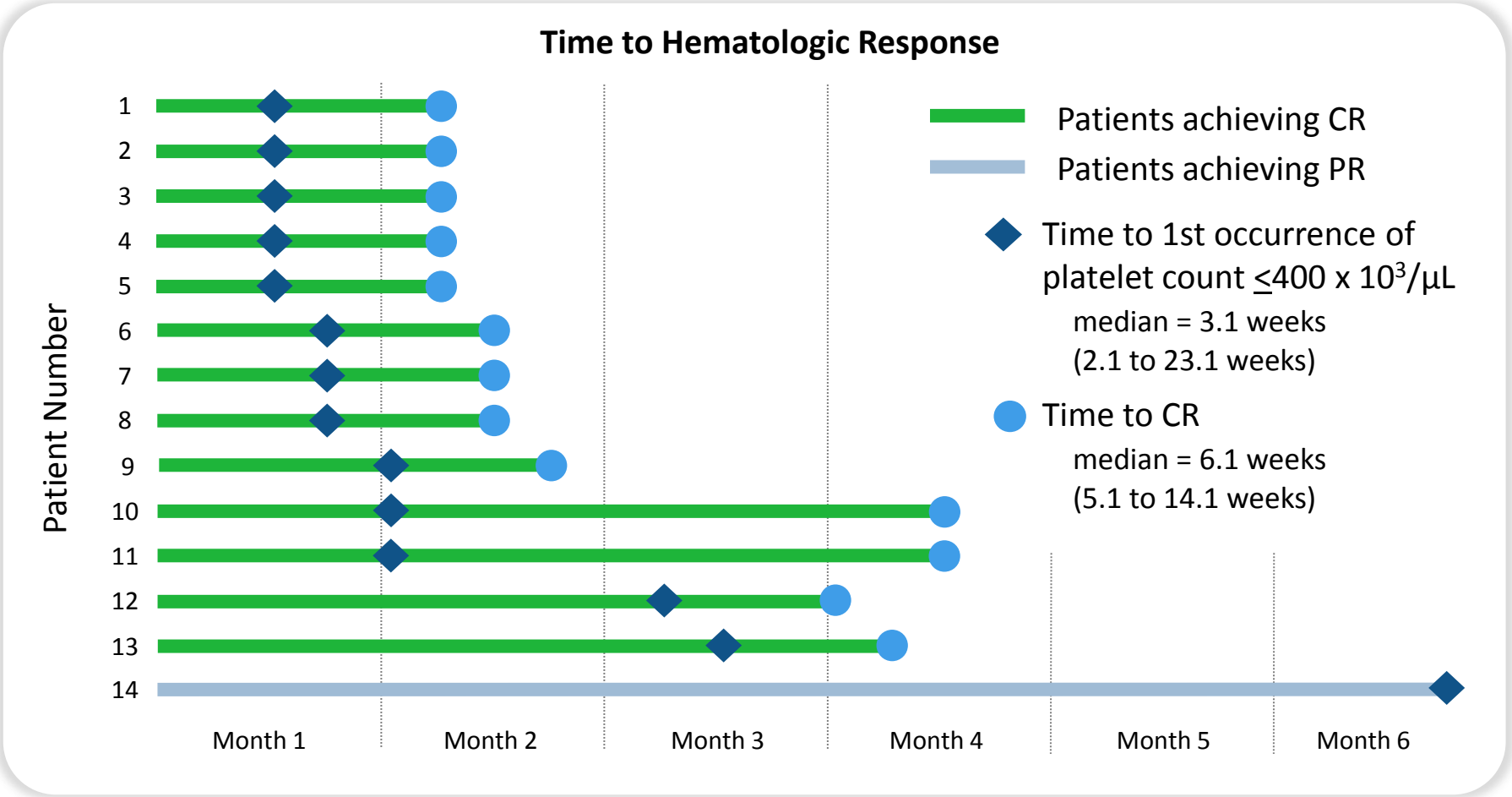
Characteristic Median (Range)	Total (N=14)
Age	59.5 years (21-83)
Years Since Initial Diagnosis	5.8 (0.3-24.9)
Median Baseline Platelet Count	787.5 x 10^3/µL (521-1359)
Median Baseline WBC Count	6.6 x 10^3/µL (3.0-14.6)
Pts with JAK2 V617F Pts with MPL W515^{mt}	7 (50%) 2 (14.3%)
More than one prior therapy (anagrelide +/- IFN)*	9 (64%)
Resistant to at least one prior therapy	7 (50%)
Intolerant of or refused at least one prior therapy	11 (71%)

* All 14 patients received prior hydroxyurea (6 resistant, 8 intolerant)

RESULTS: Primary Endpoint--Hematologic Response

Overall hematologic response in 100% of patients (n = 14)

- Complete Response in 13 of 14 (92.9%) patients
- Partial Response in 1 of 14 (7.1%) patients



RESULTS: Dosing Frequency in Maintenance

- 13 patients had a hematologic CR and began maintenance therapy

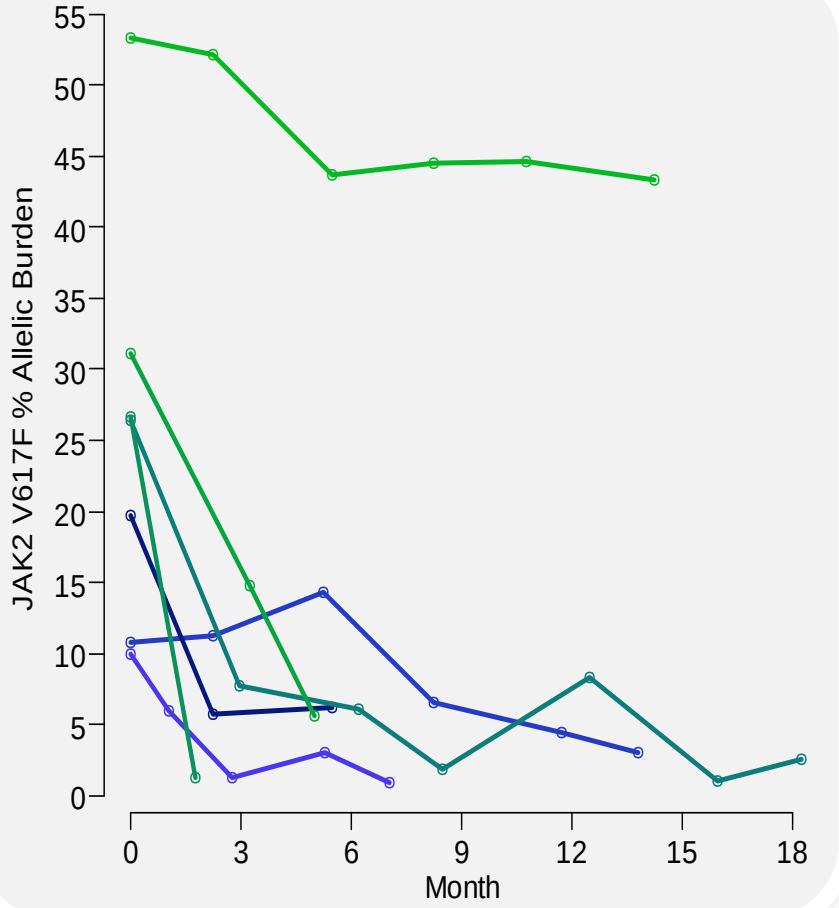
- Maintenance dosing frequency generally decreased with time (range weekly to Q7 weeks) with the majority (84.6%) of patients receiving imetelstat every 2 weeks or less frequently (based on median)

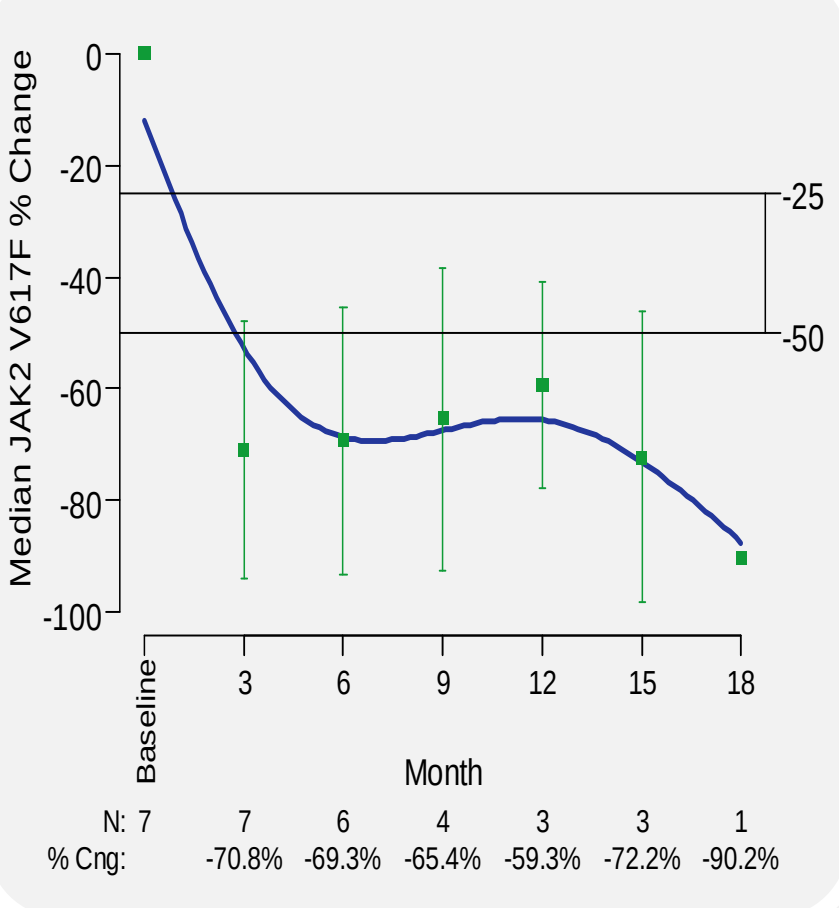
Median Frequency of Therapy	N=13
Weekly	2 (15.4%)
Every 2 weeks	3 (23.1%)
Every 3 weeks	2 (15.4%)
>Every 3 weeks	6 (46.1%)

- 85.7% (6/7) of patients who are eligible to remain on therapy after 1 year have continued maintenance therapy

RESULTS: Secondary Endpoint--JAK2 V617F Allelic Burden

- % JAK2 V617F allelic burden decreases over time in all patients
- PR observed in 6/7 patients (85.7%)



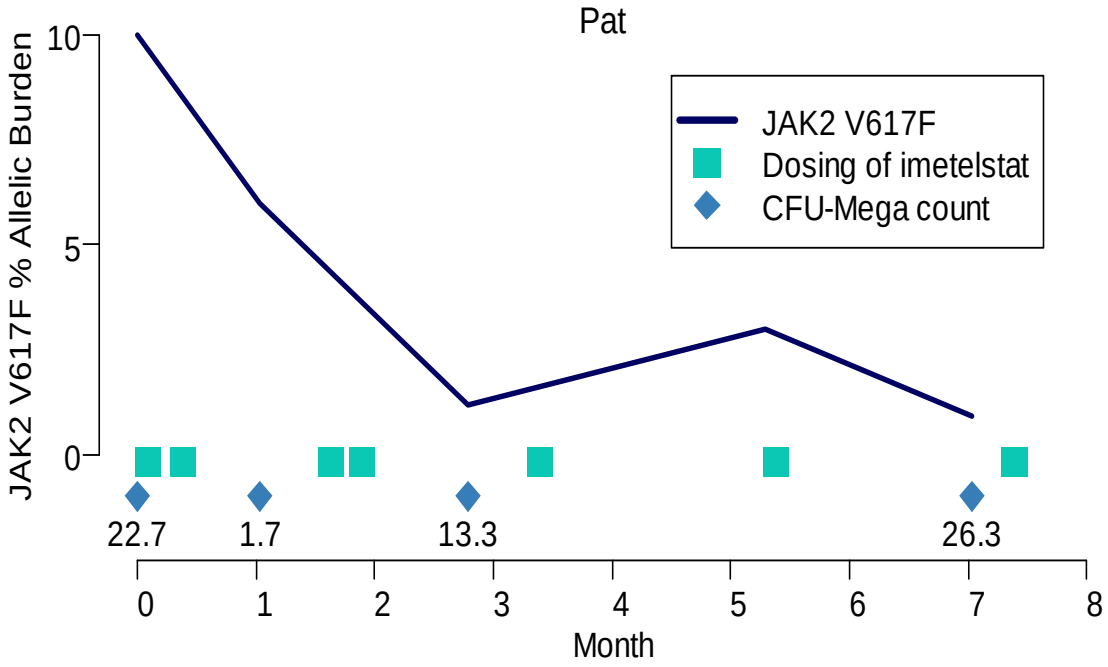


RESULTS: Exploratory Endpoint--CFU-Mega

- A reduction in the spontaneous growth of CFU-Mega was also observed in the 2 pts tested, with 93% and 96% reduction from baseline, respectively

Patient #	Baseline	1 month
4	22.7	1.7
8	8.0	0.3

- Spontaneous growth of CFU-Mega did not correspond with the reduction in JAK2 V617F allelic burden in one patient (pt #4)



RESULTS: Safety--Clinically Significant Frequent Non-Hematologic Adverse Events

Frequent Non-Hematologic Adverse Events	All Grades (N=14)	Grade 3 (N=14)
GI Events (Nausea/Diarrhea/Constipation)	14 (100%)	0
Infections	12 (85.7%)	1* (7.1%)
Fatigue	9 (64.3%)	1 (7.1%)
Musculoskeletal Disorders (Pain)	9 (64.3%)	0
Bleeding Events	8 (57.1%)	1** (7.1%)
Headache	7 (50.0%)	1 (7.1%)
Cough	7 (50.0%)	0
Decreased Appetite	7 (50.0%)	0
Dizziness	6 (42.9%)	
Infusion Reactions	4 (28.6%)	1*** (7.1%)

* Grade 3 cellulitis/wound infection
** Grade 3 post-operative hemorrhagic anemia
*** Grade 3 syncope; patient remains on treatment

- One Grade 4 Adverse event : imetelstat unrelated femoral neck fracture
- No Grade 5 Adverse events
- No thromboembolic events were reported

RESULTS: Safety--Laboratory Abnormalities

Laboratory Parameter	All Grades (N=14)	Grade 3 (N=14)	Grade 4
ALT/AST (change from grade at baseline)	13 (92.9%)	2 (14.3%)	0
Neutropenia	11 (78.6%)	4 (28.6%)	2 (14.3%)
Anemia (change from grade at baseline)	9 (64.3%)	1 (7.1%)*	0
Thrombocytopenia	6 (42.9%)	0	0

*Post-operative hemorrhagic anemia

- No cases of febrile neutropenia were reported

CONCLUSIONS

- **Imetelstat** was generally **well tolerated.**
- **100% hematologic responses (92.9% CR)** achieved in patients with ET who have failed or are intolerant to conventional therapies. **All patients** who have attained a hematologic CR **remain on treatment.**
- **Molecular responses (PR)** were reached **in 6 of 7 (85.7%) patients** with JAK2 V617F **within a 3-6 month** range.
- **Reduced neoplastic clonogenic growth ex-vivo after 1 month** was demonstrated in the 2 patients tested, confirming prior *ex vivo* data**.** CFU-Mega did not correspond with the reduction in JAK2 V617F burden in one patient.
- Of the 13 patients who achieved a hematologic CR, **11 (84.6%)** subsequently **reduced their frequency of imetelstat administration. Six of 7 (85.7%)** eligible patients **remain on treatment beyond one year.**
- The data suggest that **imetelstat** has a **relatively selective inhibitory effect on the growth of the neoplastic clone(s)** which drive MPNs such as ET and has the **potential to modify the underlying biology** of the disease.

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