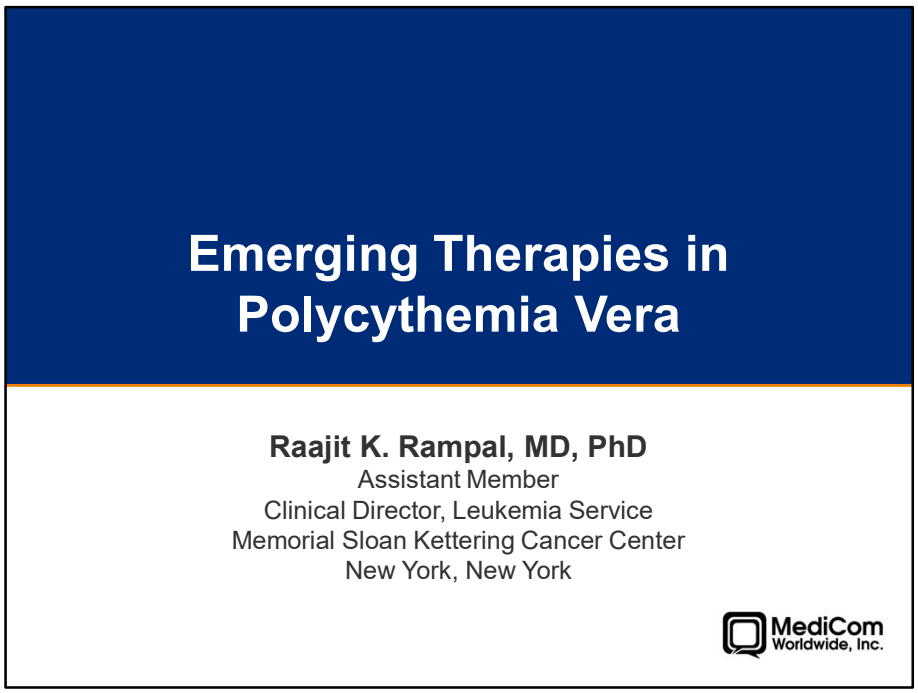
Emerging Therapies in Polycythemia Vera



Hello and welcome to *Managing MPN*. I am Dr. Raajit Rampal and today, I will discuss emerging therapies in polycythemia vera.

Disclosures

- Dr. Raajit Rampal has received honoraria related to formal advisory activities, as well as consultant fees from AbbVie Inc., Blueprint Medicines, Celgene Corporation - A Bristol-Myers Squibb Company, CTI BioPharma, Galecto Biotech, Incyte Corporation, Jazz Pharmaceuticals plc, Kartos Therapeutics, and PharmaEssentia Corporation. He has received grant support related to research activities from Constellation Pharmaceuticals, Incyte, and Stemline Therapeutics, Inc.

These are my disclosures.

Case Study: Polycythemia Vera

- Mr. V is a 68-year-old man who presents with plethora, mild splenomegaly
- Recently found to have a DVT in the left leg following a 7-hour car trip
- Upon evaluation, found to have:
  - Hematocrit of 59.8%; WBC of 12.3K/uL; Plts of 433K/uL
- No other comorbidities
- Mild splenomegaly
- What is the diagnostic approach to this patient?

Let's start with a case study. Mr. V is a 68-year-old man who presents with plethora and mild splenomegaly. He was recently found to have a DVT in his left leg following a seven-hour long car trip. Upon evaluation, he was found to have a hematocrit of 59.8%, a white count of 12.3K/uL, and platelets of 433K/uL. No other comorbidities in his history are noted. He has mild splenomegaly on exam but otherwise the exam is unremarkable. So how do we approach the diagnosis of this patient?

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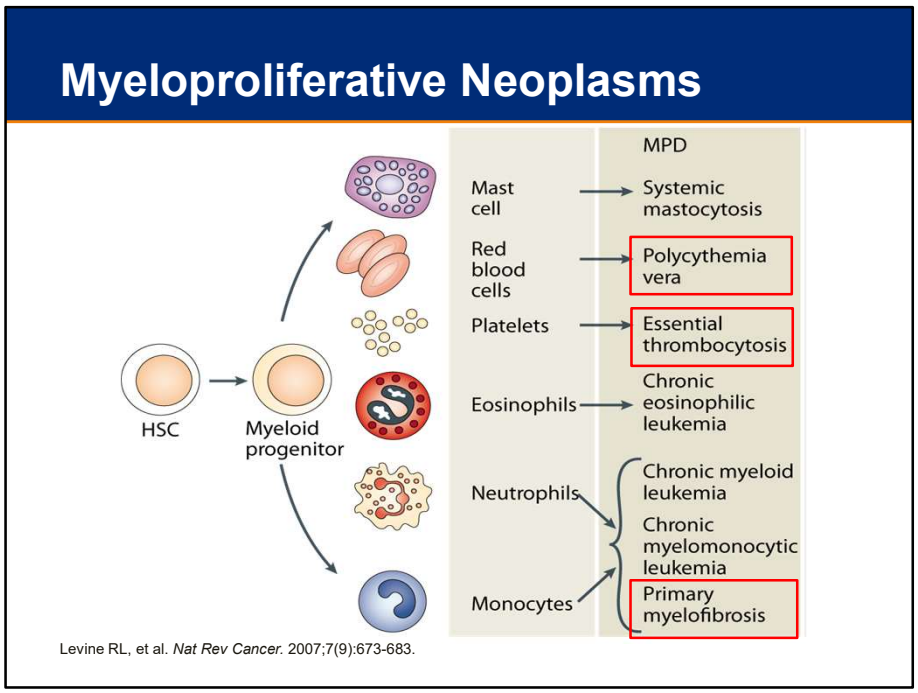

Well, talking simply the myeloproliferative neoplasms are clonal hematopoietic stem cell disorders that include primary myelofibrosis (PMF), essential thrombocythemia (ET), and polycythemia vera (PV).

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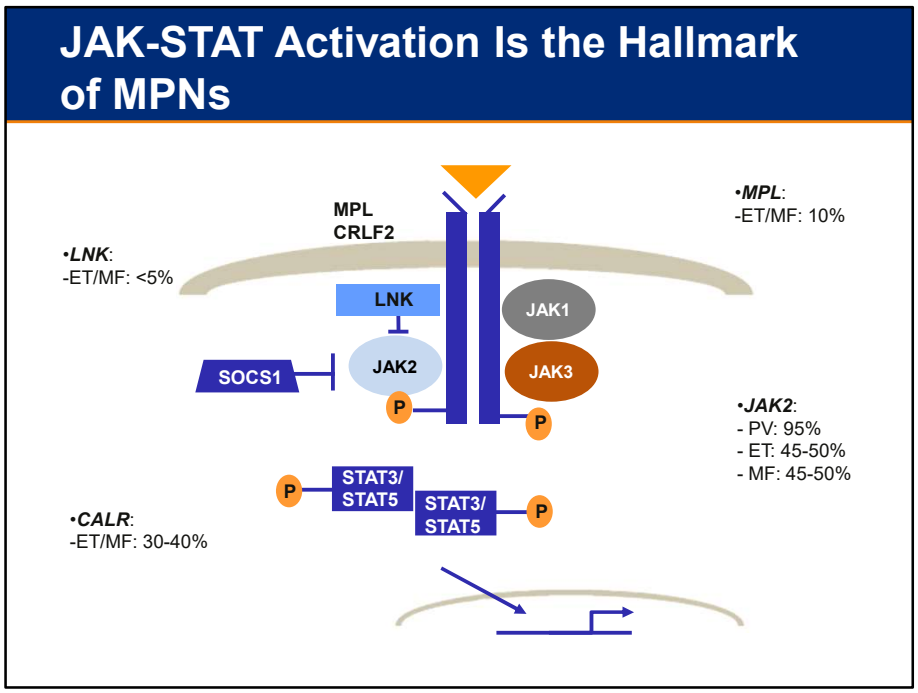

The hallmark of MPNs is activation of the JAK-STAT pathway and JAK2 mutations are found in 95% to 99% of PV patients and roughly half of ET and MF patients. Calreticulin mutations are found in about 30% to 40% of patients and MPL mutations are found in about 10% of patients. Really rare mutations like LNK mutations are found in under 5% of ET and MF patients and it's important to note, there still remains about 10% or so of patients for whom a JAK-STAT driver mutation isn't identified in the setting of having diagnostic findings on a bone marrow examination for an MPN.

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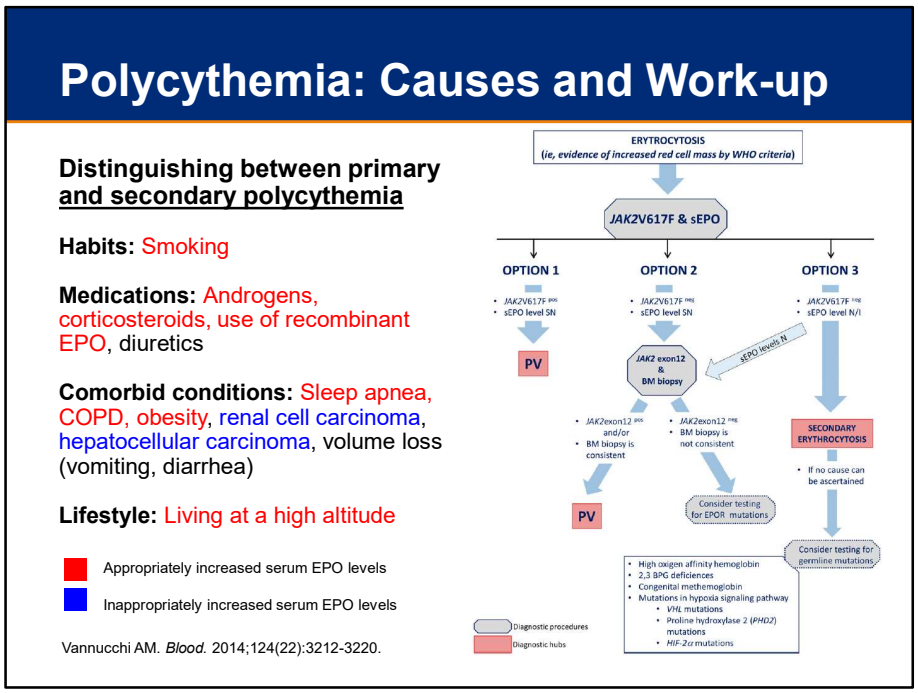

Now thinking about our patient who is clearly presenting with a polycythemia, how do we approach the managements and diagnosis of this patient? It's important to always think about and exclude other causes of polycythemia with the effort here being to distinguish between primary and secondary polycythemia. The JAK2 mutation in the context of having polycythemia as well as other features as we'll talk about in a minute, is usually conclusive to make the diagnosis of polycythemia vera, but in patients where one can't identify the mutation, a workup that includes assessing the patient's history very carefully including looking for things like smoking as well as medications like androgens, corticosteroids, or even recombinant erythropoietin is useful. Diuretics use as well can cause an elevation in the red cells. Other conditions as well such as sleep apnea, COPD, or obesity can also lead to an elevation in the hemoglobin and hematocrit. It's also important to always remember, of course, that things like renal cell carcinoma and hepatocellular carcinoma can present with polycythemia.

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Evolution of WHO PV Diagnostic Criteria

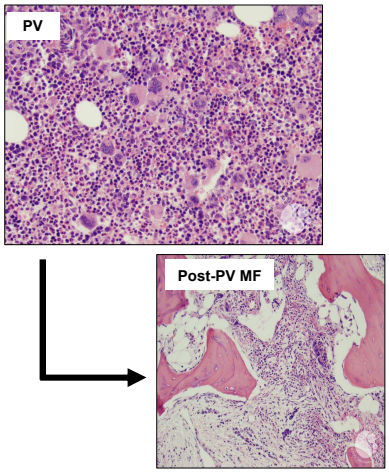
2008 WHO[1]	2016 WHO[2]
Requirement for diagnosis	
▪ 2 major and 1 minor criteria OR 1 major and 2 minor criteria	▪ All 3 major criteria OR first 2 major criteria and the minor criterion
Major criteria	
1. Hb >18.5 g/dL (men); >16.5 g/dL (women) 2. *JAK2*V617F mutation or similar (*JAK2* exon 12)	1. Hb >16.5 g/dL or Hct >49% (men); OR Hb >16.0 g/dL or Hct >48% (women); OR increased red cell mass 2. BM biopsy showing hypercellularity, trilineage growth (panmyelosis) with erythroid, granulocytic, and pleomorphic, mature megakaryocytic proliferation 3. *JAK2V617F or JAK2 exon 12 mutation*
Minor criteria	
1. Subnormal serum EPO level 2. BM trilineage proliferation 3. Endogenous erythroid colony growth	1. Subnormal serum EPO level

[1]Thiele J, et al. *Curr Hematol Malig Rep*. 2009;4(1):33-40. [2]Arber DA, et al. *Blood*. 2016;127(20):2391-2405.

Talking specifically about polycythemia vera, the WHO criteria changed as of 2016 for this diagnosis. The diagnosis is based on the finding of an elevated hemoglobin or hematocrit as well as a bone marrow examination that shows a hypercellular bone marrow with panmyelosis and finally, the finding of a JAK2 mutation, whether this is the canonical VC617F mutation and exon 14 or the exon 12 mutation. Minor criterion include a subnormal erythropoietin level. It is important to note that the differences between the 2016 and the 2008 criteria include a lowering of the hematocrit threshold and hemoglobin threshold for diagnosis and this was based on the observation that there are patients who didn't quite meet the threshold, as was denoted in 2008, but were still having manifestations of disease and bone marrow findings consistent with polycythemia vera. As well, a bone marrow examination is now been added to the criteria for the diagnostic workup. This is not required in every single case. It depends on the hemoglobin and hematocrit levels that exceeds a certain threshold that a bone marrow examination is not absolutely required by the WHO criteria.

Bone Marrow Testing in PV Diagnosis

- **Bone marrow biopsy may not be required for diagnosis** if sustained Hb levels >18.5 g/dL (men) or >16.5 g/dL (women) where *JAK2* mutated and EPO suppressed[1]
- **Biopsy may identify fibrosis at diagnosis**
  - Prevalence: 14% to 48% with grade 1 fibrosis at diagnosis; consequences include a higher rate of overt, fibrotic progression[2,3]
- **Biopsy required to diagnose post-PV MF[4]**
  - Progression prevalence: 5% to 19% at 15 years
  - Risk factors: age ≥60 years, disease duration, WBC count >15K at diagnosis, *JAK2*+ >50%, and possibly non-*JAK2* mutations (*ASXL1, IDH, SRSF2*)
  - **Diagnosis also requires clinical criteria**



[1]Arber DA, et al. *Blood.* 2016;127(20):2391-2405. [2]Barbui T, et al. *Blood.* 2012;119(10):2239-2241. [3]Barraco D, et al. *Blood Cancer J.* 2017;7(3):e538. [4]Cerquozzi S, et al. *Blood Cancer J.* 2015;5(11):e366.

Why do the bone marrow at all if the patient has an elevated hemoglobin or hematocrit and has a JAK2 mutation? There are a couple of things to think about. One is that the bone marrow can help to identify the presence of fibrosis, and that is important prognostically because patients with fibrosis have a higher rate of overt fibrotic progression and fibrosis is present in 14% to 48% of patients at a level of grade 1 or so at baseline and so, it's an important thing to consider as a prognostic marker. In general, having a bone marrow examination at baseline for MPN patients can provide a lot of useful information aside from just meeting WHO criteria.

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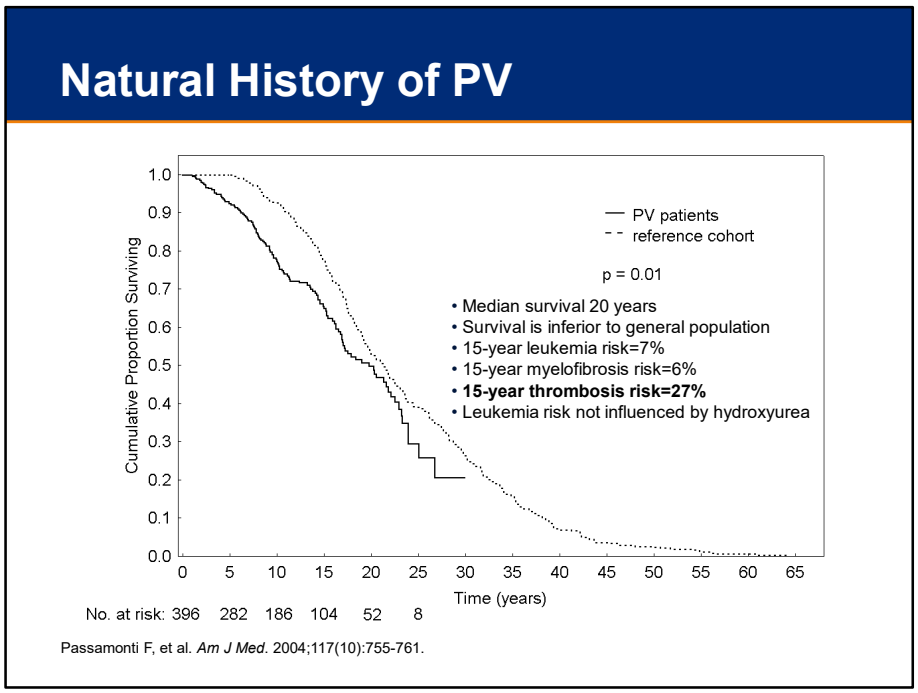

What is the natural history of a polycythemia vera? We know that patients have an impaired overall survival versus the general population. There is a risk of leukemic transformation, about 7% at 15 years. There is a risk of progression to myelofibrosis and other MPN, about 6% at 15 years but there is most importantly, a risk of thrombosis which is 27% at 15 years. This is certainly not small and is really one of the main areas that we focus on in terms of our treatment of these patients.

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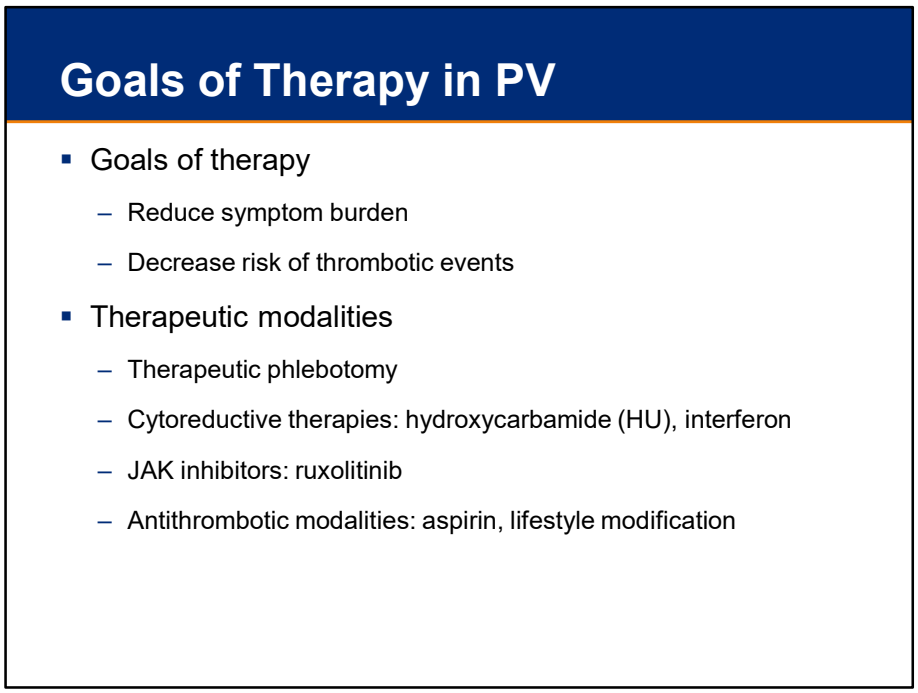

Some of the goals of therapy, as such, are to reduce the risk of thrombotic events and also to reduce the symptom burden in patients. Patients with polycythemia vera and MPNs in general can have a wide range of different symptoms, and these include night sweats, fevers, itching, myalgias, arthralgias, early satiety, abdominal discomfort, and most notably, fatigue, and so it's important to keep the symptom burden in mind when you are managing a patient with polycythemia not just focus on the hematocrits.

How do we approach patients? We use their phlebotomies, we use cytoreductive therapy, in some cases, we use JAK inhibitors as well, but it's also important to remember simple things like giving patients aspirin and lifestyle modifications, and this means emphasizing to your patients that control of their cholesterol, control of their weights, control of their blood glucose, control of their blood pressure, are all fundamentally important considerations in managing their disease.

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Stratification for Thrombohemorrhagic Complications in PV

Low-risk	Age<60 years *and* No history of thrombosis *and* Platelet count<1.5 million *and* No cardiovascular risk factors	Thrombosis risk is not significantly increased compared to controls
High-risk	Age≥60 years *or* Previous thrombosis	Thrombosis risk is significantly increased
Indeterminate risk	Neither low nor high risk	Thrombosis risk is not well studied

Finazzi G, Barbui T. *Leukemia*. 2008;22(8):1494-1502.

The approach to the management of patients with polycythemia vera is really based on the idea that there are different risks of thrombotic events. We group people into the low-risk category if they're under the age of 60 and who've never had a thrombotic event. We group them into high risk if they are over age 60 or have had a thrombotic event. These relative terms because low risk does not mean no risk and in general, the risk of thrombotic events even the low-risk patients is greater than that in the general population. This is a relative tool but it does change how we manage patients. In general, patients with low-risk disease are managed with phlebotomy and those with high-risk disease are managed with cytoreductive agents.

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- Mr. V is a 68-year-old man who presents with plethora, mild splenomegaly
- Recently found to have a DVT in the left leg following a 7-hour car trip
- Upon evaluation, found to have:
  - Hematocrit of 59.8%; WBC of 12.3K/uL; Plts of 433K/uL
  - No leukoerythroblastosis
  - BMBX consistent with PV by WHO 2016 criteria
  - *JAK2* V617F mutation detected
- No other comorbidities
- Mild splenomegaly
- What is the optimal approach to therapy for this patient?
  - Pegylated interferon? Hydroxyurea?

Coming back to the case of Mr. V, he undergoes a bone marrow examination, is found to have polycythemia vera by 2016 criteria, he does have a JAK2 mutation. He has no other comorbidities and on exam he has mild splenomegaly, so what's the approach to the treatment of this patient? Remember that he is 68 and therefore falls into the high-risk category. Therefore, it is reasonable to put him on cytoreductive therapy as well as aspirin 81 mg or low-dose aspirin, but full-dose aspirin is not required. In terms of cytoreductive therapy, what is the right agent? The agents that have been traditionally used in the frontline setting include pegylated interferon as well as hydroxyurea. How do you choose what the right frontline treatment is for such a patient?

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Aspirin

Double-blind, placebo-controlled trial of ASA (100 mg) in patients with PV

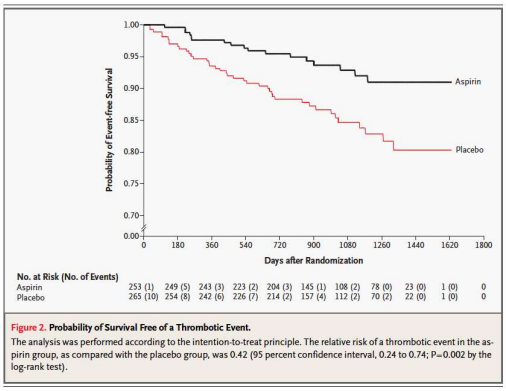

Figure 2. Probability of Survival Free of a Thrombotic Event.
The analysis was performed according to the intention-to-treat principle. The relative risk of a thrombotic event in the aspirin group, as compared with the placebo group, was 0.42 (95 percent confidence interval, 0.24 to 0.74; P=0.002 by the log-rank test).

Table 3. Rates and Relative Risks of Bleeding Episodes in the Two Groups.*

Type of Bleeding Episode	Aspirin Group (N=253)	Placebo Group (N=265)	Relative Risk (95% CI)	P Value
	no. (%)			
Any bleeding	23 (9.1)	14 (5.3)	1.82 (0.94–3.53)	0.08
Major bleeding	3 (1.2)	2 (0.8)	1.62 (0.27–9.71)	0.60
Gastrointestinal	2 (0.8)	0		
Intracranial	1 (0.4)	2 (0.8)		
Minor bleeding	20 (7.9)	12 (4.5)	1.83 (0.90–3.75)	0.10
Hematoma	2 (0.8)	2 (0.8)		
Gastrointestinal	7 (2.8)	3 (1.1)		
Hematuria	1 (0.4)	3 (1.1)		
Epistaxis	9 (3.6)	1 (0.4)		
Other	2 (0.8)	4 (1.5)		

Landolfi R, et al. *N Engl J Med.* 2004;350(2):114-124.

Starting with aspirin, it's important to remember that randomized trials have demonstrated that there is a benefit to aspirin and in this case this study was utilizing a 100 mg daily of aspirin, but 81 mg seems to have the similar effect compared to placebo in terms of event-free survival, there was a clear statistical benefit for using aspirin.

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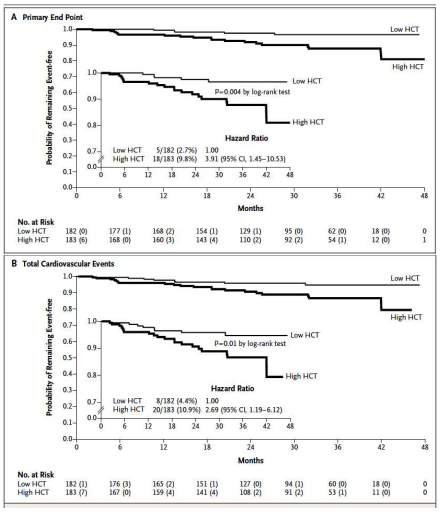
Therapeutic Phlebotomy: What Is the Optimal Goal?



Low-hematocrit group (<45%)
vs
High-hematocrit group (45-50%)

Is this the optimal HCT goal for women?

Is <42% more appropriate?

Marchioli R, et al. *N Engl J Med.* 2013;368(1):22-23.

What about our goals for hematocrits, both from therapeutic phlebotomy or from cytoreductive therapy? This was examined in a phase 3 trial in which patients were randomized to two groups. One, a low hematocrit group, less than 45 hematocrit, versus a high hematocrit group with a threshold of hematocrit between 45 and 50. What was demonstrated in this study was that the patients kept in the lower hematocrit group had a lower incidence of cardiovascular events and lower incidents of mortality, and so therefore, the threshold of less than 45% has been established as standard of care whether they're using phlebotomy or using cytoreductive agents. Now, one question remains is, is this the appropriate hematocrit for female patients? The majority of patients in this particular study were male and we do know that at baseline, males and females don't have the same baseline hematocrit, and there is evidence to suggest that a hematocrit of less than 42% may be more suitable for female patients, but nonetheless, 45% as the upper limit remains the standard.

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Additional Studies of HU for Frontline Cytoreduction in Patients With PV

Study/Organization	Pts, N	Intervention	Comparator	Thrombosis
French PV Study Group[1]	292 <65 yrs (median FU: 7 yrs)	HU (randomized)	Pipobroman	No significant difference
French PV Study Group[2]	285 (median FU: 16 yrs)	HU (randomized)	Pipobroman	No significant difference
PV cohort of ECLAP study[3]	1042 (median FU: ~30-35 mos)	HU (propensity matching)	Phlebotomy	CV events/100 PY: HU: 3.0 Phlebotomy: 5.8
Retrospective study[4]	235 with thrombosis history	Cytoreduction; 77% received HU	None	Cytoreduction reduced recurrence rates

[1]Najean Y, et al. *Blood*. 1997;90(9):3370-3377. [2]Kiladjian JJ, et al. *J Clin Oncol*. 2011;29(29):3907-3913. [3]Barbui T, et al. *Am J Hematol*. 2017;92(11):1131-1136. [4]De Stefano V, et al. *Haematologica*. 2008;93(3):372-380.

What do we know about cytoreductive therapies? Hydroxyurea has been studied in in a variety of settings and sometimes, it was in randomized trials versus historical agents such as pipobroman, which are no longer utilized and so that data is really not quite so relevant anymore. But if propensity matching analysis when examining patients who received phlebotomy versus those received hydroxyurea, there was a trend towards a lower number of cardiovascular events in the patients who received hydroxyurea versus those who just received phlebotomy.

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PegIFN for Patients With PV

Study	Population	Findings
PVN[1,2] ▪ PegIFN α-2a	▪ N = 37 ▪ Newly diagnosed pts	▪ CHR: 95%; CR: 82% in extended FU – 0 thromboembolic events in 6 yrs ▪ CMR: 8 (28%); sustained improvements after d/c of treatment ▪ Grade 1/2 AEs: 89%; d/c for toxicity (1 yr): 24%
MDACC[3,4] ▪ PegIFN α-2a	▪ N = 43 ▪ ~50% previous cytoreductives ▪ Median FU: 83 mos	▪ Median response duration: hematologic: 65 mos; molecular: 58 mos – Failure to achieve CMR: more likely to have/acquire nondriver mutations ▪ Thrombosis and progression can occur ▪ Toxicity continued over time (new grade 3/4 events in 10% to 17% of PY); d/c for AEs: 22%
PEGINVERA[5,6] ▪ RopegIFN α-2b	▪ N = 51 ▪ HU pretreated: 33% ▪ Median FU: 80 wks	▪ CR: 43% to 57%; PR: 43%; CMR: 21% ▪ 1 TIA, 1 DVT during study period ▪ AEs (any): 88%; d/c for AEs: 20%

[1]Kiladjian JJ, et al. *Blood.* 2008;112(8):3065-3072. [2]Turlure P, et al. *Blood.* 2011;118(21):280. [3]Quintas-Cardama A, et al. *Blood.* 2013;122(6):893-901. [4]Masarova, et al. *Lancet Haematol.* 2017;4(4):3165-e175. [5]Gisslinger H, et al. *Blood.* 2015;126(15):1762-1769. [6]Clinicaltrials.gov. NCT01193699.

What about interferon? Interferon has been widely used in patients with polycythemia vera as well as essential thrombocythemia and myelofibrosis, and pegylated interferon has demonstrated the ability to control the patient's blood counts and drive down the JAK2 allele burden which is in an area that is being increasingly studied in terms of its implications. But how do you choose between the agents?

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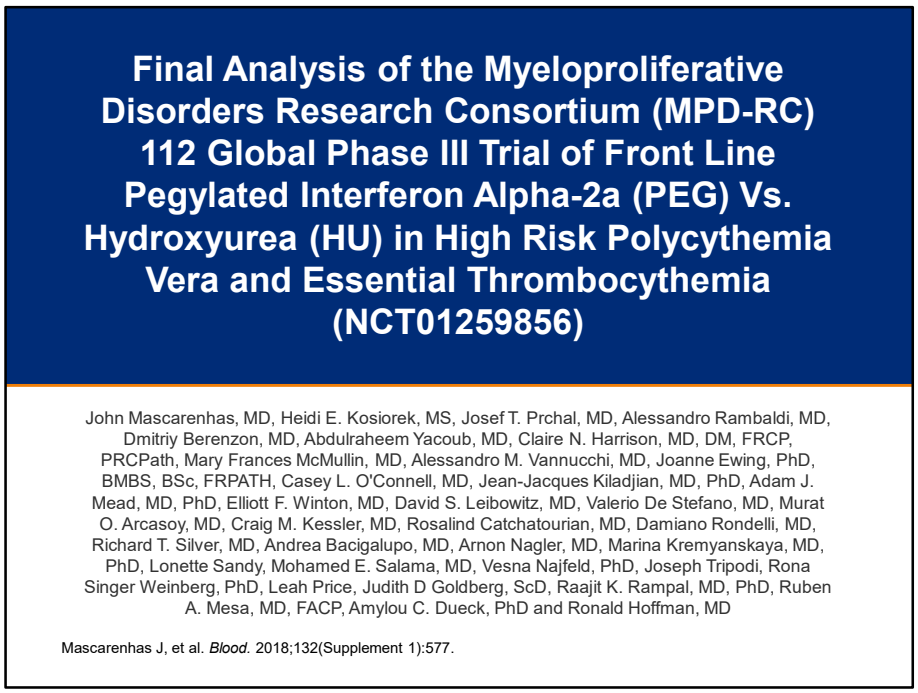

This has been the subject of a couple of different studies. The first was the Myeloproliferative Neoplasms Research Consortium 112 Study; which was a randomized global phase 3 of frontline pegylated interferon alpha-2a versus hydroxyurea in patients with polycythemia vera or essential thrombocythemia.

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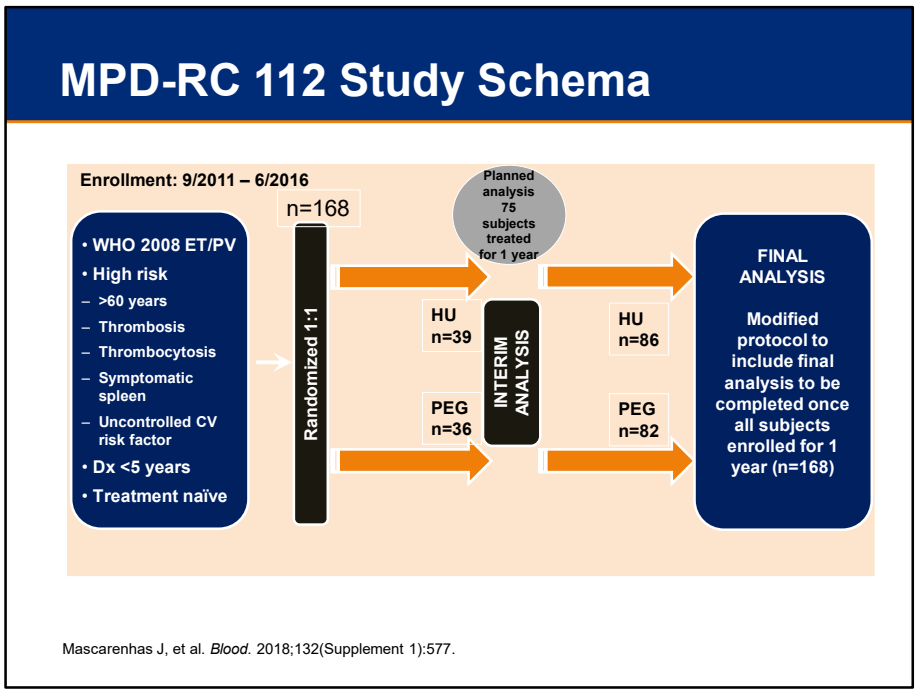

Mascarenhas J, et al. *Blood.* 2018;132(Supplement 1):577.

Patients were randomized one to one to hydroxycarbamide versus pegylated interferon. An interim analysis was carried out at the 12 months.

24-Month Response Data

- When considering all 106 patients who were eligible to receive treatment for 24 months (due to study closure)

	HU (n=54)			PEG (n=52) *P*=0.22		
	ET	PV	Total	ET	PV	Total
CR	6 (25%)	5 (16.7%)	11 (20.4%)	9 (37.5%)	7 (25%)	15 (28.8%)
PR	2 (8%)	9 (30%)	11 (20.4%)	5 (20.8%)	10 (35.7%)	16 (30.8%)
ORR	**8/24 (33.3%)**	**14/30 (46.7%)**	**22 /54 (40.7%)**	**14/24 (58.3%)**	**17/28 (60.7%)**	**31/52 (59.6%)**
			22/48 (45.8%)	***P*=0.22**		**31/52 (59.6%)**

Mascarenhas J, et al. *Blood.* 2018;132(Supplement 1):577.

With regards to the data at 24 months, the overall response rates between hydroxyurea at 40.7% and pegylated interferon at 59.6% was essentially statistically the same. The CR rate, and this is displayed here in red, was 20.4% in the hydroxyurea arm and 28.8% in the pegylated interferon arm.

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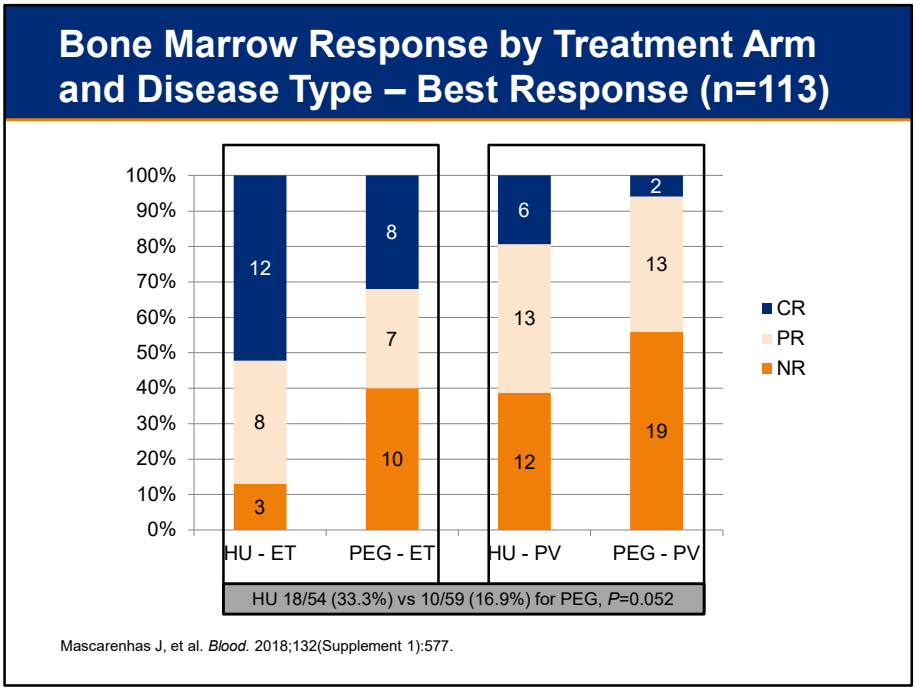

No statistical difference was found in terms of the overall response. Now, in terms of bone marrow response by histopathologic criteria, there was a slight increase actually in the hydroxyurea arm, 33% versus 16.9%, which was borderline significant, but it's important to remember that this was not all patients that were assessed from the study.

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Number of Patients with Any Grade AEs Regardless of Attribution Occurring in ≥10% of Patients in Either Arm

Non-Hematologic

Adverse Event	Hydroxyurea n=80		PEG N=82	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Fatigue	42 (53.0%)	2 (2.6%)	19 (23.2%)	5 (6.1%)
Pain	20 (25.0%)	3 (3.9%)	30 (36.6%)	2 (2.4%)
Headache	10 (12.5%)		18 (21.9%)	3 (3.7%)
Diarrhea	8 (10.0%)	1 (1.3%)	14 (17.1%)	
Cough	9 (11.3%)		11 (13.4%)	
Flu like symptoms	2 (2.5%)		18 (21.9%)	2 (2.4%)
Pruritus	4 (5.0%)		13 (15.9%)	2 (2.4%)
Nausea	6 (7.5%)		13 (15.9%)	
Arthralgia	6 (7.5%)	1 (1.3%)	11 (13.4%)	
Dizziness	8 (10.0%)		8 (9.8%)	
Upper respiratory infection	5 (5.3%)		11 (13.4%)	
AST increased	3 (3.8%)	1 (1.3%)	10 (12.2%)	2 (2.4%)
Dyspnea	4 (5.0%)		9 (11.0%)	2 (2.4%)
Abdominal pain	3 (3.8%)		11 (13.4%)	
Blurred vision	4 (5.0%)		9 (11.0%)	
Constipation	9 (11.3%)		4 (4.9%)	
Peripheral sensory neuropathy	3 (3.8%)	1 (1.3%)	9 (11.0%)	
Depression	2 (2.5%)		10 (12.2%)	
Hypertension		2 (2.6%)	3 (3.7%)	6 (7.3%)
Mucositis	8 (10.0%)	1 (1.3%)	1 (1.2%)	

Hematologic

Adverse Event	Hydroxyurea		PEG	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Leukopenia	5 (6.3%)		18 (21.9%)	
Anemia	11 (13.8%)		10 (12.2%)	1 (2.1%)
Neutropenia		2 (2.6%)	7 (8.5%)	2 (2.4%)

Mascarenhas J, et al. *Blood.* 2018;132(Supplement 1):577.

In terms of side effects, notable side effects of course include fatigue, headaches, flu-like symptoms, abdominal pain, depression, and most of these were seen more frequently in the pegylated interferon arm. Hematologic side effects were notable for mild anemia as well as neutropenia, which in terms of the neutropenia, was roughly equivalent between the two arms.

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That dataset would argue that really, at least at the time of 24 months, there doesn't appear to be an overtly significant difference between PV patients or ET patients treated with interferon versus those treated with hydroxycarbamide. By contrast, a similar study was undertaken with the new drug called ropeginterferon. This is a longer-lasting interferon that's administered every two weeks rather than every week as is pegylated interferon. In this particular study, randomized patients only with polycythemia vera to ropeginterferon versus hydroxyurea.

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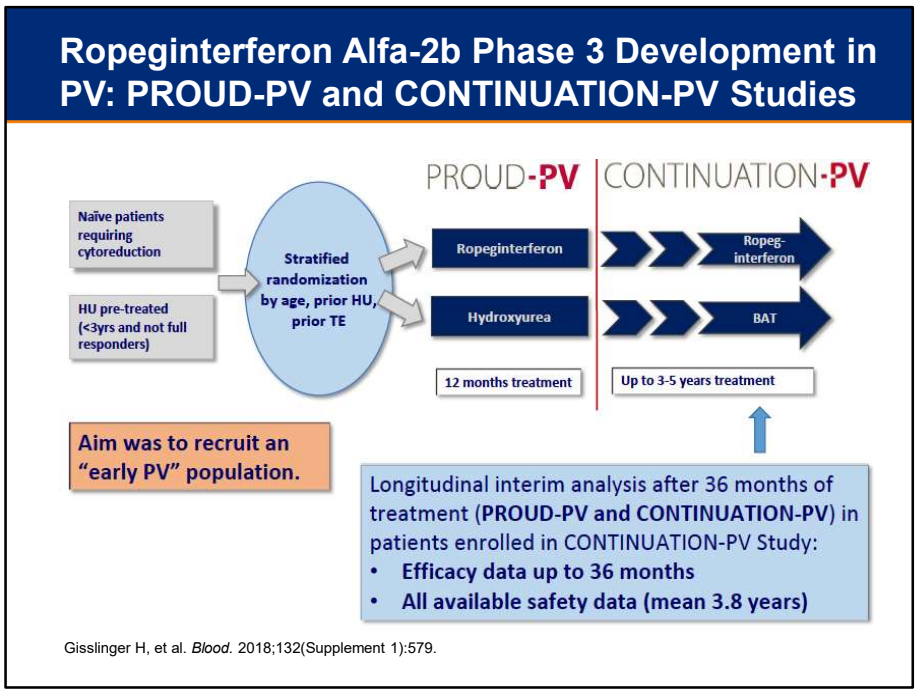
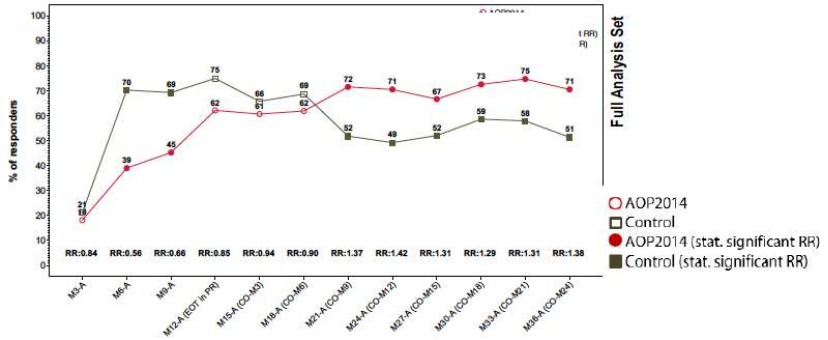


Gisslinger H, et al. *Blood.* 2018;132(Supplement 1):579.

This was the PROUD-PV study which was assessed after 12 months and then there was a continuation portion of this study which went up to five years.

Emerging Therapies in Polycythemia Vera

Complete Hematologic Response



Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	59/95	62.1	57/76	75.0	0.1201	0.85 [0.70-1.04]
MONTH 24	67/95	70.5	33/67	49.3	0.0111	1.42 [1.08-1.87]
MONTH 36	67/95	70.5	38/74	51.4	0.0122	1.38 [1.07-1.79]

Gisslinger H, et al. *Blood.* 2018;132(Supplement 1):579.

The study initially had results that were similar to what I've described with the MPN-RC 112 study; in which at about 12 months' time, it appeared that there was no real difference, although by the proportion of responders, there seemed to be some increase in patients responding in the hydroxyurea arm versus the interferon arm, which is in red. But interestingly, with more prolonged time in the curves invert and in fact, the response rate does increase over time in the ropeginterferon treated arm as we go into month 36, with 70.5% of patients deemed to be responders in the ropeg arm, whereas 51.4% of the hydroxyurea-treated patients were responders at month 36, which meant statistical significance.

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Treatment-related Adverse Events in >10% of Patients

Treatment-related AE	Ropeg (n=95) n (%)	Control (n=76) n (%)
Thrombocytopenia	24 (25.3%)	**25 (32.9%)**
Leukopenia	21 (22.1%)	**23 (30.3%)**
Anaemia	10 (10.5%)	**22 (28.9%)**
Increased gamma-glutamyltransferase	**11 (11.6%)**	2 (2.6%)
Alanine aminotransferase increased	**10 (10.5%)**	-
Platelet count decreased	-	**8 (10.5%)**
Myalgia	**10 (10.5%)**	3 (3.9%)

Gisslinger H, et al. *Blood.* 2018;132(Supplement 1):579.

In terms of adverse events, there were hematologic side effects including thrombocytopenia, leukopenia, and anemia noted in both treatment arms. An increase in the liver function tests (LFTs) was noted in the ropeginterferon-treated patients as well, as well as some myalgias, but in general, it appeared that the treatment was well-tolerated.

Case Study: Polycythemia Vera-2

- Patient achieves initial count control with hydroxycarbamide 1000 mg daily, but still requires phlebotomy every 3 months
- Dose of hydroxycarbamide increased to 2000 mg daily
- However, patient becomes leukopenic due to increased dose of hydroxycarbamide
- What are the options for this patient?

Based on these, the ropeginterferon has actually been approved in the European Union for frontline treatment of patient with polycythemia vera who are high risk. This is still undergoing regulatory review in the United States and may possibly be an option for our patients in the United States in the relatively near future. Nonetheless, this data does at least give us some evidence on which to base of the initial treatment decision of hydroxyurea versus, in this case, ropeg interferon.

In our patient's case, our patient is initially started on hydroxyurea at 1000 mg daily, which is a reasonable and appropriate thing given the data that I've shown you, but the patient is still requiring phlebotomy every three months, which is still a substantial phlebotomy burden. The dose of hydroxycarbamide is increased to 2000 mg daily but the patient now encounters hematologic side effects, namely leukopenia at the dose of hydroxycarbamide that's required to control the hematocrit. What do we do for this patient now? What are our treatment options?

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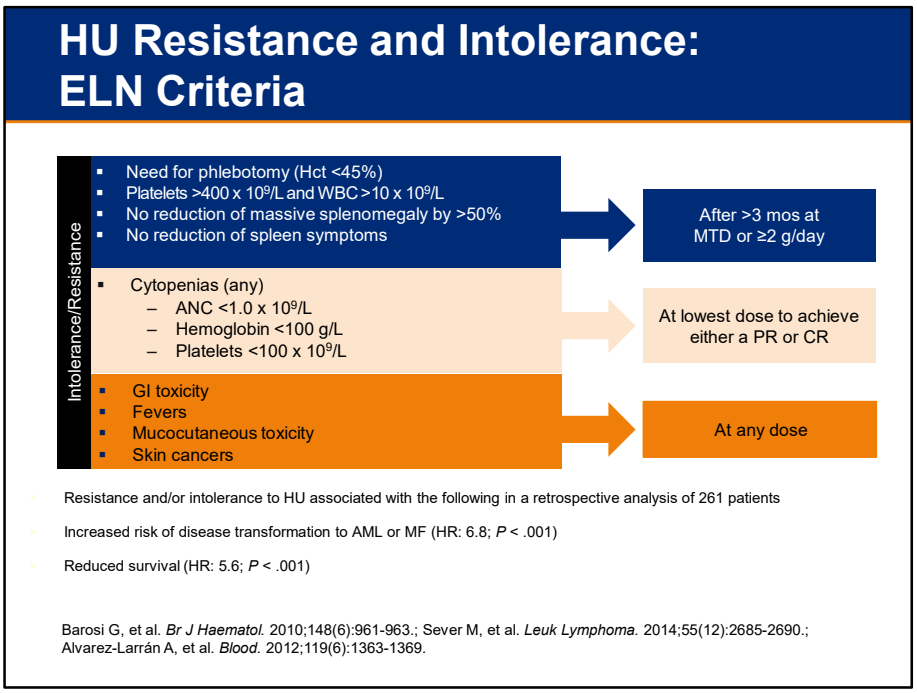

Well, it's important to realize that there are established definitions for hydroxyurea resistance and intolerance. These are ELN criteria. Patients are deemed to be intolerant if they have side effects such as GI toxicity, fevers, mucocutaneous ulcers or skin ulcers at any dose. Intolerance is also deemed to be cytopenias at doses that are required to achieve hematocrit control and so, incurring neutropenia or anemia or even thrombocytopenia at a dose of hydroxycarbamide that you need to control hematocrit, would meet that definition. As well, resistance is defined as still needing phlebotomy when on a dose of 2 grams or greater per day of hydroxyurea, platelets over 400,000 at that dose, no reduction in massive splenomegaly at that dose, and no reduction in spleen symptoms at that dose of 2 grams per day.

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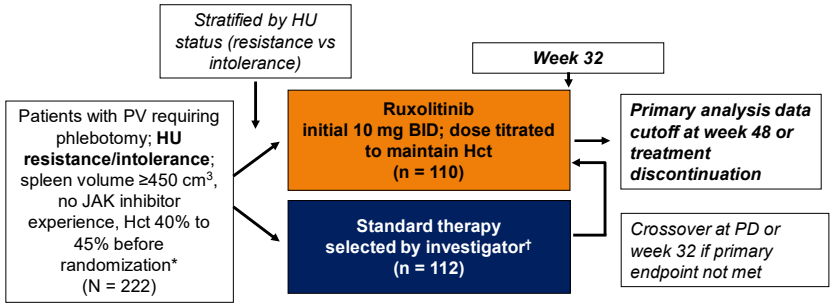
RESPONSE: Ruxolitinib vs Standard Therapy in Pts With PV and HU Resistance/Intolerance

- International, multicenter, randomized, open-label phase 3 study
  - **Ruxolitinib**: JAK112 inhibitor



All patients received low-dose ASA.
*Pts with Hct <40% or >50% entered Hct control period prior to randomization.
†Excluding ^{32}P, busulfan, and chlorambucil.

Vannucchi AM, et al. *N Engl J Med.* 2015;372(5):426-435.

Based on these criteria, a trial called the RESPONSE trial was carried out and this was a trial for patients who met the definition of hydroxyurea resistance or intolerance, who were randomized to receive the JAK1/2 inhibitor ruxolitinib at a dose of 10 mg twice daily, or standard therapy as selected by the investigator. In most cases, this did turn out to be hydroxyurea. Patients were randomized and were assessed at week 32.

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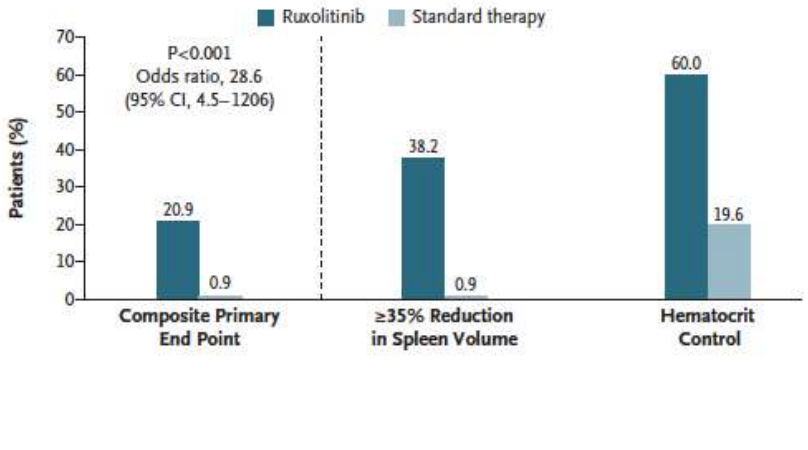
Ruxolitinib



Vannucchi AM, et al. *N Engl J Med.* 2015;372(5):426-435.

The endpoint of the study was hematocrit control and spleen size reduction. If we look at the composite primary endpoint, this was achieved by 20.9% of patients in the ruxolitinib arm, but only 0.9% of patients in the standard therapy arm. Breaking this down by the components of the endpoint, 38% or so of patients achieved this spleen volume reduction of 35% versus 0.9 in the control arm or standard therapy arm, but importantly, hematocrit control was achieved in 60% of patients who got ruxolitinib versus only 19.6% of patients who got standard therapy.

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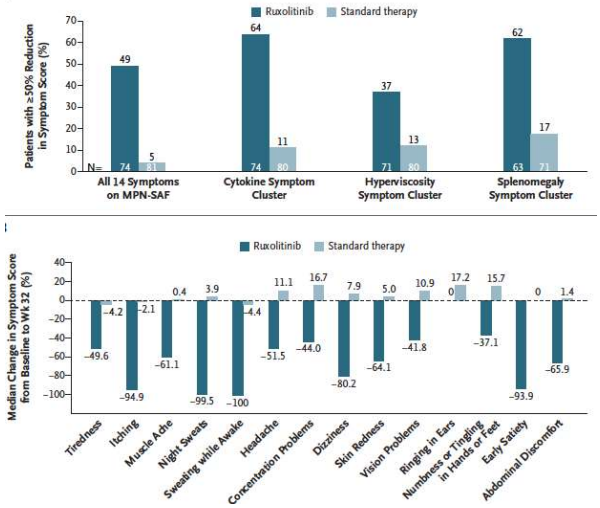
Ruxolitinib



Vannucchi AM, et al. *N Engl J Med.* 2015;372(5):426-435.

In terms of the symptom profile, there was a decrease in the total symptoms score burden that patients who were treated with the ruxolitinib face. As you can see here, symptom clusters such as cytokines symptom clusters or hyperviscosity or splenomegaly related symptoms all improved on patients treated with ruxolitinib at a higher degree than that what was seen with standard therapy arm. But more importantly, if we break this down by the individual components, so things like headaches or sweating or night sweats, all decreased substantially when patients are treated with ruxolitinib, whereas in some cases on the standard therapy, these symptoms did in fact increase.

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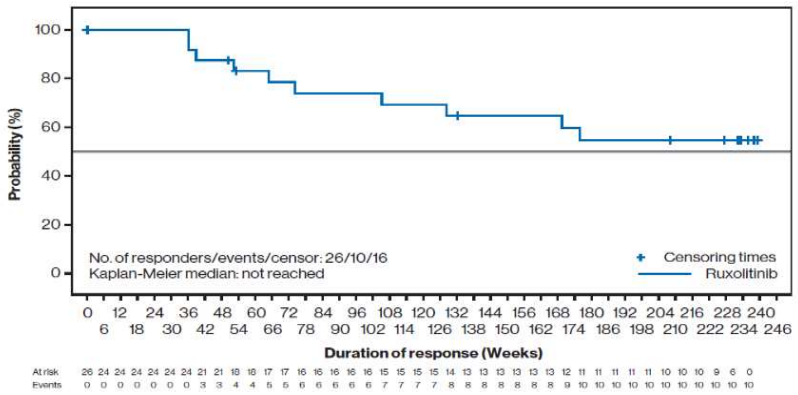
Durability of Response to Ruxolitinib



Kiladjian JJ, et al. *Blood.* 2018;132: Abstract 1753.

Now, what about the durability of response? As it turns out, the response to ruxolitinib in these patients seems to be rather durable. The most recent updated data has shown that the majority of patients, now several years out from this randomization, appeared to still continue to tolerate and benefit from ruxolitinib therapy. This has been approved by the FDA for patients who are resistant or intolerant to hydroxyurea and represents the standard of care option for polycythemia vera patients.

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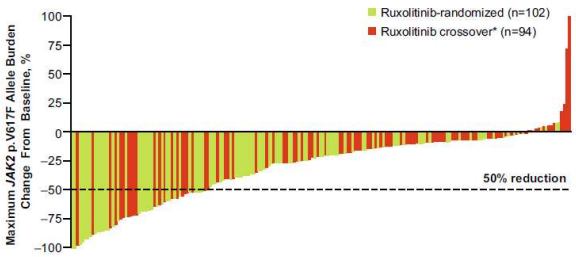
Ruxolitinib Reduces JAK2 V617F Allele Burden in Patients with PV (RESPONSE)



Ruxolitinib treatment for up to 4 years provides progressive reductions in *JAK2 V617F* allele burden in patients with PV who are resistant/intolerant to HU

Vannucchi AM, et al. *Ann Hematol.* 2017;96(7):1113-1120.

Notably, the JAK2 allele burden does appear to decrease in the majority of patients treated with ruxolitinib. A large proportion of patients did actually achieve a 50% reduction in their JAK2 allele burden which meets definition for a partial molecular response, and in fact, several patients did approach almost 100% reduction in the JAK2 allele burden, but these were the minority of patients.

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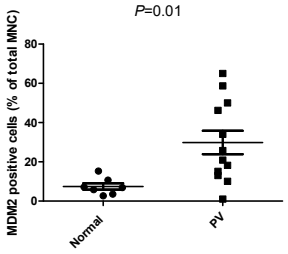
MDM2 Inhibition: Idasanutlin (MPN-RC 115)



	Not evaluable (NE)	No response (NR)	Partial Response (PR)	Complete Response (CR)	Overall Response (PR+CR)
PART A (n=12)	1*	4†	3‡	4	7 (58%)
PART B (n=4)†		2	1	1	2 (50%)
				PART A + PART B ORR	9 (75%)

*NE due to patient decision to withdraw from study after 4 cycles because of gastrointestinal toxicity.
†Four patients from part A who had NR entered part B combination idasanutlin + IFN-α.
‡Residual splenomegaly likely resulting from known portal vein thrombosis in 1 patient, likely a CR (n = 1)
Mascarenhas J, et al *Blood.* 2019;134(6):525-533.

Now, beyond ruxolitinib, in the second line, one can also switch to interferon if one has started with hydroxyurea and vice versa if one starts treating the patient with interferons, one could always switch to hydroxyurea, so the options are really two drugs more or less that are available and then can be used in patients who failed their initial cytoreductive therapy for polycythemia vera. What else is out on the horizon? Well, one class of drugs that is being intensely studied in patients with MPNs in general and in particular, patients with polycythemia vera are MDM2 inhibitors. So, MDM2 is an ubiquitin ligase that binds to and leads the degradation of p53 and in fact, in analysis of primary patient samples, levels of MDM2 seemed to be higher in patients with MPNs and PV in particular versus normal controls. The therapeutic approach, our thought here is that if one inhibits MDM2, the activity of p53 may be restored and therefore, leading to apoptosis of the MPN cells and in fact, this has been studied and demonstrated in pre-clinical settings and so, this has led to the idea that this could be utilized as a clinically active therapeutic strategy. This was studied in the MPN-RC, the Myeloproliferatives and Neoplasms Research Consortium 115 Study in which patients received an MDM2 inhibitor or an MDM2 inhibitor plus interferon. If we just look at PART A in which patients received the MDM2 inhibitor, the overall response rate, which was both a CR and PR, was about 58%. It is a relatively small number of patients who are evaluated in the study, but nonetheless, this is at least proof of a clinical activity of this inhibitor and of this therapeutic concept in general.

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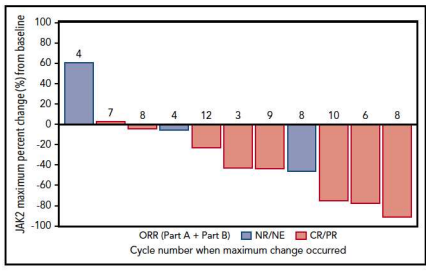
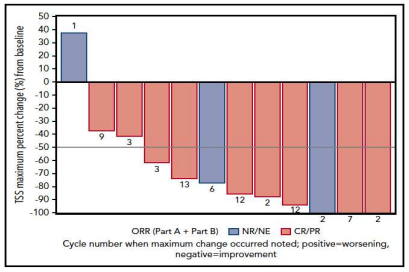
MDM2 Inhibition: Idasanutlin (MPN-RC 115)

JAK2V617F Allele Burden



TSS



Mascarenhas J, et al *Blood.* 2019;134(6):525-533.

The JAK2 allele burden in patients who were treated with the MDM2 inhibitors actually did increase over the time of treatment and in only one or two cases did the allele burden actually go up, but in most cases there was a reduction, and in some case are pretty marked reduction in the JAK2 allele burden. As well, the symptom scores did decrease in the majority of patients who were treated on the study.

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MDM2 Inhibition: Idasanutlin (MPN-RC 115)

	n (%)				
	100 mg (n = 6)		150 mg (n = 6)		Total (N = 12)
	Grade 1/2	Grade 3	Grade 1/2	Grade 3	All grades
Diarrhea	5 (83.3)	1 (16.7)	5 (83.3)		11 (91.7)
Fatigue	4 (66.7)	2 (33.3)	3 (50.0)	1 (16.7)	10 (83.3)
Constipation	6 (100)		4 (66.7)		10 (83.3)
Nausea	5 (83.3)		5 (83.3)		10 (83.3)
Headache	4 (66.7)	1 (16.7)	2 (33.3)		7 (50)
Abdominal pain	4 (66.7)		2 (33.3)		6 (50)
Upper respiratory tract infection	1 (16.7)		4 (66.7)		5 (41.7)
Dry skin	2 (33.3)		2 (33.3)		4 (33.3)
Pain	2 (33.3)	1 (16.7)	1 (16.7)		4 (33.3)
Pruritus	2 (33.3)		2 (33.3)		4 (33.3)
Vomiting	3 (50.0)		1 (16.7)		4 (33.3)
Arthralgia	3 (50)				3 (25)
Dizziness	3 (50)				3 (25)

Mascarenhas J, et al *Blood.* 2019;134(6):525-533.

In terms of side effects, a vast majority of patients, 83% of patients experienced GI toxicity mainly diarrhea that was grade 1 or 2 with about 16% to 17% obtaining grade 3 level of diarrhea. Fatigue was a notable side effect in 66% of patients at grade 1 or 2, and at 33% of patients at a level of grade 3. Other notable side effects included nausea as well in this particular study.

Stratification for Thrombohemorrhagic Complications in PV

Low-risk	Age<60 years *and* No history of thrombosis *and* Platelet count<1.5 million *and* No cardiovascular risk factors	Thrombosis risk is not significantly increased compared to controls
High-risk	Age≥60 years *or* Previous thrombosis	Thrombosis risk is significantly increased
Indeterminate risk	Neither low nor high risk	Thrombosis risk is not well studied

Finazzi G, et al. *Leukemia*. 2008;22(8):1494-1502.

Now, other approaches for us to think about, we will shift gears and talk a little bit more about changing how we fundamentally approach our PV patients. As I've talked about at the beginning of our discussion today, we stratify patients into the low-risk, into the high-risk groups and our approach has been traditionally to give cytoreductive therapy to only the high-risk patients and really focus on phlebotomy and aspirin for low-risk patients. But the question remains is, is this the right approach? Could low-risk patients with PV still benefit from having cytoreductive therapy?

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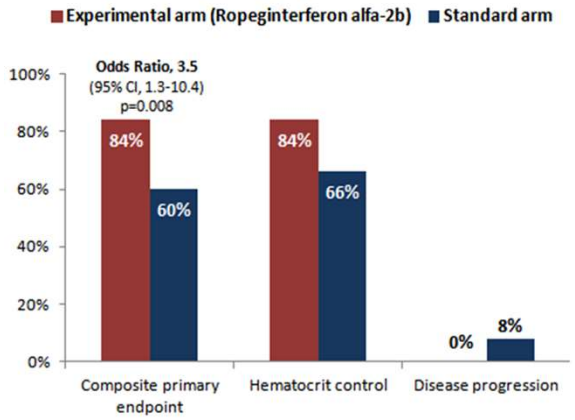
Phase 3 RCT Comparing Ropeginterferon vs Phlebotomy in Low-risk Patients with PV

Results of the Pre-planned Interim Analysis



Barbui T, et al. EHA Library. 06/14/20. 303391;LB2602.

This question has begun to be addressed in a study that was presented at the European Hematology Association as a plenary talk in 2020 and the study was a phase 2 randomized study that compared ropeg interferons, so again, this is the long-acting interferon given every two weeks versus phlebotomy in low-risk PV patients. The study looked at hematocrit control as well as disease progression. In fact, if we look at the composite endpoints, a higher number of patients, 84% of patients, achieve the endpoints of those treated with ropeg interferon versus 60% in standard therapy. In terms of hematocrit control, the proportions were roughly the same, 80% achieved control versus 66% in the standard arm, but interestingly, 8% of patients in the standard arm had disease progression, which was not observed in patients treated with ropeg interferon. This data is intriguing and raises the question, should we intervene earlier with therapeutics such as interferon which we think may have some disease-modifying ability? This is an important question and in fact the data safety monitor board of the study stopped the study based on these results. There is further follow-up coming, but the study was halted because of these results. It does now raise the question, should we intervene earlier? We will need to see more data in larger numbers of patients, but it is quite possible that the entire paradigm that we've talked about today in terms of approaching the treatment of these patients may change in the very near future.

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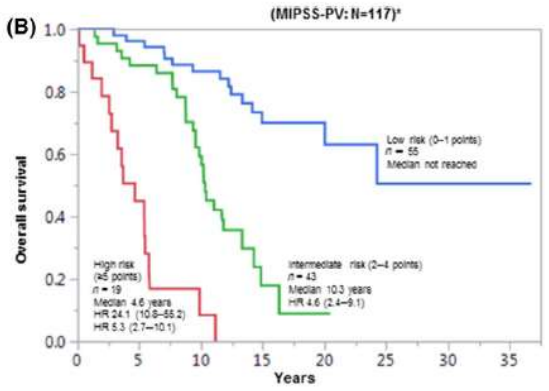
MIPSS-PV



- *SRSF2* mutation
- Abnormal karyotype
- Age >67
- Leukocyte count ≥15 x10^9/l

Tefferi A, et al. *Br J Haematol.* 2020;189(2):291-302.

Finally, the last point I will touch upon on today's presentation is that, we've talked extensively and almost exclusively today about thrombotic risk, and again, the reason for that is the greatest risk facing our PV patients is thrombotic events as well as bleeding events, but it's important to remember that progression to myelofibrosis or to acute leukemia remain significant risk for our patients and I think that this risk may increase with time. This risk assessment is important in somebody who is relatively younger. In somebody who may be diagnosed at the age of 80, the relevance may not be so great, but if somebody is diagnosed at the age of 50 who would otherwise have decades of life ahead, that risk of transformation to a more severe phase of the disease remains a very significant consideration. Now, we don't really have great prognostic tools in general to figure out who the progressors are going to be. This remains an open and important question in the MPN field. How can we predict which of our patients are going to have progressive disease? One tool that has been recently put forward is to use genomic data. So in general in patients with myelofibrosis, we have become quite good at using clinical factors as well as genomic factors to try to predict which patients will have the highest risk of progression. We are only beginning to do this now in patients with polycythemia vera and essential thrombocythemia. One risk-scoring tool has been published and put forth by the Mayo Clinic group, is the mutation-enhanced prognostic scoring system for polycythemia vera in which a number of variables emerged as potentially heralding disease progression and these include the presence of an SRSF2 mutation, which is a splicing-factor mutation, and has been implicated in the leukemic transformation of myelofibrosis patients, an abnormal karyotype, and age of diagnosis over the age of 67, and a leukocyte count over 15,000. Now these data remained to be validated in other studies, but at least this gives us the beginnings of a tool and a perspective to think about how we might prognosticate who are patients at highest risk of disease transformation are.

Emerging Therapies in Polycythemia Vera

Conclusions

- Goals of therapy in PV are aimed at symptom alleviation and reduction of thrombotic risk
- Prognostication of thrombosis as well as disease progression remain major challenges
- Cytoreductive therapies are usually reserved for patients refractory to, or intolerant of phlebotomy, as well as those at high thrombotic risk
- The order of therapies in first-line (hydroxycarbamide vs interferon) is under investigation. Notably, ropeginterferon was approved in first-line for PV based on phase 3 data
- Ruxolitinib is approved (US) for patients resistant or intolerant of hydroxycarbamide
- Several agents are under investigation for patients who fail current conventional therapies
- New data regarding the timing of cytoreductive therapy suggest a possible benefit for earlier intervention

To summarize, the goals of therapy in polycythemia vera are aimed at symptom alleviation and the reduction of the thrombotic risk. Prognostication of thrombosis as well as disease progression remains major challenges. We have no perfect tool to tell us who's going to have a clot and who is going to progress, but these are active areas of investigation. Cytoreductive therapies are usually reserved for patients who are refractory to or intolerant to phlebotomy, as well as those who fall into the high-risk thrombotic category but as we've talked about, that might change in the near future. The order of therapies in first line, hydroxycarbamide versus interferon is under investigation and notably, ropeginterferon was approved in the first line in the European Union based on phase 3 data. Ruxolitinib, a JAK1/2 inhibitor is approved in the United States for patients who fit the criteria of being intolerant or resistant to hydroxyurea as well as several other pathways are being investigated for patients who fail our current conventional therapies and we've talked about MDM2 inhibitors as an example of that. Finally, new data regarding the timing of cytoreductive therapy suggest a possible benefit for earlier intervention in our patients.

With that, I'd like to conclude and thank you for your attention.