10 Anni di *Highlights*

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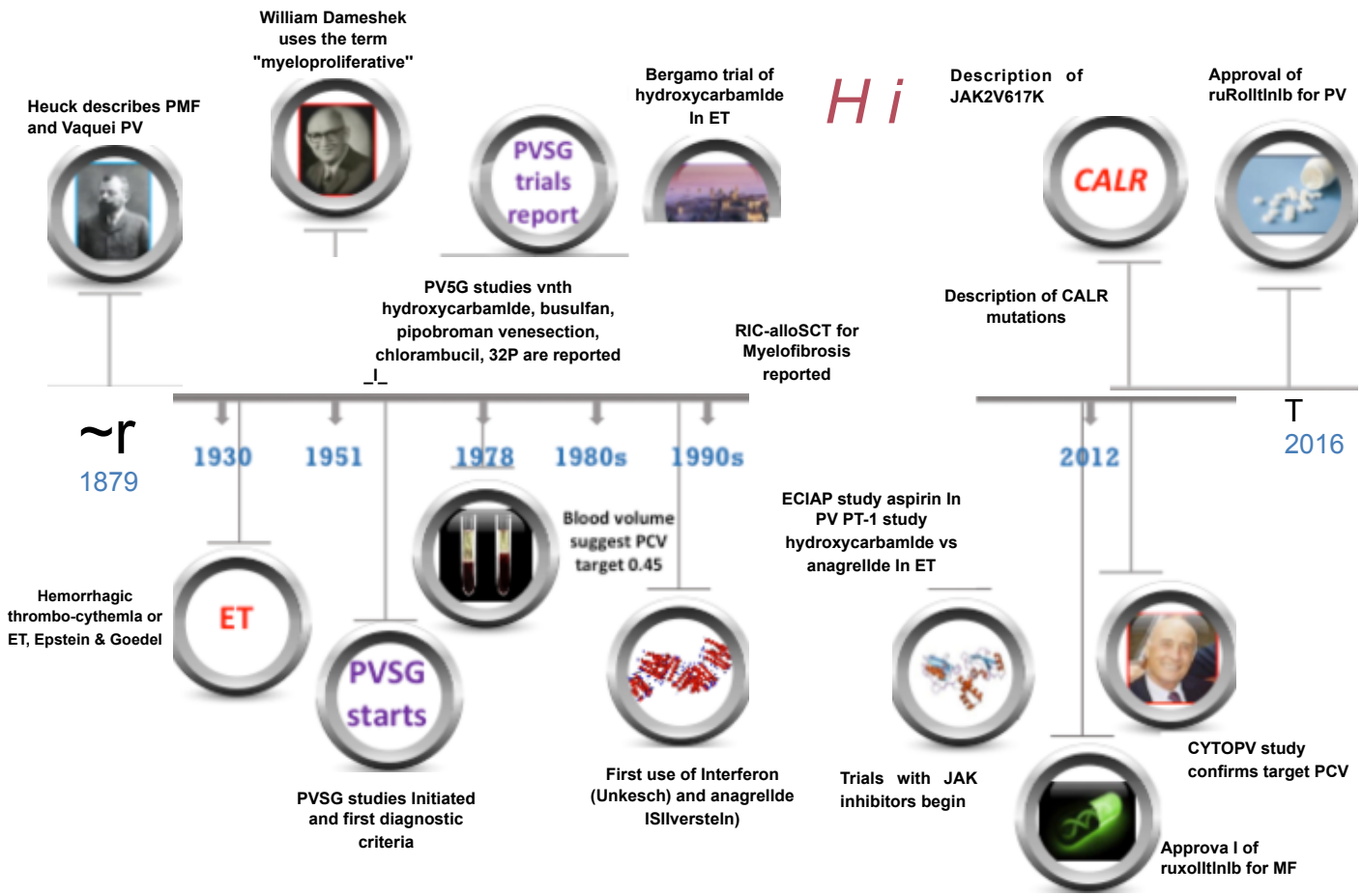
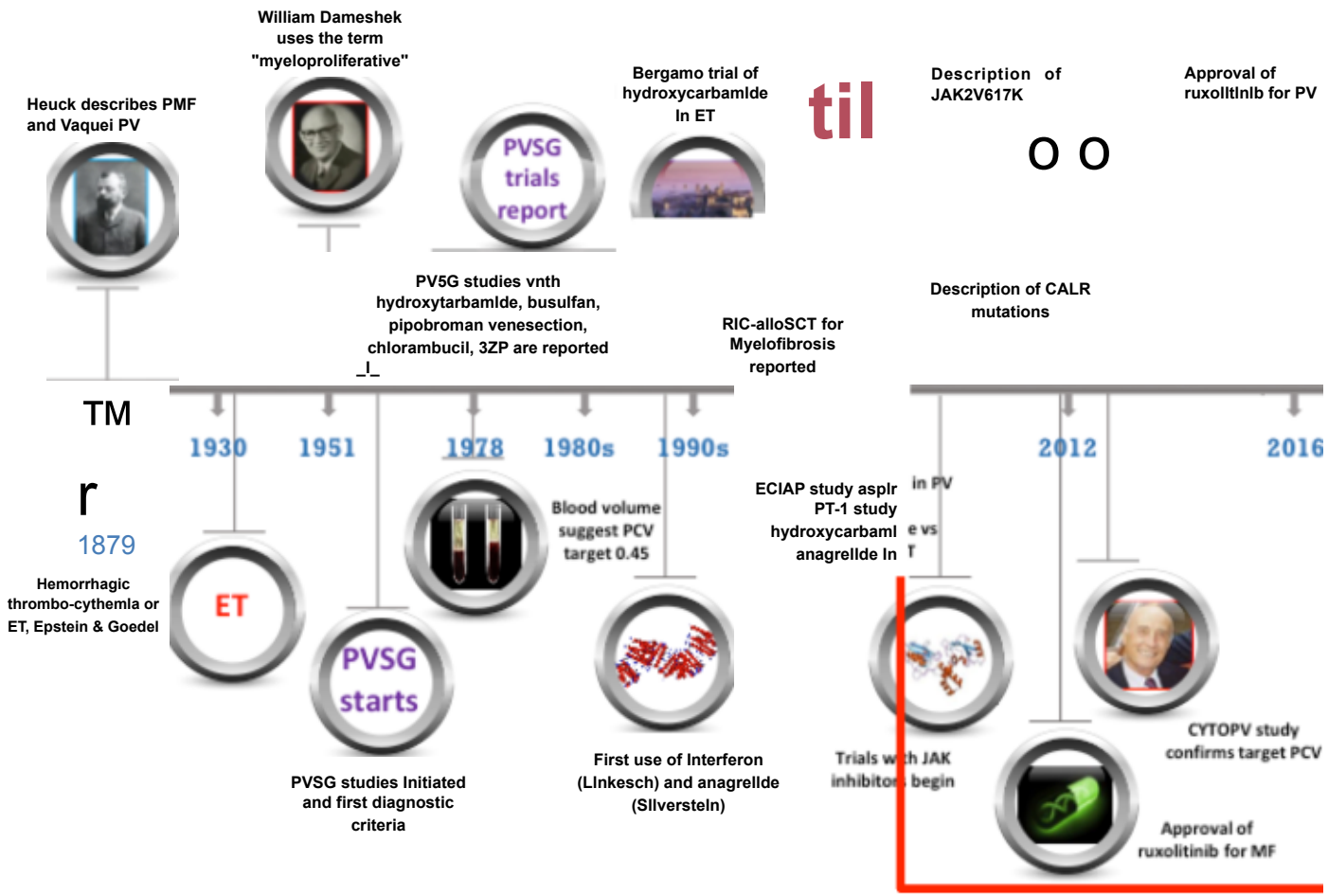
Figure 1: MPN timeline: critical research and clinical data

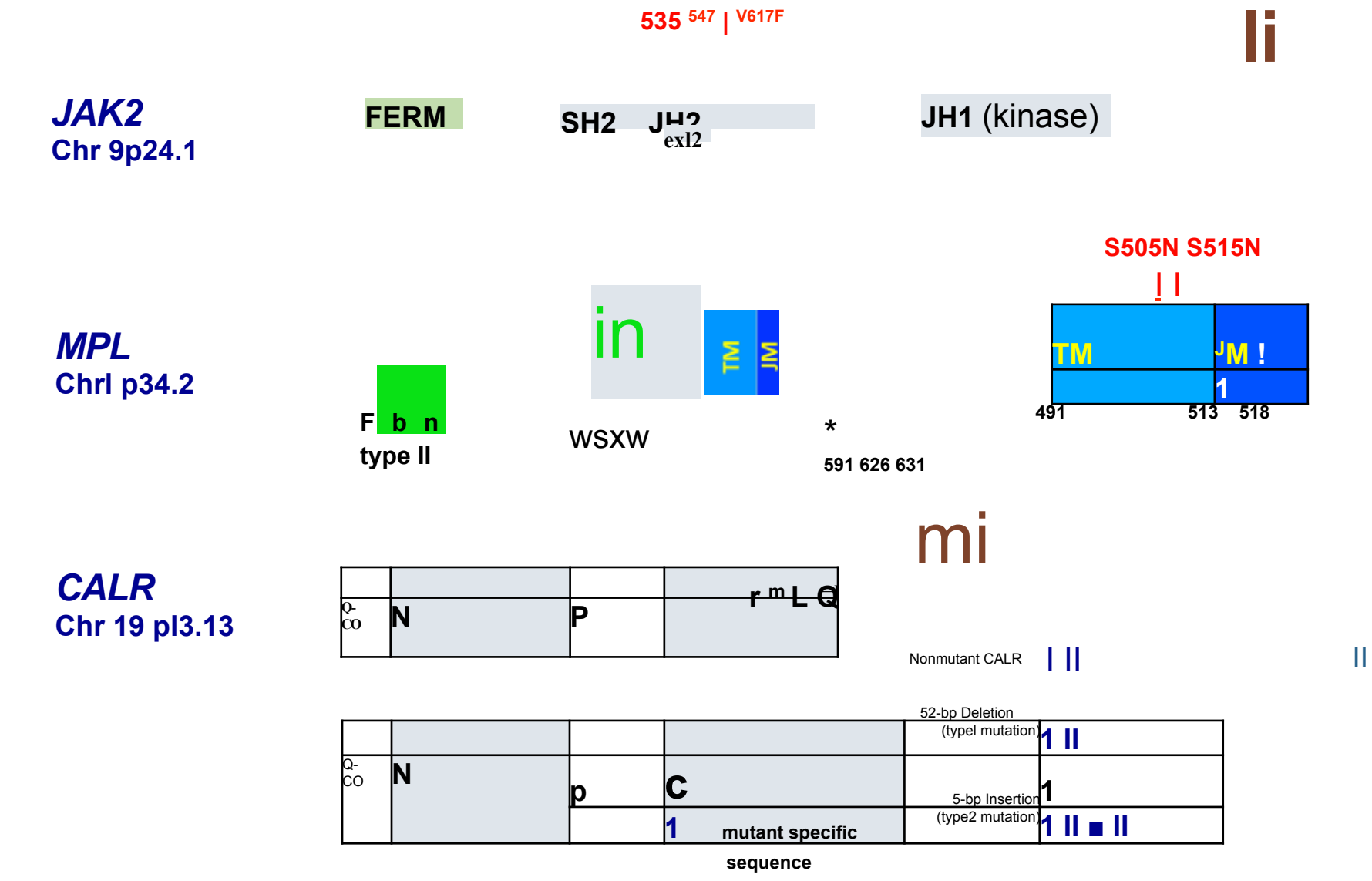


AM Vannucchi, C Harrison, unpublished, 2

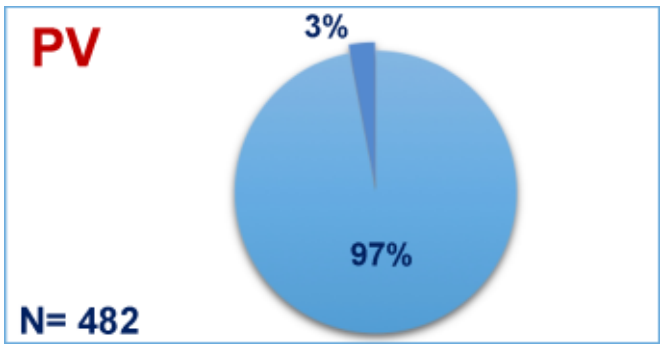
Figure 1: MPN timeline: critical research and clinical data

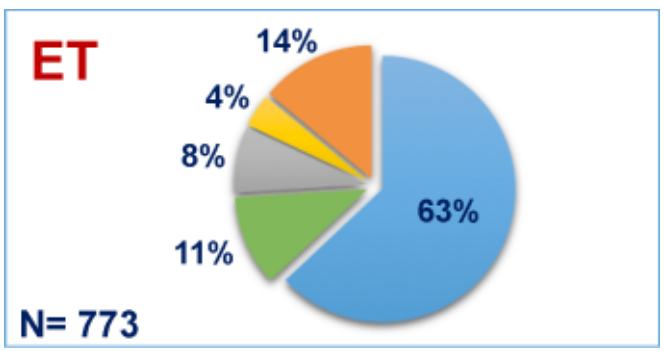


Biologia molecolare delle MPN Highlightsfrom EH/



Biologia molecolare delle MPN Highlightsfrom EH/





Type 2-like
39% Type -I _like
57%

Essential thrombocythemia

Type 2-like
15%

Type 1-like
83%

Primary myelofibrosis

***JAK2V617F* B**

JAK2* Exl 2 *CALR

Typel *CALR* Type2

MPZ.W515 Triple

Negativ

Pre- 5O, **PMF 6%**

10%

12%

67%

N= 286

Overt-PMF 6%

14%

4%

58%

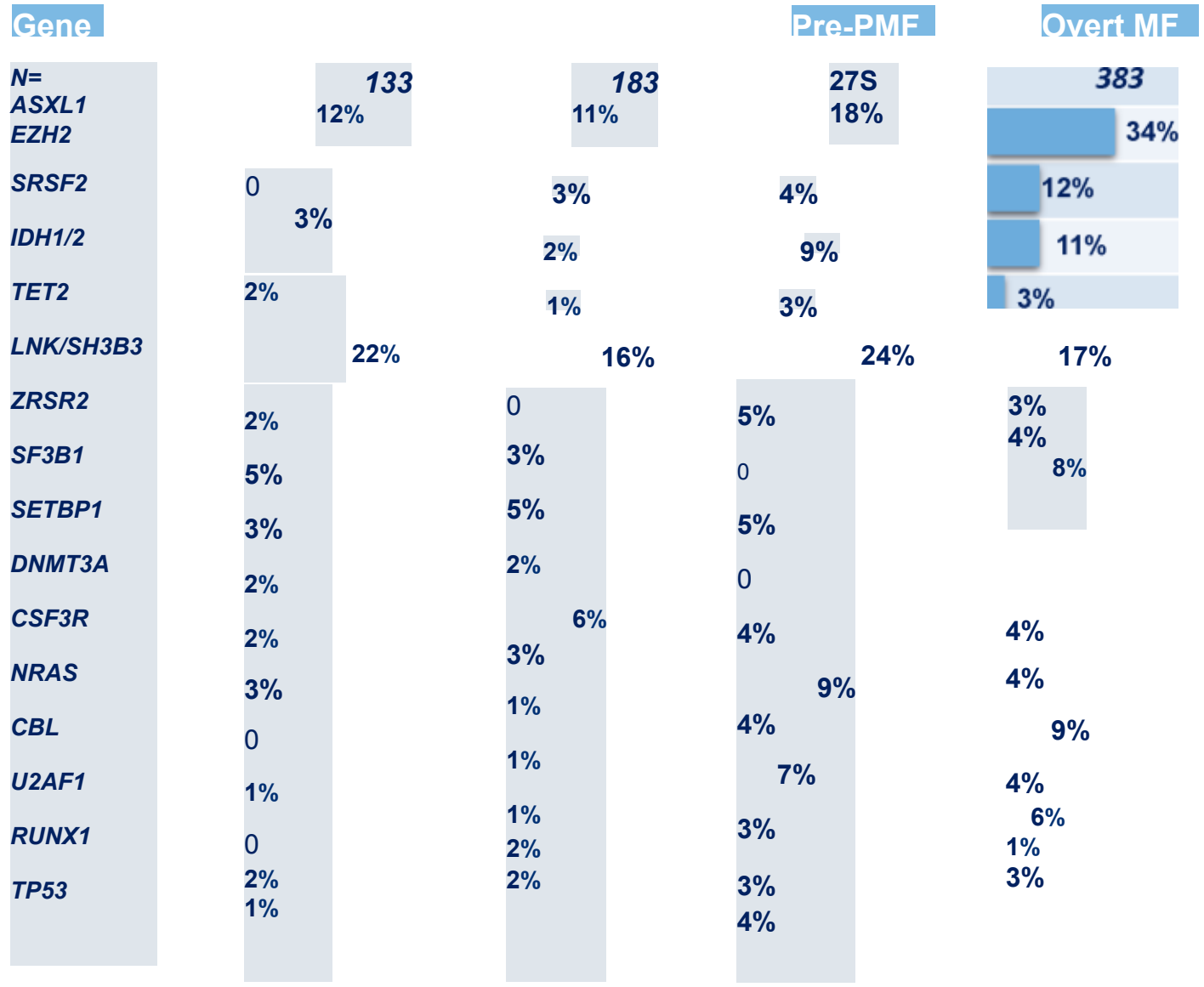
18%

N= 390

Pietra D et al, Leukemia 201
(30:431-8;

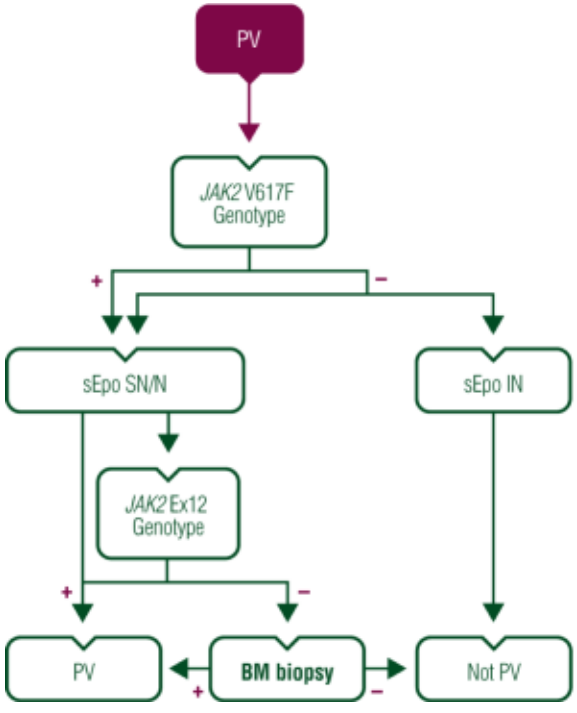
PV, ET: Database of CRIMM; Florence; PMF: Database AGIMM, Guglielmelli Petal, Blood 2017; 129:3227-36.

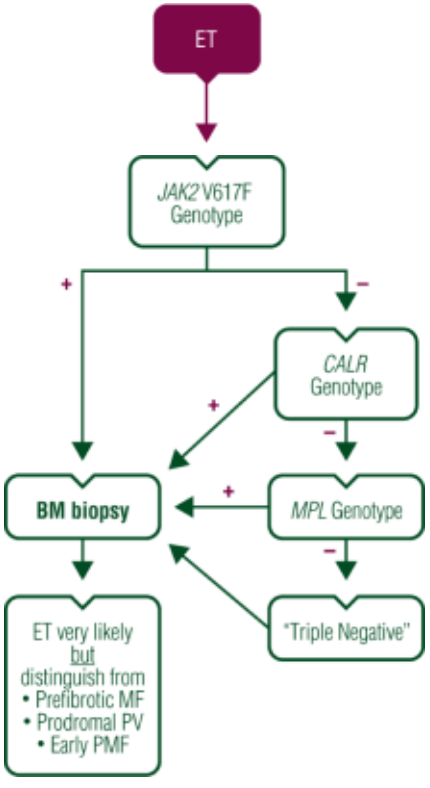
Biologia molecolare delle MPN Highlightsfrom EH/

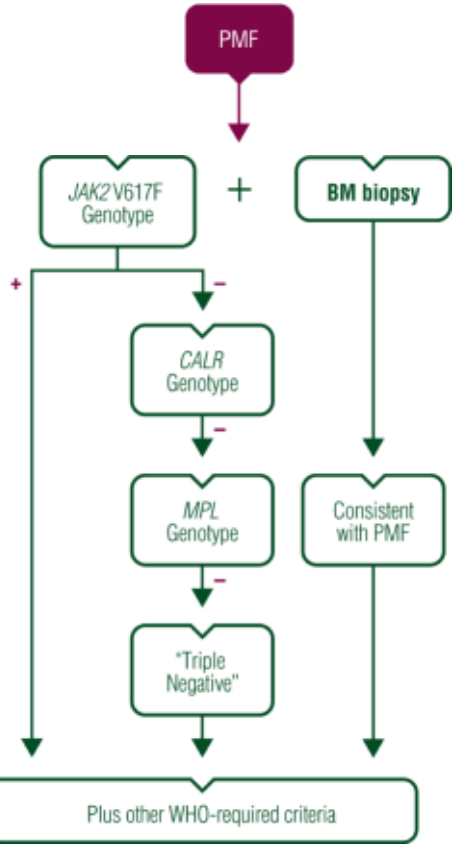


Vannucchi AM etal, Leukemia 2013; 27:1861-9. TefferiAet al, BoodAdv 2016; 1:21-30; TefferiAetal, Blood Adv 2016; 1:105-111; Guglielmelli Pet al, Blood; 2017:129:3227-3

Biologia molecolare delle MPN Highlightsfrom EH/







clinical practice guidelines

Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

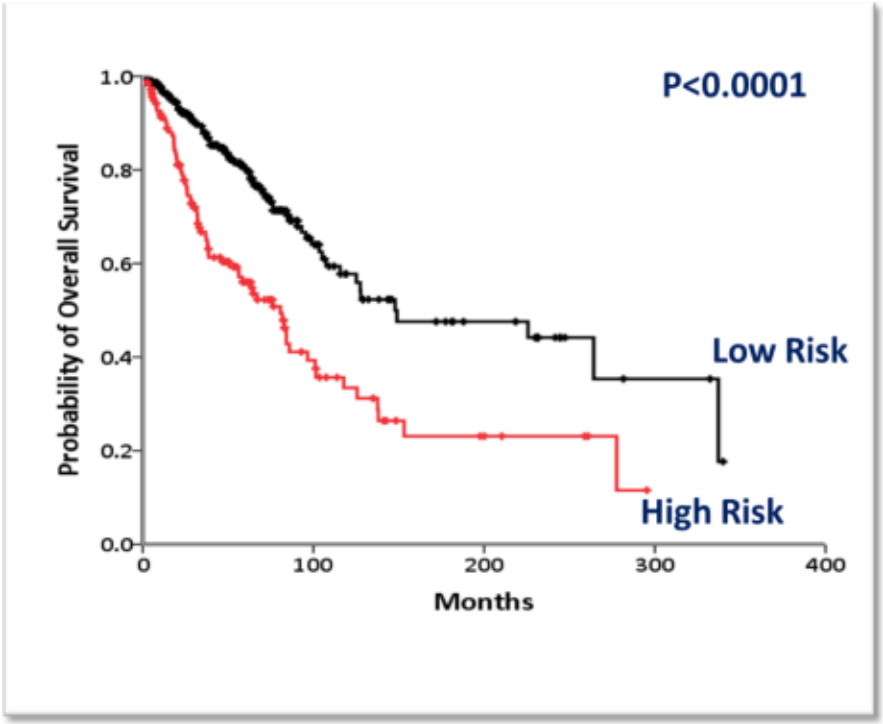
Vannucchi AM et al, Ann Oncol 2015; 26: v85-v9<

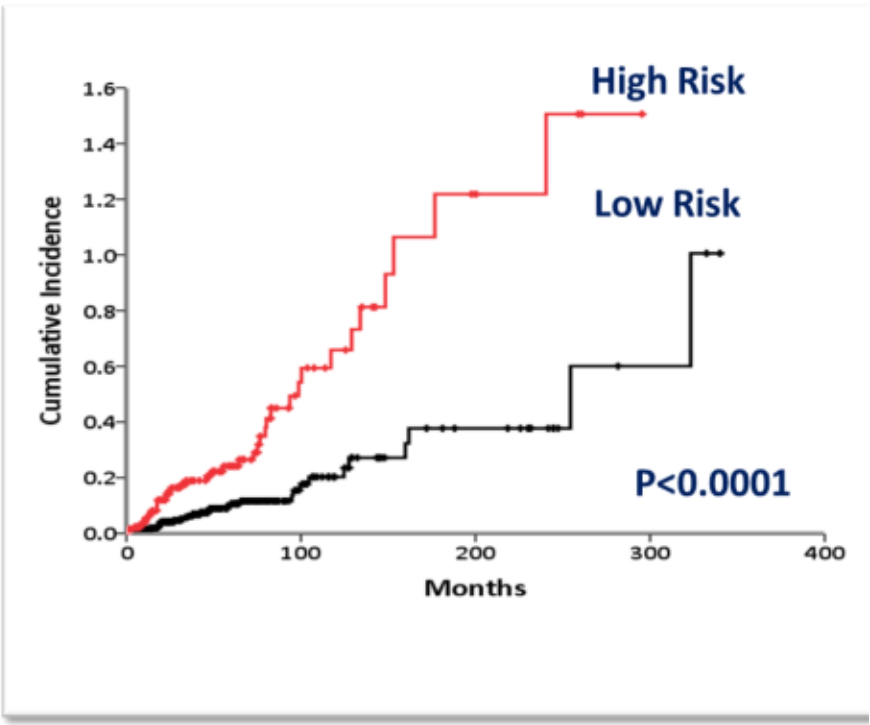
Biologia molecolare delle MPN Highlightsfrom EH/

High Molecular Risk Prognostic Category

harboring >1 mutation in any one of ***ASXL1, EZH2, SRSF2, IDH1/2***

Overall Survival Blast Transformation



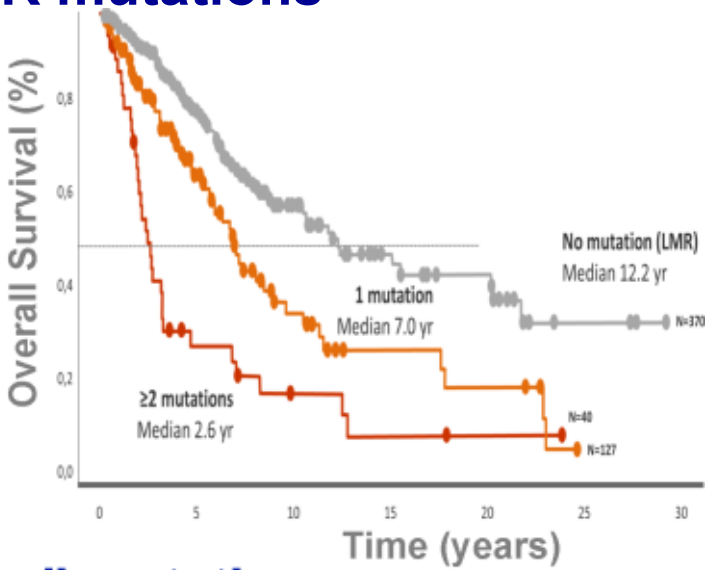


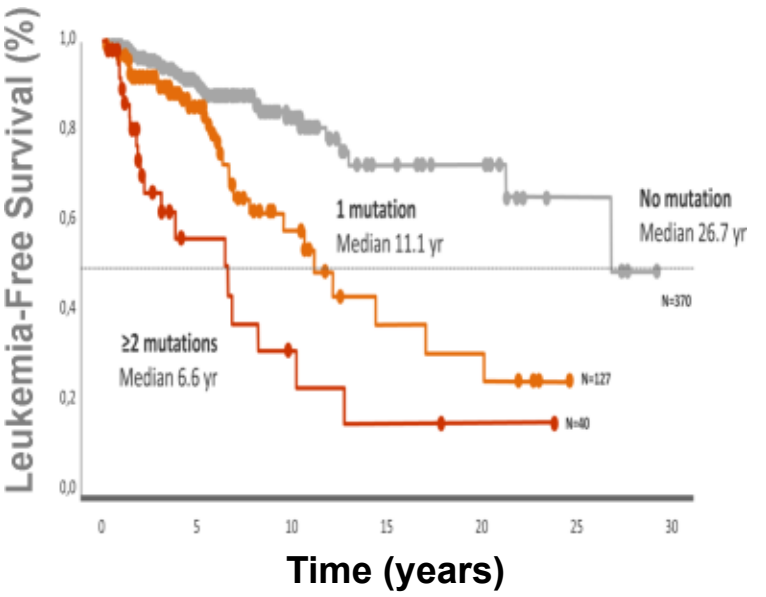
• A HMR status is associated with reduced OS and increased risk of blast transformation ir PMF patients independent of IPSS/DIPPS-plus

Vannucchi AM, et al. Leukemia. 2013;27:186

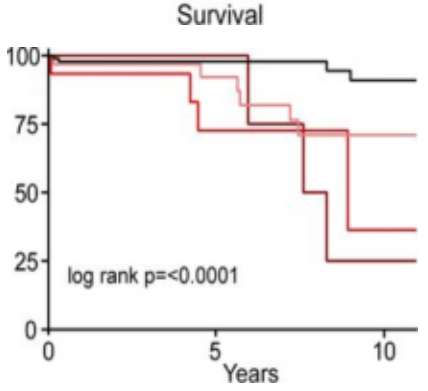
Influence of the Number of Mutations on OS and LFS in PMF

HMR mutations

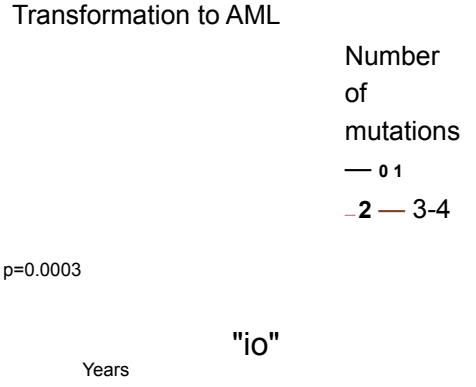




Any" mutation

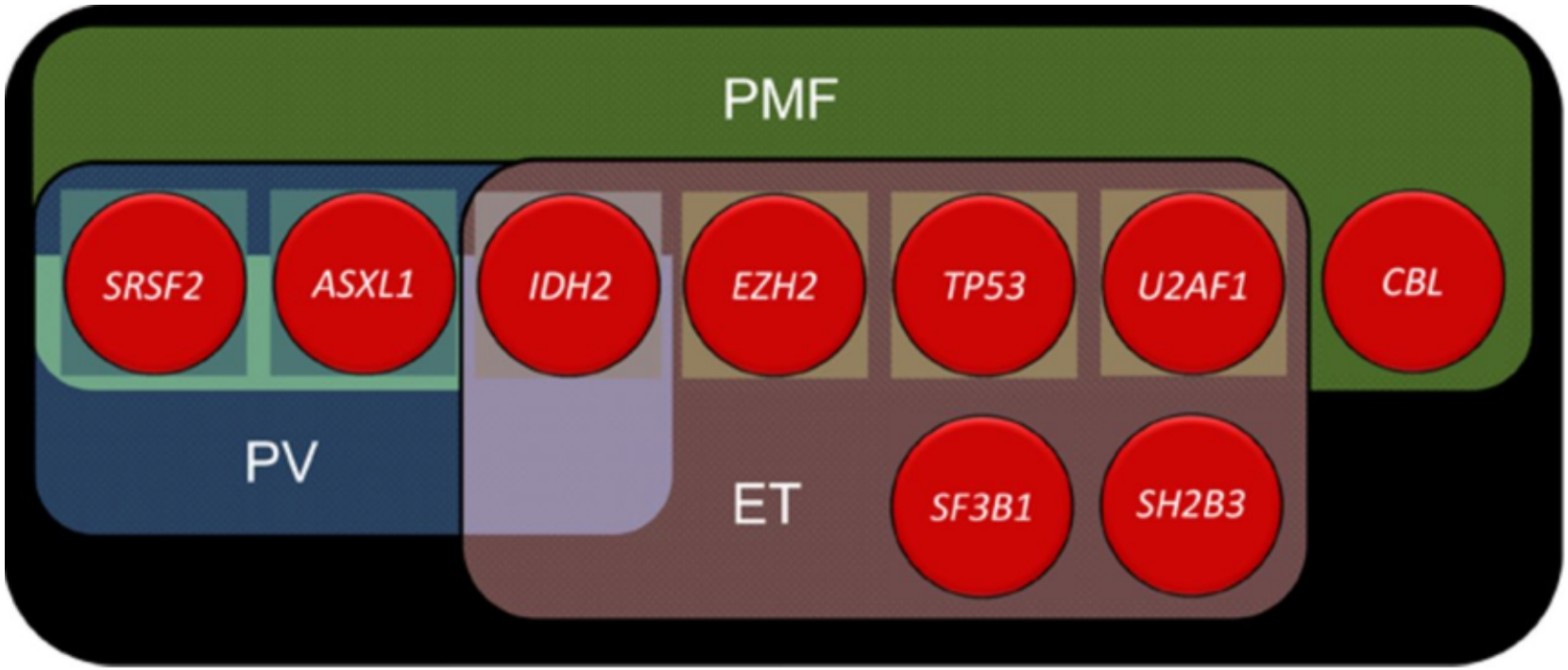


Number of mutations
0
1
2
3-4



Guglielmelli P, et al. Leukemia. 2014; 28: 1804-1810. Lundberg P et al. Blood 2014;123:2220-2

Prognostically Relevant Non-Driver Gene Mutations in PV and ET



PV= 133 Mayo, 215 Florence 27-gene panel
ET= 183 Mayo, 174 Florence PMF= 182 Mayo

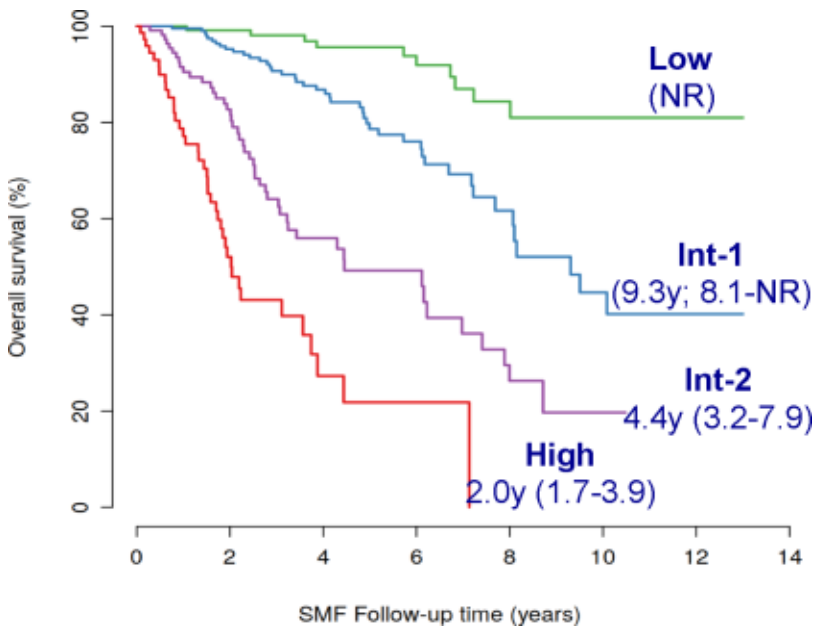
Tefferi A. et al. Blood Adv 2016:1:21-30

MYSEC (MYelofibrosis SECondarv to PV and ET)-PMF a Molecular-Enriched Prognostic Model

- Includes 685 patients, 397 with PET-MF and 384 with PPV-M

Co variate	HR (95% CI)	P value	Points
Age at MF dx*	1.07 (1.05-1.09)	<.0001	0.15
Hb <11 g/dL	2.3 (1.6-3.3	<.0001	2
Pit <150xl0^9/L	1.7 (1.2-2.5)	.006	1
PB blasts >3%	2.9 (1.8-4.8	<.0001	2
CALR wt	2.6 (1.2-5.3)	.001	2
Const, symptoms	1.5 (1.0-2.0)	.03	1

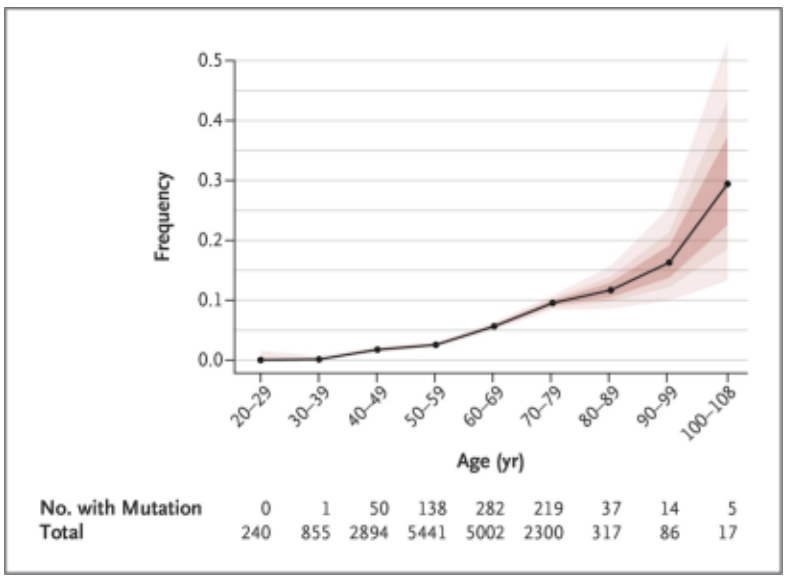
* continuous, 0.15 point/year

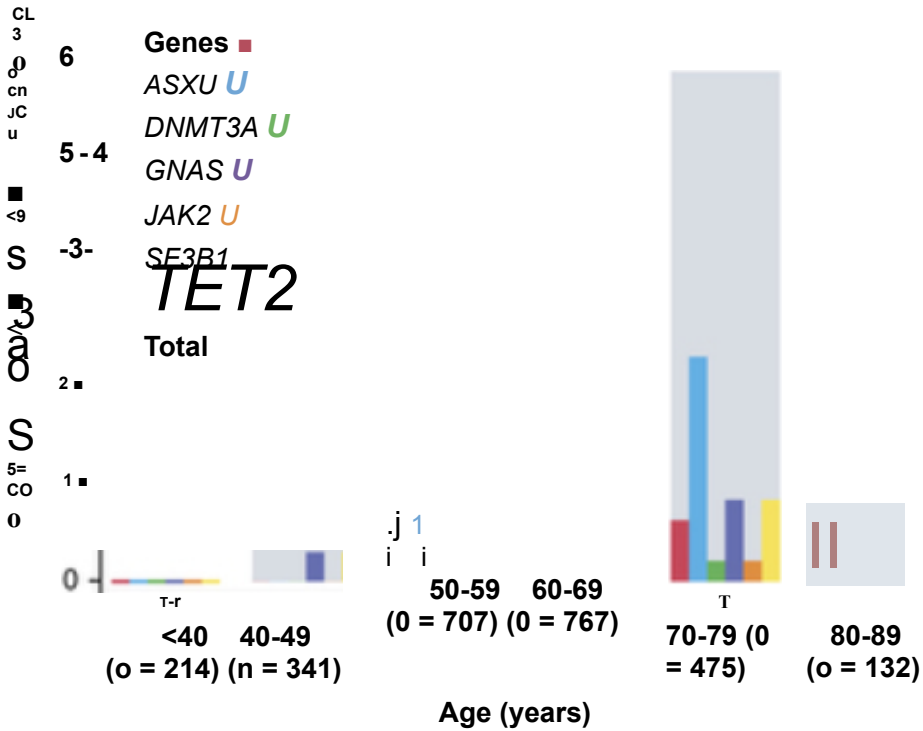


- Of the HMR mutations, only *SRSF2* mutations were significant for reduced OS in PET-MF.

Passamonti F et al. Leukemia 2017, in press; Rotunno G et al, AJH, 2016;91:6(

Clonal Hematopoiesis of Indetermined Potential





• Clonal hematopoiesis is increasingly common with aging (10% of persons older than 65 vs 1 % of <50y).

Thorsten Klampfl et al. *Blood* 2011;118:167-176; Xie M et al. *Not Med.* 2014 ;20(12):1472-8; Jaiswal S et al. *N Engl JI* 2014 Dec 25;371(26):2488-98; Genovese G et al. *N Eng! J Med.* 2014 25;371(26):2477-8; Jaiswal S et al, NEJM,:

Biologia molecolare delle MPN Highlightsfrom EH/

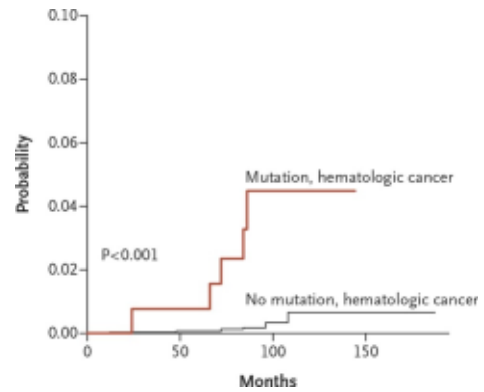
Association with the risk of Hematologic Cancers and Coronary Heart Disease/Early MI

A

Hematologic Cancer	Events/No. at Risk	Hazard Ratio (95% CI)	P Value
No mutation (referent)	11/3208		
JHS	10/2326		
MEC	1/882		
Mutation	5/134		<0.001
JHS	3/83	-■- 7.1 (2.0-25	0.002
MEC	2/51	-*-I 36 (4.9-270	<0.001
Mutation, VAF ^0.10	5/57	M 49 (21-120	<0.001
JHS	3/34	-■- 21 (5.7-80	<0.001
MEC	2/23	-*m* 90 (29-280	<0.001

|-1-■ ... M|-1.....
1 10 100

B



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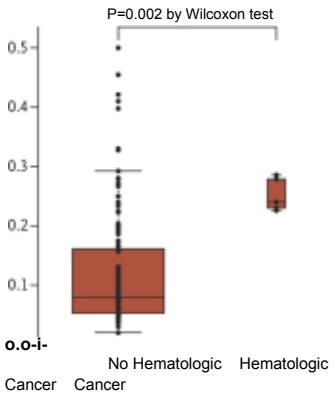


A CHIP and Coronary Heart Disease

No. of Participants with

Subgroup	Coronary Heart Disease/ No. at Risk
Biol mage	
No mutation (reference)	94/326
Mutation	19/44
MDC	
No mutation (reference)	299/607
Mutation	21/33

Hazard Ratio (95% CI) P Vali

Fixed-effects meta-analysis

0.7

L0 5 4.0

1.8 (1.1-2.9) 0.03

2.o (1.2-3.i) o.oo:

1.9 (1.4-2.7) <0.00!

B CHIP and Early-Onset Myocardial Infarction

No. of Participants with Myocardial Infarction/
Subgroup No. at Risk Odds Ratio (95% CI)

P Vali

ATVB
No mutation (reference) 1716/3293
Mutation PROMIS No 37/43
mutation (reference)
Mutation 2488/3844
Fixed-effects meta-analysis 52/65

<o.oo

<o.o
o:
<o.o
o:

0.5 1 2 4 8 16

Jaiswal S et al. N Engl J Med 2014;371:2488-2498

Jaiswal S et al. N Engl J Med 2017;377:111

Criteri Diagnostici

CUILIV-HN

Highlightsfrom EH/

PV	ET	Pre-PMF
Maior criteria	**Maior criteria**	**Maior criteria**
1. Hb >16.5g/dL in men, or 16.0 g/dL in women, or Hct >49% and 48%, or increased RCM	**1.** Platelet count >450xl0^9/L	1. BM biopsy with Mk proliferation and atypia, w/o reticulin fibrosis >G1; with incr. cellularity, granulocytic prolifer. and often decreased erythr'iesis
2. BM biopsy with hyper-cellularity with panmyelosis and Mk proliferation with pleomorphic Mks	2. BM biopsy with proliferation mainly of the Mk lineage with mature enlarged Mk with hyperlobulated nuclei	2. Not meeting WHO criteria for other myeloid neoplasms
3. Presence of *JAK2MS17?* or *JAK2* exl2 mutation	3. Not meeting WHO criteria for other myeloid neoplasms **4. Presence of *JAK2MS17?*, CALR or *MPL* mutation**	**3. Presence of *JAK2MSYJ?*, *CALR* or *MPL* mutation, or in the absence of these mutations, presence of another clonal marker,** or absence of minor reactive BM reticulin **Minor criteria** I.Anemia
Minor criteria	**Minor criteria**	2.Leucocytosis >IIxl0^9/L
1. Subnormal sEPO levels	**1.** Presence of a clonal marker, or absence of evidence of reactive thrombocytosis	3.Palpable splenomegaly 4.Increased LDH
3 major or first 2 major + minor	**4 major or first 3+ minor**	**3 major + >1 minor**

Overt PMF

Major criteria

1. BM biopsy with Mk proliferation and atypia with either reticulin fibrosis G2-3 and/or collagen
2. Not meeting WHO criteria for other myeloid neoplasms
4. **Presence of *JAK2MS11?*, *CALR* or *MPL* mutation, or in the absence of these mutations, presence of anothei clonal marker,** or absence of reactive myelofibrosis

Minor criteria

1. Anemia
2. Leucocytosis >IIxl0^9/L
3. Palpable splenomegaly
4. Increased LDH
5. Leukoerythroblastosis

3 major + >1 minor

In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ***ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1)*** are of help in determining the clonal nature of the disease.

Arber DAetal, Blood 2016; 127:2391-4

1JAK inhibitor (Company)	MF	PV/ET	Note
	phase, status		
CEP701 (Cephalon)			STOP
AZD1480 (AstraZeneca)			STOP
XL019 (Exelixis)			STOP
NS-018 (NS Pharma)	1		?
BMS-911543 (BMS)	I/II		?
LY2784544 (Lilly)	II	1	STOP
Momelotinib (Gilead)	III, Ist/2nd line		COMPLETE --->
Pacritinib (CTI)	III, Ist/2nd line		COMPLETE, on Hold-->re-test
Fedratinib (Sanofi)	III, Ist/2nd line	I/II	STOP
Ruxolitinib (Incyte/Novartis)	111(2)	II (ET,PV) III (PV)	**MF & PV 2nd line APPROVED**

Studi Clinici

Highlightsfrom EH/

COMFORT I

Patients with MF (N = 309) → Randomized 1:1 <

- Ruxolitinib 15 mg BID or 20 mg BID
- Placebo BID

Primary Endpoint

- Number of subjects achieving >35% reduction in spleen volume* from baseline to week 24

Secondary Endpoint

- Proportion of patients with >50% reduction in Total Symptom Score (mod. MFSAF v2.0 electronic diary)

COMFORT II

Patients with MF (N = 219) → Randomized / 2:1 \

- Ruxolitinib 15 mg BID or 20 mg BID
- Best available therapy (BAT)

Primary Endpoint

- Number of subjects achieving > 355 reduction in spleen volume* from baseline to week 48

Secondar/Exploratorv endpoints

- Changes in functioning and sympto

Ruxolitinib MTD: 25 mg twice daily or 100 mg once daily with thrombocytopenia as DLT

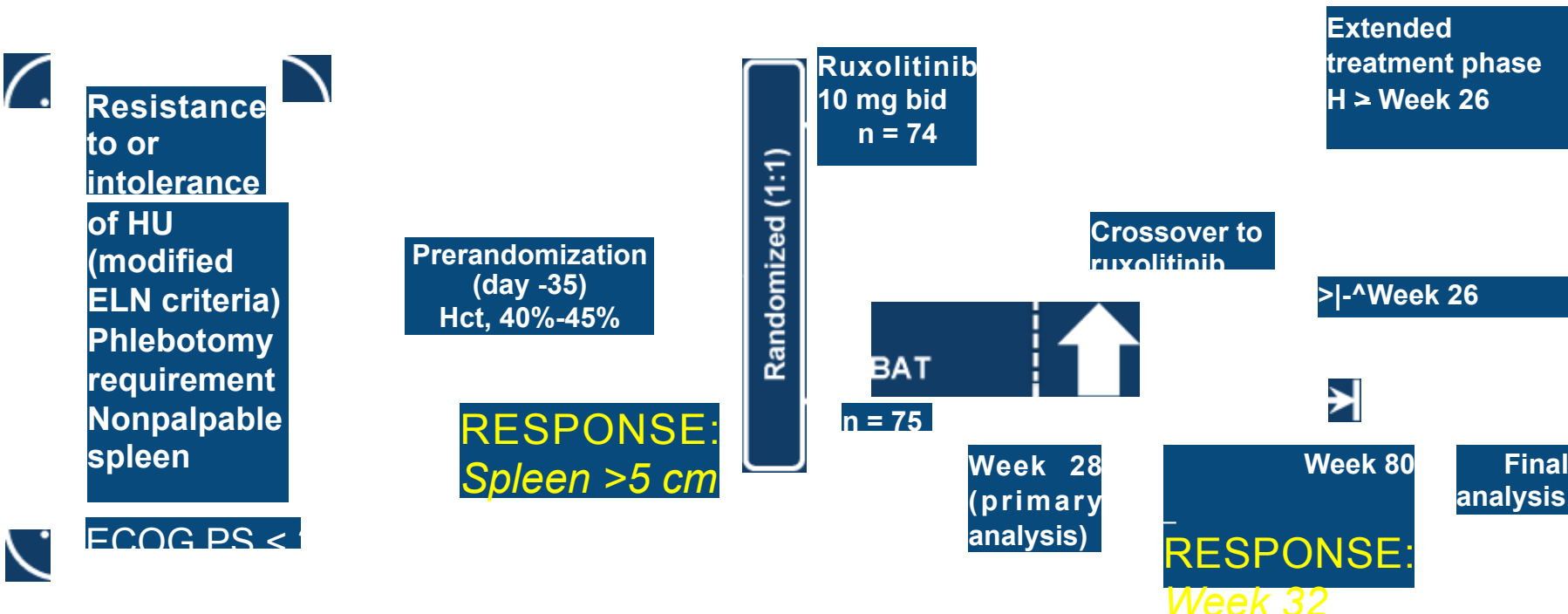
* As measured by MRI/CT scan

Verstovsek S et al. NEJM 2012; 366:799-807; Harrison C et al. NEJM 2012; 366:787

Studi Clinici

I VS CUII IvIN

Highlightsfrom *EHP*



- Ruxolitinib-randomized patients had their doses individually titrated for efficacy and safety (to a maximum of 25 mg bid)
- Investigator-selected BAT as monotherapy included HU (at a tolerated dose if the patient were likely to receive benefit), interferon (IFN)/peg-IFN, anagrelide, pipobroman, immunomodulatory drugs, or observation
- All patients received low-dose aspirin unless medically contraindicated

bid, twice daily;

VannucchiAM et al, NEJM2015; 372:426; Passamonti F et al, Lancet Oncol 2017; 18:88-'

Target Hematocrit for Optimal Management of PV: Results of the CYTO-PV Stud

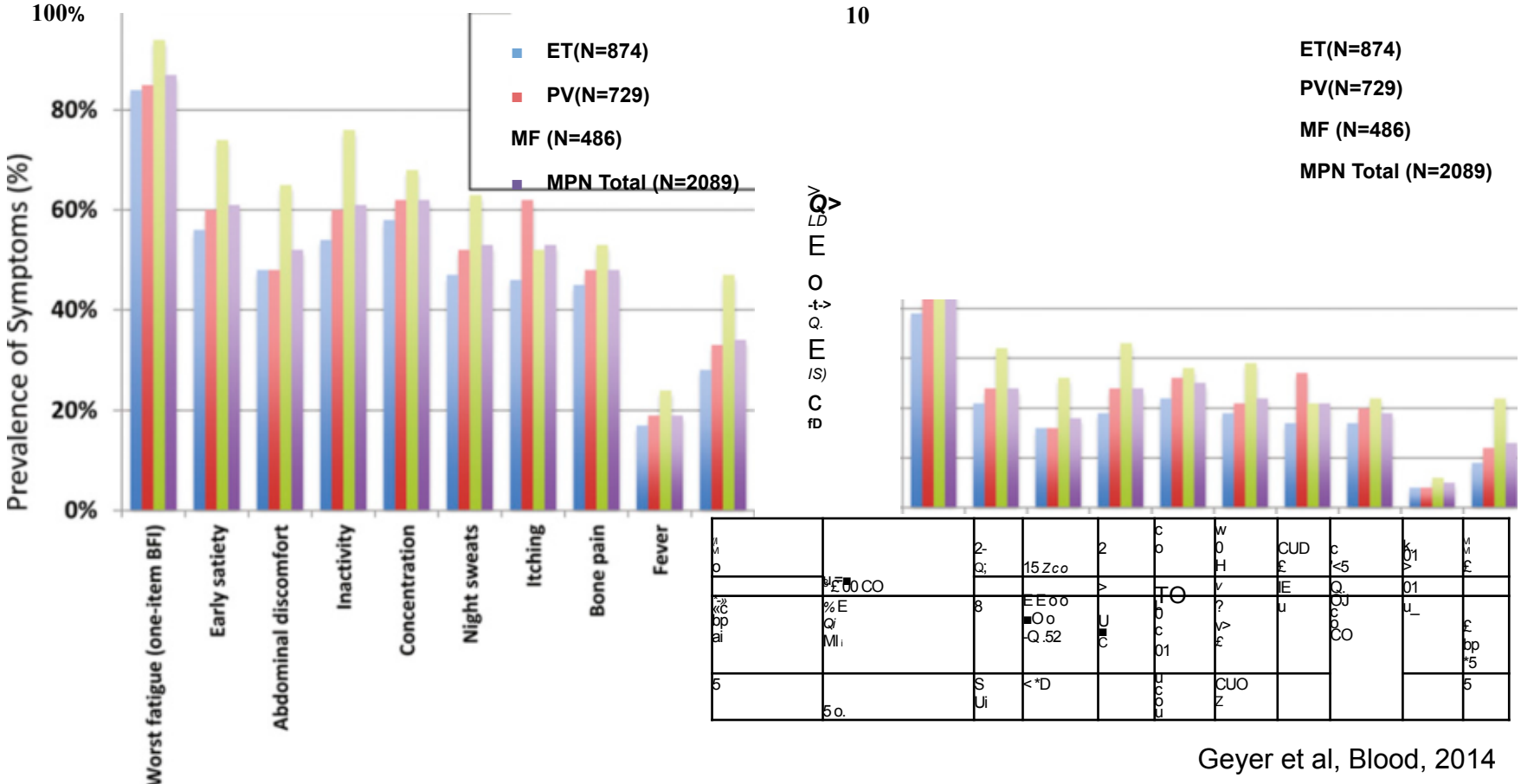
n

	HCT <45% N = 182	HCT 45-50% N=183	HR (95%CI)	P
Primary Endpoint (CV death, MI, stroke, PAT, DVT, PE, TIA, abdominal thrombosis)	5 (2.8%)	18 (9.8%)	3.91 (1.45-10.53)	0.005
IR % person/year	1.1	4.4		
Total CV events (Primary plus superficial vein thrombosis)	8 (4.4%)	20 (10.9%)	2.69 (1.19-6.12)	0.012
IR % person/year	1.9	5.0		

Marchioli R, et al. NEJM. 2013; 368:22-

Symptoms burden in MPN

Significant symptom heterogeneity exists within each MPN subtype, sometimes independent c disease features or prognosis, i.e. symptoms are prominent even in low-risk MPN populations.



Geyer et al, Blood, 2014

CUIIIVJIN

Highlightsfrom EH/

PHYSICIANS

ET

- Prevent vascular events -Slowor delay condition Healthy blood counts ■ Better QoL ^Symptom improvement Reduction in spleen size Reduce frequency of phlebotomy

PV

- Prevent vascular events -Slowor delay condition Healthy blood counts ■ Better QoL ^Symptom improvement Hematocrit <45% Reduce phlebotomies Reduce spleen size

MF

— Prevent vascular events
— Slow or delay condition Healthy blood counts
— Better QoL ^Symptom improvement Anemia treatment Reduce blood transfusion Reduce spleen size

PATIENTS

ET

- Prevent vascular events
- Slow or delay condition Healthy blood counts
- Better QoL ^Symptom improvement Reduction in spleen size Reduce frequency of phlebotomy

PV

- Prevent vascular events
- Slow or delay condition Healthy blood counts
■ Better QoL
- Symptom improvement Hematocrit <45% Reduce phlebotomies Reduce spleen size

MF

— Prevent vascular events
— Slow or delay condition Healthy blood counts
■ Better QoL ^Symptom improvement Anemia treatment Reduce phlebotomies Reduce spleen size

Mesa R et al, 2i

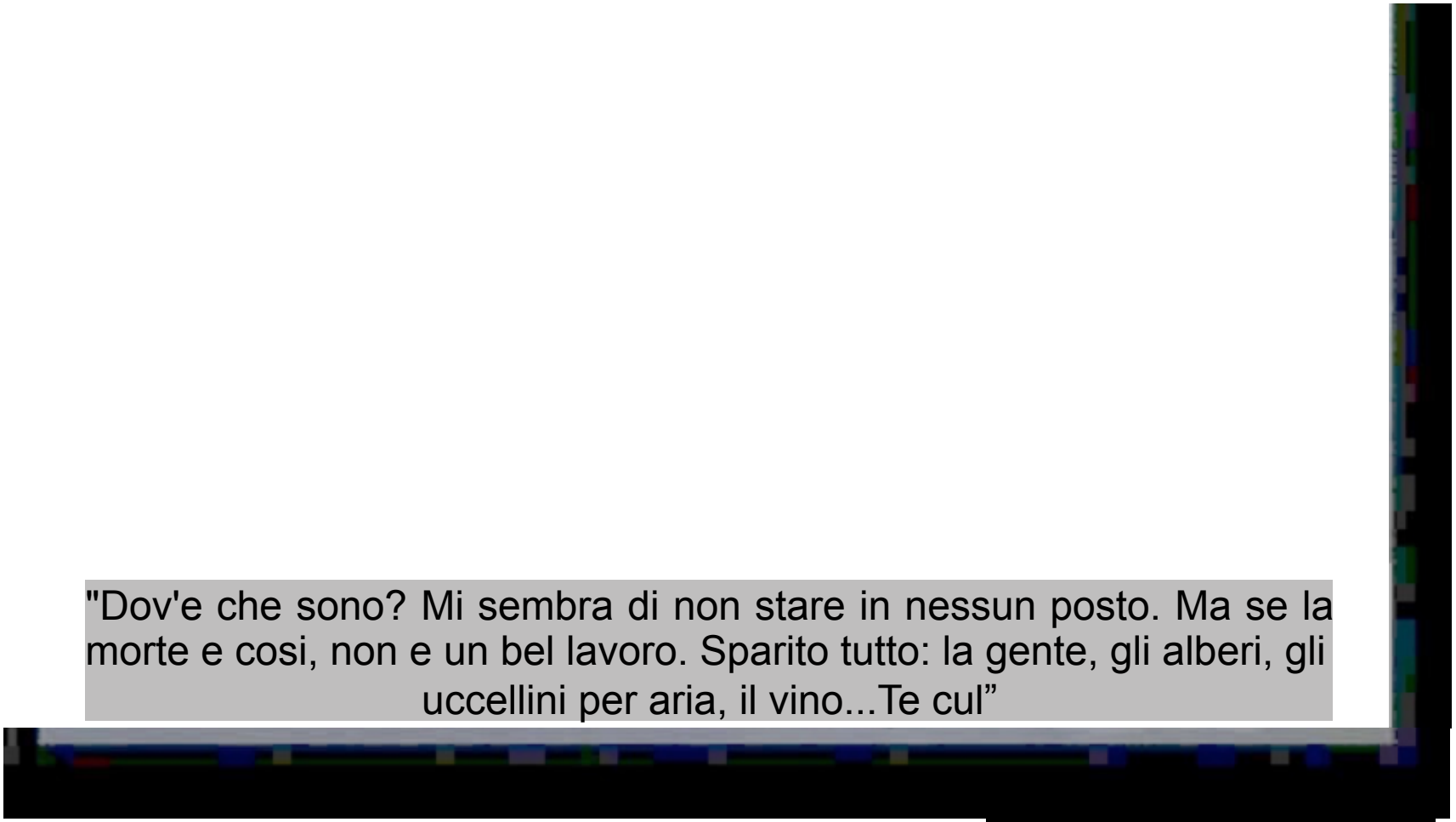
Prossimi 10 anni: wish list

- Definire le forme Triplo-Negative
- Sviluppare score molecolari piu performanti
- Diagnosi multiparametrica (senza BOM?)
- Parametri predittivi di evoluzione in sMF e LA
- Terapie “eradicanti” (?)
- Rischio di trombosi ancora elevato
- Immunoterapia (?)
- Controllo duraturo della patologia

Il Futuro negli Studi clinici nelle MPN — c o m e la

Il Futuro negli Studi clinici nelle MPN — c o m e la

"Dov'e che sono? Mi sembra di non stare in nessun posto. Ma se la morte e cosi, non e un bel lavoro. Sparito tutto: la gente, gli alberi, gli uccellini per aria, il vino...Te cul”



AMARCORD, Federico Fellini (1973)

Report del gruppo di lavoro

- F Silvestri Udine
- L Pedrazzi Modena
- C Gasparrini Campobasso
- S Santini Prato
- E Ruggeri Milano
- L Cimarosto Belluno
- F Ballerini Genova
- 0 Racchi Genova
- G Lo Scocco Firenze
- R La Tagliata Roma
- AM Vannucchi Firenze
- A. Tondo Firenze-Meyer
- G Musardo Faenza
- E Raviolo Cuneo
- F Faccinelli Perugia
- T Petrucci Roma

Report del gruppo di lavoro

- F Silvestri Udine
- L Pedrazzi Modena
- C Gasparrini Campobasso
- S Santini Prato
- E Ruggeri Milano **G TOdt f U11!!!!!**
- L Cimarosto Belluno
- F Ballerini Genova
- 0 Racchi Genova
- G Lo Scocco Firenze
- R La Tagliata Roma
- AM Vannucchi Firenze
- A. Tondo Firenze-Meyer
- G Musardo Faenza
- E Raviolo Cuneo
- F Faccinelli Perugia
- T Petrucci Roma

Cugina 73 anni

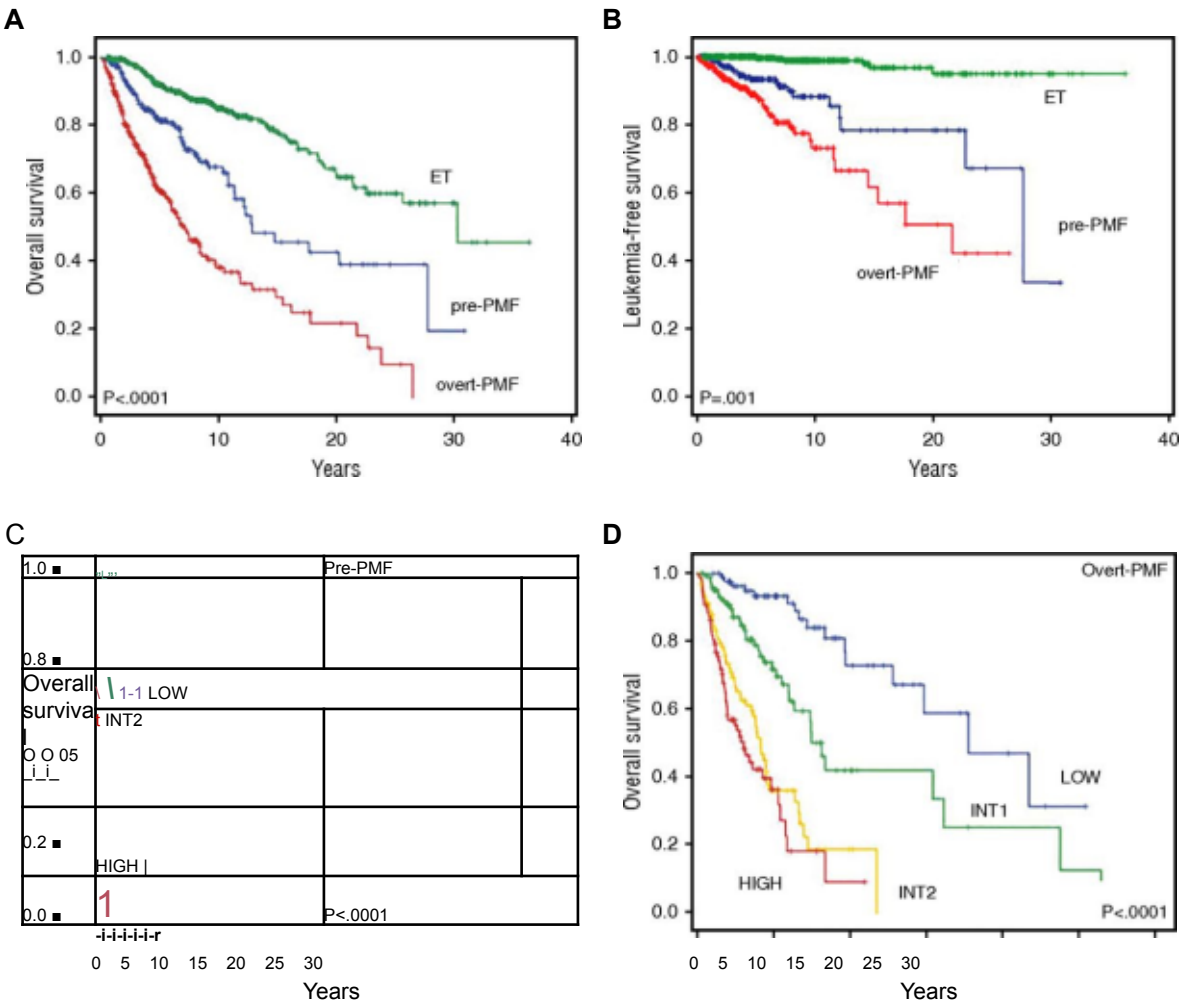
1- BOM: si per conoscenza scientifica

2- BOM: potrebbe essere non tanto ET o prePMF ma una PMF iniziale

3- Regole WHO: difensiva nostra?

4- Cambia trattamento ? NO 4- prospettiva ?

OS and LFS in relation to diagnosis and IPSS risk categories in study patients population.



Paola Guglielmelli et al. Blood 2017;129:3227-3236

* blood

Diagnosi di Policitemia Vera:

Qunti sani giovani hanno un valore a livello WHO?

Come rendere cost-effective il percorso dx Iter

mutazionale

Apnee notturne

Triple-negativity

- Istopatologia: non differenze evidenti
- Fenotipo clinico

- Permane incertezza ???

- Forte implicazione diagnostica nella MF

- Implicazioni di gestione nella ET

Albumina

- And so what?
- Critica interpretazione
- Utilizzazione terapeutica ??
- Si va verso score “oggettivi”

Interferone:

- Dati???

- Progressione???
- Non pud cambiare OGGI il nostro approccio terapeutico

Ruxolitinib:

- PV: quanti e quali pazienti?
- MF: basse dosi?
- Precoce
- Discussione sulle inicazini in base alia classe di rischio

Timing del trapianto (Carella)