

# Novel drugs in MPNs: Histone-Deacetylase Inhibitors

# 1st Annual Florence MPN Meeting

## April 16, 2011

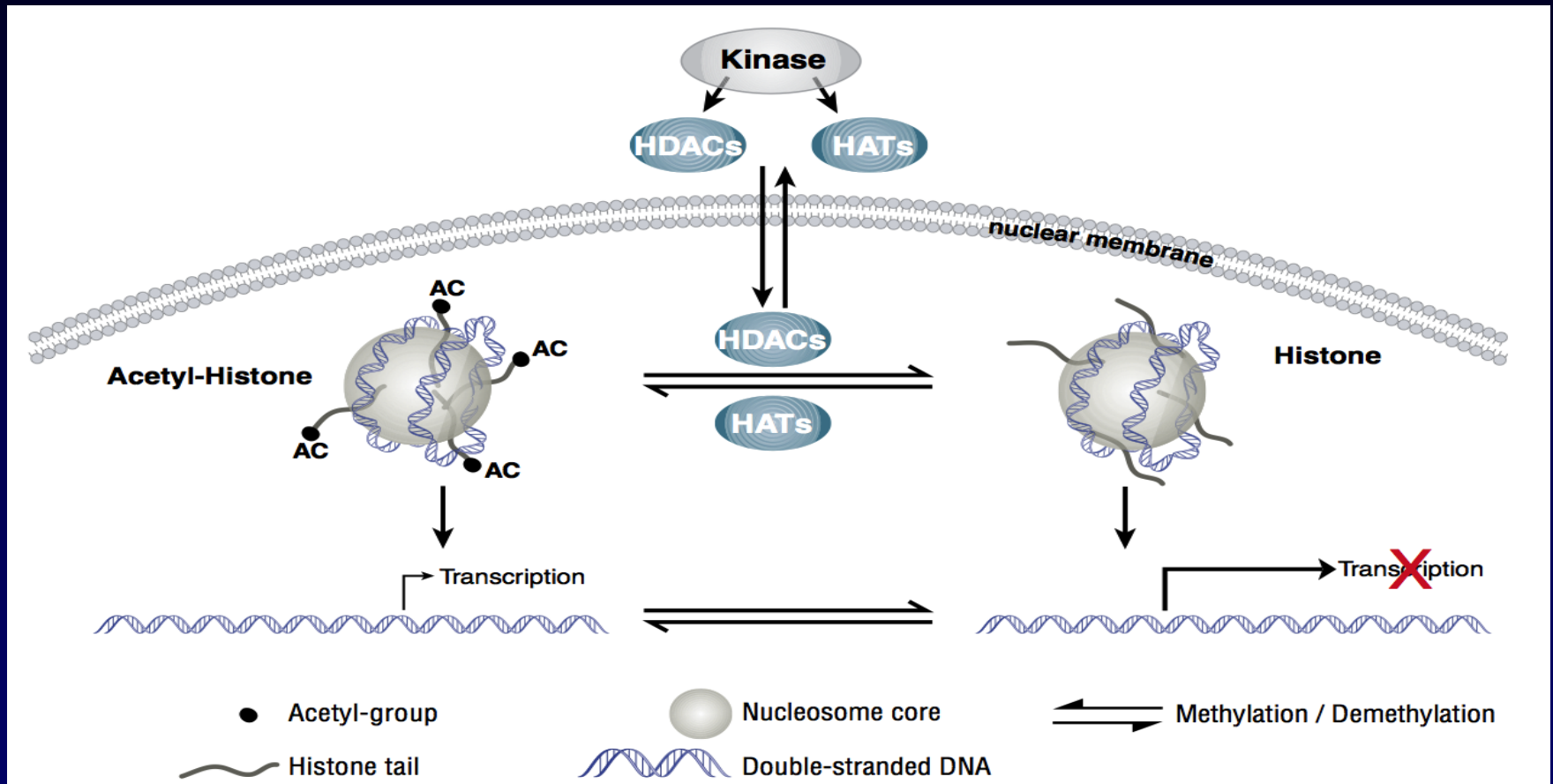
# Guido Finazzi

# Chronic Myeloproliferative Neoplasm Unit

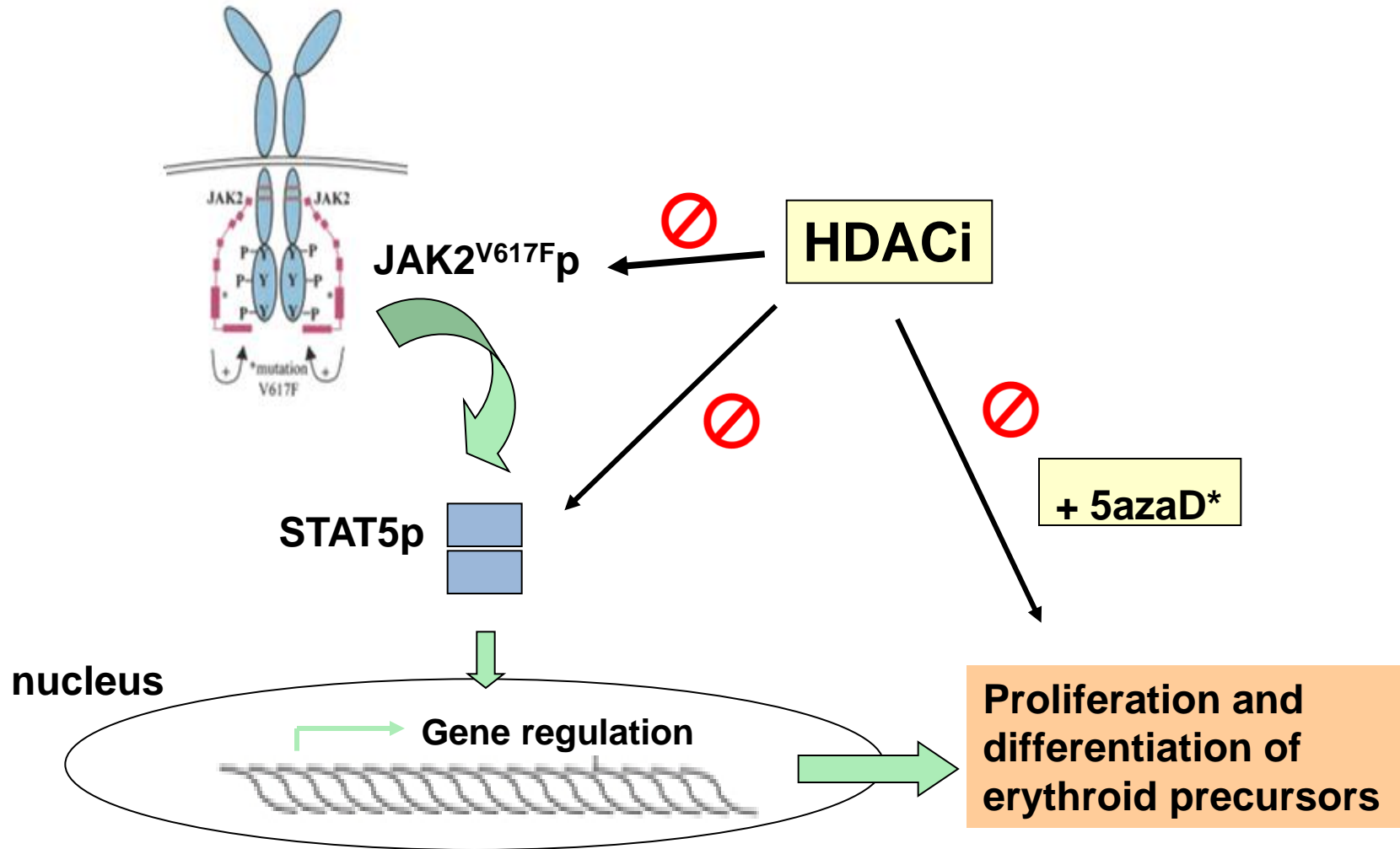
# Division of Hematology

# Ospedali Riuniti di Bergamo, Italy

# Mechanism of action of HDAC inhibitors



# Specific effects of HDAC inhibitors in MPN



# Histone Deacetylase Inhibitors

Family	Compounds
Hydroxamate	<ul style="list-style-type: none"><li>• <b>Vorinostat (SAHA)</b></li><li>• <b>Panobinostat (LBH589)</b></li><li>• <b>Givinostat (ITF2357)</b></li><li>• Dacinostat (NVP-LAQ824)</li><li>• Belinostat (PXD-101)</li></ul>
Cyclic peptide	<ul style="list-style-type: none"><li>• <b>Depsipeptide</b></li></ul>
Aliphatic acid	<ul style="list-style-type: none"><li>• Valproic acid</li><li>• Phenybutyrate</li></ul>
Benzamide	<ul style="list-style-type: none"><li>• Entinostat (MS-275)</li><li>• Mocetinostat (MGCD0103)</li></ul>



## **Efficacy of Vorinostat in a murine model of Polycythemia Vera**

**Akada H, Hamada S, Mohi G**

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**An inducible JAK2 V617F knock-in mouse model reproducing all the features of human PV was generated (Blood 2010; 115:3589)**

**In this model, Vorinostat significantly reduced the increase in RBC, hematocrit and spleen size compared to vehicle-treatment**

**Furthermore, Vorinostat selectively inhibited the clonogenic growth of primary erythroid progenitors expressing JAK2V617F without significant toxicity towards wild-type JAK2-expressing normal hematopoietic progenitors**

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**A phase II trial of **Panobinostat**, an orally available HDACi in patients with primary, post-ET and post-PV myelofibrosis**

**DeAngelo D, Tefferi A, Fiskus W, Mesa RA et al.**

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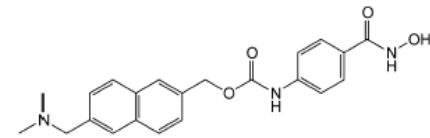
**31 MF pts. with IPSS 2 or 3 and symptomatic splenomegaly or anemia were enrolled in an ongoing trial**

**Initial Panobinostat dose was 40 mg three times a week, but most pts. required dose reduction for toxicity, mainly hematological and gastrointestinal.**

**Correlative studies showed decline in the protein level of STAT3 and STAT5 and depletion of JAK2V617F allelic burden by 10-90%**

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# Givinostat: a novel HDAC inhibitor



At nanomolar concentrations, Givinostat inhibits

Gene expression and synthesis of  $\text{TNF}\alpha$  and  $\text{IFN}\alpha$  by mononuclear cells

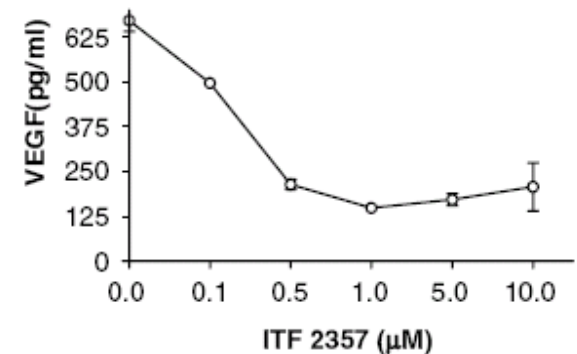
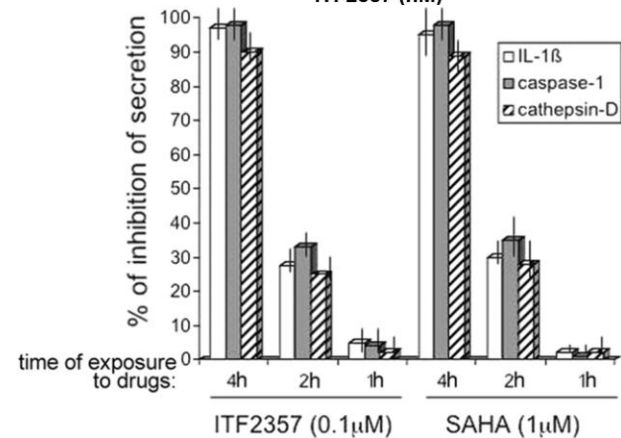
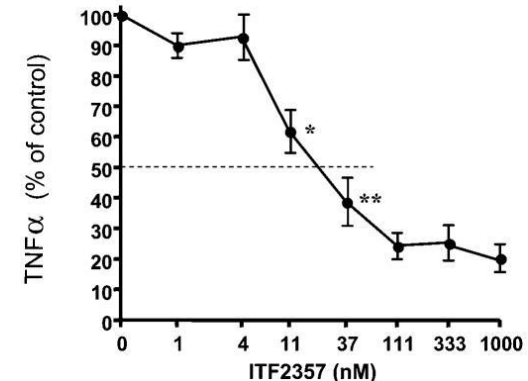
*Leoni, Mol Med. 2005*

Secretion of  $\text{IL-1}\beta$  by preventing the exocytosis of  $\text{IL-1}\beta$ -containing secretory lysosomes

*Carta, Blood 2006*

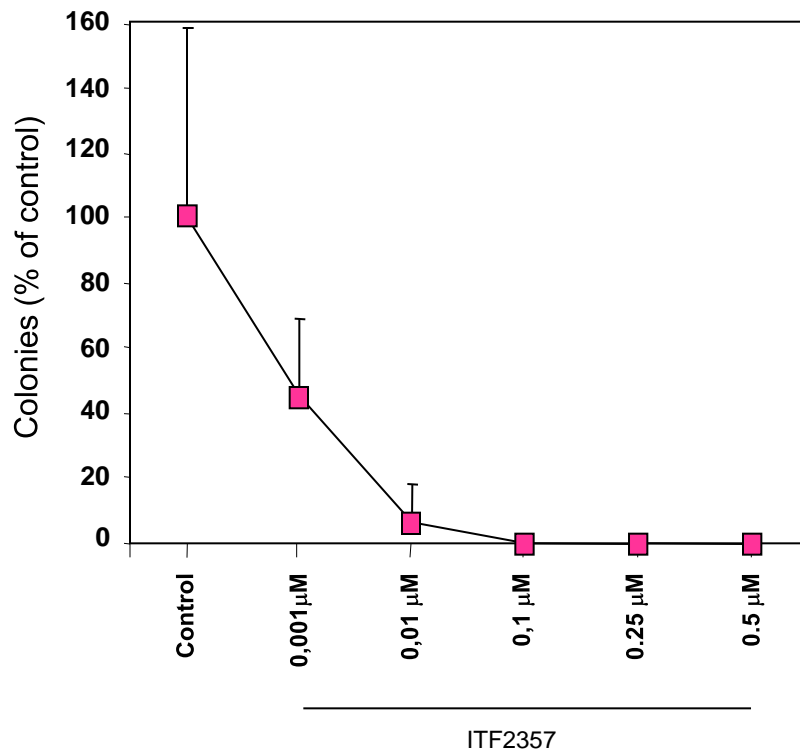
Secretion of  $\text{IL-6}$ ,  $\text{VEGF}$  and  $\text{IFN-}\gamma$  by mesenchymal stromal cells

*Golay, Leukemia 2007*

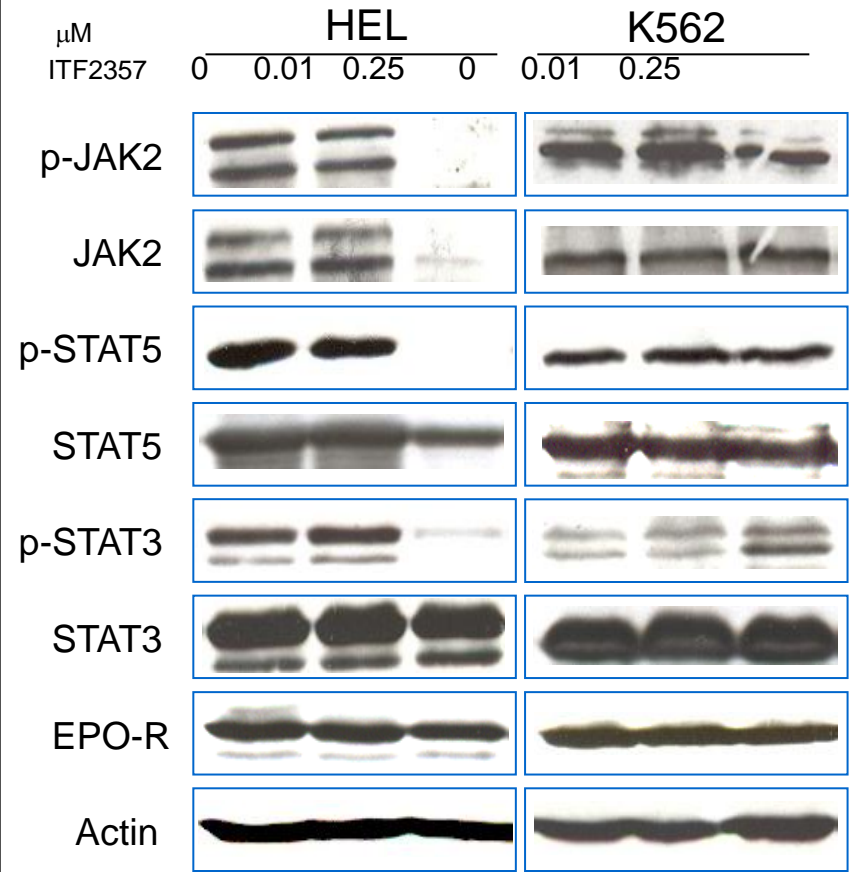


# Inhibition of EEC assay and JAK2 signal transduction by Givinostat

*Inhibition of EEC assay in JAK2<sup>V617F</sup> TE (n=7) and PV (n=6)*



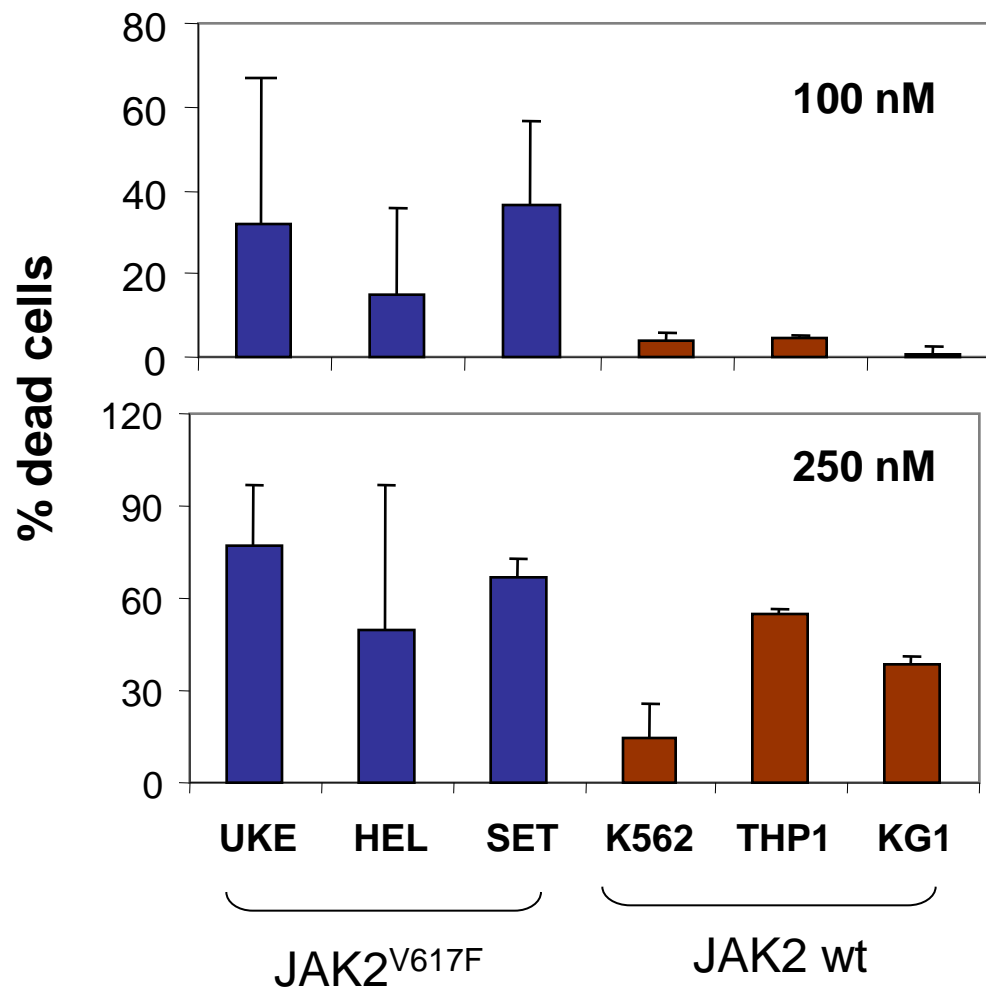
Down-modulation of JAK2<sup>V617F</sup>, pSTAT5 and pSTAT3



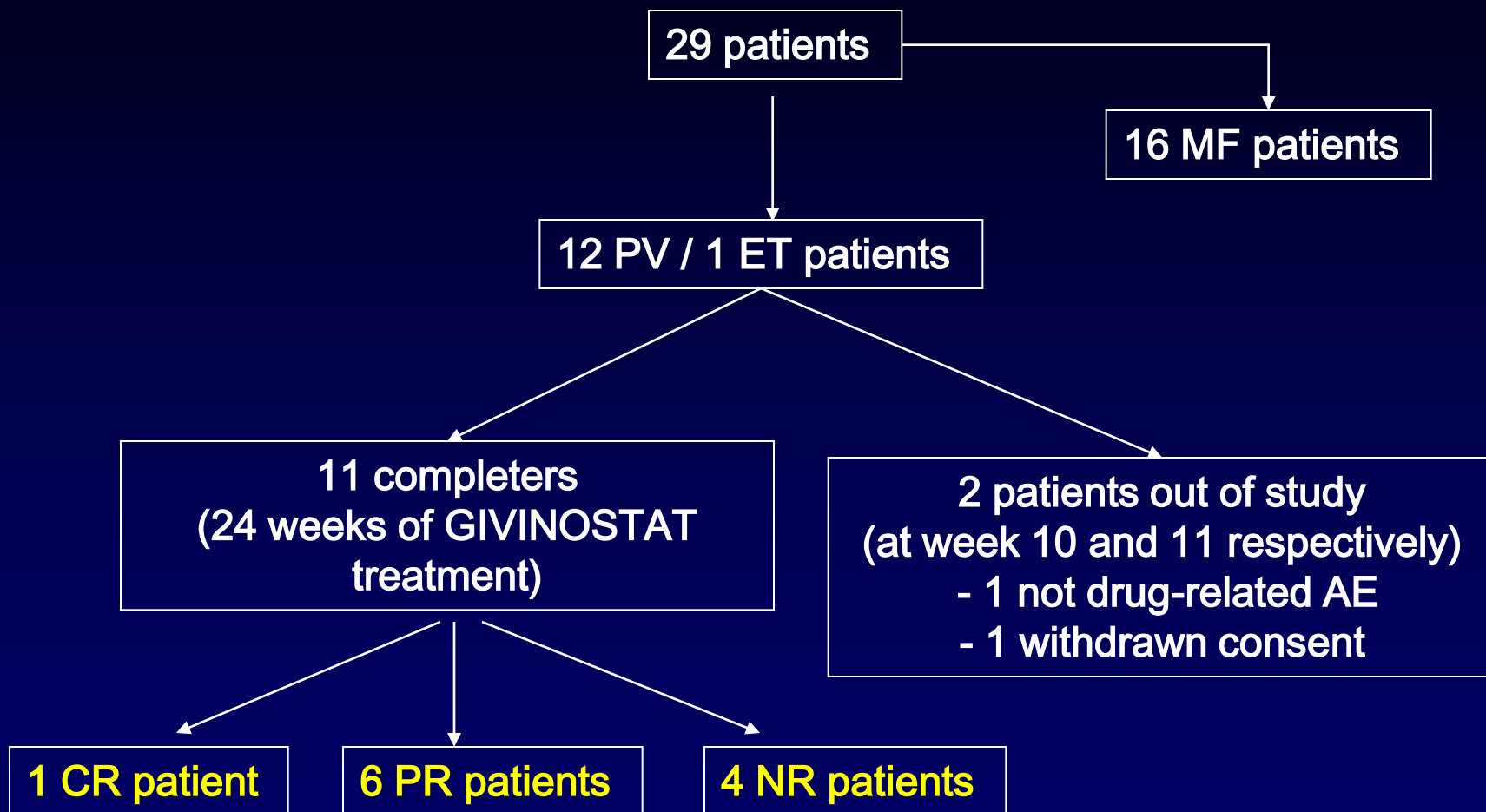


**Givinostat** modulates key hematopoietic genes and induces cell death in JAK2<sup>V617F</sup> cells from MPN patients

Amaru A et al.



# A phase II pilot study of Givinostat in Patients with JAK2<sup>V617F</sup> Positive Chronic Myeloproliferative Neoplasms



# Clinical Response in PV/ET patients

	Baseline	Week 12	Week 24
<b>Phlebotomy requirement</b>	7/13	2/12	2/11
<b>Platelets <math>\geq 450 \times 10^9/L</math></b>	<b>11/13</b>	<b>6/12</b>	<b>6/11</b>
Median (range)	865 (347-1458)	565 (279-1071)	453 (233-1602)
<b>WBC <math>\geq 10 \times 10^9/L</math></b>	<b>11/13</b>	<b>7/12</b>	<b>7/11</b>
Median (range)	16 (4.9-45)	11 (4-32)	13.3 (3.6-35)
<b>Splenomegaly</b>	8/13	3/12	3/11
<b>Pruritus</b>	11/13	2/12	1/11

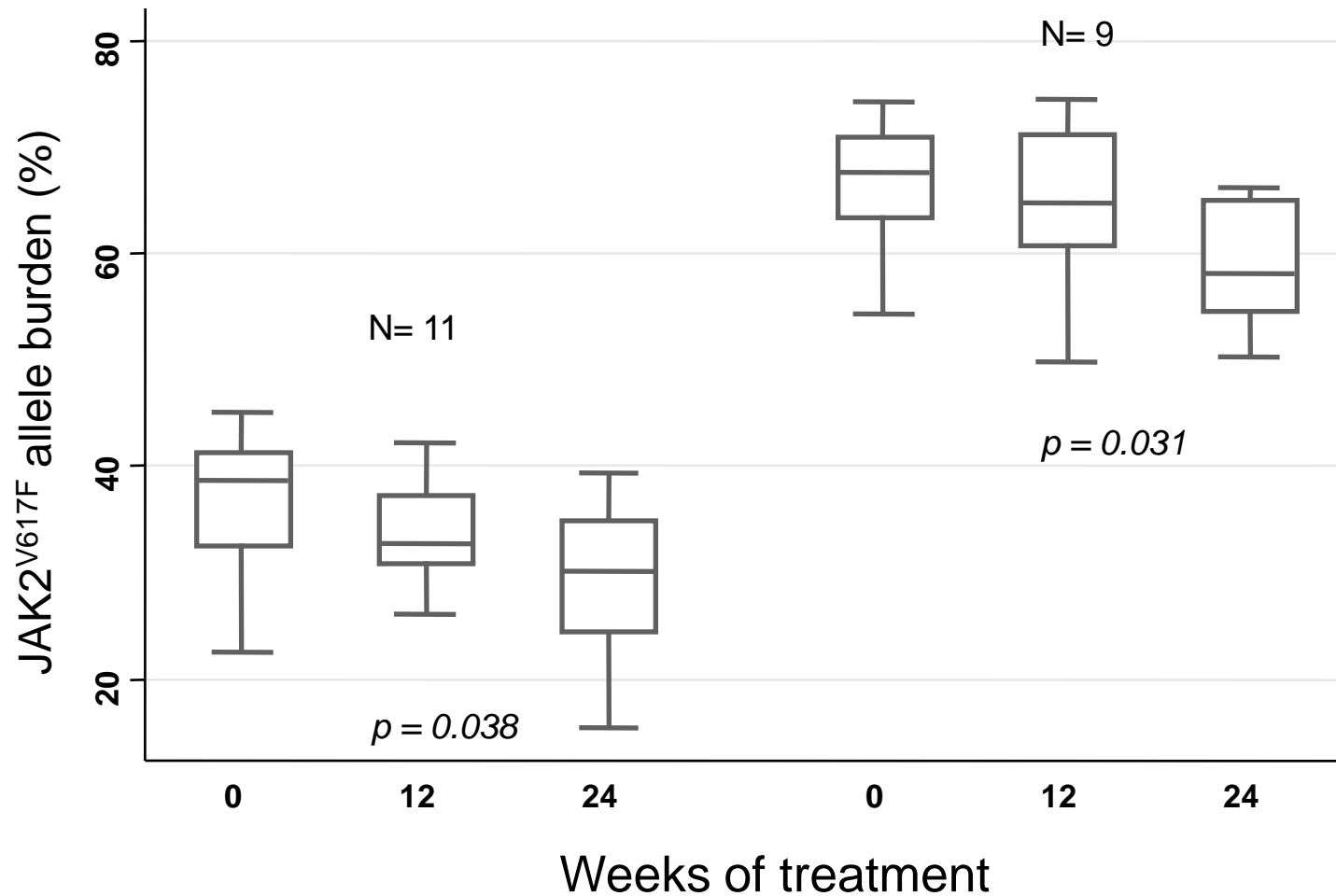
# Clinical Response in MF patients

	Week 12	Week 24
<b>Response in anemia</b>		
Complete	1/10	1/10
Partial	1/10	1/10
<b>Response in splenomegaly</b>		
Complete	0/13	0/13
Partial	3/13	3/13
<b>Response in platelets</b>		
Complete	1/5	1/5
Partial	1/5	1/5
<b>Response in WBC</b>		
Complete	0/10	0/10
Partial	1/10	1/10
<b>Response in systemic symptoms</b>	2/15	2/15

# Toxicity

ADVERSE EVENT	G1	G2	G3	TOTAL (%)
Diarrhea	9/28	7/28	1/28	17/28 (60)
Fatigue	2/28	5/28	-	7/28 (25)
Anemia	5/28		1/28	6/28 (21)
Dyspepsia/Nausea	4/28	1/28	-	5/28 (18)
Epigastric/abdominal pain	1/28	3/28	-	4/28 (14)
Weight loss	2/28	2/28	-	4/28 (14)
Skin rash	2/28	-	1/28	3/28 (11)
Thrombocytopenia	2/28	1/28	-	3/28 (11)
Anorexia	2/28	-	-	2/28 (7)
Chronic renal failure	2/28	-	-	2/28 (7)
Fever	1/28	-	1/28	2/28 (7)
Neutropenia	-	2/28	-	2/28 (7)
Hypertriglyceridemia	-	1/28	-	1/28 (3,5)
Hyperkalemia	-	-	1/28	1/28 (3,5)
Long QT	1/28	-	-	1/28 (3,5)

# JAK2<sup>V617F</sup> allele burden in PMN during treatment



# Comments

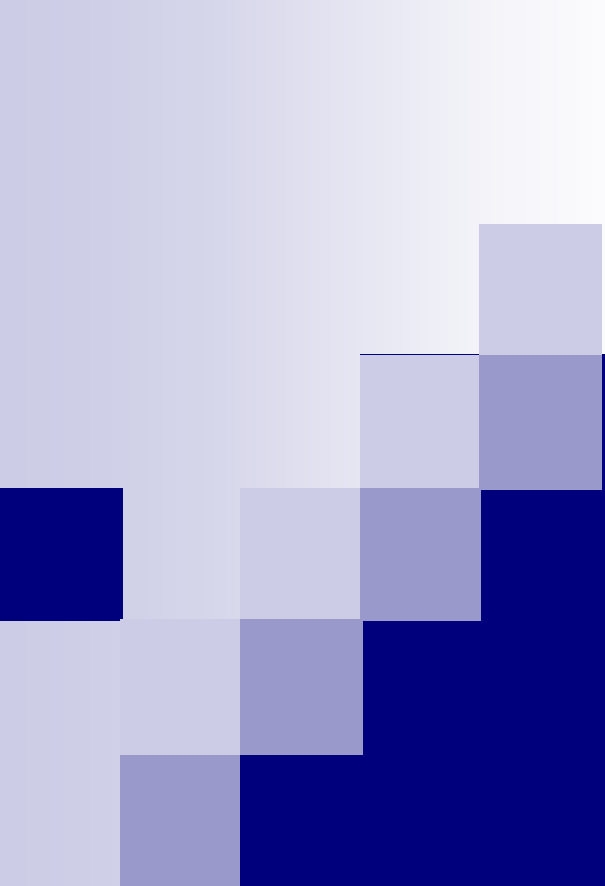
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Givinostat was **well tolerated** and could induce haematological response, particularly in PV patients.

This response was mainly seen on clinical symptoms, such as **pruritus and splenomegaly**, often resistant to conventional cytoreductive therapy with hydroxyurea

**Clinical studies of combined therapy (Givinostat and HU) may be worthwhile**

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Phase II study of the histone-deacetylase inhibitor GIVINOSTAT (ITF2357) in combination with hydroxyurea in patients with JAK2<sup>V617F</sup> positive Polycythemia Vera non-responder to hydroxyurea monotherapy.



# Study Plan

Hydroxyurea non-responder patients

HCT normalisation during the pre-study time  
(HCT = 45%)

Randomization (1 : 1)

12 Weeks

Hydroxyurea  
+

GIVINOSTAT (ITF2357) 50 mg o.d.

Hydroxyurea  
+

GIVINOSTAT (ITF2357) 50 mg b.i.d.

Primary endpoint assessment → Overall response rate

12 weeks

Response

continue

No Response

GIVINOSTAT (ITF2357) daily dose increase by 50 mg

# Conclusions

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**Several HDACi have shown significant activity in vitro and in vivo against PMF and other MPNs**

**Clinical trials are ongoing to define their place in the overall strategy of patients treatment**

**There are indications that new (and old) drugs can be combined to improve the benefit/risk ratio in MPNs: in this context, HDACi may play an important role.**

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