Les syndromes myéloprolifératifs Ph négatifs

Ph Rousselot 2011

Myeloproliferative neoplasms

- ✓ Incidence

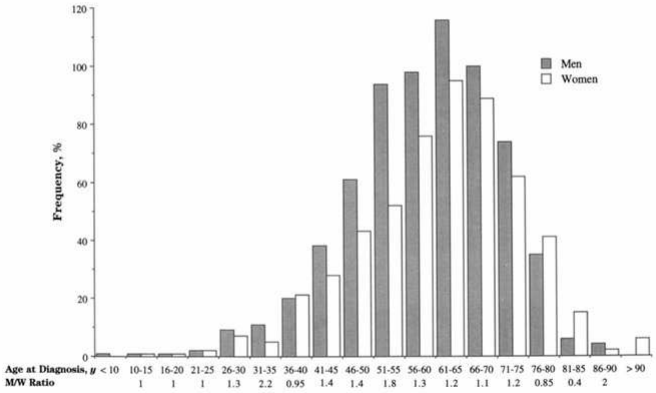
TABLE II. Characteristics of Chronic Myeloproliferative Disorders*

	AMM[a]	ET[a]	PV[b]
No. of patients, 1976–1995	21	39	50
Median age at Dx (range, year)	67 (43–84)	72 (18–90)	
Males, no.	8	14	31
Females, no.	13	25	19
Median Hb concentration at Dx (range, g/dL)	10.6 (6.2–15.7)	13.8 (8.7–17.1)	
Median platelet count at Dx (range, $\times 10^9$/L)	312 (16–984)	914 (649–1,696)	
Incidence rate (95% CI) (Patients/100,000/year) (U.S. white population 1990)	1.46 (0.82–2.09)	2.53 (1.77–3.40)	2.3 (1.4–2.5)
Median survival, months	36	130	86

Mesa, Am J Hematol, 1999

Myeloproliferative neoplasms

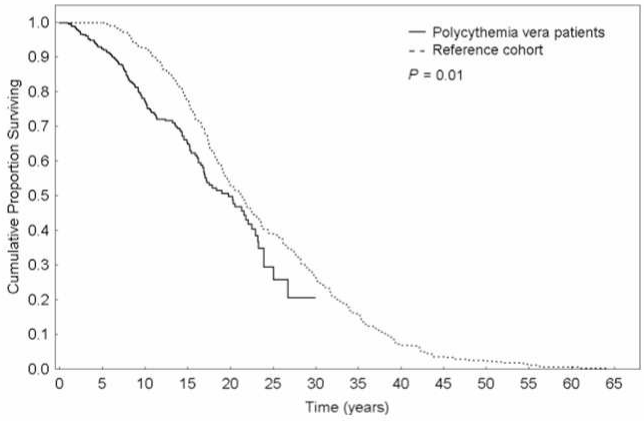
- ✓ Age at diagnosis (PV)



GISP, Ann Intern Med, 1995

Myeloproliferative neoplasms

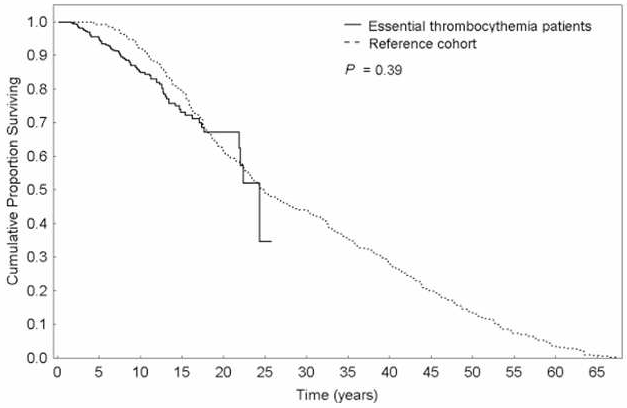
- ✓ Life expectancy (PV)



Passamonti, Am J Med, 2004

Myeloproliferative neoplasms

✓ Life expectancy (ET)



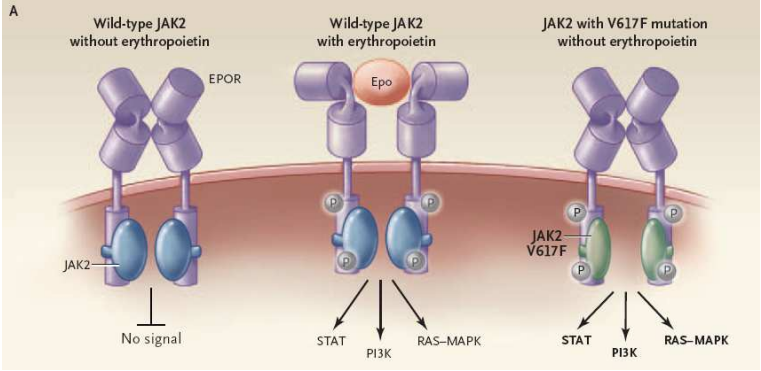
Passamonti, Am J Med, 2004

Circonstances de diagnostic

- NFS systématique

- Hyperhémie cutanée, conjonctivale
- Splénomégalie
- Signes d'hyperviscosité
  - Céphalées, vertiges, troubles visuels, confusion
- Complication thrombotique
  - Veineuse
  - Artérielle
  - Erythromélalgies
- Complication hémorragique (rare)
- Prurit

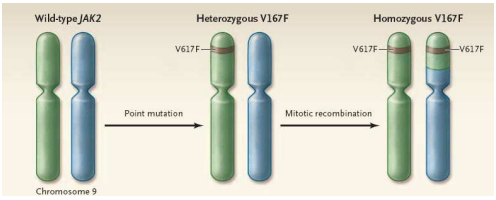
Physiopathologie



Kralovics R. N Engl J Med 2005 ; 352 : 1779-1790.
Goldman J. N Engl J Med 2005 ; 352 : 1779-1790
James C. Nature 2005 ; prepublished
Baxter E. Lancet 2005 ; 365 : 1054-1061.

Physiopathologie

- Mutation V617F ou exon 12
  - Pousse spontanée BFU, Mega
  - Perte d'hétérozygotie dans les PV



- > 95% des PV
- 50% des TE
  - Autres : MPL, …

Critères diagnostiques PV

Table 1. 2001 WHO criteria for polycythemia vera

2001 criteria for PV
A-criteria
AVANT : MASSE SANGUINE
2. No cause of secondary erythrocytosis, including:
a. Absence of familial erythrocytosis
b. No elevation of erythropoietin caused by:
i. Hypoxia (arterial $pO_2 \leq 92\%$)
ii. High oxygen affinity hemoglobin
iii. Truncated erythropoietin receptor
iv. Inappropriate erythropoietin production by tumor
3. Splenomegaly
4. Clonal genetic abnormality other than Philadelphia chromosome or *BCR-ABL* fusion gene in marrow cells
5. Endogenous erythroid colony formation
B-criteria
1. Thrombocytosis $> 400 \times 10^9$/L
2. Leukocytosis $> 12 \times 10^9$/L
3. Bone marrow biopsy showing panmyelosis with prominent erythroid and megakaryocytic proliferation
4. Low serum erythropoietin levels

Diagnosis requires the presence of the first 2 A-criteria together with either any 1 other A-criterion or 2 B-criteria.

Critères diagnostiques PV

Table 2. Proposed revised WHO criteria for polycythemia vera

Proposed criteria for PV
Major criteria
1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume*
2. Presence of tation such as *JAK2* exon 12 mut **MAINTENANT : jak2**
Minor criteria
1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. Serum erythropoietin level below the reference range for normal
3. Endogenous erythroid colony formation in vitro

Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria.

Evolution hématologique

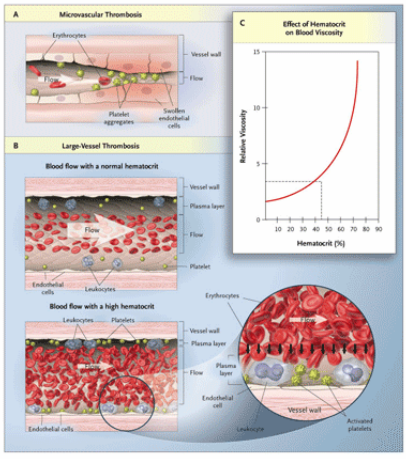
- Complications hématologiques : PV > TE
  - Myélofibrose
  - Myélodysplasie

    5 à 15% à 10 ans
  - Leucémies aiguës
- Facteurs de risque
  - Age
  - Durée d'évolution
  - Traitement par P32, pipobroman, busulphan

Finazzi G. Blood 2005 ; 105 : 2664-2670.

Risque vasculaire

- Complications vasculaires : PV
  - Risque de thrombose : 40% au cours de l'évolution
  - 20% des causes de décès
- Facteurs de risque
  - Taux Ht
  - Terrain (age, ATCD)



Spivak J. N Engl J Med 2004 ; 350 : 99-100.

Traitement : PV

- Prise en charge du risque vasculaire
  - Etude ECLAP : 518 patients randomisés (cohorte de 1638 patients dans 12 pays)
  - Aspirine 100 mg/j vs placebo
- Contrôle de l'hématocrite
  - Libre dans l'étude ECLAP

Landolfi R. N Engl J Med 2004 ; 350 : 114-124.

ECLAP : résultats

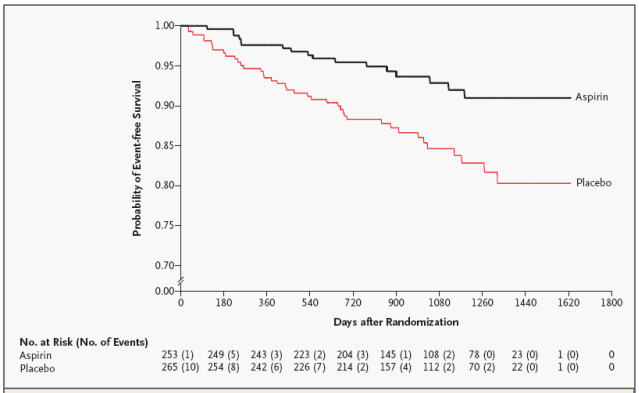
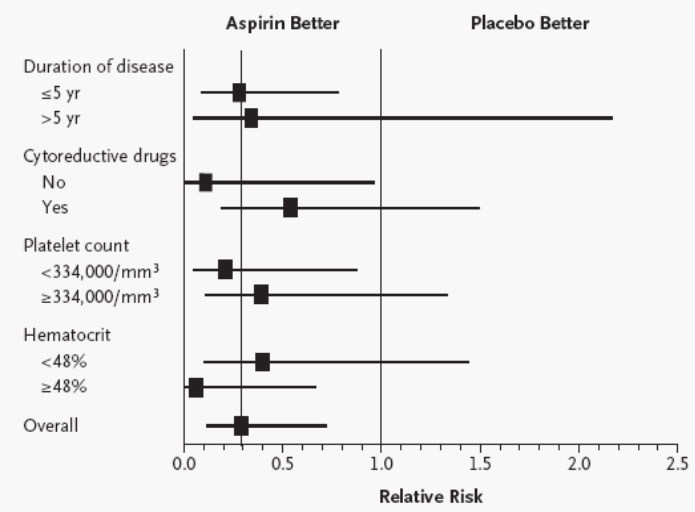


Figure 2. Probability of Survival Free of a Thrombotic Event.
The analysis was performed according to the intention-to-treat principle. The relative risk of a thrombotic event in the aspirin group, as compared with the placebo group, was 0.42 (95 percent confidence interval, 0.24 to 0.74; P=0.002 by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

ECLAP : résultats



Contrôle de l'hématocrite

- Saignées : à la phase initiale (Ht > 45%)
- Hydroxyurée (Hydréa®) : pas de risque leucémogène
- Pipobroman (Vercyte®) : risque leucémogène discuté
- P32 : pratiquement abandonné

Nouveaux traitements

- Interféron pegylé
  - Tolérance difficile chez le sujet agé
- Inhibiteurs de JAK2
  - Essais en cours

Critères diagnostiques de la thrombocytémie essentielle

Table 3. 2001 World Health Organization criteria for essential thrombocythemia

2001 criteria for ET
Positive criteria
1. Sustained platelet count ≥ 600 × 10^9/L
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes
Criteria of exclusion
1. No evidence of polycythemia vera
a. Normal red cell mass or hemoglobin < 18.5 g/dL in men, 16.5 g/dL in women
b. Stainable iron in marrow, normal serum ferritin, or normal MCV
c. If the former condition is not met, failure of iron trial to increase red cell mass or hemoglobin levels to the PV range
2. No evidence of chronic myeloid leukemia: no Philadelphia chromosome and no *BCR-ABL* fusion gene
3. No evidence of chronic idiopathic myelofibrosis
a. Collagen fibrosis absent
b. Reticulin fibrosis minimal or absent
4. No evidence of myelodysplastic syndrome
a. No del(5q), t(3;3)(q21;q26), inv(3)(q21q26)
b. No significant granulocytic dysplasia, few, if any, micromegakaryocytes
5. No evidence that thrombocytosis is reactive caused by
a. Underlying inflammation or infection
b. Underlying neoplasm
c. Prior splenectomy

Tefferi, Blood 2007

Critères diagnostiques de la thrombocytémie essentielle

Table 4. Proposed revised WHO criteria for essential thrombocythemia (ET)

Proposed criteria for ET
1. Sustained platelet count ≥ 450 × 10^9/L*
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis
3. Not meeting WHO criteria for PV,† PMF,‡ CML,§ MDS,¶ or other myeloid neoplasm
4. Demonstration of *JAK2*617V>F or other clonal marker, or in the absence of a clonal marker, no evidence for reactive thrombocytosis‖

Diagnosis requires meeting all 4 criteria.

* During the work-up period.

† Requires the failure of iron replacement therapy to increase hemoglobin level to the PV range in the presence of decreased serum ferritin. Exclusion of PV is based on hemoglobin and hematocrit levels, and red cell mass measurement is not required.

‡ Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow for age accompanied by megakaryocyte morphology that is typical for PMF– small to large with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous or irregularly folded nuclei and dense clustering.

§ Requires the absence of *BCR-ABL*.

¶ Requires absence of dyserythropoiesis and dysgranulopoiesis.

‖ Causes of reactive thrombocytosis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders. However, the presence of a condition associated with reactive thrombocytosis does not exclude the possibility of ET if the first three criteria are met.

Tefferi, Blood 2007

Frequences des complications

- Complications thrombotiques: 11–25% des patients[1]
- Hémorragie: 13–63% des patients[2-5]
- Occlusions microvasculaires: 30–40% des patients[6]
- Progression en LA: rare[7]

1. Elliot MA, Tefferi A. *Brit J Haematol* 2004; 128: 275-290
2. Buss DH et al. *Am J Hematol* 1985; 20: 365-372
3. Bellucci S et al. *Cancer* 1986; 58: 2440-2447
4. Hehlmann R et al. *Cancer* 1988; 61: 2487-2496
5. Kessler CM et al. *Brit J Haematol* 1982; 50: 157-167
6. Barbui T. *Semin Hematol* 2003; 40 (1) (Suppl 1): 22-25
7. Brière JB. *Orphanet J Rare Dis* 2007; 2 (3): 1-17

Importance de l'âge et des ATCD thrombotiques

Risque de thromboses dans les TE[1]

Risk factor	Rate of thrombotic events (Percent/ patient-year)	Odds ratio (95% confidence limits)	p value
Previous thrombosis			
No	3.4	1.0*	
Yes	31.4	13 (4.07 – 41.52)	< 0.0005
Age (years)			
<40	1.70	1.0*	–
40–60	6.3	3.88 (0.70 – 21.5)	NS
>60	15.1	10.28 (2.05 – 51.5)	< 0.001

Abbreviation: NS, not seen, *Reference category

1. Cortelazzo S et al. *J Clin Oncol* 1990; 8 (3): 556-562

Stratification par groupes de risque

Faible risque	**Patients <60 ans et:** Pas d'ATCD de thromboses Plaquettes <1500 x 10^9/L
Intermediaire	**Patients 40–60 ans et:** Présence de facteurs de risques cardiovasculaires ou thrombophilie familiale Plaquettes < 1500 x 10^9/L
Haut risque	**Patients >60 years Ou présence de:** ATCD de throboses ou accident hémorragique majeur **OU** Plaquettes >1500 x 10^9/L

1. Finazzi G, Harrison C. *Semin Hematol* 2005; 42: 230-238

JAK2 V617F et risque thrombotique

Publication	N	Any correlation with thrombotic risk
Cheung *et al.* 2005[1]	60	**Yes**
Campbell *et al.* 2005[2]	776	**Yes***
Wolanskyj *et al.* 2005[3]	150	**No**
Kittur *et al.* 2007[4]	176	**Yes****
Speletas *et al.* 2007[5]	111	**No**
Arellano-Rodrigo *et al.* 2006[6]	49	**No**
Heller *et al.* 2006[7]	50	**Yes**
Carobbio *et al.* 2007[8]	439	**No**
Finazzi *et al.* 2007[9]	179	**Yes**
Ohyashiki *et al.* 2007[10]	51	**Yes**
Pemmaraju *et al.* 2007[11]	80	**No**

Considerations:

- **Methodologies differentes**
- **Le temps (avant ou après le diagnosique) et le type (arterielle or veineuse) de thromboses peuvent interférer.**

*Only significant in year before diagnosis, venous thrombosis

**Only significant during follow up, venous thrombosis

1. Cheung B, Radia D, Pantelidis P, *et al. Br J Haematol* 2005;132:244-250
2. Campbell PJ, Scott LM, Buck G, *et al. Lancet* 2005;366:1945-1953
3. Wolanskyj AP, Lasho TL, Schwager SM, *et al. Br J Haematol* 2005;131:208-213
4. Kittur J, Knudson RA, Lasho TL, *et al. Cancer* 2007;109:2279-2284
5. Speletas M, Katodritou E, Daiou C, *et al. Leuk Res* 2007;31:1053-1062
6. Arellano-Rodrigo E, Alvarez-Larrán A, Reverter JC, *et al. Haematologica* 2006;91:169-175
7. Heller PG, Lev PR, Salim JP, *et al. Eur J Haematol* 2006;77:210-216
8. Carobbio A, Finazzi G, Guerini V, *et al. Blood* 2007;109:2310-2313
9. Finazzi G, Rambaldi A, Guerini V, *et al. Haematologica* 2007;92:135-136
10. Ohyashiki K, Aota Y, Akahane D, *et al. Leukemia* 2007;21:1097-1099
11. Pemmaraju N, Molterno AR, Williams DM, *et al. Leukemia* 2007;21:2210-2212

Thrombose et hyperleucocytose

Carobbio et al, Blood, Mai 2007

Série de 439 patients

Risk factors	Baseline analysis	Time-dependent analysis
Sex	.1	.2
Standard Risk factors	.004	.04
HU		.02
Antiplatelets		.02
WBC>8.7 G/L	**.001**	.06
Hb>14g/dL	.07	.07
Hct>42%.6	.6	.4
PLT>784 G/L	.1	.7

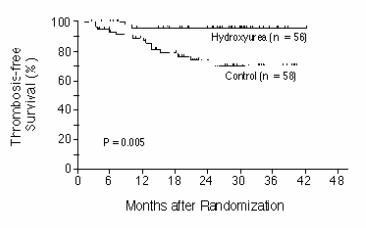
Traitement

- Prise en charge du risque vasculaire
  - Hydroxyurée : si haut risque ou risque intermédiaire
  - Antiagrégants

Table 2. Incidence of Thrombosis in 114 Patients with Essential Thrombocythemia.

Type of Thrombosis	Hydroxyurea Group (N=56)	Control Group (N=58)
	no. (%)	
Arterial	2 (100)	11 (79)
Transient ischemic attacks	0	5
Digital microvascular ischemia	0	5
Stroke	1	1
Myocardial infarction	1	0
Venous	0	3 (21)
Superficial thrombophlebitis	0	2
Iliofemoral venous thrombosis	0	1
Total (% of treatment group)	2 (3.6)	14 (24)*

*There was a difference of 20.4 percentage points in the rate of thrombosis between the groups (95 percent confidence interval, 8.5 to 32 percent, chi-square with Yates' correction, 8.2, 1 df; P = 0.003).



Cortelazzo S. N Engl J Med 1995 ; 332 : 1132-1137.

Anagrélide

- Etude MRC PT1
- Anagrélide + aspirine vs Hydréa + aspirine
- 809 patients à haut risque (age, plaquettes)
- Suivi médian de 89 mois
- Risque complication vasculaire : 1.57 (p=0.03)

	Anagrelide	Hydroxyurée	OR
Thromboses artérielles	37	17	2.16
Thromboses veineuse	3	14	0.27
Hémorragies	22	8	2.61

Green A. ASH 2004 abst 6.

- Complications
  - Cardiomyopathies réversibles

EXELS Study

Evaluation of Xagrid® Efficacy and Long-term Safety

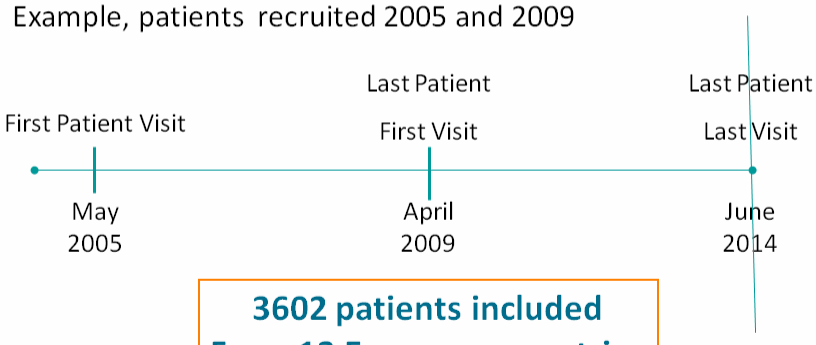
- ✓ EXELS is being conducted in Europe, where Xagrid® (anagrelide) is licensed as an orphan drug for thrombocythemia in at-risk ET patients as second-line therapy
- ✓ The data presented were collected from analyzes performed in June 2010

EXELS
EVALUATION OF XAGRID EFFICACY AND LONG-TERM SAFETY

Study Design

6-monthly data collection during 5 years for each patient

Example, patients recruited 2005 and 2009



3602 patients included
From 13 European countries

Age at registration

Age categories, n

< 50	607
< 60	1169
> 60	2340
> 80	**469**

Gender by age group

Gender	**< 60**	**60 - 69**	**> 80**
Female	62 %	60 %	66 %
Male	38 %	40 %	34 %

History of vascular events by age group

Previous vascular event	< 80	> 80
Yes	**36 %**	**41 %**
No	61 %	56 %
Missing data	*3 %*	*3 %*

Anti aggregation by age group

	< 60	60 - 69	> 80
Yes	66 %	70 %	69 %
No	34 %	30 %	31 %

Cytoreductive therapy
at any time in the study

	Number of Patients
Hydroxyurea	2647 (62%)
Xagrid®	1123 (26%)
Interferon alpha	248 (6%)
Pipobroman	129 (3%)
Busulphan	65 (2%)
P32	3
Other	35

	All patients	Anagrelide	Other
Mean age (yrs)	64	55	67

Subjects changing therapy
by age categories

From \ To	No switch	HU	Other	Ana	Ana + HU
HU < 60	78 %	0	9 %	6 %	7 %
60 - 79	87 %	0	8 %	3 %	3 %
> 80	87 %	0	11 %	1 %	1 %
Other	55 %	6 %	30 %	10 %	0
	73 %	9 %	13 %	4 %	0
	61 %	3 %	36 %	0	0
Anagrelide	79 %	4 %	9 %	0	8 %
	75 %	8 %	9 %	0	7 %
	57 %	10 %	26 %	0	7 %
Ana + HU	56 %	16 %	1 %	26 %	0
	64 %	11 %	4 %	21 %	0
	50 %	17 %	8 %	25 %	0

Time to first switch
by age categories

Median, days	< 60	60 - 79	> 80
HU	200	304	285
Anagrelide	261	206	337

Reasons for switch
by age categories

	< 60	60 - 79	> 80
Intolerance	**32 %**	**41 %**	**31 %**
Non-efficacious	**21 %**	**17 %**	**14 %**
Subject preference	10 %	4 %	1 %
Other	37 %	38 %	45 %
Unknown	5 %	3 %	8 %

Predefined events reported

	< 60	60 - 79	> 80
Any PDE	75 (6.5%)	253 (13%)	94 (20%)
MI + angina	1 (0.08%)	19 (0.9%)	8 (1.7%)
Stroke	4 (0.3%)	47 (0.2%)	5 (1%)
TIA	4 (0.3%)	8 (0.4%)	1 (0.2%)
Venous thrombosis	1 (0.08%)	20 (1%)	8 (1.7%)
Severe hemorrhage	9 (0.7%)	16 (0.8%)	4 (0.8%)
Transformation	11 (0.9%)	20 (1%)	9 (1.9%)

Myeloproliferative neoplasms

- ✓ Risk stratification

ET	PV
Age	**Age**
History of thrombosis	History of thrombosis
Platelet count	
Leukocytosis?	*Leukocytosis?*
% JAK2V617F?	*% JAK2V617F?*

Conclusion

- Pas de véritable spécificité du sujet agé
- AGE : facteur de risque
- Profil de tolérance des traitements (HU, anagrélide) similaire
- Peu ou pas d'expérience avec Interféron