

# Focus on aggressive polycythemia vera



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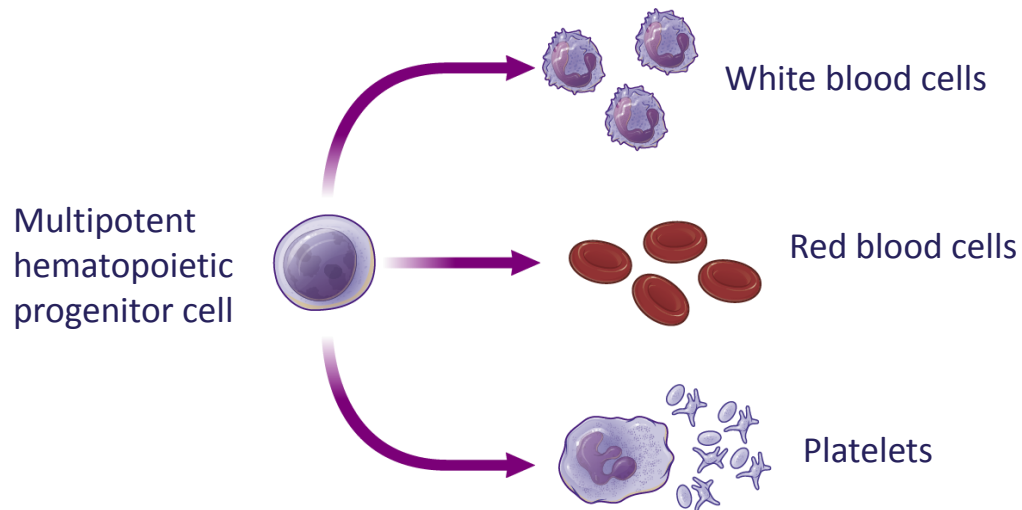
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## Disclosure

*These slides were developed by Incyte Corporation (Wilmington, DE) from an interview with Jerry L. Spivak, MD, conducted in May 2015. Dr Spivak has served as a consultant for Incyte Corporation and was compensated for his participation.*

## Introduction to polycythemia vera (PV)

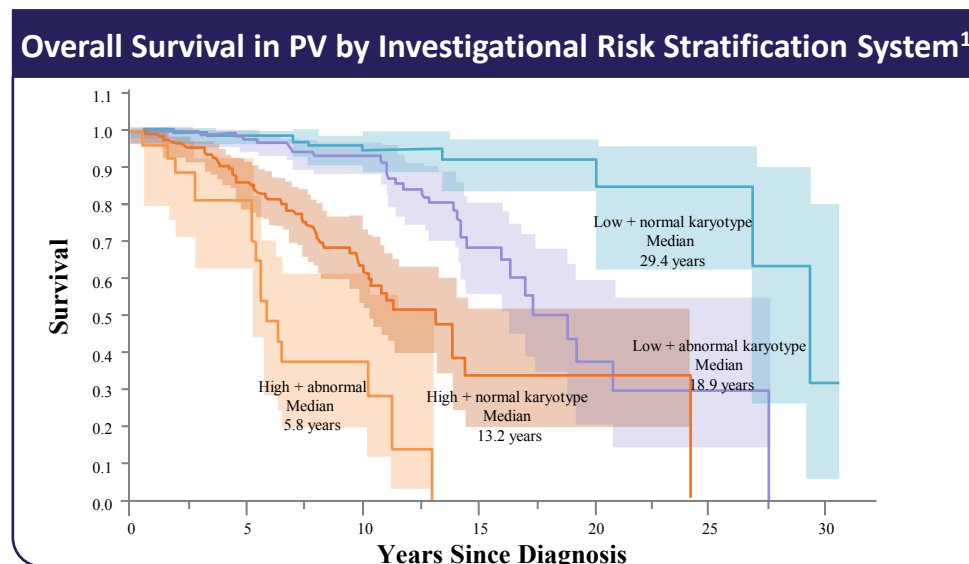
- A clonal disorder involving a multipotent hematopoietic progenitor cell<sup>1</sup>
- Characterized by the accumulation of phenotypically normal red blood cells, white blood cells, and platelets, alone or in combination, in the absence of a definable stimulus<sup>1</sup>



**Reference:** 1. Spivak JL. *Blood*. 2002;100(13):4272-4290.

## There is an aggressive subtype of PV

- One study found a subset of patients with PV with a much lower median survival rate, estimated at 5.8 years<sup>1</sup>
- This is consistent with the median survival in primary myelofibrosis<sup>2</sup>



Risk-stratified survival that considers karyotype in 631 patients with PV.

PV, polycythemia vera.

**References:** 1. Tefferi A et al. *Leukemia*. 2013;27(9)(suppl):1874-1881. 2. Tefferi A et al. *Blood*. 2014;124(16):2507-2513.

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## No guidelines exist for identifying PV with an aggressive course

- Patients with PV who are aged <60 years and have no history of thrombosis are generally considered “low risk”<sup>1</sup>
- This stratification is designed to estimate the likelihood of thrombotic complications in PV, but not survival<sup>1</sup>
- The phenotypic variability of PV provides some clues to outcomes<sup>2</sup>
- In addition, a study using gene expression profiling of CD34+ hematopoietic stem cells was able to accurately identify a subset of patients with aggressive PV<sup>3</sup>

**References:** 1. Tefferi A et al. *Am J Hematol*. 2015;90(2):163-173. 2. Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE. 3. Spivak JL et al. *N Engl J Med*. 2014;371(9):808-817.

## The phenotypic variability of PV

- PV may present as erythrocytosis, leukocytosis, or thrombocytosis, alone or in combination

Presenting Blood Counts at Time of Diagnosis of PV	
Isolated erythrocytosis	18% <sup>1</sup>
Isolated leukocytosis	Case study <sup>2</sup>
Isolated thrombocytosis	7%-20% <sup>3,4</sup>
Erythrocytosis and thrombocytosis	16%-30% <sup>5,6</sup>
Erythrocytosis and leukocytosis	13%-31% <sup>1,5,6</sup>
Erythrocytosis, thrombocytosis, and leukocytosis	40% <sup>1</sup>

PV, polycythemia vera.

**References:** 1. Szur L et al. *Q J Med.* 1959;28:397-424. 2. Taylor KM et al. *Leukemia.* 1989;3(6):419-422. 3. Moliterno AR et al. *Exp Hematol.* 2008;36(11):1480-1486. 4. Jantunen R et al. *Ann Hematol.* 1999;78(5):219-222. 5. Berglund S et al. *Eur J Haematol.* 1992;48(1):20-26. 6. Berlin NI. *Semin Hematol.* 1975;12(4):339-351.

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## Isolated erythrocytosis in PV

- In our practice, isolated erythrocytosis is seen in fewer than 20% of cases of PV<sup>1,2</sup>
- Excess red blood cell production is readily controlled by periodic phlebotomy, which immediately<sup>3,4</sup>:
  - reduces erythrocyte mass
  - lowers blood viscosity

### Threshold for Erythrocytosis<sup>5</sup>



Females: >16.5 g/dL

Males: >18.5 g/dL

**References:** 1. Szur L et al. *Q J Med.* 1959;28:397-424. 2. Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE. 3. Segel N et al. *Clin Sci.* 1967;32(3):527-549. 4. Dameshek W. *Blood.* 1968;32(3):488-491. 5. Tefferi A et al. *Leukemia.* 2008;22(1):14-22.

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## Leukocytosis in PV

- While uncommon, isolated leukocytosis can be the presenting manifestation of PV<sup>1</sup>
- In the author's experience, a minor degree of leukocytosis has no clinical significance and requires no therapy in asymptomatic patients with uric acid >9 mg/dL<sup>2</sup>
- Progressive leukocytosis is a harbinger of extramedullary hematopoiesis or disease acceleration and can thus serve as a guide to disease control

### Threshold for Leukocytosis<sup>3</sup>



>10 × 10<sup>9</sup>/dL

**References:** 1. Taylor KM et al. *Leukemia*. 1989;3(6):419-422. 2. Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE. 3. Barosi G et al. *Blood*. 2013;121(23):4778-4781.



## Isolated thrombocytosis in PV

- Occurs in 7% to 20% of patients with PV (particularly women)<sup>1,2</sup>
- PV should be considered in the differential diagnosis of isolated thrombocytosis<sup>3</sup>
- Thrombocytosis in PV is associated with transient microvascular blockage manifested by erythromelalgia<sup>4,5</sup> or a constellation of neurologic symptoms that include intractable migraine<sup>6</sup>
  - These can be reversed or prevented by aspirin-induced platelet inactivation or a reduction in the platelet count<sup>7,8</sup>

### Threshold for Thrombocytosis<sup>9</sup>



>400 × 10<sup>9</sup>/dL

**References:** 1. Moliterno AR et al. *Exp Hematol*. 2008;36(11):1480-1486. 2. Jantunen R et al. *Ann Hematol*. 1999;78(5):219-222. 3. Spivak JL. Interview. May 20, 2015. Incyte Corporation, Wilmington, DE. 4. Edwards EA et al. *JAMA*. 1970;214(8):1463-1467. 5. Michiels JJ. *Semin Thromb Hemost*. 1997;23(5):441-454. 6. Michiels JJ et al. *Neurology*. 1993;43(6):1107-1110. 7. van Genderen PJ et al. *Thromb Haemost*. 1995;73(2):210-214. 8. Rinder HM et al. *Blood*. 1998;91(4):1288-1294. 9. Barosi G et al. *Blood*. 2013;121(23):4778-4781.

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## Erythrocytosis, leukocytosis, and thrombocytosis in PV

- Approximately 40% of patients with PV present with hyperproliferation of all 3 cell lines<sup>1</sup>
  - This form of the disease is generally more aggressive and frequently associated with splenomegaly and constitutional symptoms<sup>2</sup>

**References:** 1. Szur L et al. *Q J Med.* 1959;28:397-424. 2. Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE.

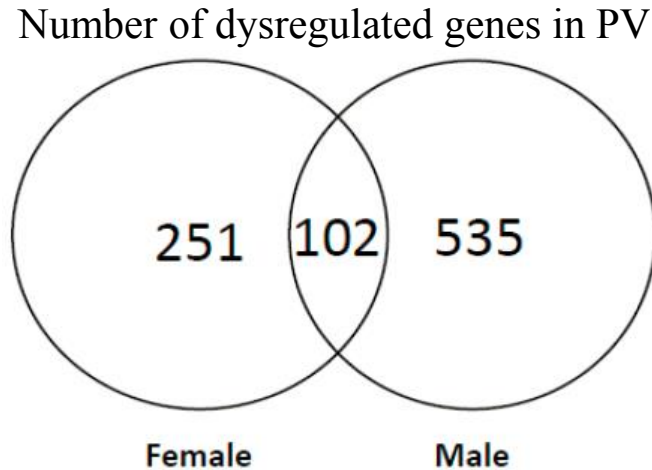
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## The genetics of high-risk patients

- A study suggests that gene expression profiling may make it possible to identify the subset of patients with aggressive PV<sup>1</sup>
  - These patients might benefit from early intervention before myelofibrosis or marrow failure ensues
- Most previous gene expression studies were performed with granulocytes and provided some diagnostic but no prognostic information
- The new study analyzed gene expression in CD34+ peripheral-blood hematopoietic stem cells using oligonucleotide microarray technology after correcting for potential confounding by sex<sup>1</sup>

**Reference:** 1. Spivak JL et al. *N Engl J Med.* 2014;371(9):808-817.

## Dysregulated genes in men and women with PV



Adapted with permission from Massachusetts Medical Society.

- Men with PV had twice as many upregulated or downregulated genes as women with PV, but there was a core of 102 genes that were consistently dysregulated in the disease process<sup>1</sup>
- 55 of these 102 genes are also dysregulated in chronic myelogenous leukemia<sup>2</sup>

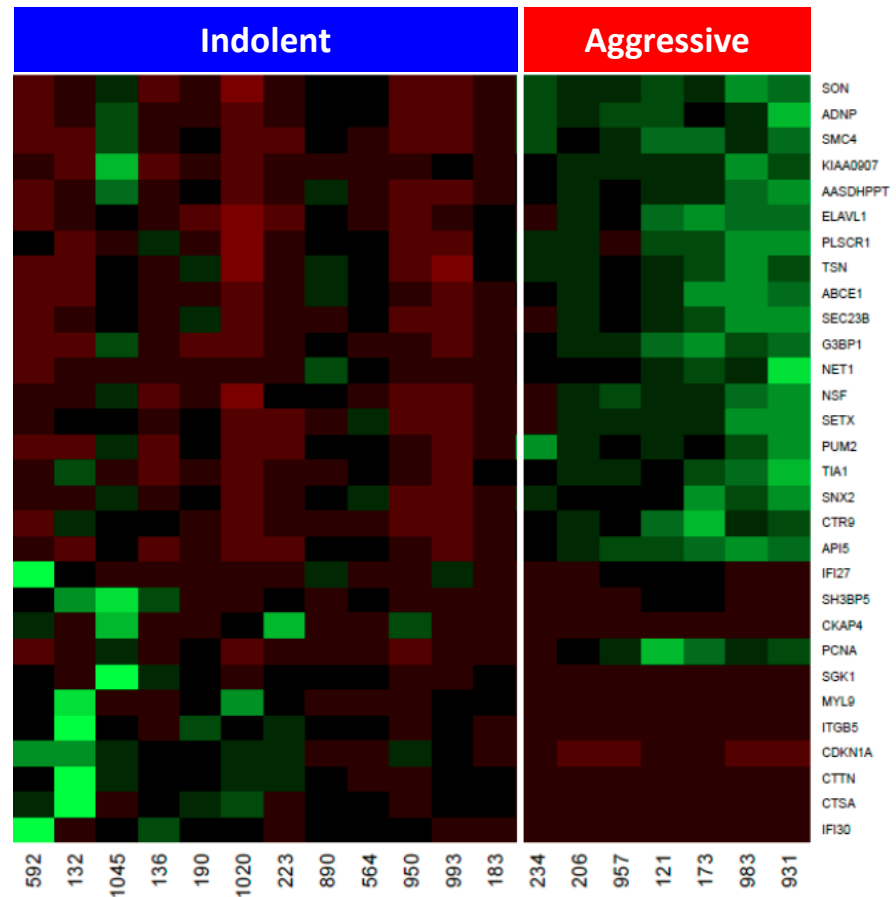
PV, polycythemia vera.

**Reference:** 1. Spivak JL et al. *N Engl J Med.* 2014;371(9)(suppl):808-817. 2. Spivak JL et al. *N Engl J Med.* 2014;371(9):808-817.

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## Prediction of aggressive vs indolent PV

- These 102 core genes were used to identify a subset of patients with increased thrombotic events, increased transformation to acute leukemia, and decreased survival<sup>1,2</sup>
- The number of genes required for distinguishing indolent from aggressive PV could be reduced to 10<sup>1,2</sup>



**References:** 1. Spivak JL et al. *N Engl J Med.* 2014;371(9):808-817. 2. Spivak JL et al. *N Engl J Med.* 2014;371(9)(suppl):808-817.

## Conclusions

- The course of PV may span decades, but a subset of patients has aggressive disease with outcomes comparable to those of myelofibrosis<sup>1,2</sup>
- No guidelines exist to identify PV that is aggressive with respect to splenomegaly, leukemic or fibrotic transformation, or survival
- In some cases, the type(s) of cell(s) overexpressed may provide some clues to outcomes<sup>3</sup>
- A study using gene expression profiling of CD34+ hematopoietic stem cells was able to accurately identify the subset of patients with increased thrombotic events, increased transformation to acute leukemia, and decreased survival<sup>4</sup>

**References:** 1. Tefferi A et al. *Leukemia*. 2013;27(9)(suppl):1874-1881. 2. Tefferi A et al. *Blood*. 2014;124(6):2507-2513. 3. Spivak JL. Interview. May 20, 2015. Incyte Corporation. Wilmington, DE. 4. Spivak JL et al. *N Engl J Med*. 2014;371(9):808-817.

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