



SCOTTSDALE  
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# NOVEL THERAPIES IN PV AND ET

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- Clinical needs in PV and ET
- Old drugs... new data :
  - Alpha Interferon: PVN1 & MD Anderson (phase 2)
  - Anagrelide: ANAHYDRET (phase 3)
- New drugs :
  - JAK inhibitors: INCB18424, CEP701
  - HDAC inhibitors: Givinostat, Vorinostat
  - Other inhibitors
- Conclusion

# Clinical needs in PV and ET

- International experts, European LeukemiaNet

Tiziano Barbui, Giovanni Barosi, Gunnar Birgegard, Francisco Cervantes, Guido Finazzi, Martin Grieshammer, Claire Harrison, Hans Carl Hasselbalch, Rudiger Hehlmann, **Ronald Hoffman**, Jean-Jacques Kiladjian, Nicolaus Kröger, **Ruben Mesa**, Mary F. Mc Mullin, **Animesh Pardanani**, Francesco Passamonti, Alessandro M. Vannucchi, Andreas Reiter, **Richard T. Silver**, **Srdan Verstovsek**, **Ayalew Tefferi**

# Clinical needs in PV and ET

- International experts, European LeukemiaNet
  - Avoid first occurrence or recurrence of thrombosis and hemorrhage
  - Minimize the risk of hematological transformation
  - Control systemic symptoms
  - Manage risky situations (surgery, pregnancy,...)

# Old drugs... new data

- pegylated Interferon- $\alpha$  2a
  - PVN1 (phase 2)
  - MD Anderson (phase 2)
- Anagrelide
  - ANAHYDRET (phase 3)

# Peg-IFN $\alpha$ -2a - PVN1 study

- Multicenter, phase 2 study of peg-IFN $\alpha$ -2a in PV
- 40 PV patients included
- **Haematological response** at 12 months : 100%, including 91% CR
- **Molecular response:**
  - Diminution %V617F in 26/29 (90%)
  - 7 patients (24%) in molecular CR
- **Tolerance:** 3 withdrawals for toxicity (8%) during the first year



## **Update - 35 patients, FU 55 months**

**Peg-IFN discontinuations: n=19 (54%)**

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**9 (26%) for toxicity**, after a median time on peg-IFN of 12 months

immunological disorders (n=2, auto-Abs)

allergy (n=2)

neutropenia (n=1) after 9 months

depression, fatigue (n=1) after 14 months

peripheral neuropathy (n=1) after 12 months

liver enzyme elevation (n=1) after 12 months

arthralgia (n=1) after 27 months

## Peg-IFN discontinuations

### Off-study use

**66 patients:** 14 PV, 16 ET, 6 PMF, 30 SVT with MPN

**13 (20%) discontinuations:**

3/14 PV (21%)

2/16 ET (12%)

2/6 PMF (33%)

7/30 SVT (23%)

Fatigue:

6 (46%)

Depression, mood:

4 (30%)

Arthralgia, myalgia:

2 (15%) (*Sjögren + myositis in 1*)

Immune thrombocytopenia:

1 (8%) (*after 10*)

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## Update - 35 patients, FU 55 months

### Peg-IFN discontinuations: n=19 (54%)

**9 (26%) for toxicity**, after a median time on peg-IFN of 12 months

### **8 (23%) for sustained hematologic CR**

median peg-IFN therapy: 31.5 months (15 - 43)

7/8 still in hemato-CR, 1 PR (platelets)

7/8 still off cytoreduction, 1 on HU

7 patients (20%) off therapy for 20 mos median (12 - 43):

all in hem-CR

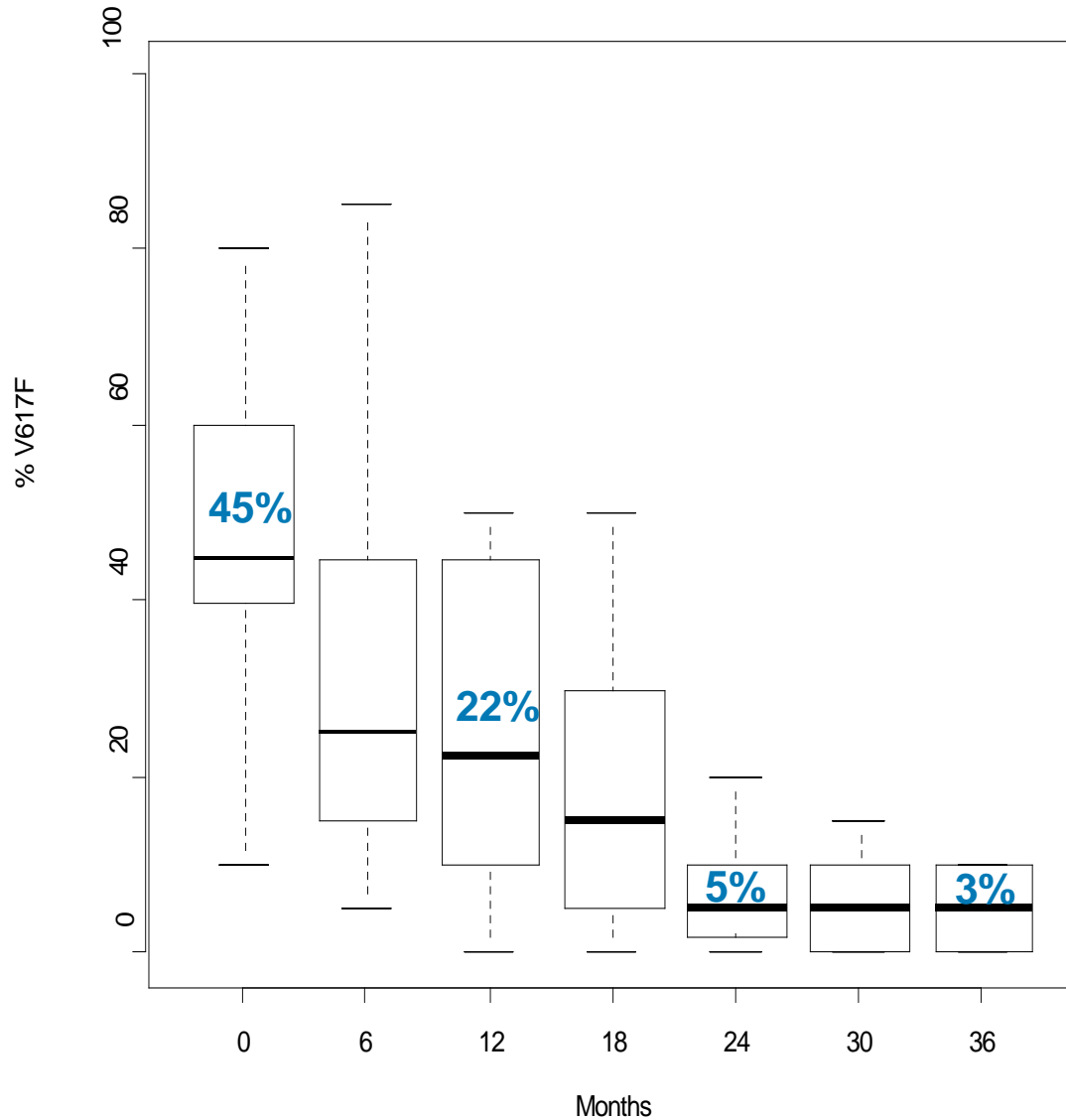
1 also in mol-CR for 35+ months

2 had achieved mol-CR for 6 months, but

relapsed

last %V617F: 5% in 4, 10% in 1, 20% in 1

# RESULTS - molecular response



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## *Complete Molecular Responses:*

- ✓ 10/29 (35%) patients

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### *Complete Molecular Responses:*

- ✓ 10/29 (35%) patients
- ✓ 4 still in molecular-CR
  - 48 months (on peg-IFN)
  - 40 months (off cytoreductive therapy for 26 months)
  - 25, and 26 months (switched to HU)

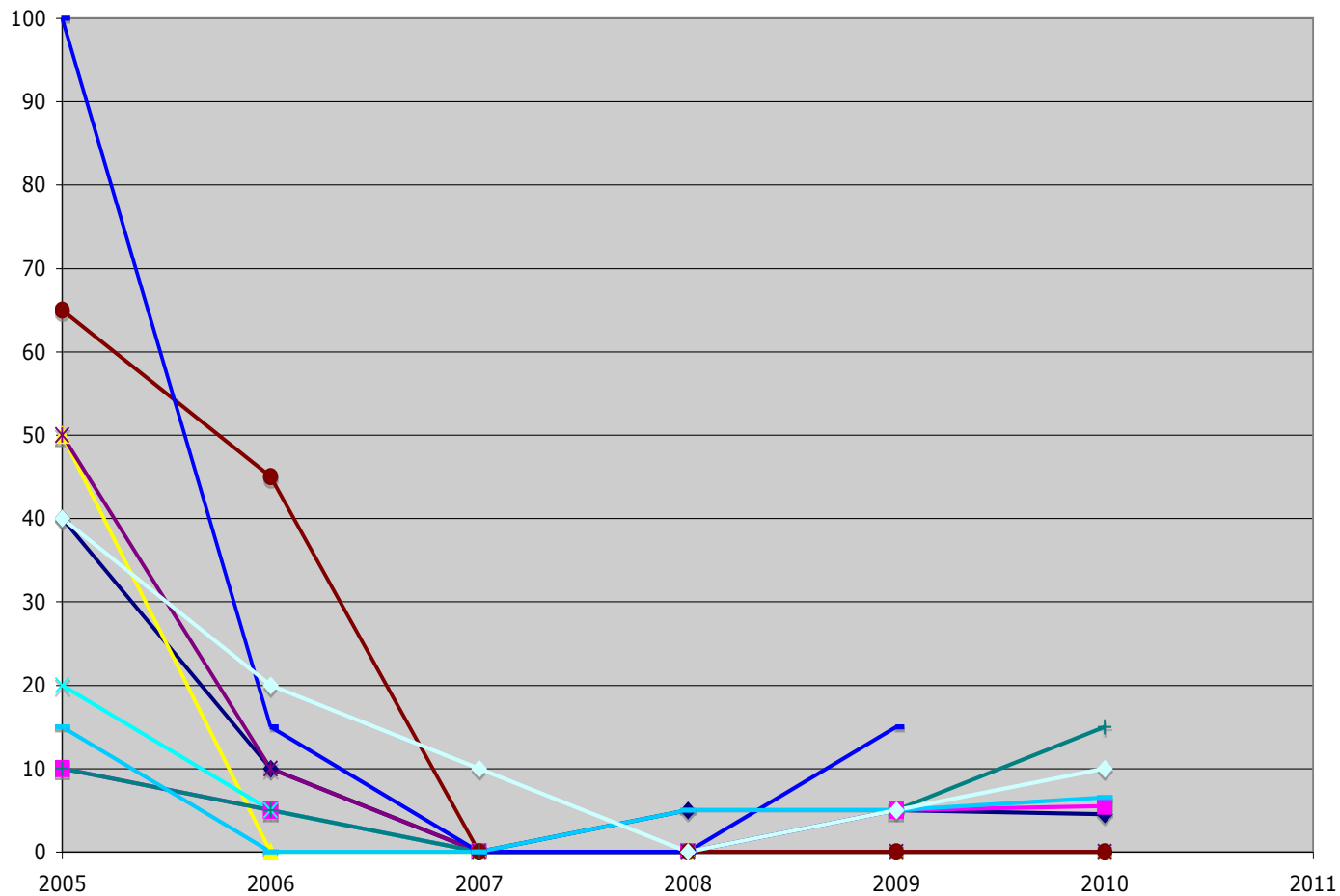
## RESULTS - molecular response

### *Complete Molecular Responses:*

- ✓ 10/29 (35%) patients
- ✓ 4 still in molecular-CR
- ✓ Molecular relapse in 6 patients, all still in hem-CR

# RESULTS - molecular response

## *Complete Molecular Responses:*



Patients in  
molecular CR

**0**

**2**

**9**

**8**

**4**

**4**

# New genes: the molecular era

MPL

LNK

TET2

EZH2

~~JAK2~~

CBL

ASLX1

IKZF1

IDH1 / IDH2

## Conclusion: peg-IFN $\alpha$ -2a

- ✓ No new safety issues after long term use of IFN, but:
  - ✓ Fatigue and psychological changes are the most frequent causes of discontinuation (80%):  
Prevention? Maintenance therapy at the lowest possible dose?
  - ✓ Immunologic abnormalities in about 20% of patients, including asymptomatic auto-Abs but also clinical manifestations: monitoring?

# Peg-IFN $\alpha$ -2a - M.D. Anderson

- ✓ 40 PV, 39 ET
- ✓ Median follow up : 21 months
- ✓ Discontinuation: n=17 (22%), including **8 (10%) AE-related**

|                    | PV (n=40)  | ET (n=39)  |
|--------------------|------------|------------|
| CR                 | 70%        | 76%        |
| PR                 | 10%        | 5%         |
| No response        | 20%        | 19%        |
| %V617F baseline    | 64% (n=35) | 23% (n=16) |
| Molecular response | 54%        | 38%        |
| Molecular CR       | 14% (n=5)  | 6% (n=1)   |

# Old drugs... new data

- pegylated Interferon- $\alpha$  2a
  - PVN1 (phase 2)
  - MD Anderson (phase 2)
- **Anagrelide**
  - ANAHYDRET (phase 3)

# Anagrelide - ANAHYDRET study

- Phase 3, HU vs. *anagrelide*
- *double blind*
- *ASA not recommended*
- *ET according to WHO*
- *newly diagnosed*
- *non inferiority* : platelets, WBC, Hb, vascular events
- *258* high risk ET patients
- Median FU: 2,1 years
- BMB review : ET/WHO confirmed in 82 %
- JAK2V617F+ : 52 %

# Anagrelide - ANAHYDRET study

|                               | Ana (n=122) | HU (n=136) |
|-------------------------------|-------------|------------|
| <b>Events :</b>               | 59          | 54         |
| Arterial maj.                 | 5           | 7          |
| Venous maj.                   | 2           | 4          |
| Hemorrh. maj.                 | 3           | 2          |
| Arterial min.                 | 28          | 25         |
| Hemorrh. min.                 | 18          | 13         |
| <b>JAK2+ patients :</b>       | 20 (37%)    | 19 (36%)   |
| Arterial                      | 5           | 4          |
| Venous                        | 1           | 3          |
| Hemorrh.                      | 3           | 1          |
| <b>Treatment discontin. :</b> | 25          | 20         |
| AE                            | 17          | 13         |
| Failure                       | 8           | 7          |

**Non inferiority of anagrelide / HU in WHO-ET**

# Novel therapies

- JAK inhibitors
  - INCB 18424
  - CEP 701
- HDAC inhibitors
  - givinostat
  - vorinostat
- Other inhibitors

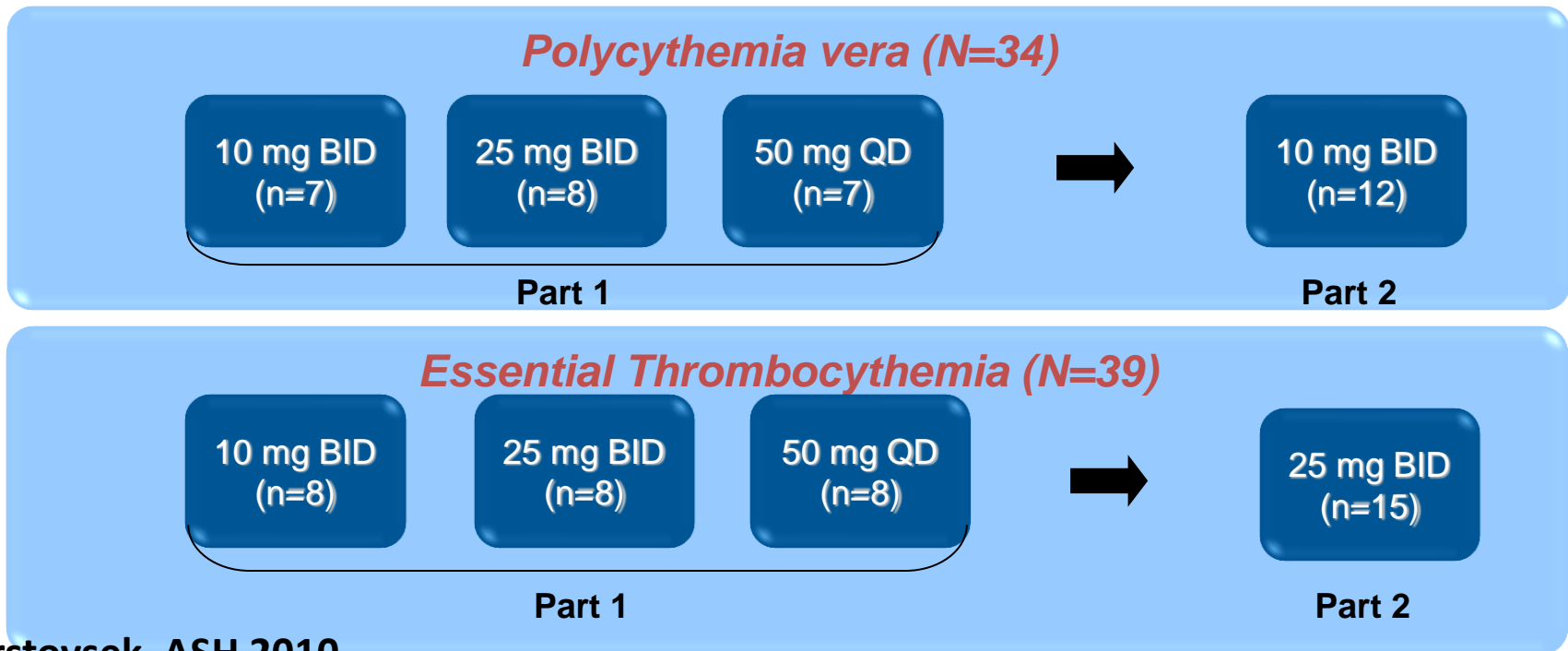
# JAK inhibitors

- Shared characteristics
  - PO
  - Not specific against V617F mutated form
  - Not specific against JAK2 (activity against other “JAK family” kinases)
  - Good short-term tolerance
  - Rapid “anti-inflammatory” effect

# Phase II Study of INCB 18424 in Patients with Advanced ET and PV

## Eligibility Criteria:

- Refractory or intolerant to hydroxyurea (HU) or HU contraindicated
- PV: Hct > 45% OR phlebotomy 2 times in last 6 months, with at least one phlebotomy in last 3 months
- ET: Platelets > 650 x 10<sup>9</sup>/L unless on therapy



# Overall Safety in PV

| Treatment-related AEs* | All Grades; n (%) | Grade 3; n (%) |
|------------------------|-------------------|----------------|
| Anemia                 | 25 (74)           | 0              |
| Thrombocytopenia       | 10 (29)           | 2 (6)          |
| Leukopenia             | 5 (15)            | 0              |
| Weight increase        | 5 (15)            | 0              |
| Diarrhea               | 3 (9)             | 0              |
| Hyperuricemia          | 3 (9)             | 0              |
| Insomnia               | 3 (9)             | 0              |
| Palpitations           | 3 (9)             | 0              |

\*Occurring in at least 3 subjects; at least 'possibly' related

- ✓ No treatment-related Grade 4 AEs have occurred on study
- ✓ Hematologic AEs are generally reversible and managed with dose reduction or temporary interruption

# Overall Safety in ET

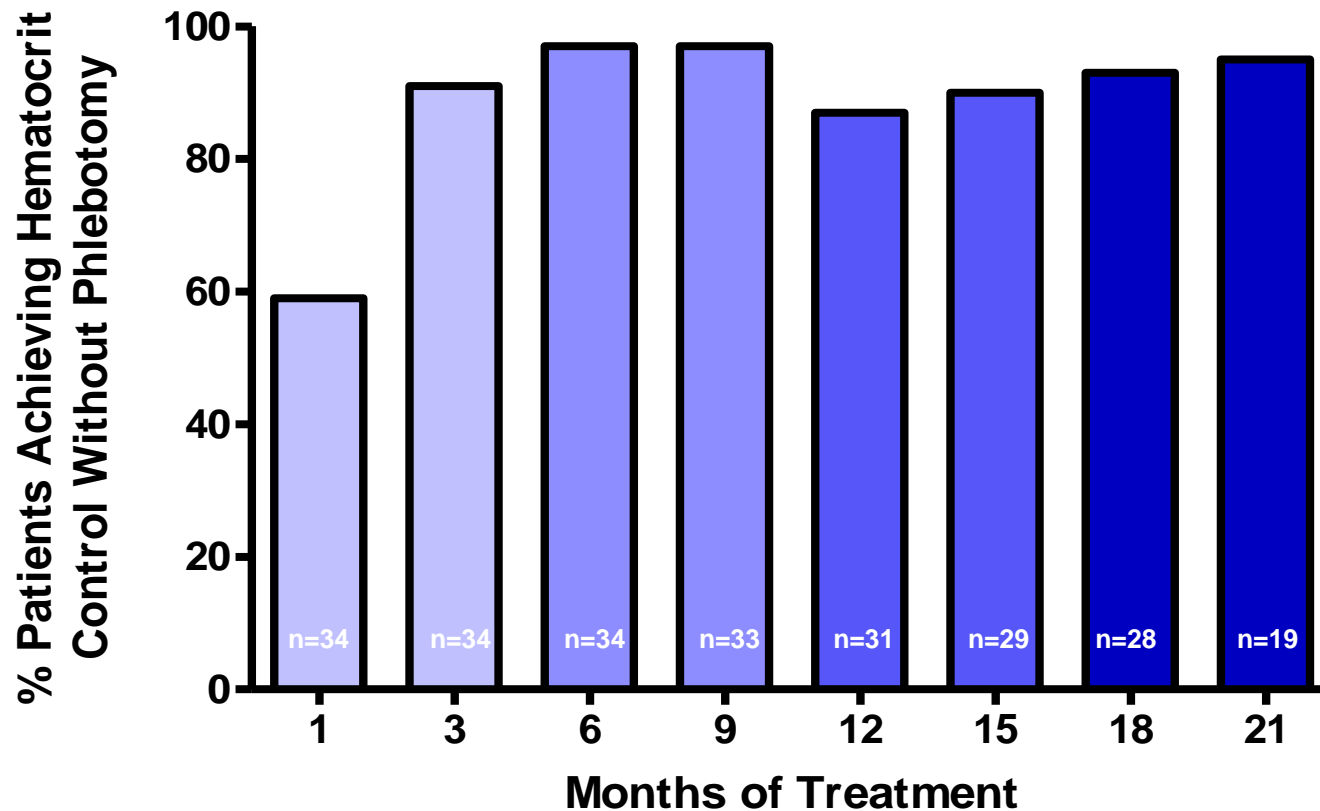
| Treatment-related AEs* | All Grades; n (%) | Grade 3; n (%) |
|------------------------|-------------------|----------------|
| Anemia                 | 29 (74)           | 0              |
| Weight increase        | 9 (23)            | 0              |
| Herpes zoster          | 2 (5)             | 0              |
| Hyperuricemia          | 2 (5)             | 0              |
| Leukopenia             | 2 (5)             | 2 (5)          |
| Pain in extremity      | 2 (5)             | 0              |
| Palpitations           | 2 (5)             | 0              |

\*Occurring in at least 2 subjects; at least 'possibly' related

- ✓ No treatment-related Grade 4 AEs have occurred on study
- ✓ Hematologic AEs are generally reversible and managed with dose reduction or temporary interruption

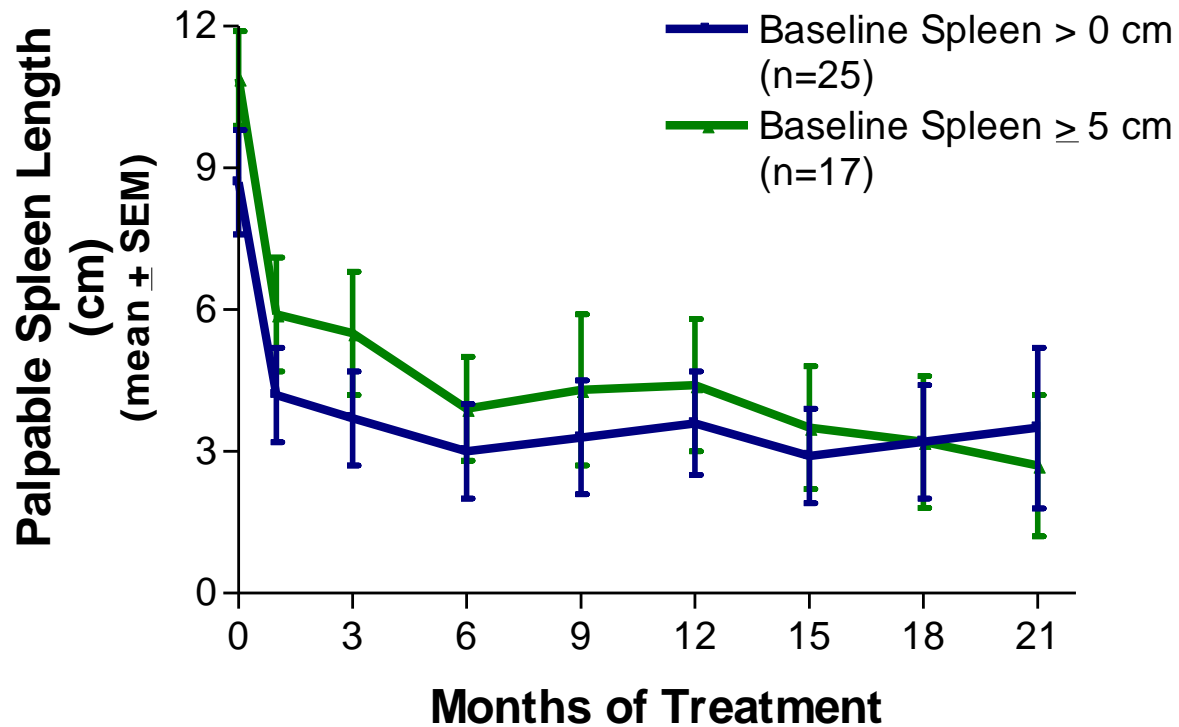
# PV Results: Hematocrit Control (Hct $\leq$ 45%) without Phlebotomy

97% of patients have achieved hematocrit  $\leq$  45%  
without the use of phlebotomy



# PV Results: Splenomegaly

## Rapid and Durable Reductions in Palpable Spleen Length



## **PV Results:**

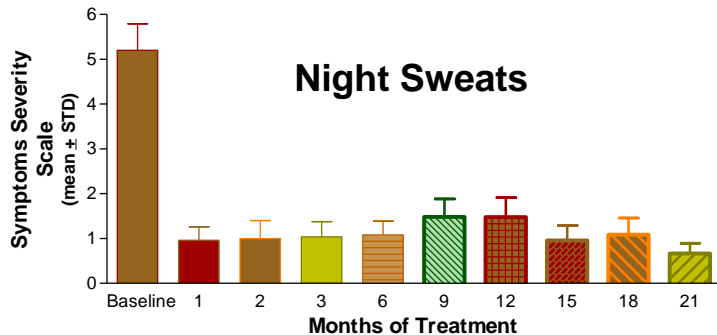
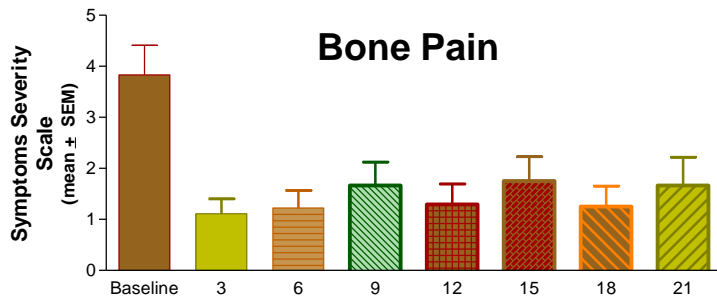
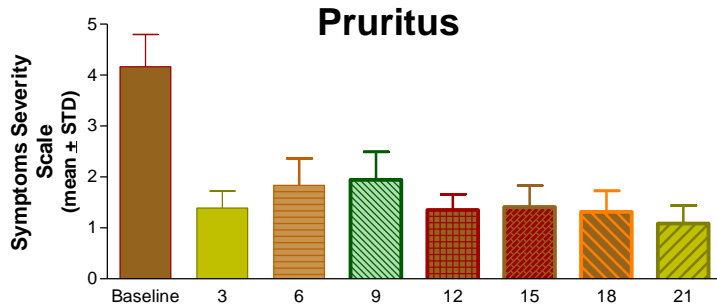
**Rapid and Durable Reductions in Palpable Spleen Length**

**Rapid and Durable Reductions in WBC counts**

**Rapid and Durable Reductions in Platelet counts**

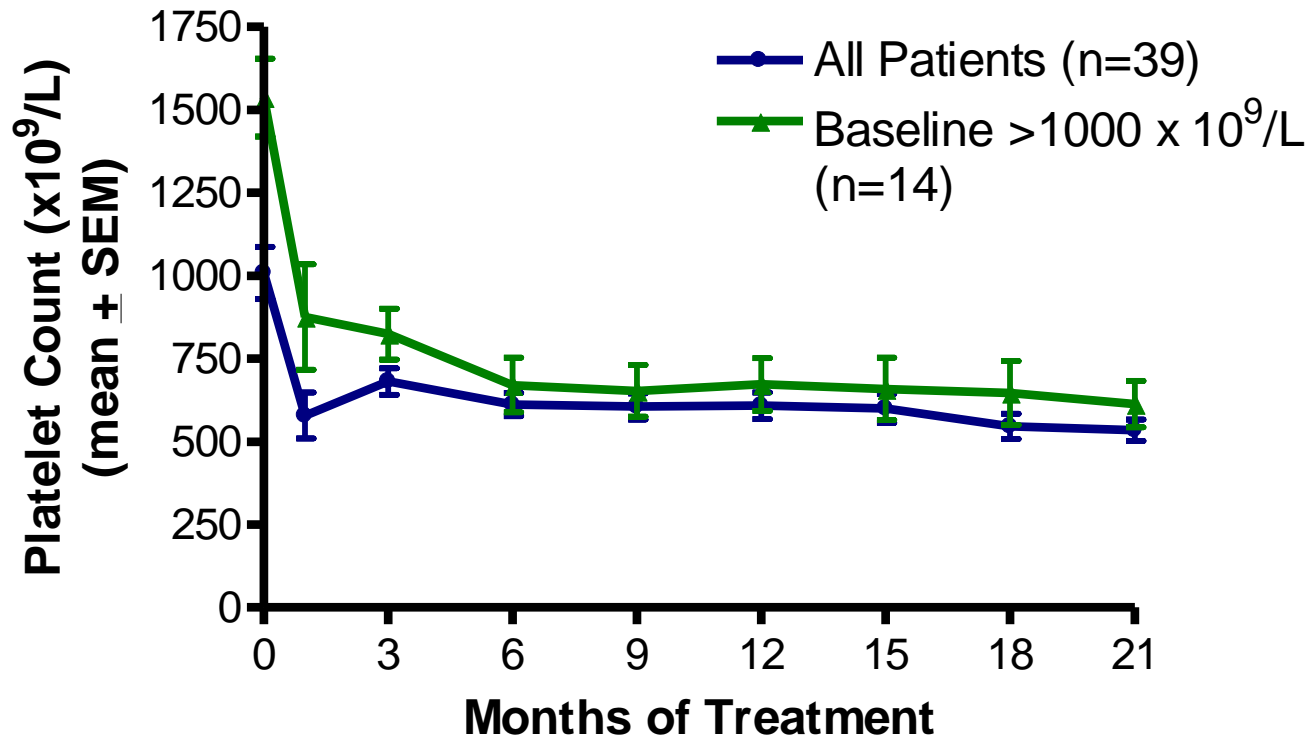
# PV Results: Symptoms

## Mean Symptom Severity Scores



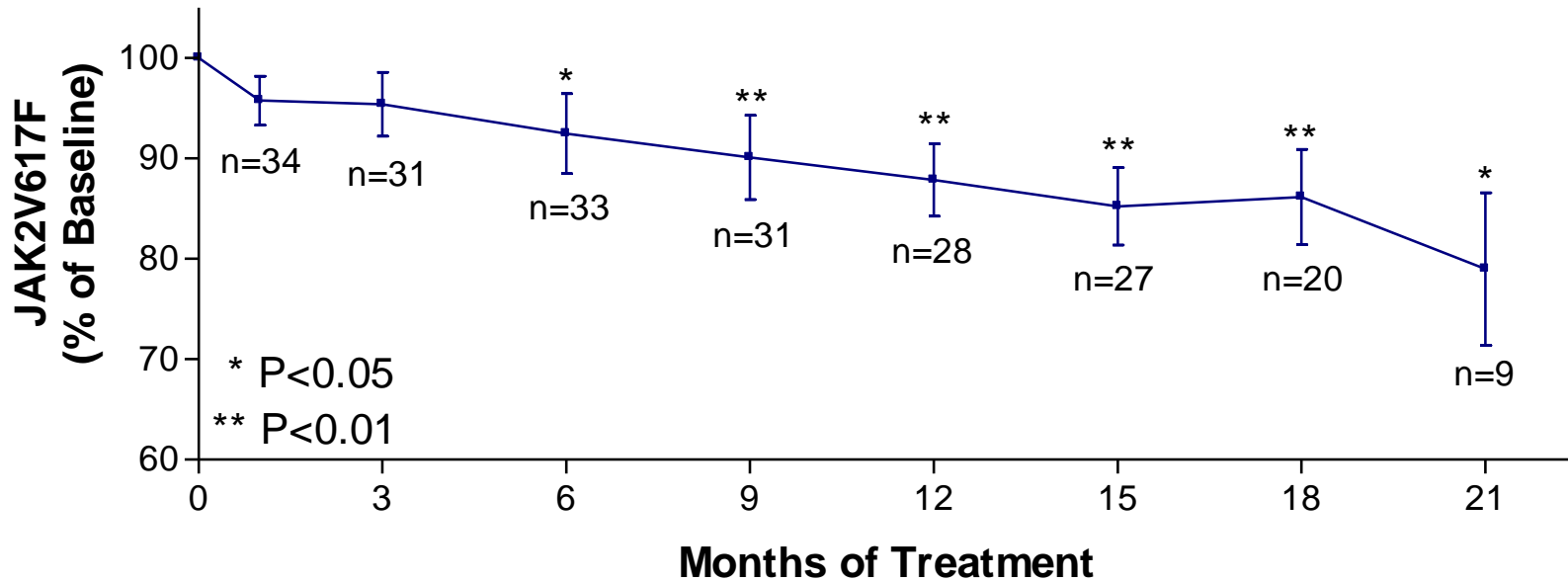
- Rapid improvements in patient reported symptom scores observed
- Responses have been durable in the majority of responding patients through the last follow-up visit

# Platelet Count Reduction in ET



# JAK2 V617F Allele Burden

## JAK2V617F % Change from Baseline in Advanced PV Patients



# INCB 18424 in ET and PV: Conclusions

- INCB 18424 is well tolerated in ET and PV patients refractory or intolerant to HU
- Durable clinical benefits in advanced ET and PV patients:
  - Resolution of splenomegaly in high percentage of patients
  - Phlebotomy independence in nearly all PV patients
  - Normalization or improvement in hematological parameters in most patients
  - Marked symptomatic benefits in both ET and PV
- Results support further development in ET and PV

# JAK inhibitors - CEP 701 (lestaurtinib)

# JAK inhibitors - CEP 701 (lestaurtinib)

- multi-kinase inhibitor (anti-flt3)
- 27 PV and 12 ET
- 15 patients have completed 18 w of treatment
  - Spleen size reduction
  - Moderate decrease phleb., little effect on WBC and plt (even increased)
  - Moderate decrease in %V617F
  - 6 patients experienced thrombosis (4 venous, 2 arterial)
  - GI toxicity

# Novel therapies

- JAK inhibitors
  - INCB 18424
  - CEP 701
- **HDAC inhibitors**
  - givinostat
  - vorinostat
- Other inhibitors

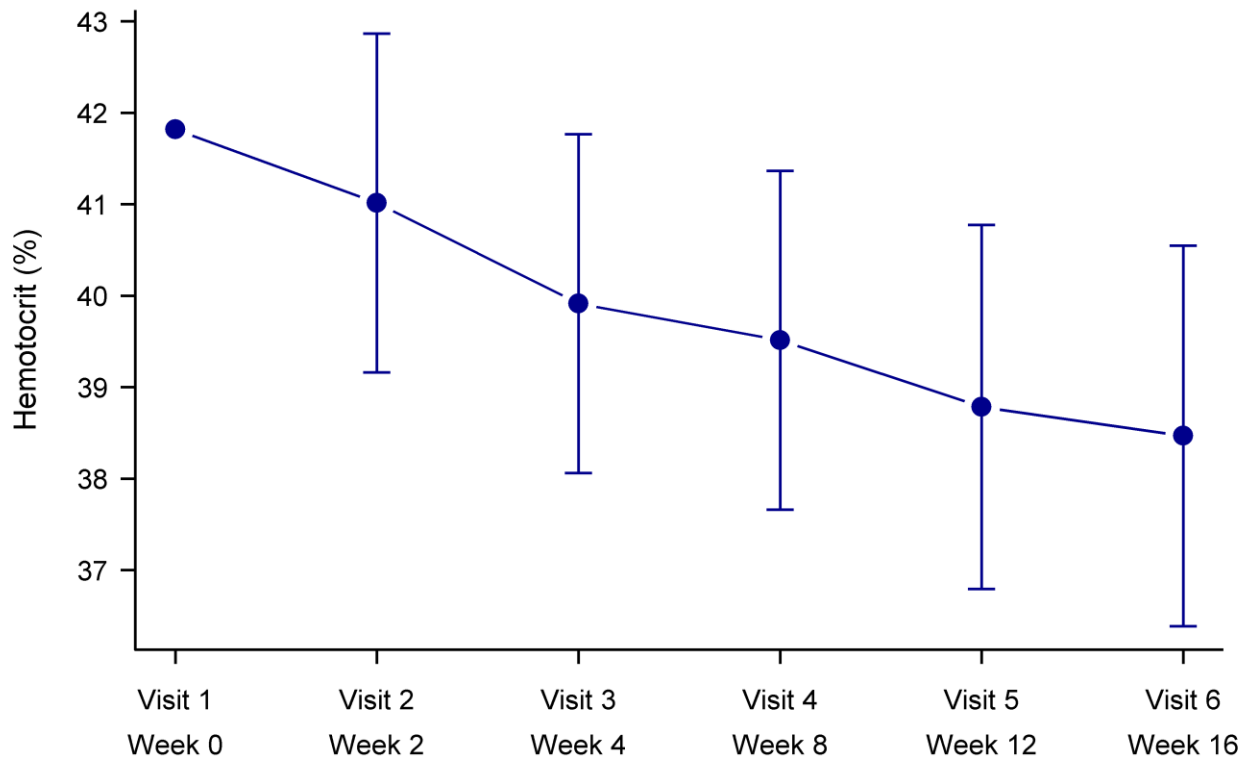
# HDAC inhibitors - Givinostat (ITF2357)

- Tested in other hematological malignancies
- Phase 2, 12 PV and 1 ET patients
  - Grade 2 GI toxicity in most patients
  - Response (24 weeks): 1 CR, 6 PR, 4 failures, 2 withdrawals
  - Reduction spleen size in 75% patients
  - Improvement of pruritus and symptoms
- New study in patients resistant to HU
- Combination of HU + givinostat

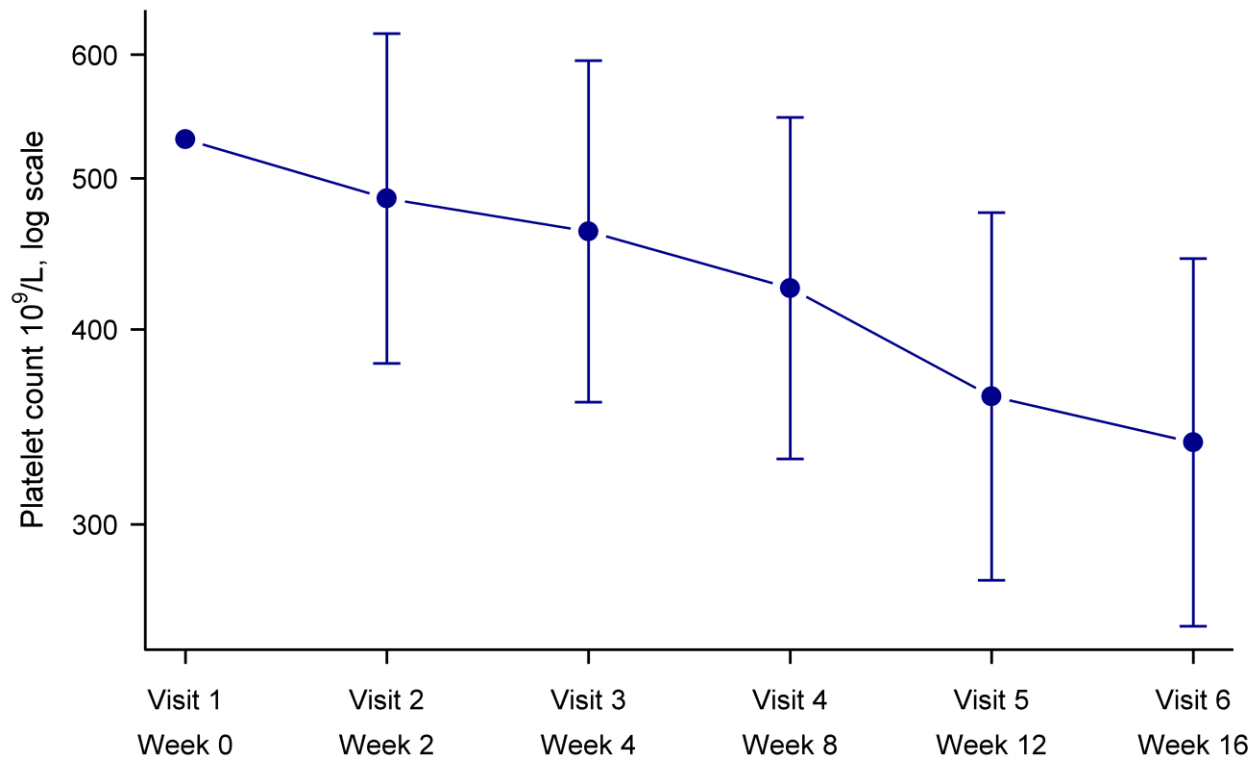
## HDAC inhibitors - Vorinostat (MK 0683)

- Phase 2 study of efficacy and safety in PV and ET (Denmark , UK, Belgium, The Netherlands, Sweden)
- 20 PV and ET patients included
- Reduction in phlebotomy requirement, reduction/normalization of WBC and platelet counts, pruritus
- Toxicity:
  - hair loss (3 patients)
  - GI toxicity (1 patient, dose reduction)
  - Neuropathy (1 patient, stop therapy)

# HDAC inhibitors - Vorinostat (MK 0683)



# HDAC inhibitors - Vorinostat (MK 0683)



# Novel therapies

- JAK2 inhibitors
  - INCB 18424
  - CEP 701
- HDAC inhibitors
  - givinostat
  - vorinostat
- **Other inhibitors...**

# Conclusion

- New clinical studies will help assess efficacy and safety of new therapeutic agents in PV and ET
- It is too early to properly evaluate the role of these novel therapies in PV and ET
- Interesting new results have been observed in studies using “good old drugs”, that may help better define subgroups of patients who could benefit of these drugs

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