FRENCH INTERGROUP MYELOPROLIFERATIVE DISORDERS

Hôpital Saint-Louis centre hospitalo-universitaire et de recherche

université PARIS DIDEROT PARIS 7

Interferon in MPN: Long-term results and future studies

Jean-Jacques KILADJIAN, MD, PhD

Clinical Investigations Center, Saint-Louis Hospital, Paris

Paris Diderot University

IWG-MRT, Florence, April 16, 2011

IFN in MPN

✓ Biological rationale for the use of interferon in MPN

✓ Clinical trials of IFN in MPDs

✓ IFN effect on the MPD clone

✓ Perspectives

INTERFERON

1957: IFN is the first cytokine discovered *(Isaacs & Lindenmann)*

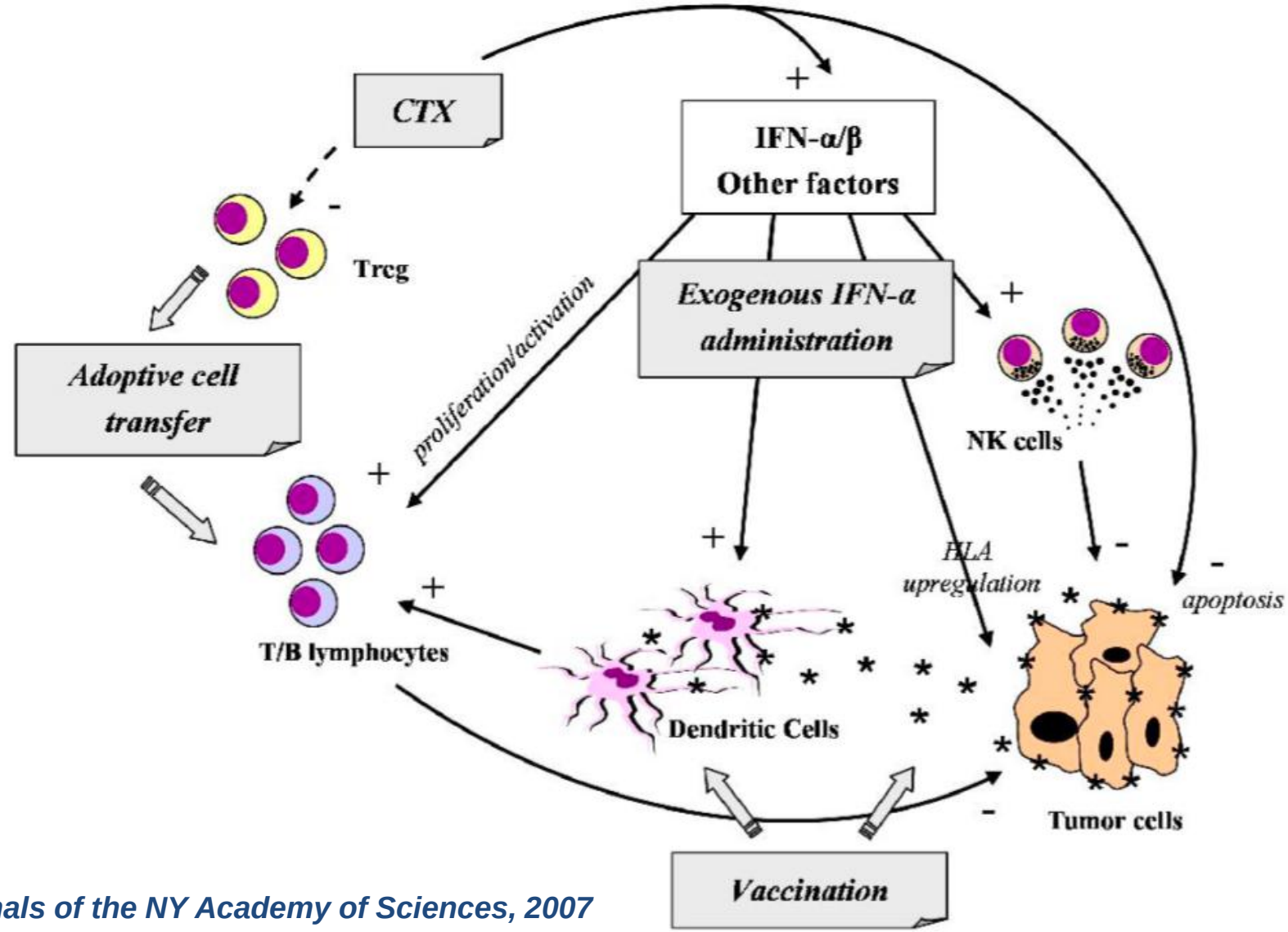
1978: purification, analyses and characterization

1980: Cloning recombinant human IFN-alpha and beta

1986: FDA approval for the treatment of Hairy cell leukemia

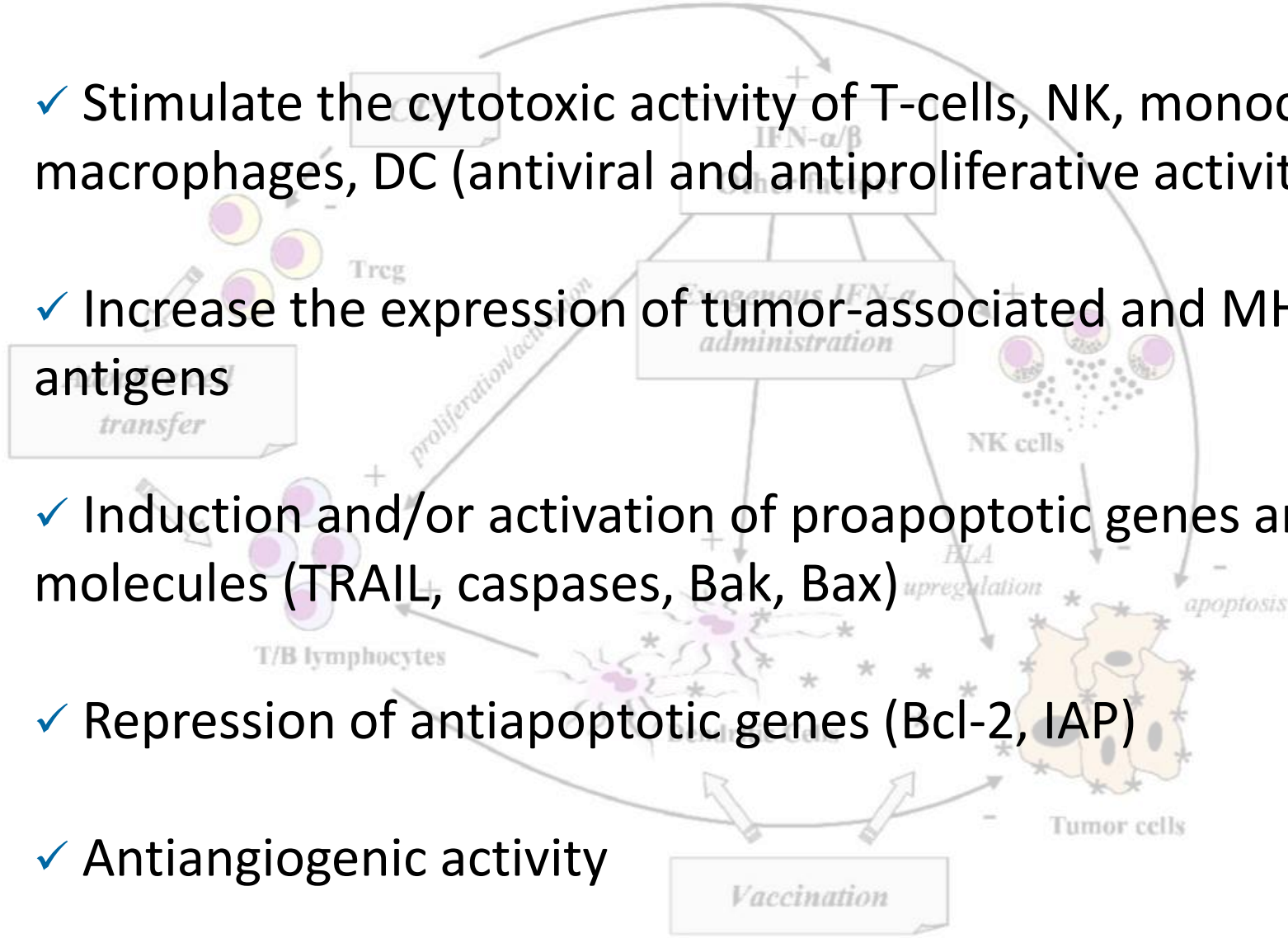
1985 - 1988: First reports of efficacy in ET *(H. Ludwig)* and PV *(R. Silver)*

ACTIVITIES OF INTERFERONS



Bracci, Annals of the NY Academy of Sciences, 2007

ACTIVITIES OF INTERFERONS



✓ Stimulate the cytotoxic activity of T-cells, NK, monocytes, macrophages, DC (antiviral and antiproliferative activities)

✓ Increase the expression of tumor-associated and MHC-I antigens

✓ Induction and/or activation of proapoptotic genes and molecules (TRAIL, caspases, Bak, Bax)

✓ Repression of antiapoptotic genes (Bcl-2, IAP)

✓ Antiangiogenic activity

ACTIVITIES OF INTERFERONS IN MPN

- ✓ Inhibit MK proliferation and TPO-induced MPL signaling

  Wang, Blood, 2000

- ✓ Inhibit EEC and endogenous MK colony growth

  Dudley, Br J H, 1990; Castello, Br J H, 1994

- ✓ Predominant activity against clonal BFU-E

- ✓ Antagonizes PDGF, inhibits the growth of marrow-derived fibroblasts

ACTIVITIES OF INTERFERONS IN MPN

✓ Induce cytogenetic remission

Hino, Ann Hematol, 1993; Messora, Br J H, 1994

✓ Reversion from monoclonal to polyclonal patterns of hematopoiesis

Massaro, Am J Hematol, 1997; Liu, Blood, 2003

IFN in MPN

- ✓ Biology of Interferons
- ✓ Clinical trials of IFN in MPNs
- ✓ IFN effect on the MPN clone
- ✓ Perspectives

Clinical Studies - PV

Author, year	Number of patients	Reduction of PHL (%)	Freedom from PHL (%)	Discontinuations 1st year (%)	Discontinuations total	Type of IFN
Cacciola, 1991[69]	11	9 (82)	5 (45)	0	NA	NA
Cimino, 1993[70]	13	10 (77)	4 (31)	0	NA	α2b
Finelli, 1993[71]	13	11 (85)	11 (85)	3 (23%)	NA	NA
Turri, 1991[72]	11	7 (64)	4 (36)	0	0	α2a
Papineschi, 1994[73]	11	9 (82)	8 (73)	NA	NA	α2a
Sacchi, 1994[74]	22	21 (95)	21 (95)	0	0	hl-IFN
Muller, 1995[75]	15	7 (47%)	NA	4 (27%)	6 (40%)	α2b
Taylor, 1996[76]	17	14 (82)	9 (53)	2 (12%)	6 (35%)	NA
Foa, 1998[77]	38	19 (50)	11 (29)	11 (29%)	16 (42%)	α2a
Gilbert, 1998[78]	31	NA	NA	NA	7 (23%)	α2b
Stasi, 1998[79]	18	17 (94)	11 (61)	0	NA	hl-IFN
Heis, 1999[80]	32	28 (87)	2 (6%)	4 (12%)	10 (31%)	NA
Radin, 2003[81]	12	5 (42)	1 (8)	NA	NA	NA
Silver, 2006[34]	55	55 (100)	53 (96)	NA	8 (14%)	α2a, α2b
Samuelsson, 2006[82]	21	7/9 (78)	4/9 (44)	NA	7/23 (30%)	peg-α2b
Kiladjian, 2008[23]	37	37 (100)	36 (97)	3 (8%)	13 (35%)	peg-α2a
Total	349	260/318 (82%)	182/303 (60%)	27/227 (12%)	82/281 (29%)	

NA: data not available, PHL: phlebotomy, hl-IFN: human leukocyte interferon.

Kiladjian, Mesa & Hoffman., Blood, 2011

Clinical Studies - ET

Clinical Studies - ET

Author, year	*Number of patients*	*Response rate (%)*	*Discontinuation n (%)*	*Type of IFN*
Bellucci, 1988[27]	12	NA	4 (33)	α2a
Giles, 1988[28]	18	100	0	α2a and α2b
Gugliotta, 1989[44]	10	100	NA	α2a
Lazzarino, 1989[45]	26	86	9 (35)	α2b
Giralt, 1991[46]	13	69	NA	α2b
Gisslinger, 1991[47]	20	85	10 (50)	α2c
Sacchi, 1991[48]	35	85	4 (11)	α2b
Turri, 1991[32]	10	70	1 (10)	α2a
Seewann, 1991[49]	19	80	6 (30)	α2b
Kasparu, 1992[50]	14	86	0	α2b
Rametta, 1994[51]	25	92	NA	α2b
Berte, 1996[52]	12	83	NA	α2a and α2b
Sacchi, 1998[53]	11	100	1 (9)	α
Radin, 2003[41]	17	88	NA	α2
Alvarado, 2003[54]	11	100	2 (18)	peg-α2b
Saba, 2005[55]	20	75	3 (15)	α2a
Langer, 2005[56]	36	75	13 (36)	peg-α2b
Samuelsson, 2006[43]	21	70	11 (55)	peg-α2b
Jabbour, 2007[57]	13	70	NA	peg-α2b
Total	343	84	23	

Abbreviations: IFN, interferon; NA, data not available.

Kiladjian, Mesa & Hoffman., Blood, 2011

Clinical Studies - PMF

Clinical Studies - PMF

Author, year	*Number of patients*	*Response rate (%)*	*Spleen size reduction (% of patients)*	*Discontinuation (%)*	*Type of IFN*
Gilbert, 1998[38]	22	NA	58	46	α2b
Tefferi, 2001[58]	11	0	18	64	α2
Heis-Vahidi-Fard, 2001[59]	9	0	20	67	γ
Radin, 2003[41]	31	3	33	NA	α2
Jabbour, 2007[57]	11	9	NA	26	peg-α2b
Total	84	3	32	51	

Abbreviations: IFN, interferon; NA, data not available.

Kiladjian, Mesa & Hoffman., Blood, 2011

Clinical Studies - PMF

Author, year	*Number of patients*	*Response rate (%)*	*Spleen size reduction (% of patients)*	*Discontinuation (%)*	*Type of IFN*
Gilbert, 1998[38]	22	NA	58	46	α2b
Tefferi, 2001[58]	11	0	18	64	α2
Heis-Vahidi-Fard, 2001[59]	9	0	20	67	γ
Radin, 2003[41]	31	3	33	NA	α2
Jabbour, 2007[57]	11	9	NA	26	peg-α2b
Total	84	3	32	51	

Abbreviations: IFN, interferon; NA, data not available.

Clinical Studies - PMF

Author, year	*Number of patients*	*Response rate (%)*	*Spleen size reduction (% of patients)*	*Discontinuation (%)*	*Type of IFN*
Gilbert, 1998[38]	22	NA	58	46	α2b
Tefferi, 2001[58]	11	0	18	64	α2
Heis-Vahidi-Fard, 2001[59]	9	0	20	67	γ
Radin, 2003[41]	31	3	33	NA	α2
Jabbour, 2007[57]	11	9	NA	26	peg-α2b
Total	84	3	32	51	

Abbreviations: IFN, interferon; NA, data not available.

Clinical Studies - standard IFN-α

- ✓ IFN-□ is an effective agent for treating PV and ET
- ✓ Recommended in PV and ET patients < 40 years

Barbui, Haematologica, 2004

McMullin, BJH, 2005

- ✓ Non leukemogenic

Silver, Semin Thromb Hemost, 2006

Schafer, NEJM, 2004

Finazzi, Blood, 2007

Mesa, Hematology, 2007

Vannucchi, CA Cancer J Clin, 2009

Cervantes, Eur J Haematol, 2007

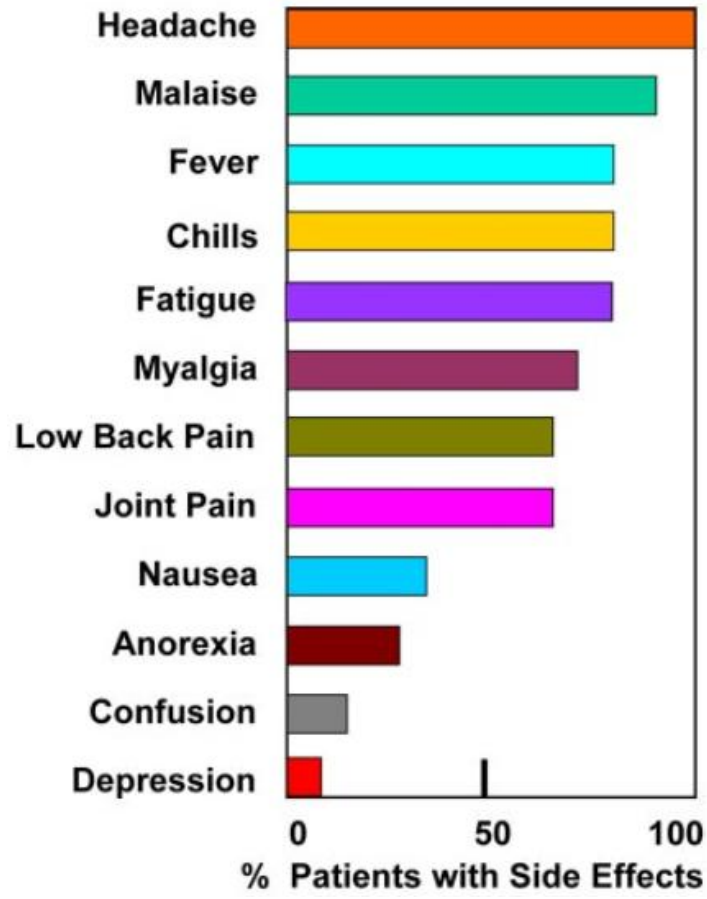
Spivak, Blood, 2002

Penninga, Drugs, 2006

McMullin, Hematol Oncol, 2007

Birgegard, Ann Hematol, 2008

Clinical Studies - standard IFN-α



Pestka, JBC, 2007

Pegylated IFN-α

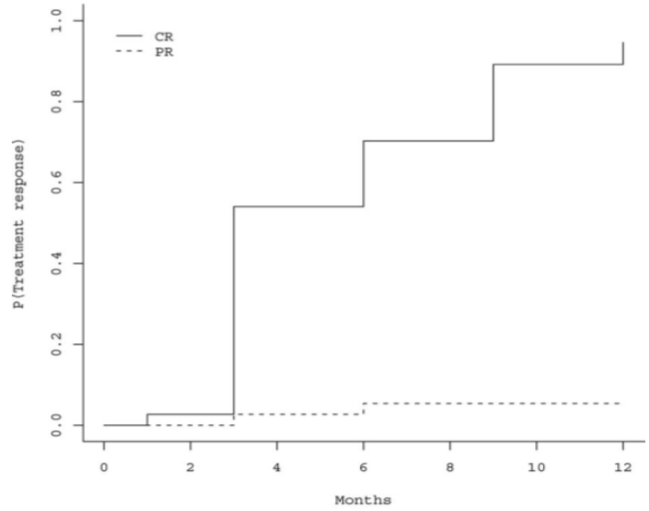
- ✓ PEG-conjugated, increases serum half-life
- ✓ Weekly administration, better compliance
- ✓ Peg-IFNa has better efficacy than standard IFNa in hepatitis C
- ✓ Peg-IFNa-2b is effective in ET, no clear advantage in terms of toxicity

Langer, Haematologica, 2005; Gugliotta, ASH, 2005

Peg-IFNα-2a in MPN

✓ Hematologic responses

	PVN-1 (PV n=37)
CR	91%
PR	9%
Failure	0%



Kiladjian, Blood, 2008

Peg-IFNα-2a in MPN

✓ Toxicity

	PVN-1 (PV n=37)	PV + ET (n=76)
Total AEs	**89%**	96%

Kiladjian, Blood, 2008

Quintas Cardama, JCO, 2009

Peg-IFNα-2a in MPN

✓ Toxicity

	PVN-1 (PV n=37)	PV + ET (n=76)
Total AEs	**89%**	96%
Discont. for tox	**8%**	10%
Discont. total	**35%**	22%

✓ Start at low dose

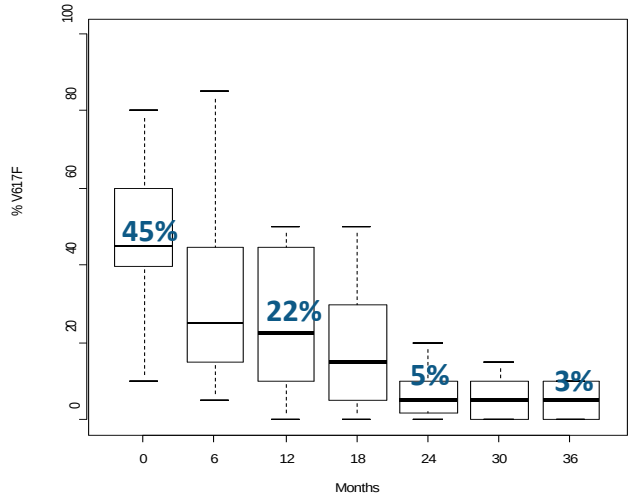
Kiladjian, Blood, 2008

Quintas Cardama, JCO, 2009

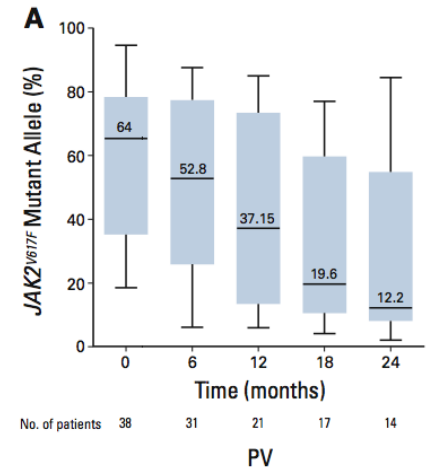
Peg-IFNα-2a in MPN

✓ Molecular responses

	PVN-1 (3 yrs FU)	PV (2 yrs FU)	ET (2 yrs FU)
CMR	7/29 (24%)	5/35 (14%)	1/16 (6%)
PMR	14/29 (48%)	11/35 (31%)	2/16 (13%)
Minor MR	5/29 (17%)	3/35 (9%)	3/16 (19%)
No response	3/29 (10%)	16/35 (46%)	10/16 (62%)%



Kiladjian, Blood, 2008

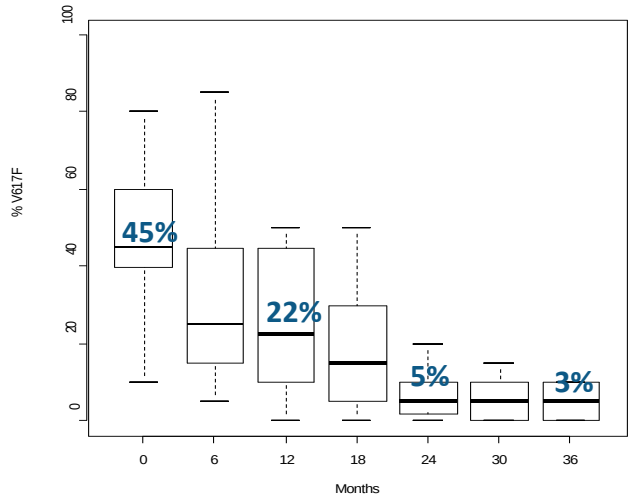


Quintas Cardama, JCO, 2009

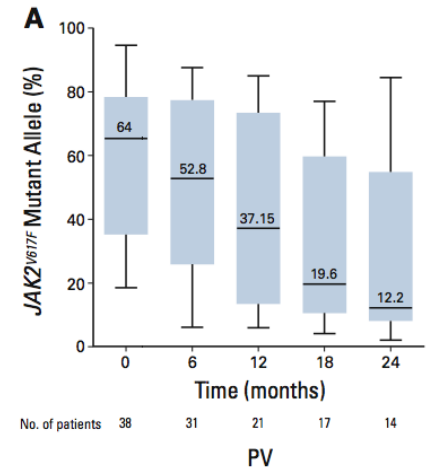
Peg-IFNα-2a in MPN

✓ Molecular responses

	PVN-1 (3 yrs FU)	PV (2 yrs FU)	ET (2 yrs FU)
CMR	**7/29 (24%)**	5/35 (14%)	1/16 (6%)
PMR	14/29 (48%)	11/35 (31%)	2/16 (13%)
Minor MR	5/29 (17%)	3/35 (9%)	3/16 (19%)
No response	3/29 (10%)	16/35 (46%)	10/16 (62%)%



Kiladjian, Blood, 2008



Quintas Cardama, JCO, 2009

PVN-1 - Update
(median FU: 55 months)

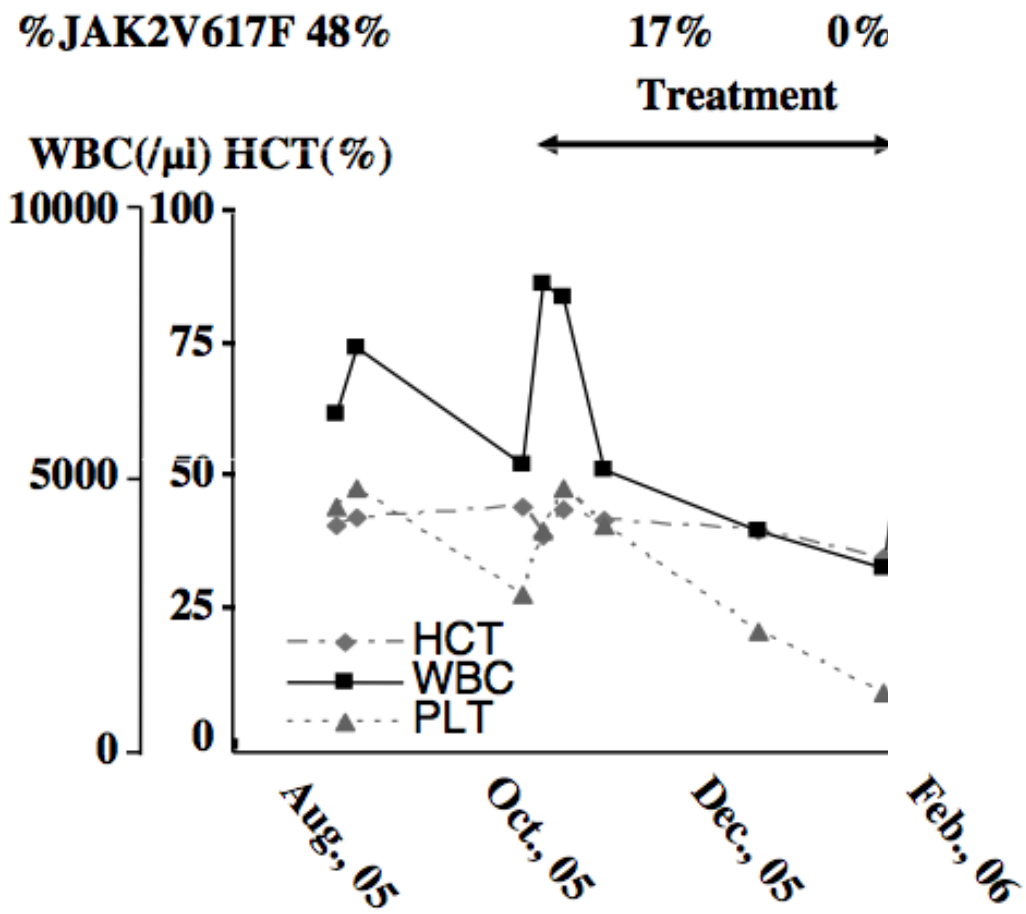
- ✓ Complete Molecular responses
- ✓ 9/29 (31%) patients
  - 4 still in mol-CR (19 - 42+ months)
  - 1 off-therapy for 26 months
- ✓ 5 molecular relapses, all in hematological CR

New question

Complete disappearance of JAK2V617F in peripheral blood granulocytes:

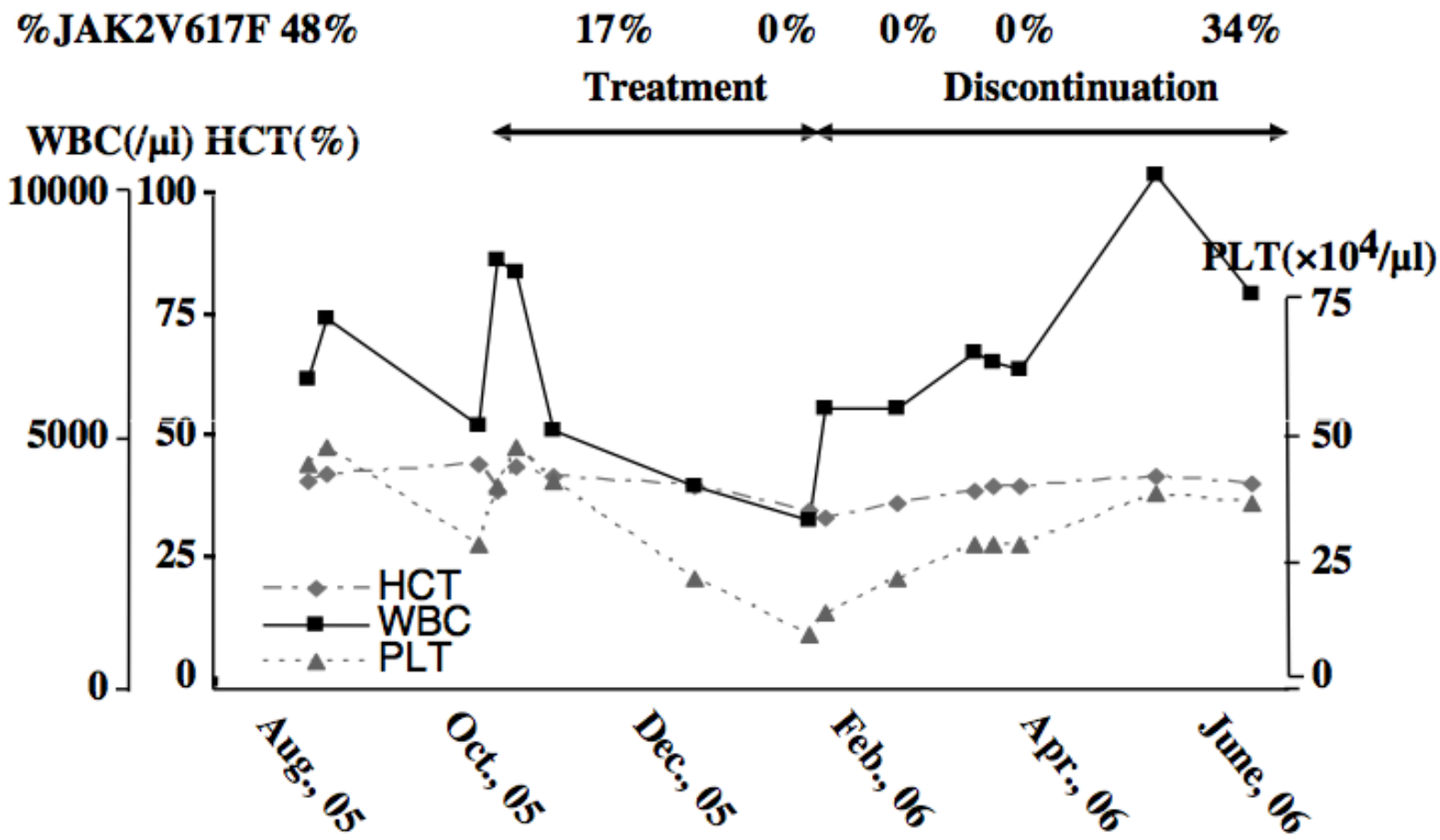
Is the JAK2-mutated clone eradicated?

Evolution of the JAK2V617F clone



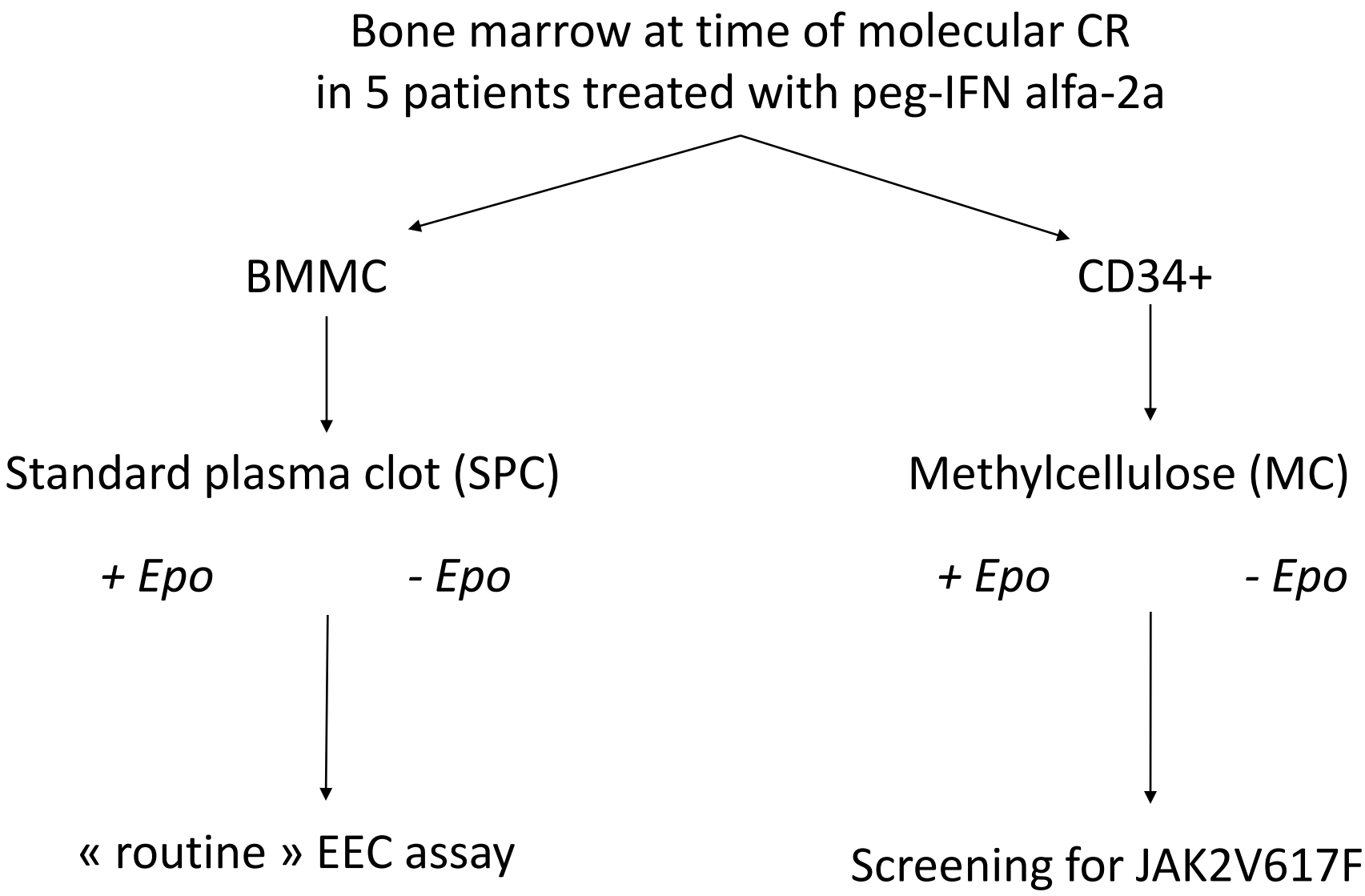
Ishii, Leukemia, 2007

Evolution of the JAK2V617F clone



Ishii, Leukemia, 2007

Evolution of the JAK2V617F clone



Evolution of the JAK2V617F clone

MC assay (CD34+)

In 1 patient, all colonies (with and without EPO) were V617F-neg

Patient	EEC	Colonies +Epo	%	V617F in EEC	V617F in col. +Epo
1	1	41	2.4	**0 / 5**	**0 / 109**
2	0	23	0	-	1 / 64
3	1	17	5.8	4 / 9	3 / 80
4	2	44	4.5	0 / 26	2 / 117
5	4	75	5.3	1 / 28	9 / 156

Kiladjian et al., Leukemia, 2010

Evolution of the MPN clone

JAK2-mutated cells: just a sub-clone?

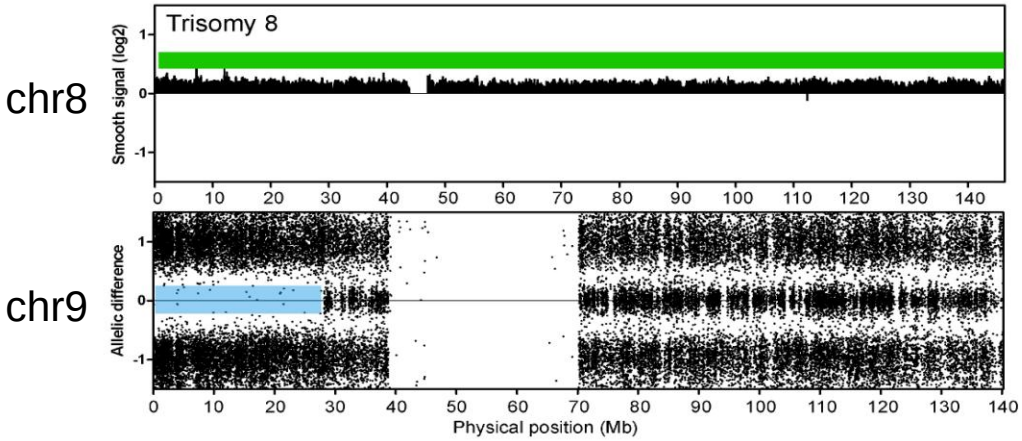
R. Kralovics

Evolution of the MPN clone

JAK2-mutated cells: just a sub-clone?

Before IFN

JAK2 V617F: 100%
Trisomy 8
9pUPD



Affymetrix SNP 6.0 microarray analysis, granulocyte DNA

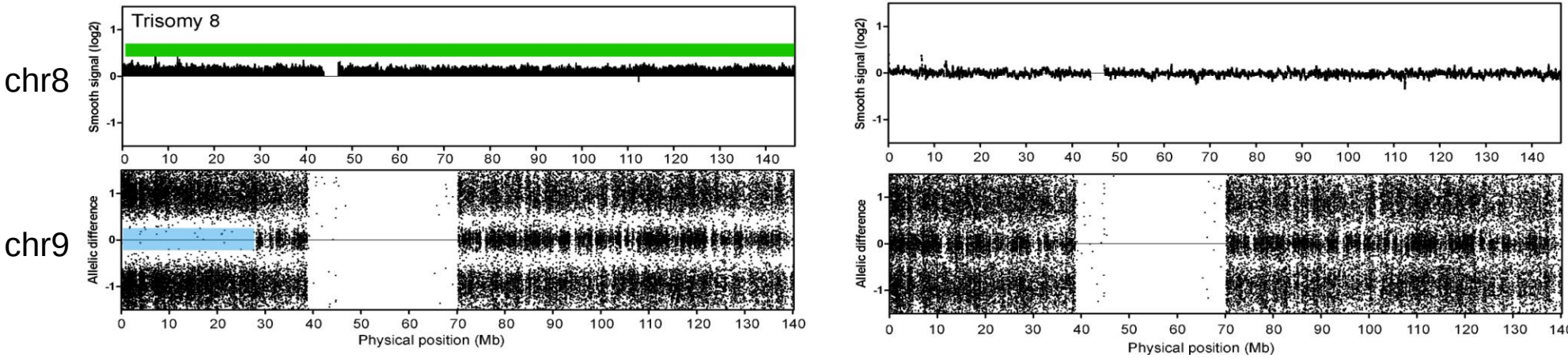
gain
UPD

R. Kralovics

Evolution of the MPN clone

JAK2-mutated cells: just a sub-clone?

Before IFN	After IFN
JAK2 V617F: 100% **Trisomy 8** **9pUPD**	**JAK2 V617F: 10%** **Normal karyotype**



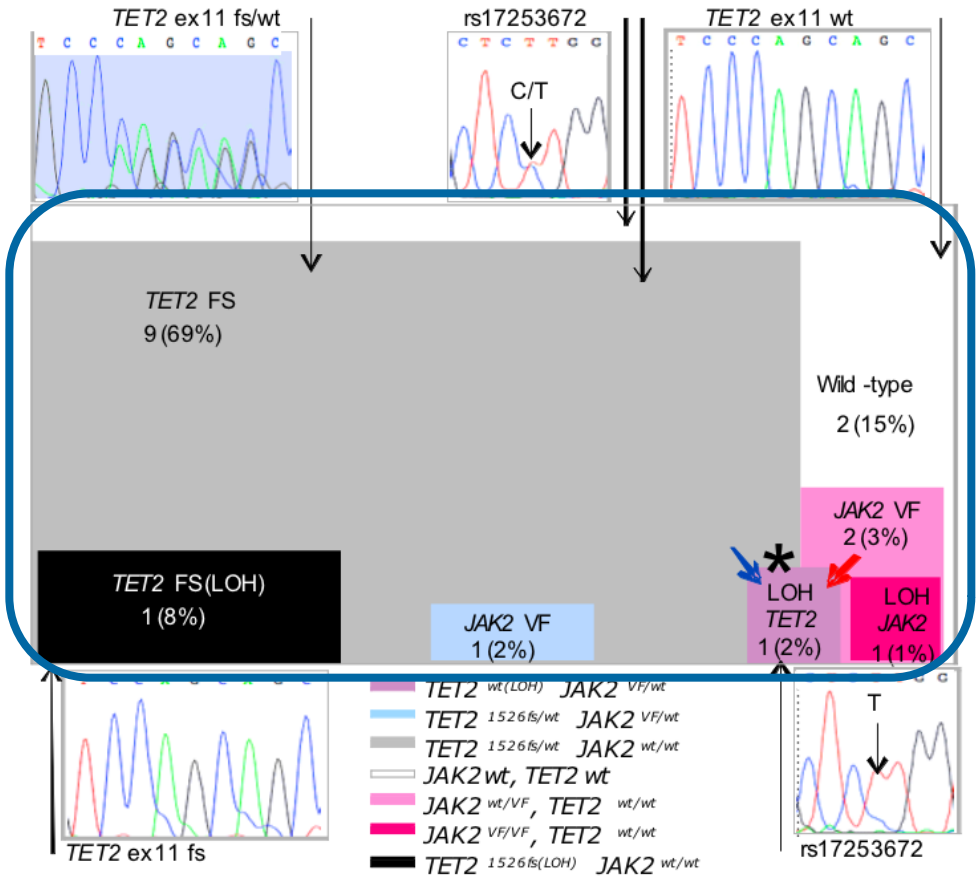
Affymetrix SNP 6.0 microarray analysis, granulocyte DNA

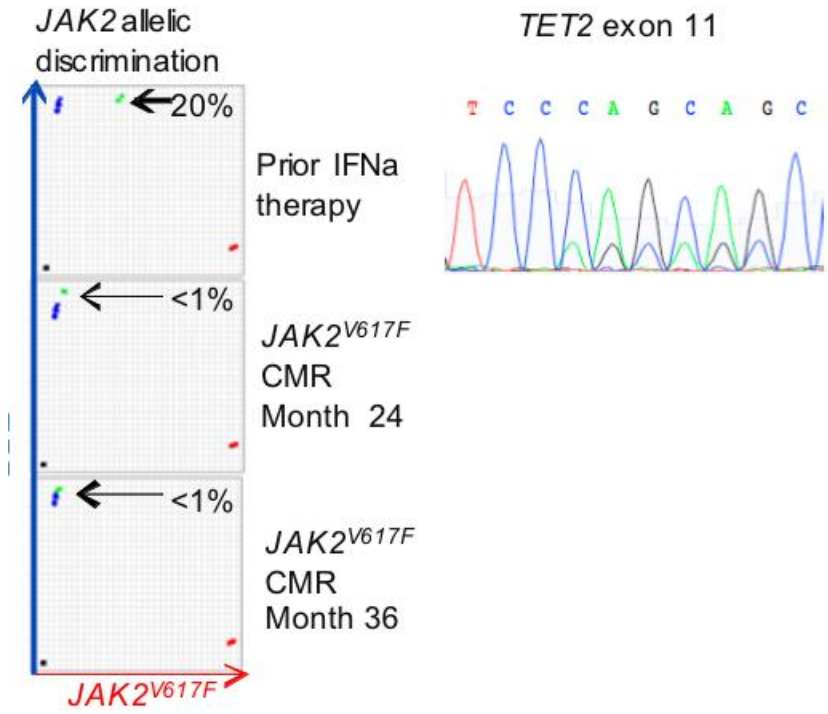
gain
UPD

R. Kralovics

Evolution of the MPN clone

JAK2-mutated cells: just a sub-clone?





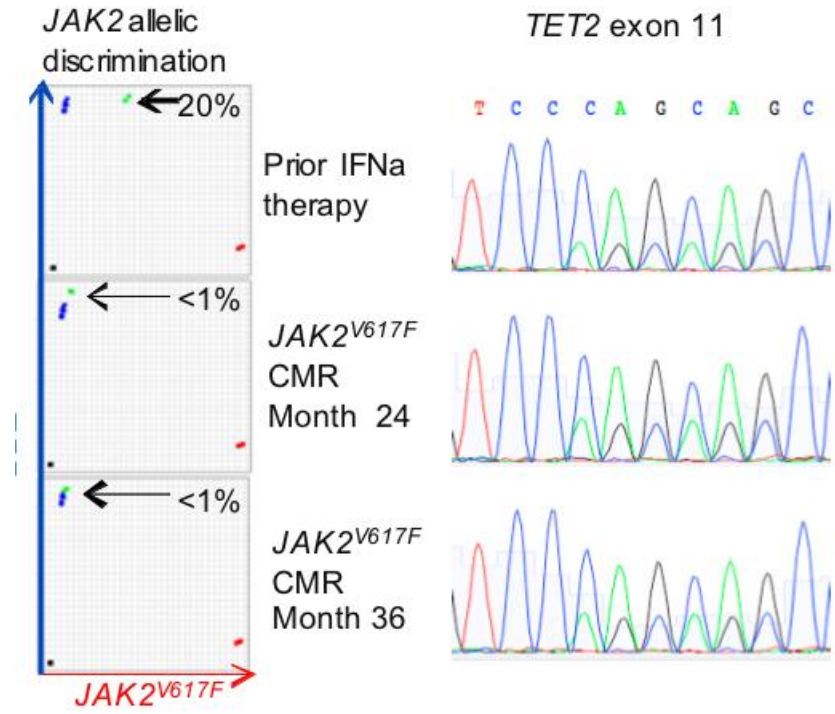
Kiladjian et al., Leukemia, 2010

Evolution of the MPN clone

JAK2-mutated cells: just a sub-clone?

- ✓ *TET2* mutated cells IFNa-resistant?
- ✓ Different stem cell compartment?
- ✓ Back to “pre-proliferative” state?

Schaub et al., Blood 2010



Kiladjian et al., Leukemia, 2010

PVN-1 - Update

✓ IFN discontinuation: 19 patients (54%)

✓ 9 (26%) for toxicity

median time on IFN: 12 months

immune disorder (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

PVN-1 - Update

- ✓ IFN discontinuation: 19 patients (54%)
- ✓ 9 (26%) for toxicity
- ✓ **8 (23%) for sustained hematological CR**
  - ➢ median peg-IFN therapy: 31.5 months (15 - 43)
  - ➢ 7/8 still in hematol-CR, 1 PR (500 000 platelets)
  - ➢ 7/8 patients off RX for 25 mos median (max: 60)
    - ▪ 3 mol-CR
    - ▪ 1 still in mol-CR for 35+ months
    - ▪ 2 mol. relapses after 6 months negativity
    - ▪ last %V617F: 0 in 1, 5% in 4, 10% in 1, 20% in 1

PVN-1 long term results

✓ After 55 months median follow up, 46% of patients are still treated with peg-IFN-2a, without new safety concern

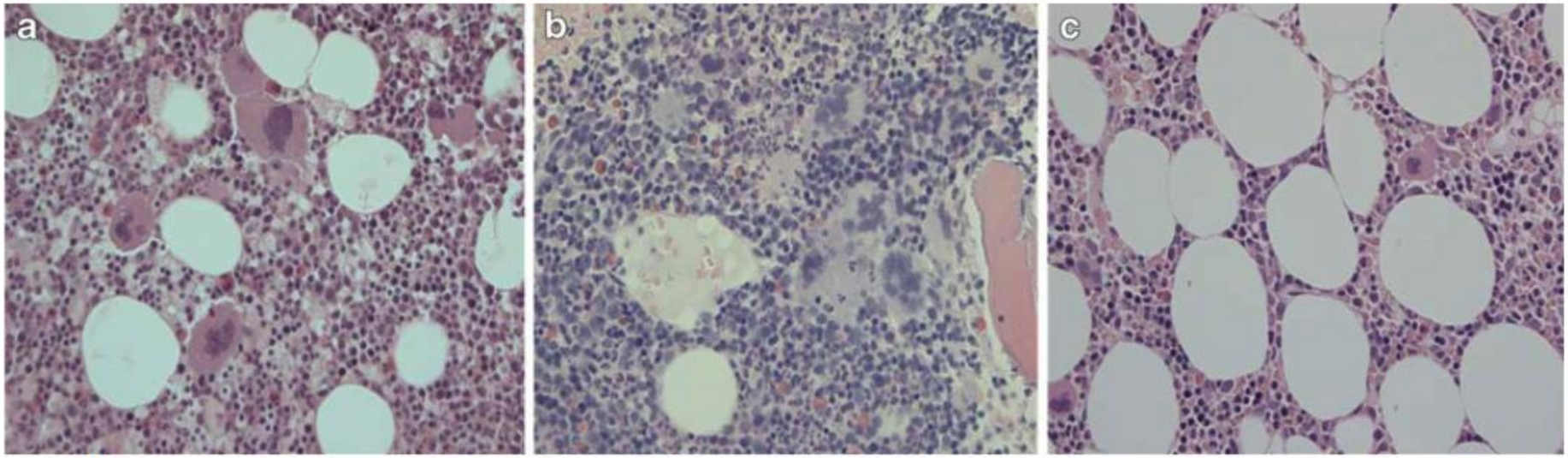
✓ About 1/4 of patients have stopped peg-IFN-2a for toxicity, but also 1/4 for sustained remission

✓ 20% of patients are in clinical remission off cytoreductive therapy for 25+ months median (up to 60 months), without clear correlation with molecular response

✓ Expected vascular events: 8; Observed: 0… *(R. Silver)*

Bone marrow response

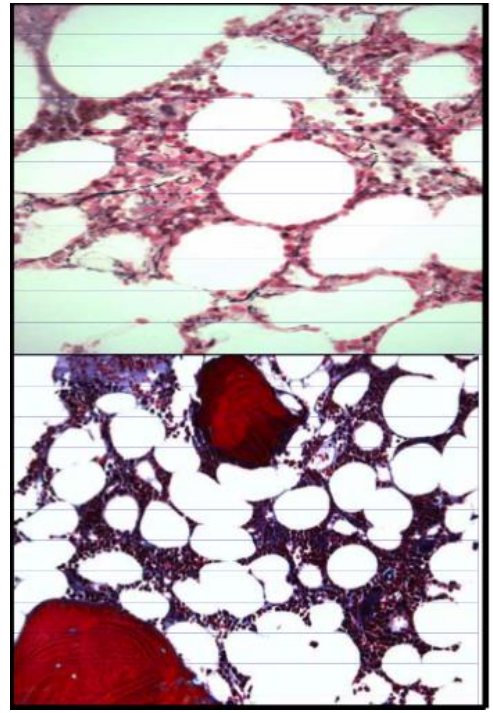
Diagnosis **Pre-IFN** **Post-IFN**



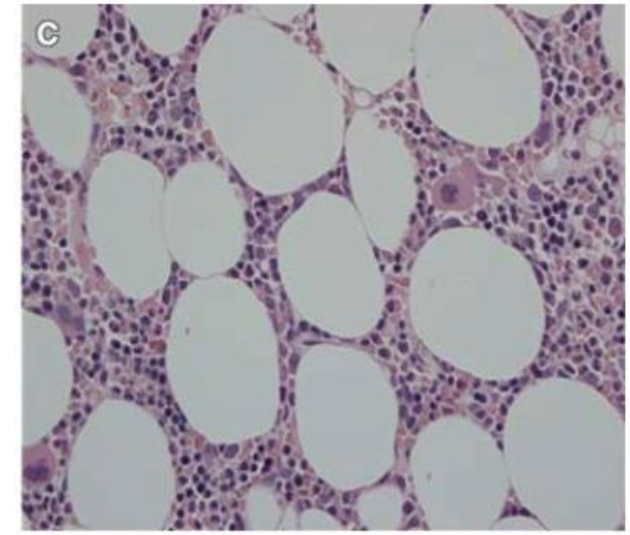
PV

Larsen, Ann Hematol, 2008

Bone marrow response



PMF



PV

Silver, Leukemia, 2009

Larsen, Ann Hematol, 2008

Advantages of IFN□ in MPN

- ✓ Reduction of the MPN clone
- ✓ Clinical remissions without cytoreductive therapy
- ✓ Reduce incidence of vascular events?
- ✓ Alter natural history of MPN (evolution to MF, MDS, AL)?

VOLUME 29 · NUMBER 6 · FEBRUARY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Philadelphia-Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations From European LeukemiaNet

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

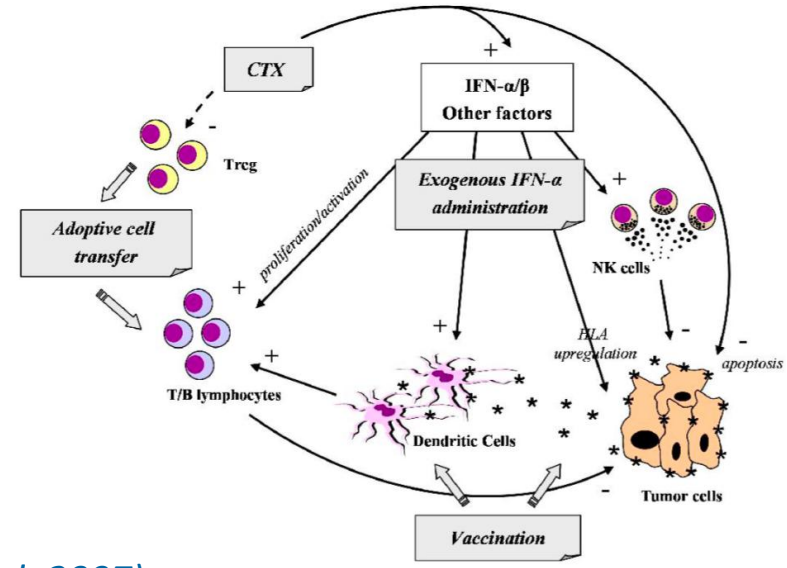
In high risk PV: "Either hydroxyurea or IFN-α is first-line cytoreductive therapy at any age"

IFN in MPN

- ✓ Biology of Interferons
- ✓ Clinical trials of IFN in MPNs
- ✓ IFN effect on the MPN clone
- ✓ Perspectives

New questions

- ✓ **Mechanisms of action of IFN?**
  - ➢ Direct effect on hematopoiesis
    - ✓ inhibition of proliferation
    - ✓ MPL signaling modulation
  - ➢ Immune-mediated?
    - ✓ PV-associated tumor Ag *(Xiong, Clin Immunol, 2007)*
  - ➢ Impact on stem cells?
    - ✓ Dormant hematopoietic stem cells *(Essers, Nature, 2009; Sato, Nat Med, 2009)*



New questions

- ✓ **Reduction of the malignant clone**:
  - ✓ Impact on long-term survival?
  - ✓ Reduction of vascular risk?
  - ✓ Diminution of evolution to MF, MDS, AL?

New questions

✓ **Is Peg-IFN?-2a the new treatment standard for MPN?**

Phase 2 open label peg-IFNa-2a (MPD-RC 111) - n= 168

- Salvage therapy of PV and ET HU resistant or intolerant,

(+ subset splanchnic vein thrombosis)

- Evaluate ability of peg-IFN to achieve CR or PR *(ELN)*

New questions

✓ Is Peg-IFN-2a the new treatment standard for MPN?

Phase 3 randomized trial (MPD-RC 112) - n= 612

- High risk PV and ET, treatment naive, peg-IFN *vs.* HU
- Primary objective: CR rates *(ELN criteria)*
- Secondary objectives:

  Toxicity, Biomarkers (JAK2 V617F, clonality, BM, cytogenetics)

  Qol - MPN-SAF (R. Mesa), Survival, Evolution to MF, MDS, or AL

  Cardiovascular events

FIM
FRENCH INTERGROUP
MYELOPROLIFERATIVE DISORDERS

B. Cassinat
M.L. Menot
G. Massonnet
C. Chomienne

S. Dupont
F. Delhommeau
J.L. Villeval
W. Vainchenker

L. Aljassem
S. Bellucci
J. Brière
N. Cambier
Y. Chait
J.L. Dutel
C. Gardin
K. Ghomari
M.J. Grange
N. Parquet
M. Roussel
P. Rousselot
P. Turlure

S. Chevret

P. Fenaux

J.D. Rain
J.F. Bernard
J. Briere
Y. Najean

université
PARIS DIDEROT
PARIS 7