MALATTIE MIELOPROLIFERATIVE CRONICHE

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Highlights from EHA 2017: some points to address today

WHO 2016 MPN classification: “hot” topics

MPN and prognosis: the simpler the better?

Prefibrotic/early PMF: a new entity

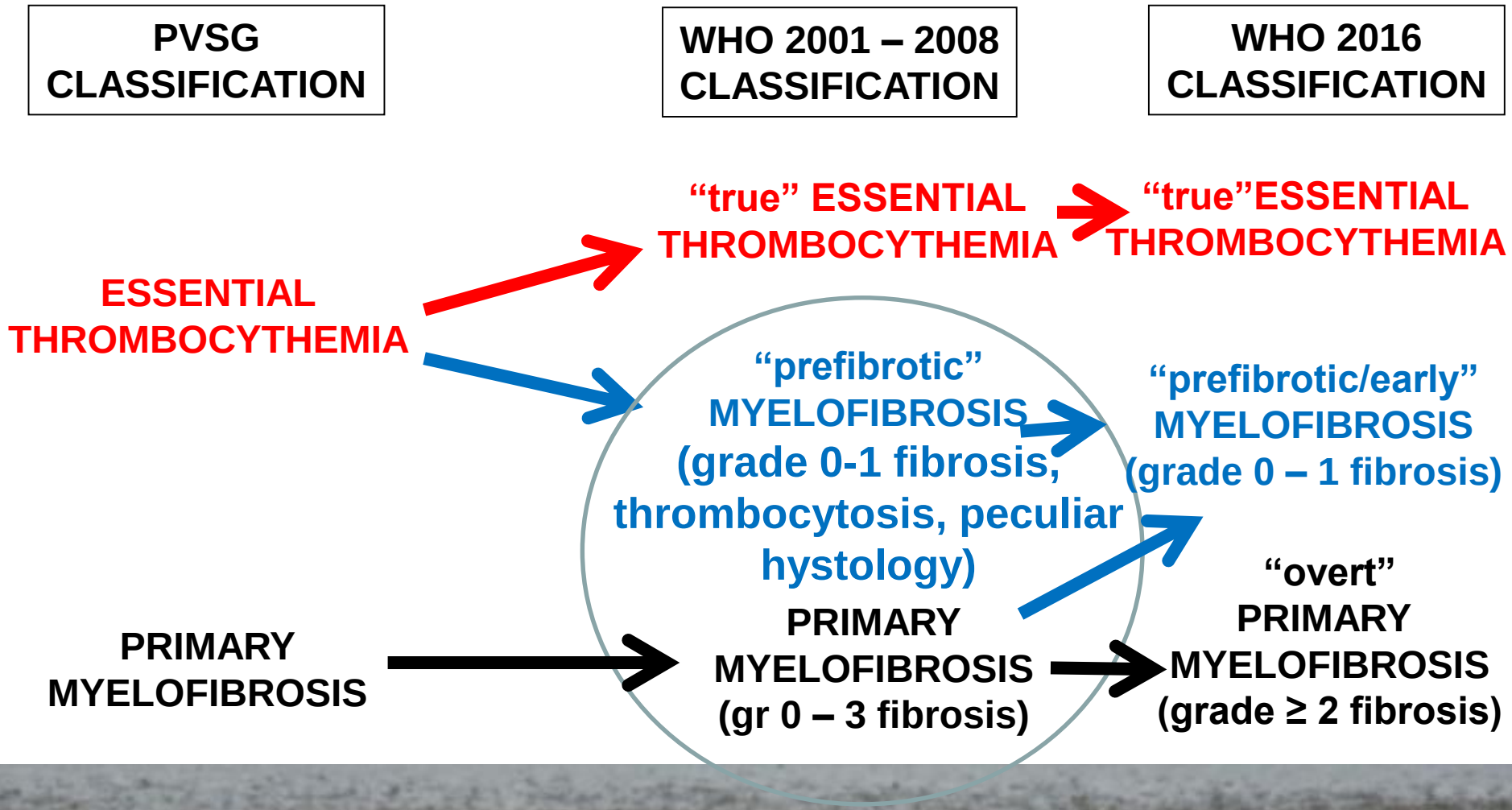
Triple negative MPN: many entities?

PV/ET treatment: what role for IFN and ruxolitinib?

PMF treatment: the ruxolitinib “empire”

PMF treatment: there is something beyond ruxolitinib?

ET, early PMF, overt PMF: the evolution of the species!



Arber DA, et Al. Blood 2016;127:2391-2405

Myeloproliferative Neoplasms in 2017: what hystological features are useful to discriminate them?

	PV	"true" ET	"prefibrotic/early" PMF	"overt" PMF
MARROW CELLULARITY	Increased	Normal	Increased	Increased→ reduced
LINEAGE INVOLVMENT	Trilinear hyperplasia	Megakaryocytic hyperplasia	Myelo-megakaryocytic hyperplasia	Myelo-megakaryocytic hyperplasia
MEGAKARYOCYTIC FEATURES	Large mature	Large mature	Variable size dysplastic	Variable size dysplastic
MEGAKARYOCYTIC CLUSTERS	No or "loose"	No or "loose"	"dense"	"dense"
GRADE OF FIBROSIS	No or mild (grado 0 – 1)	No or mild (grado 0 – 1)	No or mild (grade 0 – 1)	Moderate/severe (grade 2 -3)

Arber DA, et Al. Blood 2016;127:2391-2405

Molecular phenotype of prefibrotic MF vs overt PMF according to the revised 2016 WHO criteria

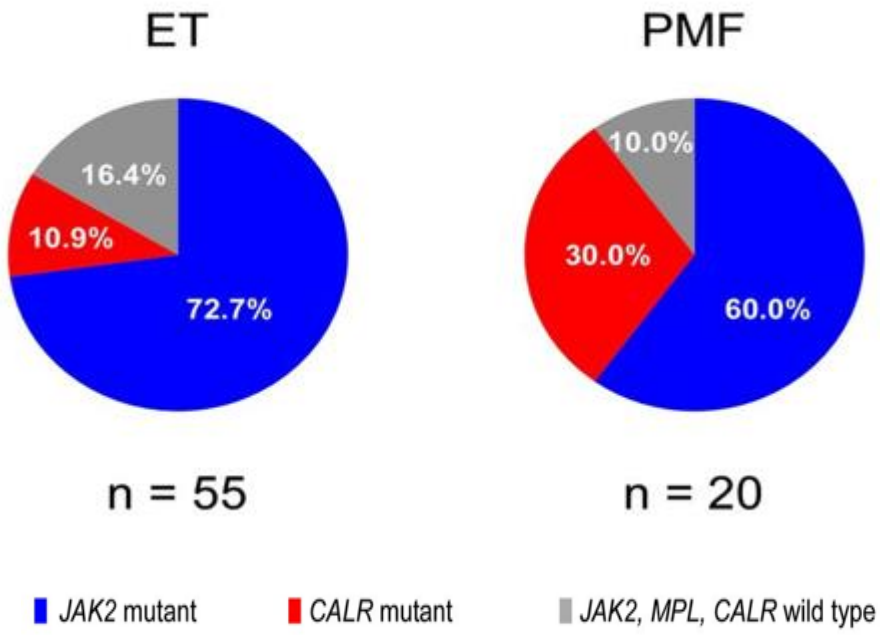
IPSS Risk Category	HMR n° (%)	HMR > 2 n° (%)	HMR n° (%)	HMR > 2 n° (%)
	Prefibrotic-PMF		Overt-PMF	
Low	23/139 (16.5)	1/139 (0.7)	22/88 (25.0)	5/88 (5.7)
	19.6%		30.6%	
Int-1	19/75 (25.3)	5/75 (6.7)	49/144 (34.0)	14/144 (9.7)
Int-2	16/37 (43.2)	2/37 (5.4)	41/96 (42.7)	12/96 (12.5)
	45.0%		52.9%	
High	16/34 (47.1)	8/34 (23.5)	58/91 (63.7)	19/91 (20.9)

Clinical phenotype of ET and prefibrotic MF according to the revised 2016 WHO criteria

	"true ET"	"early/prefibrotic" PMF	*p*
Sex (M/F), %	39/61	51/49	0.051
Median age, yrs (range)	53.1 (17.4 – 58.5)	54.7 (15.6 – 83.0)	0.938
Median Hb, g/dl (range)	14.2 (8.4 – 17.7)	13.5 (8.5 – 17.1)	**<0.001**
Median PLTS, x 10^9/l (range)	677 (450 – 2,810)	823 (98 – 3,000)	**<0.001**
Median WBC, x 10^9/l (range)	8.3 (4.2 – 28.0)	10.3 (4.7 – 23.5)	**<0.001**
Splenomegaly, %	4.5	29	**<0.001**
JAK-2 V617F, % CALR mutated, % MPL mutated, % Triple negative, %	66.5 17.8 3.4 12.3	52.3 35.8 6.4 5.5	**<0.001**

Rumi E, et al. Poster 357

Triple negative Myeloproliferative Neoplasms

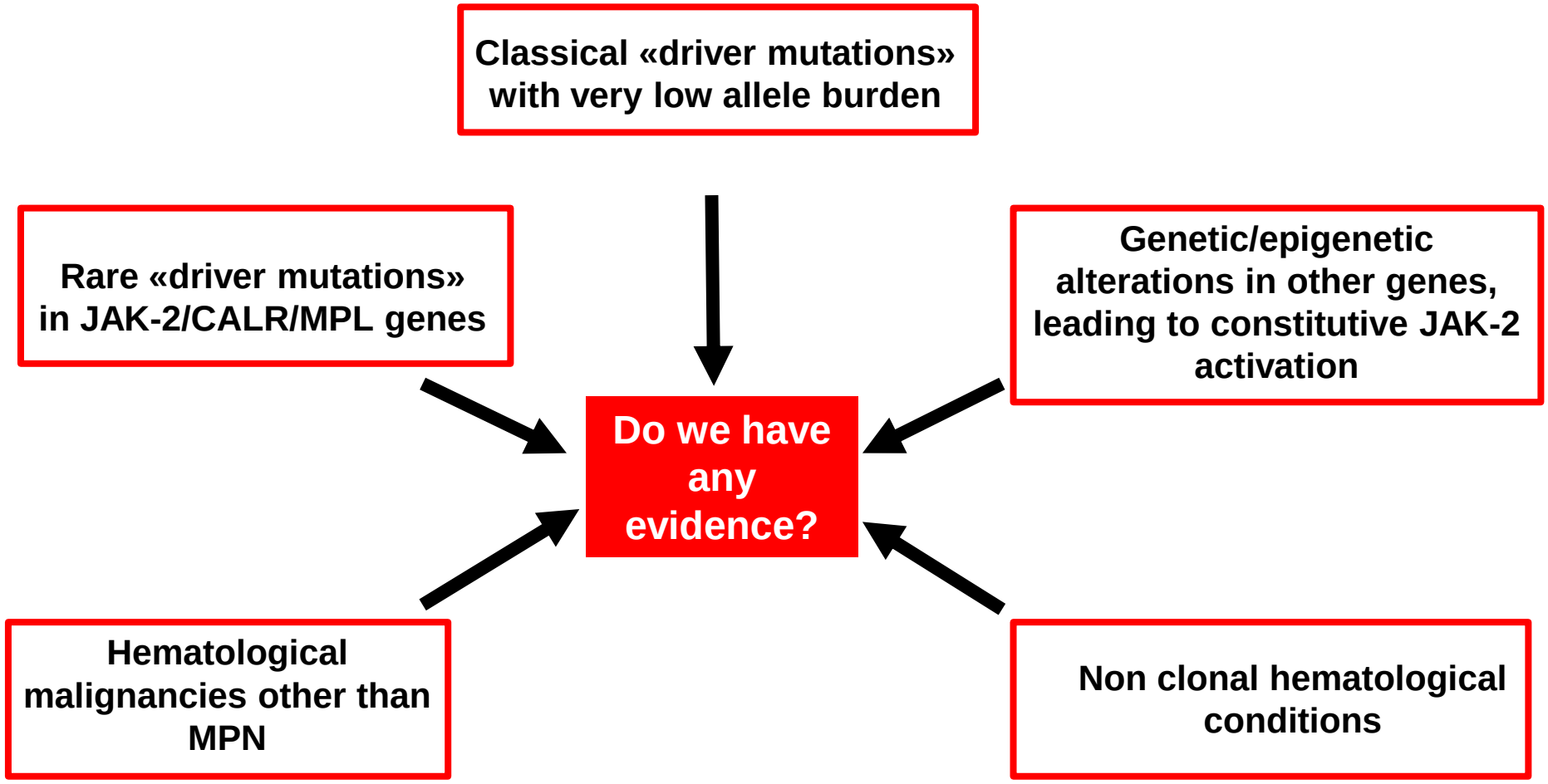


How many they are?

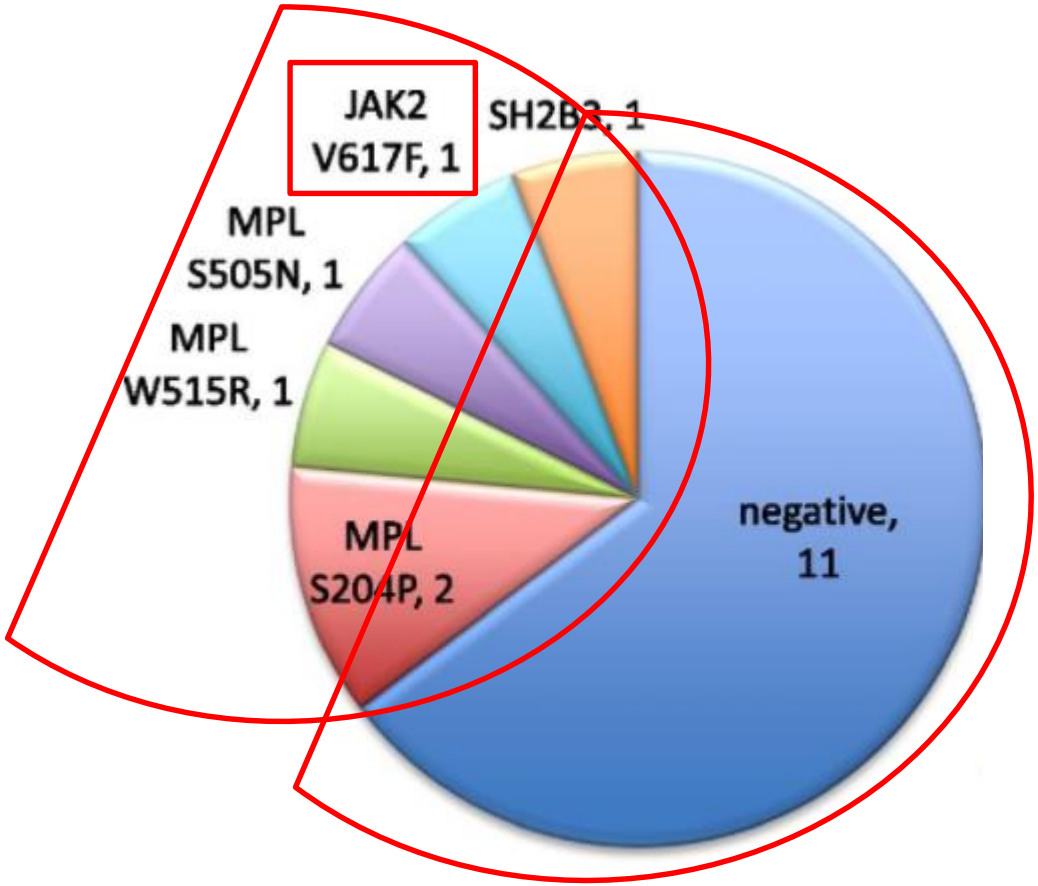
What really they are?

Elisa Rumi et al. Blood 2014;123:2416-2419

Triple negative Myeloproliferative Neoplasms: some biological/clinical hyptheses

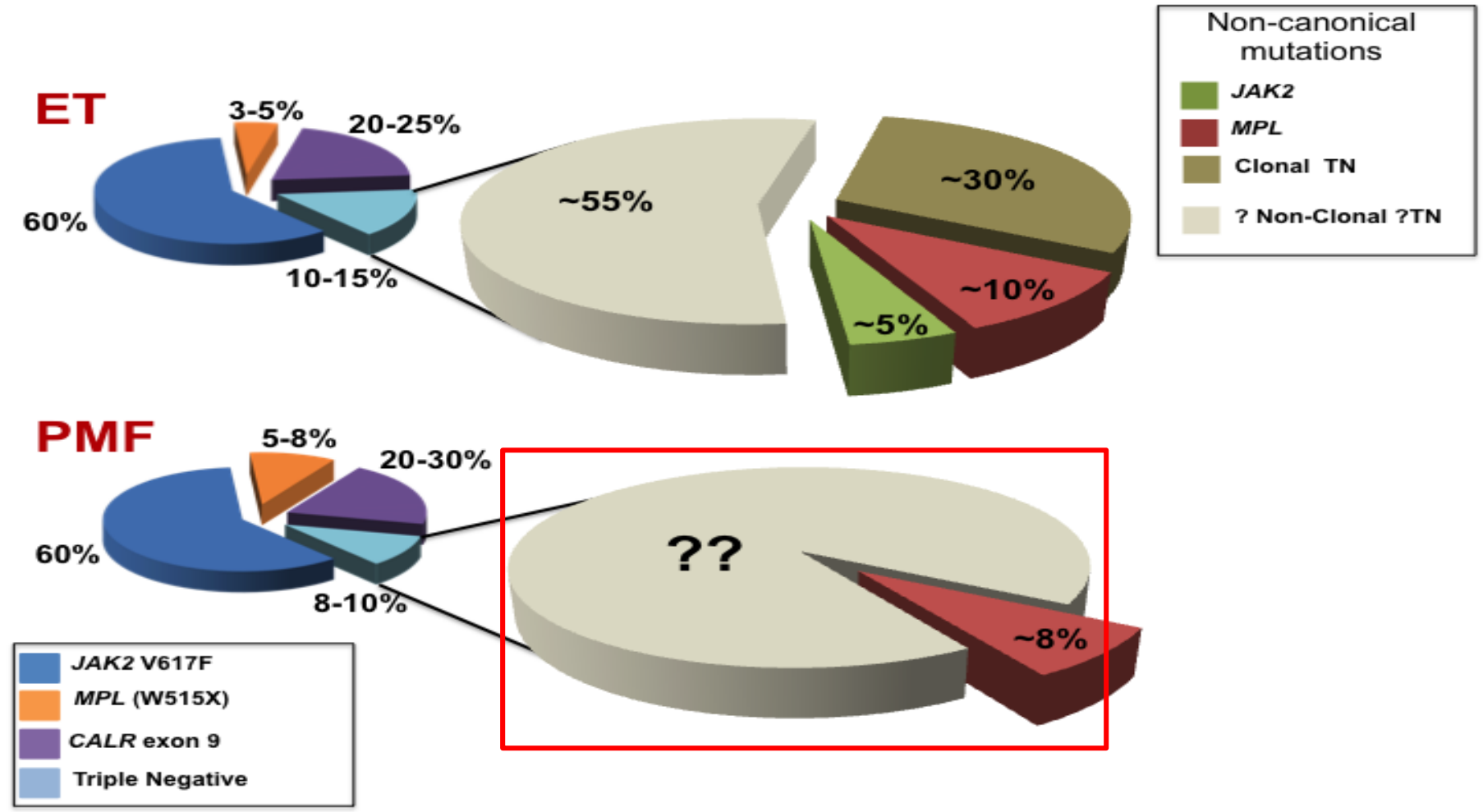


Triple negative Myeloproliferative Neoplasms: how many different diseases they are?



Cabagnols X, et al. Blood 2016, 127:333-342

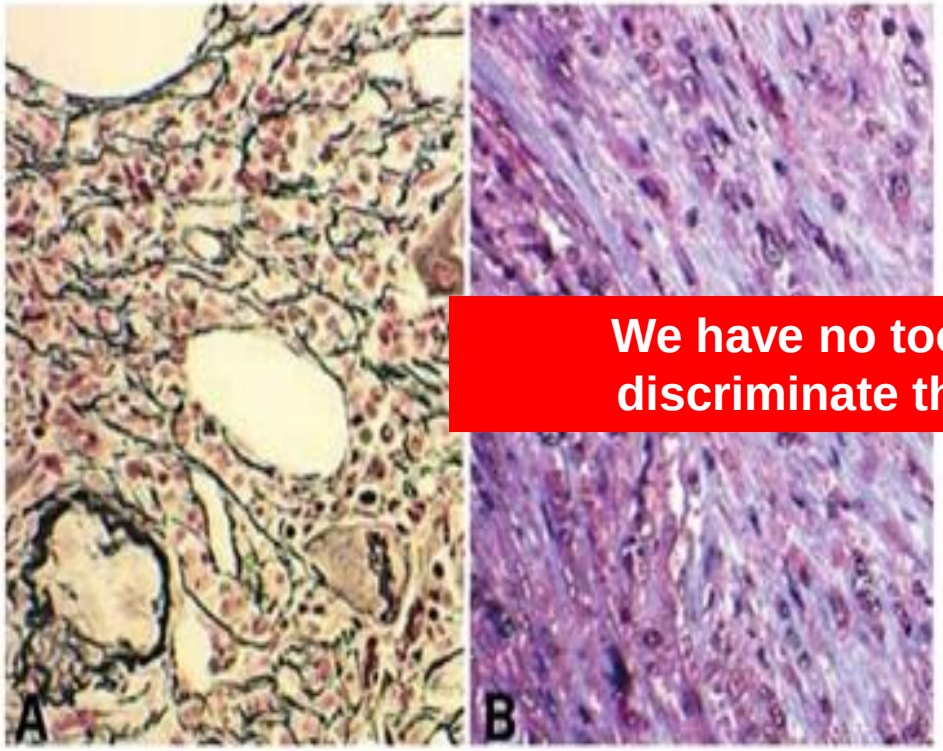
Triple negative Myeloproliferative Neoplasms: how many different diseases they are?



Claire N. Harrison, and A M. Vannucchi Blood 2016;127:276-278; Milosevic F et al, Blood 2016; 127:325-332; Cabagnols X et al, Blood 2016; 127:333-342.

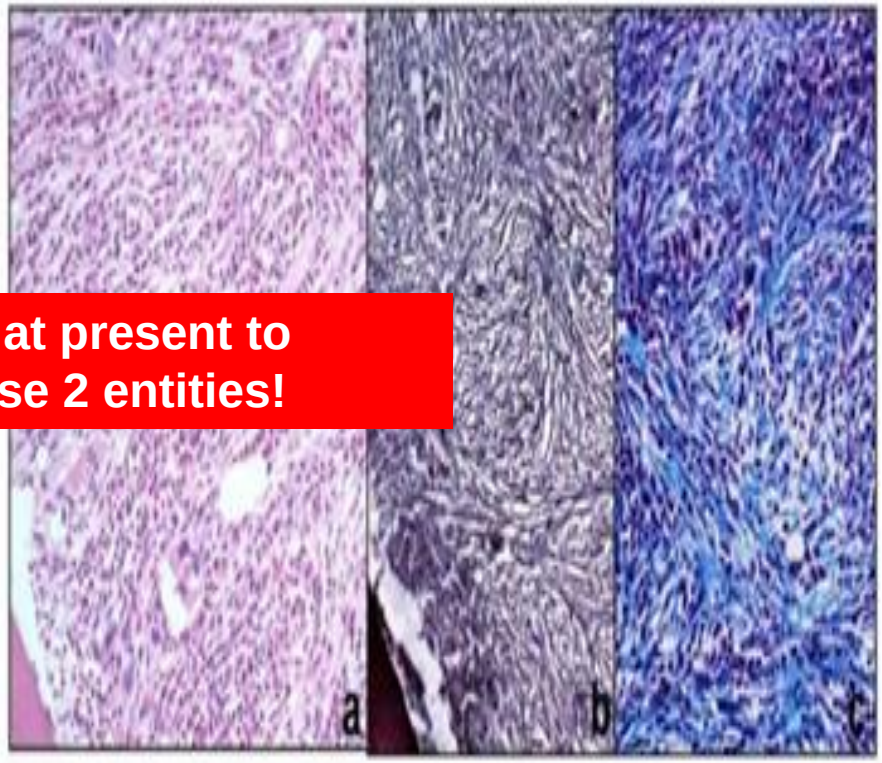
Triple negative Myeloproliferative Neoplasms: are we capable to discriminate them from MDS with fibrosis?

Patient 1



MDS with fibrosis

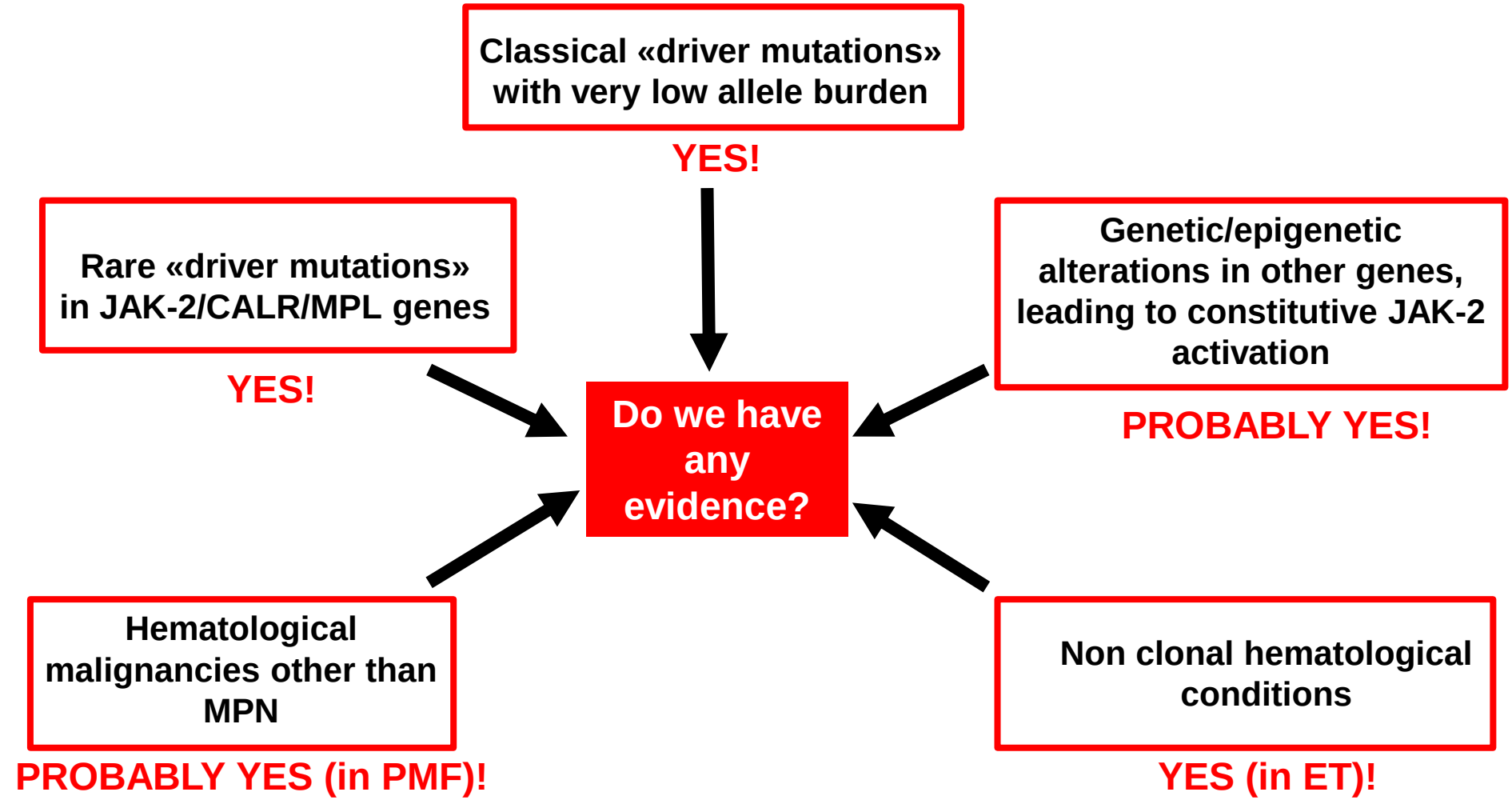
Patient 2



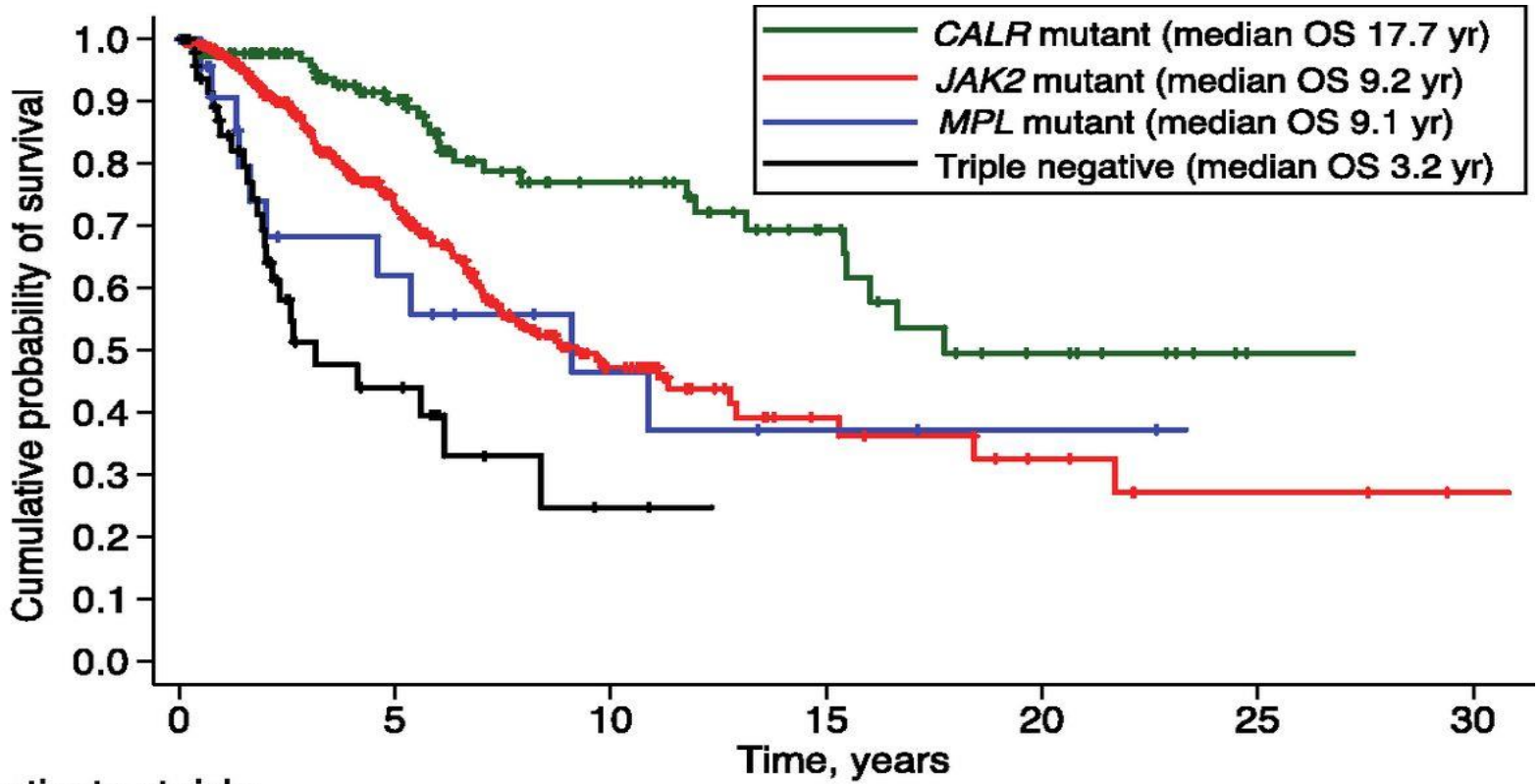
Primary myelofibrosis

We have no tool at present to discriminate these 2 entities!

Triple negative Myeloproliferative Neoplasms: some biological hyptheses



Triple negative MPN and prognosis



No. of patients at risk:

CALR mutant	140	72	37	19	9	1
JAK2 mutant	396	135	39	13	7	3
MPL mutant	25	10	5	3	2	0
Triple negative	53	11	2	0	0	0

Vannucchi A, et al. Educational session

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WHO 2016 MPN classification: “hot” topics

MPN and prognosis: the simpler the better?

PV/ET treatment: what role for IFN and ruxolitinib?

PMF treatment: the ruxolitinib “empire”

PMF treatment: there is something beyond ruxolitinib?

Currently used prognostic scores are “clinical” scores!

Variable	IPSS	DIPSS	DIPSS-plus
Age >65 y	√	√	√
Constitutional symptoms	√	√	√
Hemoglobin <10 g/dL	√	√	√
Leukocyte count >25x10^9/L	√	√	√
Circulating blasts ≥ 1%	√	√	√
Platelet count <100x10^9/L			√
RBC transfusion need			√
Unfavorable karyotype +8,-7/7q-,i(17q),inv(3), -5/5q-,12p-, 11q23 rearr.			√
	1 point each	1 point each but Hb=2	1 point each

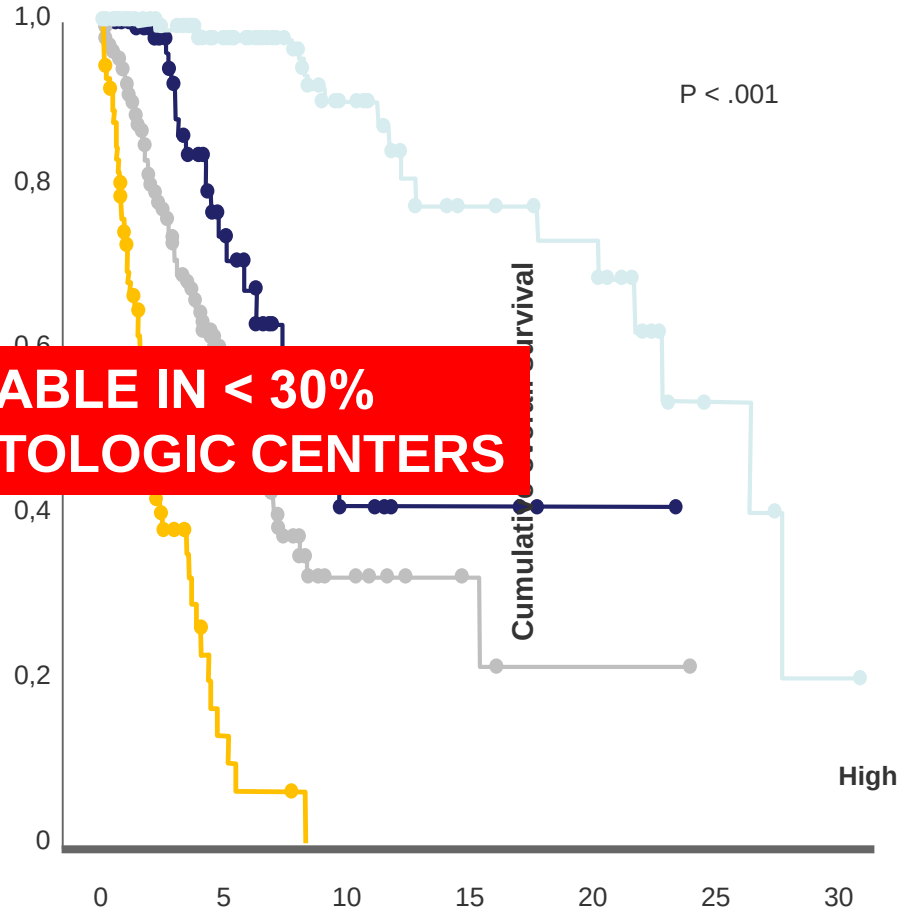
Cervantes et al. Blood. 2009;113:2895-901.
Passamonti et al. Blood. 2010; 115:1703-8.
Gangat et al. JCO. 2010; on line Dec 13.

Molecular scores are very attractive…

Genetically Driven Prognostic Model in Primary Myelofibrosis

	MIPSS	GIPSS
Age > 6	1.5	2
Constitutional Symptoms	0.5	No
Hemoglobin < 10 g/dL	0.5	No
Platelets < 200 × 10^9/L	1	
Triple Negative	1	
JAK2 or *MPL* Mutation	0.5	2
ASXL1 Mutation	0.5	1
SRSF2 Mutation	0.5	1
CALR Type 2, Type 2–Like	No	2
Unfavorable Cytogenetics*	No	3 for very high risk; 2 for high risk

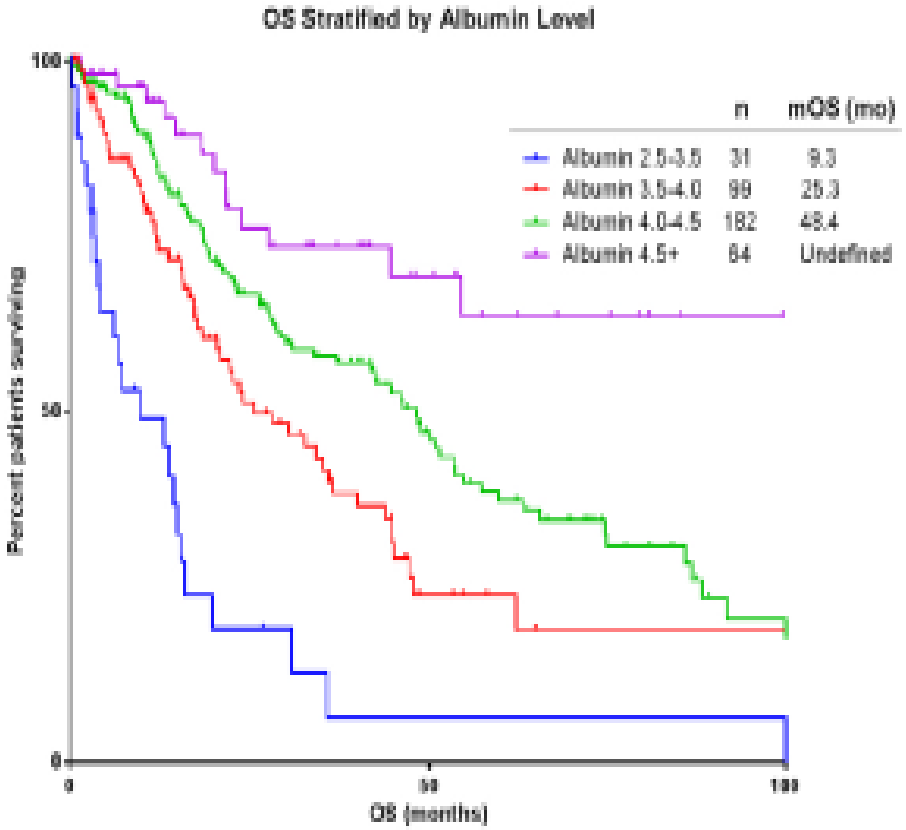
…BUT APPLIABLE IN < 30%
OF ITALIAN HEMATOLOGIC CENTERS



Vannucchi AM, et al. Blood 2014;124:405

The simpler the better? Serum albumin….

376 patients with PMF and serum albumin available within 30 days from diagnosis

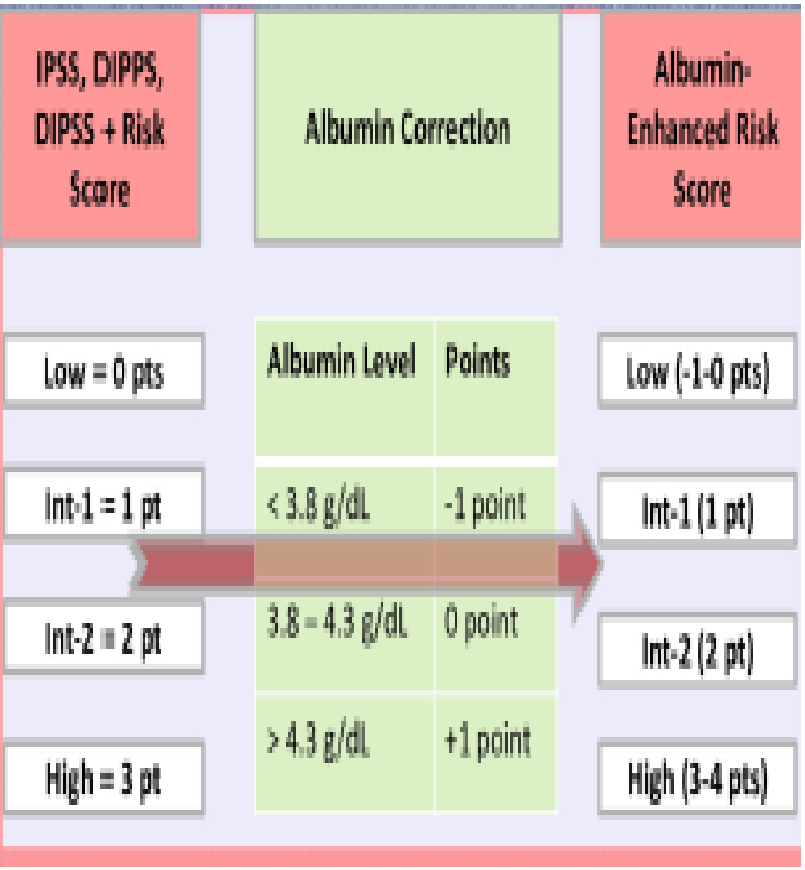


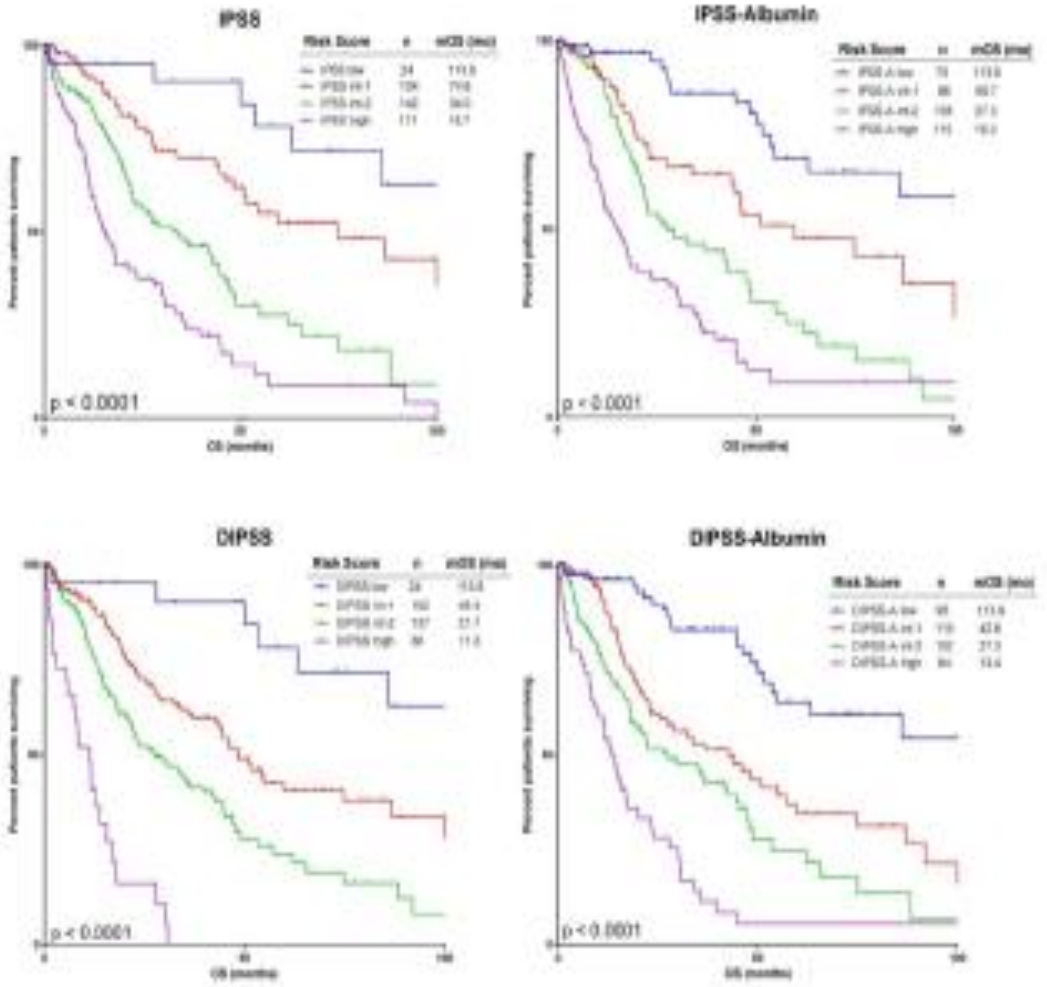
Phenotypic Correlate	P-value
Decreased hemoglobin	< 0.01
Thrombocytopenia	< 0.01
Increased age	< 0.01
Increased peripheral blasts	0.03
Increased Ferritin	< 0.01
IPSS	< 0.01
DIPSS	< 0.01
DIPSS+	< 0.01
Smoking history	< 0.01
Somatic mutation burden	0.03

Table 2. Phenotypic variables with significant correlation with serum albumin level.

Kuykendall TA, et al. Poster e1323

The simpler the better? Serum albumin….





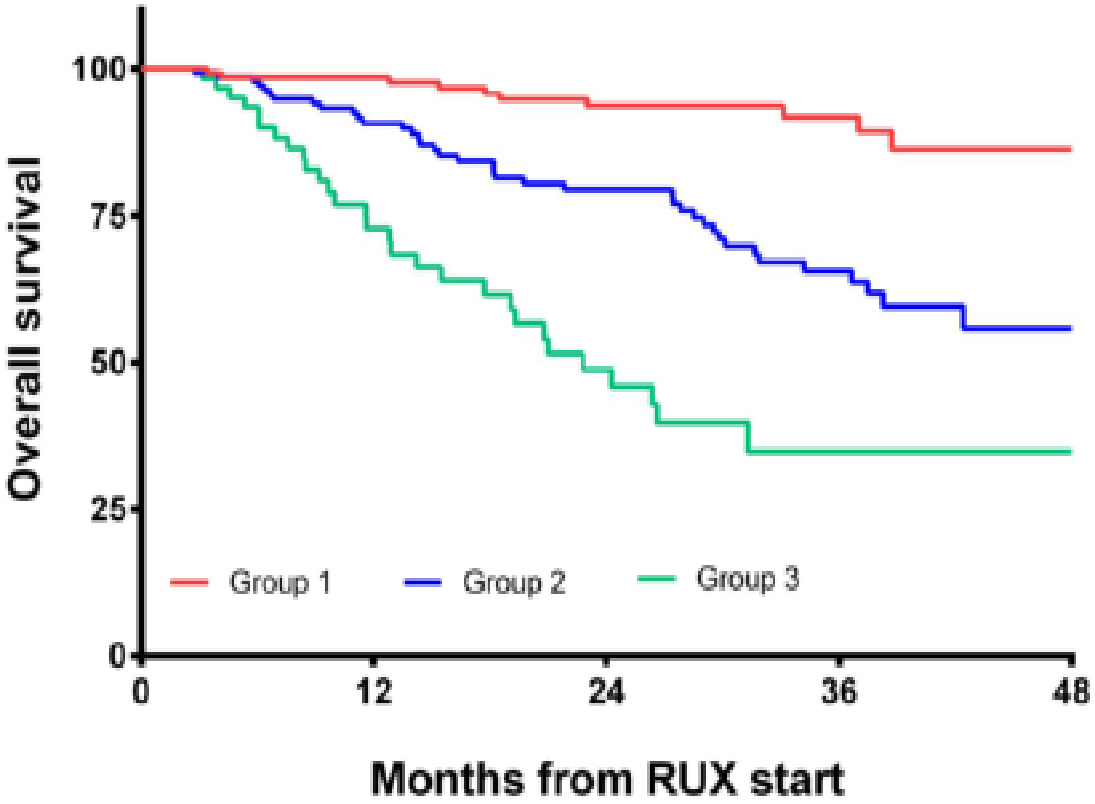
Kuykendall TA, et al. Poster e1323

The simpler the better?
Body Mass Index and Charlson Comorbidity Index…

343 patients with PMF treated with RUX in 20 Italian Centers

	Score
Transfusion dependency	1.5
CCI ≥ 3	1
BMI < 21	1
IPSS Int-2	2
IPSS High	4

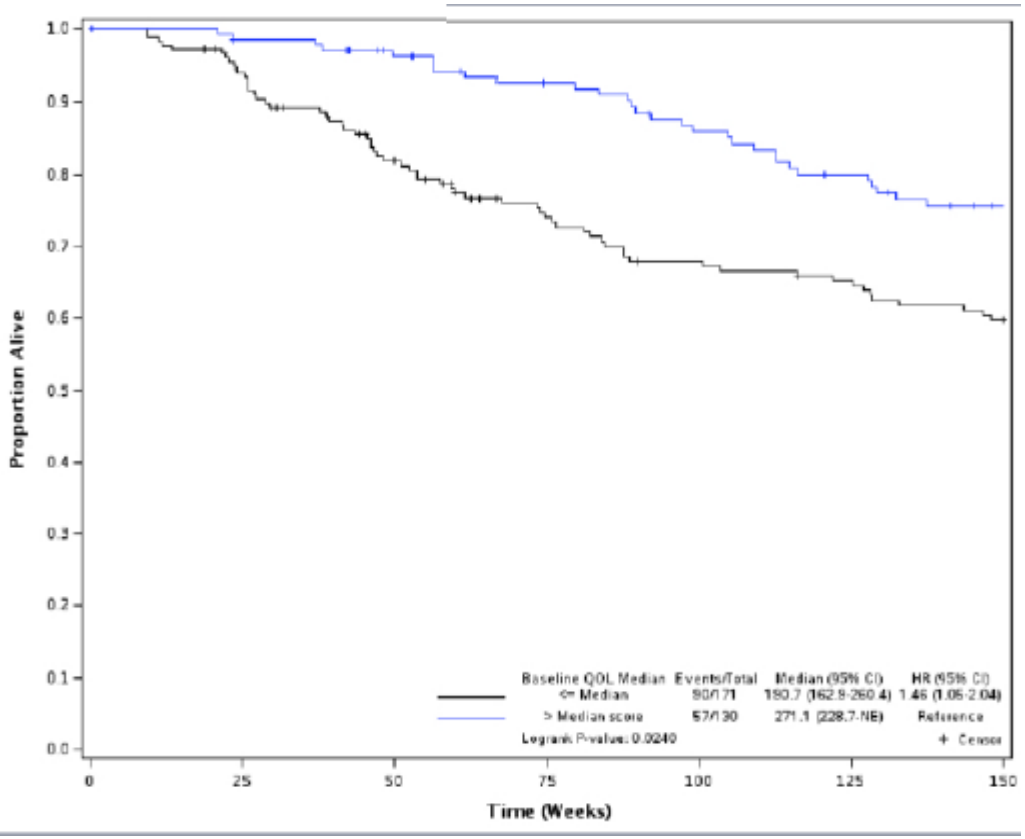
Group 1 (137 pts)	0 - 2
Group 2 (144 pts)	3 - 5
Group 3 (62 pts)	> 5



Palandri F, et al. Poster e1325

The simpler the better? Global Health QoL score

309 patients with PMF treated in the COMFORT-I study

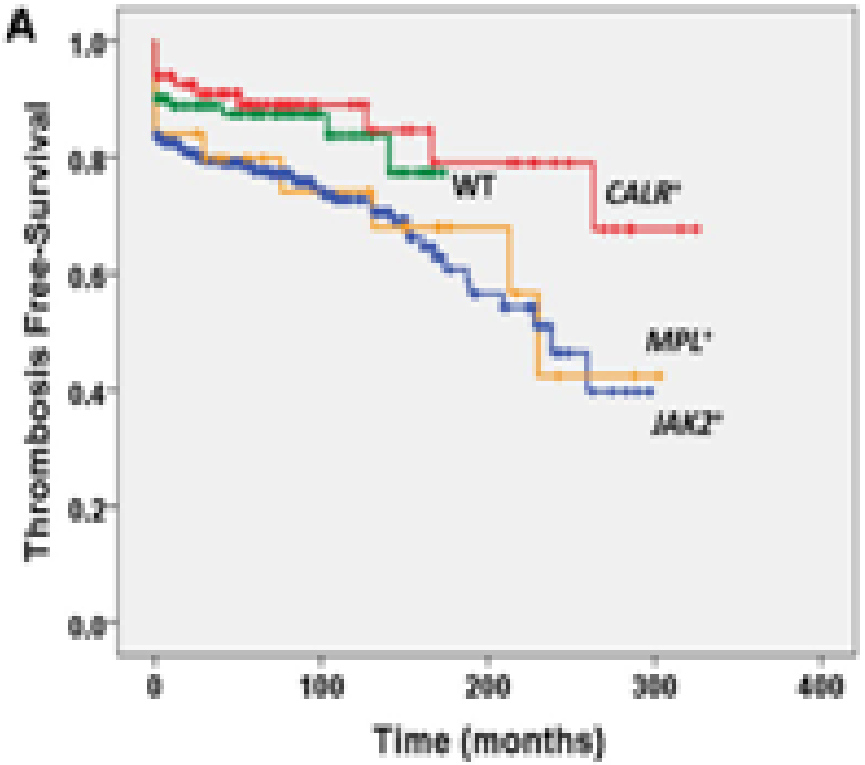


Cox Proportional Hazard Model
(censoring for placebo at crossover)

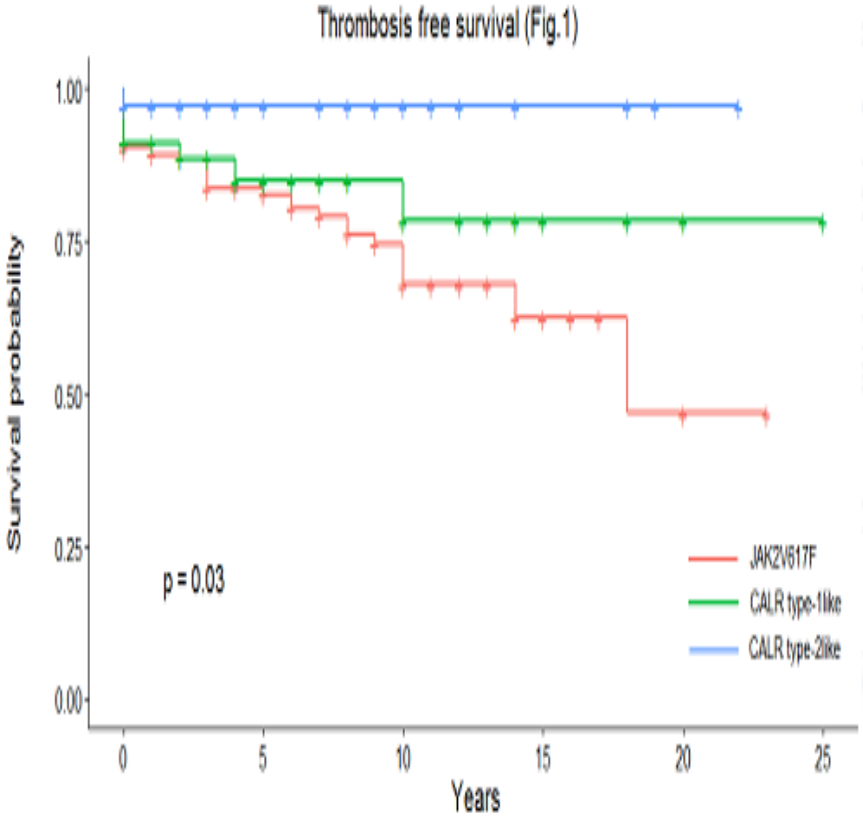
- age p<0.001
- sex p<0.001
- QoL p=0.002

Scherber R, et al. Poster e1321

Is a mutation “per se” enough for prognostication? CALR mutation and risk of thrombosis in ET



CALR mutations influence the risk of thrombosis in ET



CALR mutation **type** influences the risk of thrombosis in ET

Vannucchi A, et al. Educational session

Albuin Blanco A, et al. Poster e1327

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WHO 2016 MPN classification: "hot" topics

- **MPD RC 112 trial**
- **PROUD PV**

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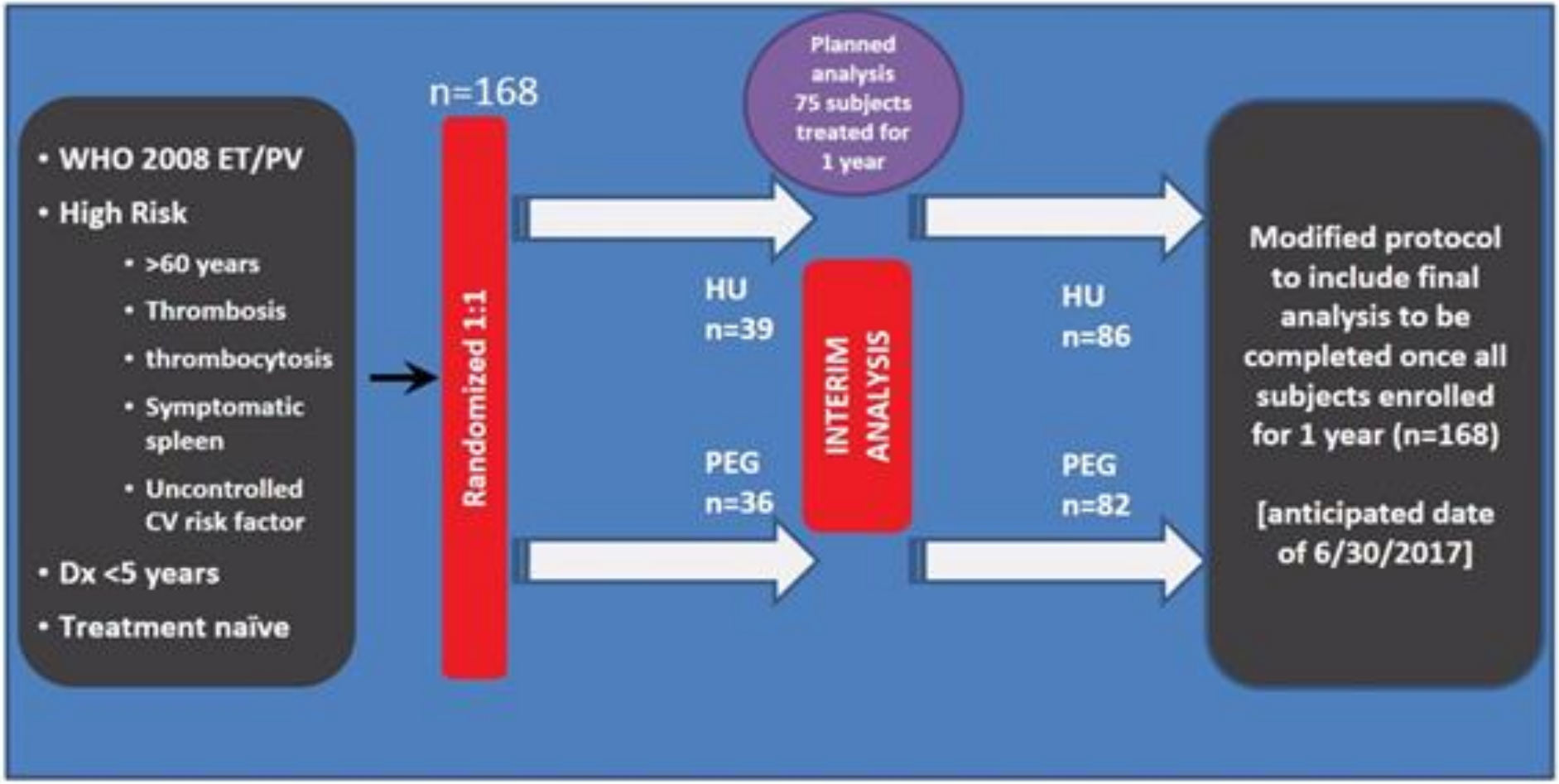
- **Response-2**
- **MAJIC ET**

PMF treatment: there is something beyond ruxolitinib?

Peg-IFN vs HU in PV/ET patients: MPD RC 112 trial



Mascarenhas J, et al. ASH 2016

MPD RC 112 trial: efficacy results at 12 months

	N° pts	Complete Hematological Response	Partial Hematological Response	Overall Response Rate	Pts with need of phlebotomy (PV only)
PEG-IFN	36	10 (28%)	19 (53%)	81% p=0.60	5/20 (20%) p=0.02
HU	39	13 (33%)	14 (36%)	69%	0/18 (0%)

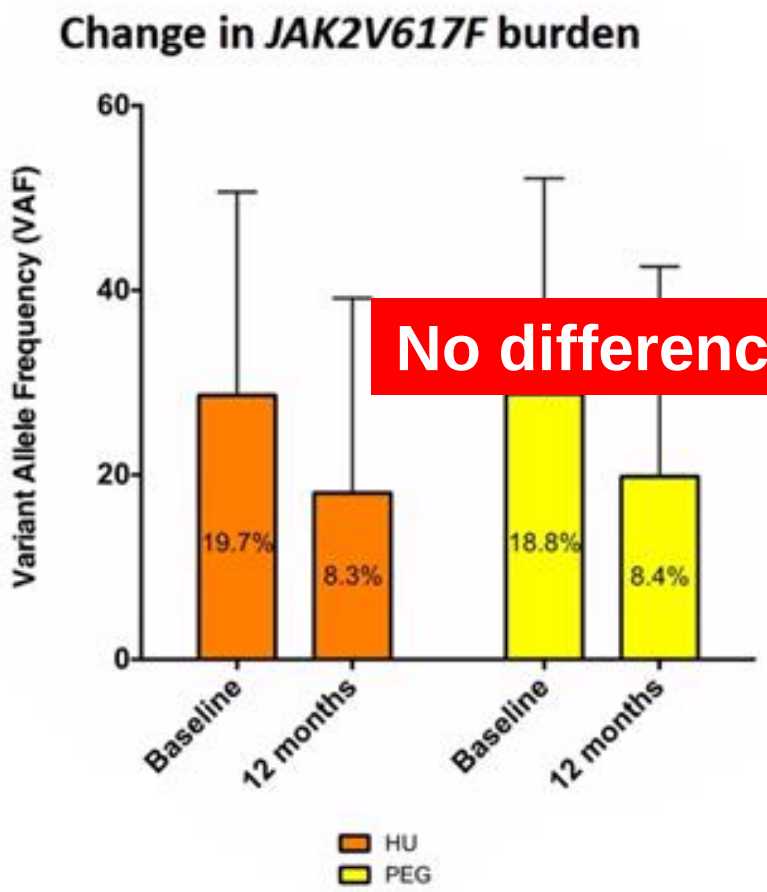
Mascarenhas J, et al. ASH 2016

MPD RC 112 trial: main adverse events (> 10%)

Adverse Event	HU (n=36)	PEG (n=36)	P Value*
Abdominal pain	1 (3%)	5 (14%)	0.09
Anemia	2 (6%)	4 (11%)	0.40
Depression	-	5 (14%)	0.02
Diarrhea	3 (8%)	4 (11%)	0.69
Dyspnea	-	5 (14%)	0.02
Fatigue	2 (6%)	6 (17%)	0.13
Flu-like symptoms	1 (3%)	4 (11%)	0.16
Injection site reaction	-	5 (14%)	0.02
Leukopenia	2 (6%)	4 (11%)	0.40
Neutropenia	4 (11%)	2 (6%)	0.40
Pain	2 (6%)	8 (22%)	0.04
Pruritus	1 (3%)	4 (11%)	0.16

Mascarenhas J, et al. ASH 2016

MPD RC 112 trial: molecular and histological responses



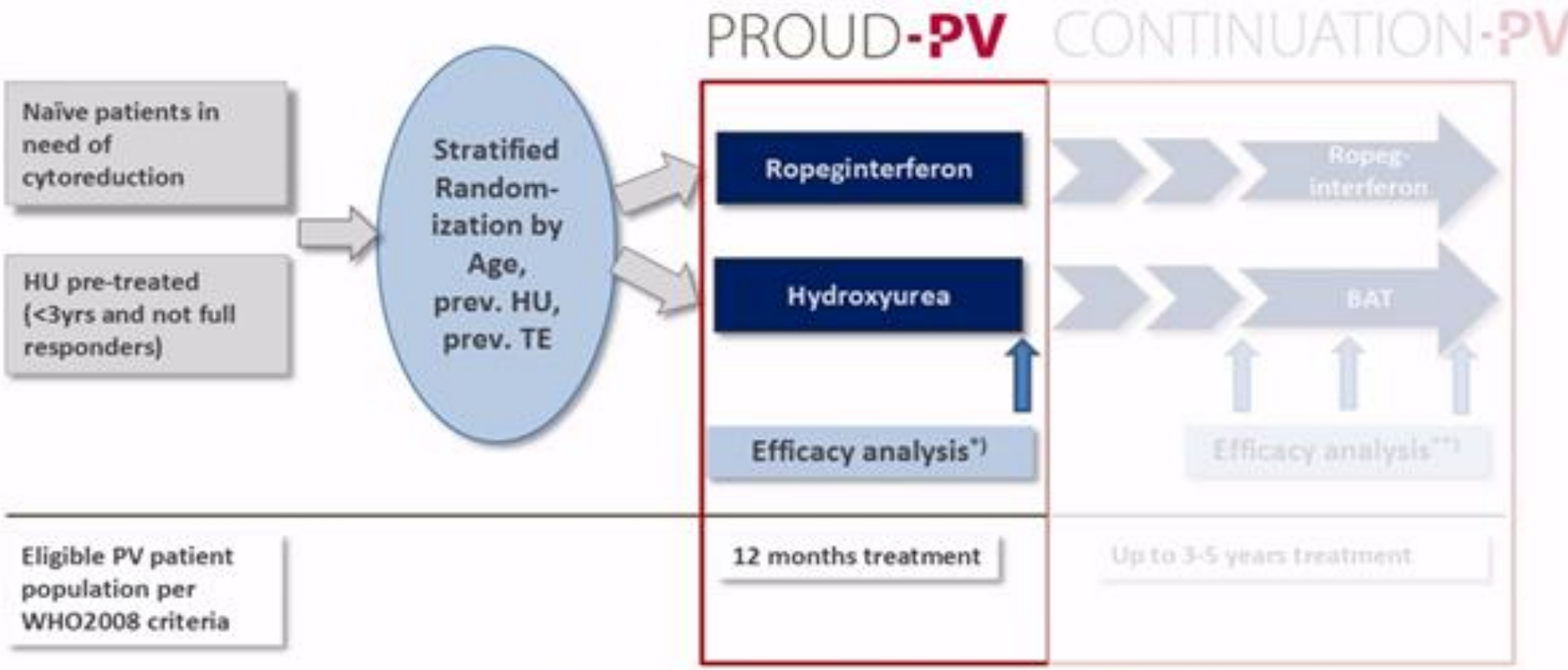
Histopathology Criteria

- Normalized BM cellularity
- < grade 2 reticulin fibrosis
- ET: Disappearance of MK hyperplasia, & abnormal MK histotopography
- PV: Disappearance of trilineage hyperplasia

No differences in both endpoints!

	HU	PEG
ET+PV	8/22	2/24
ET	5/10	2/10
PV	3/12	0/14

Peg-IFN vs HU in PV patients: PROUD-PV trial



Expected outcome: *) non-inferiority: Hematologic Response

**) benefit: durable Hematologic Response, PFS, PV symptom relief

Gisslinger H, et al. ASH 2016

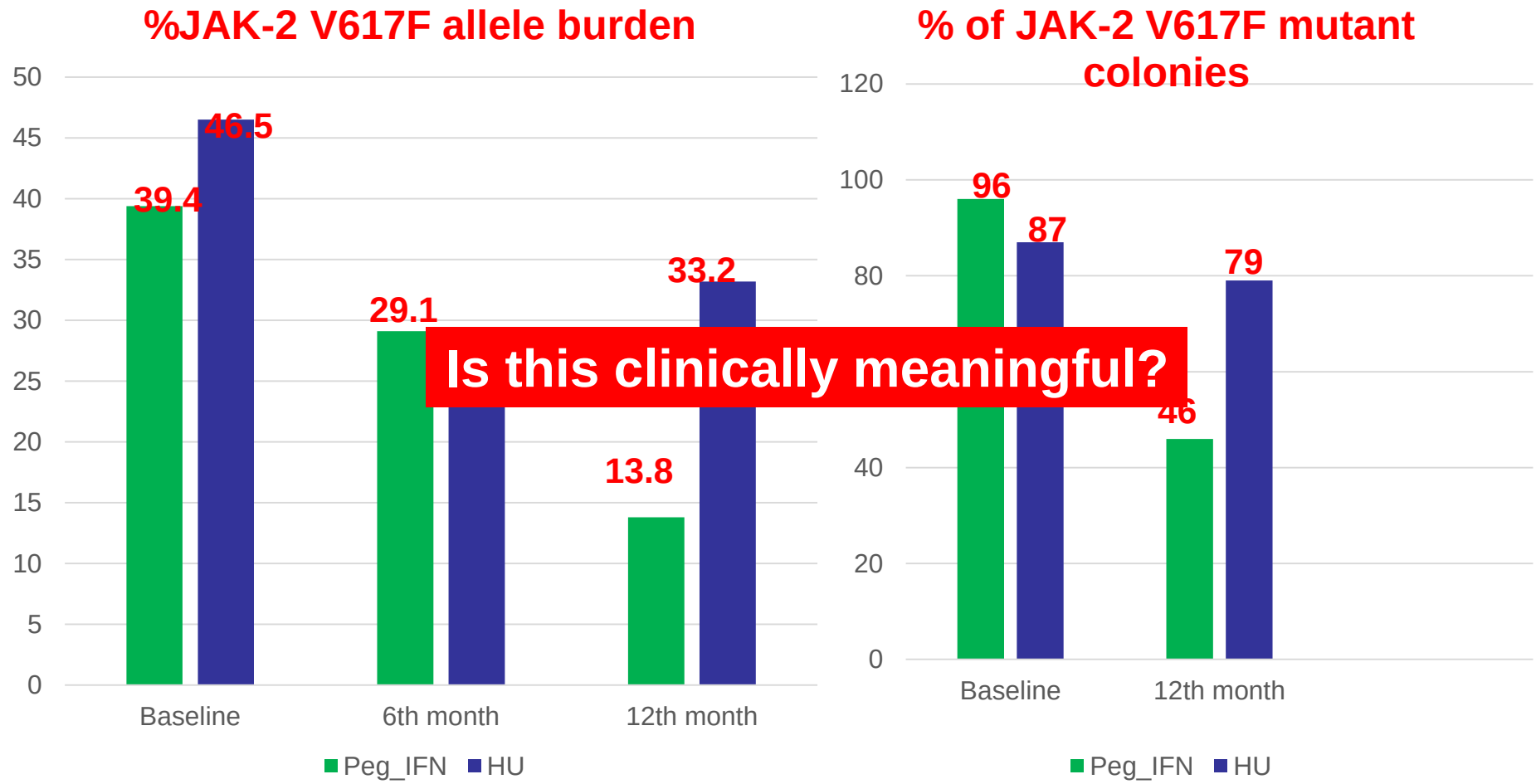
PROUD-PV trial: efficacy results at 12 months

	AOP2014	HU	Difference % (95% CI)	P-value *)
Complete hematologic response rate (ITT)	43.1%	45.6%	-2.5 (-14.9 to 9.9)	0.0028
Responding patients/n	53/123	57/125		
Complete hematologic response rate (PP)	44.3%	46.5%	-2.2 (-15.2 to 10.7)	0.0036
Responding patients/n	50/113	53/114		

→ non-inferiority is demonstrated, p=0.0028

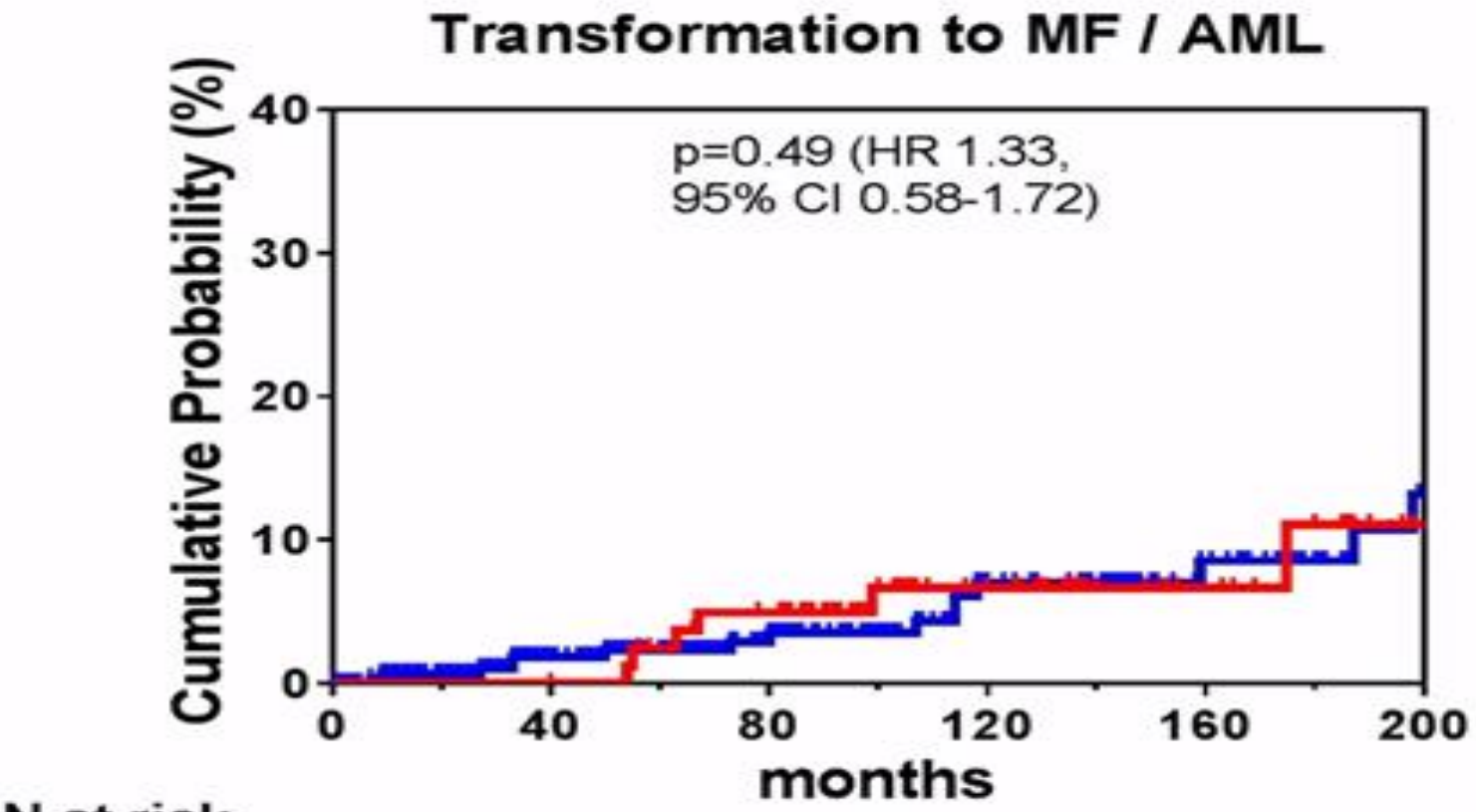
Gisslinger H, et al. ASH 2016

Molecular results of the phase III Proud PV trial (Peg-IFN vs HU in PV patients)



Kiladjian JJ, et al. S787

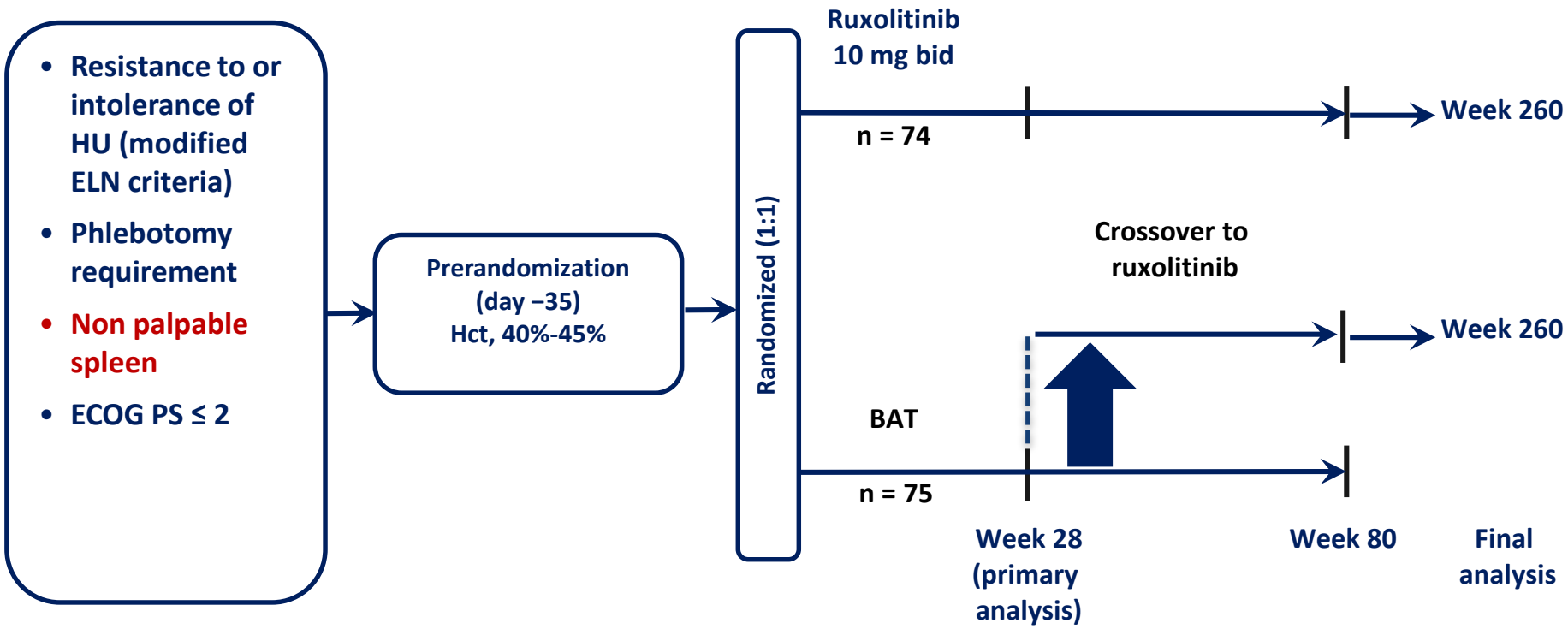
PEG-IFN in PV patients: what about myelofibrotic evolution?



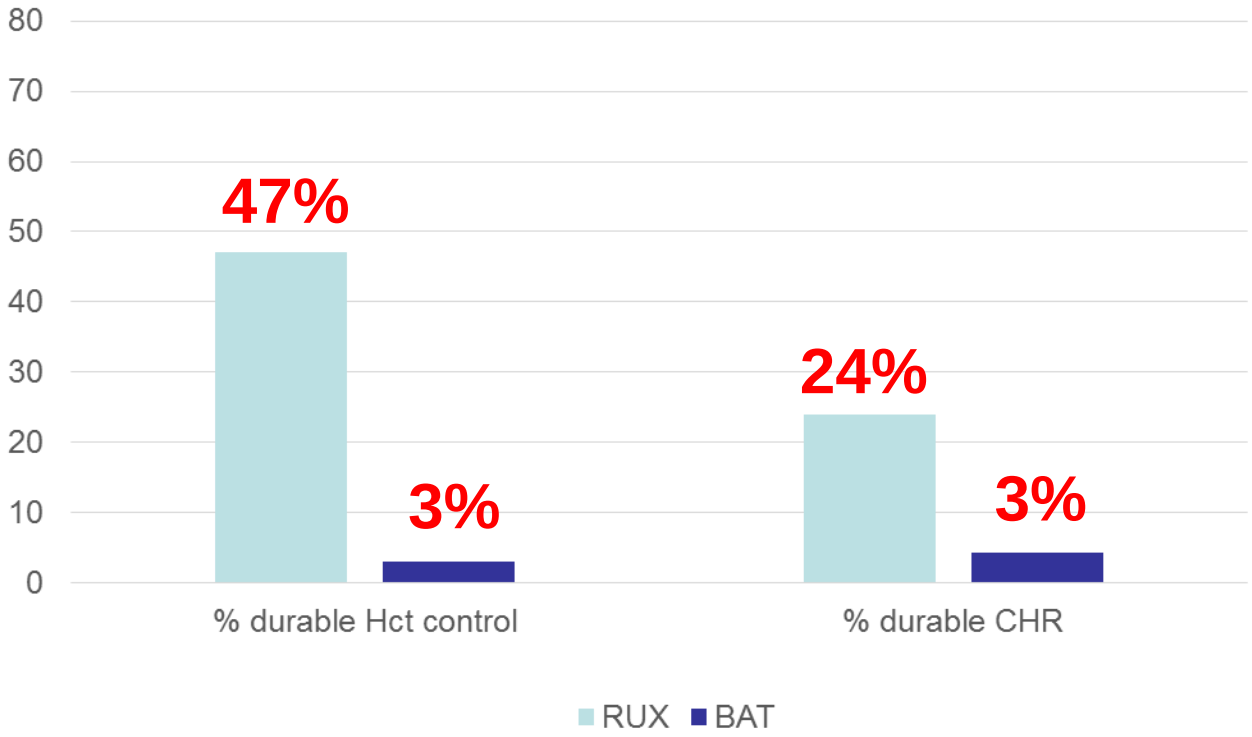
N at risk						
PEG	83	83	75	46	25	14
Control	352	224	159	97	62	35

Masarova L, et al. Lancet Hematol 2017

Results of the Response-2 trial: 80-week follow-up



Results of the Response-2 trial: 80-week follow-up



Greisshammer M, et al. S784

Results of the Response-2 trial: 80-week follow-up

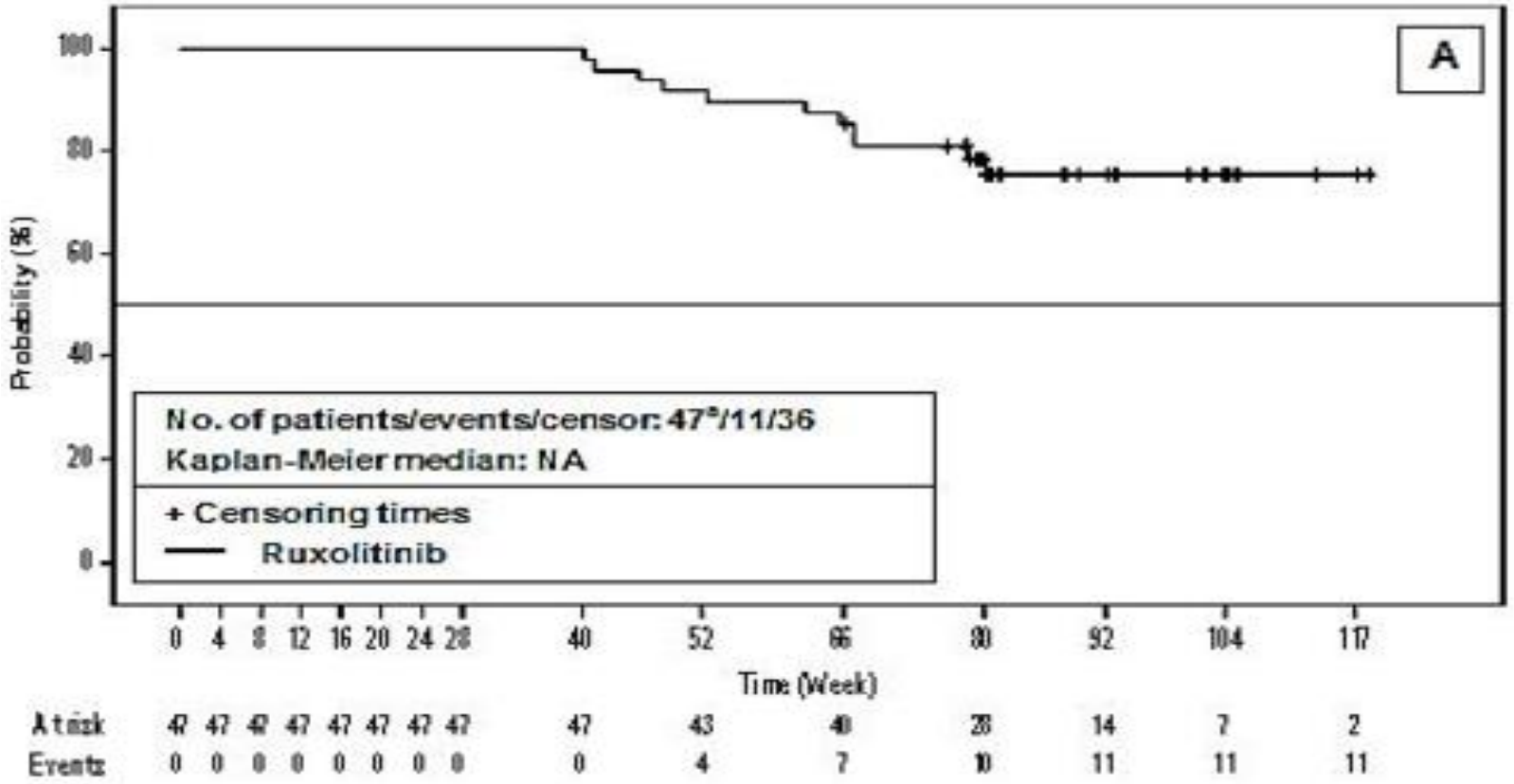
Flebotomy usage by week 80

Phlebotomy usage by week 80 (B)		
Phlebotomy frequency	Ruxolitinib, N=74, n (%)	BAT, N=75, n (%)
0	54 (72.9)	27 (36.0)
1-2	15 (20.3)	29 (38.7)
3-4	5 (6.8)	16 (21.3)
>4	0 (0)	3 (4.0)
Total number of phlebotomies	36	106

Greisshammer M, et al. S784

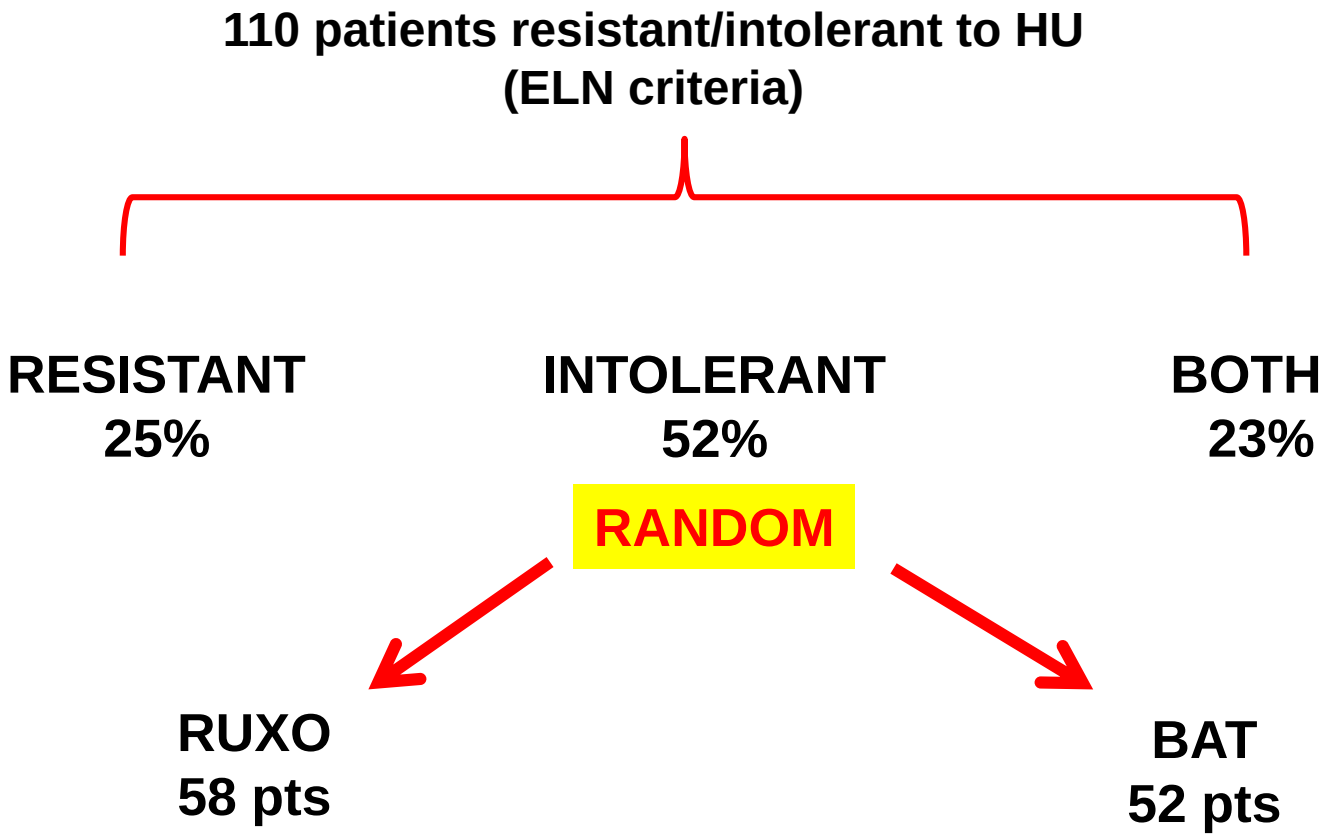
Results of the Response-2 trial: 80-week follow-up

Estimate of maintaining primary response with ruxolitinib



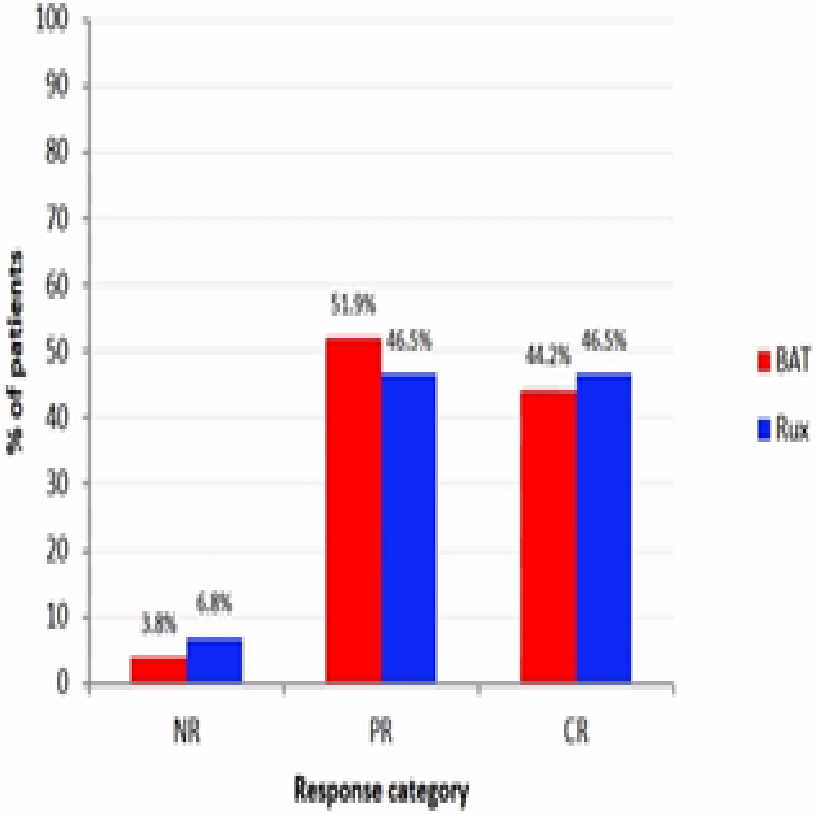
Greisshammer M, et al. S784

Ruxolitinib in ET patients: the MAJIC ET trial



Primary endpoint: Complete Hematological Response at 12 months

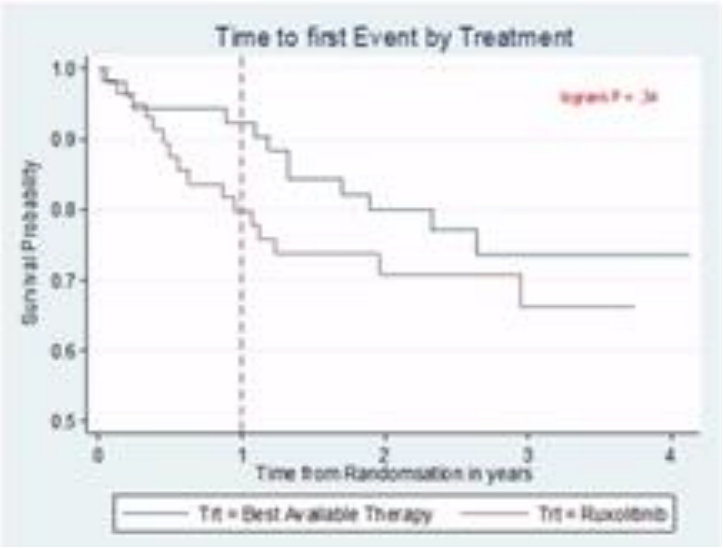
MAJIC ET trial: efficacy results and discontinuation at 12 months

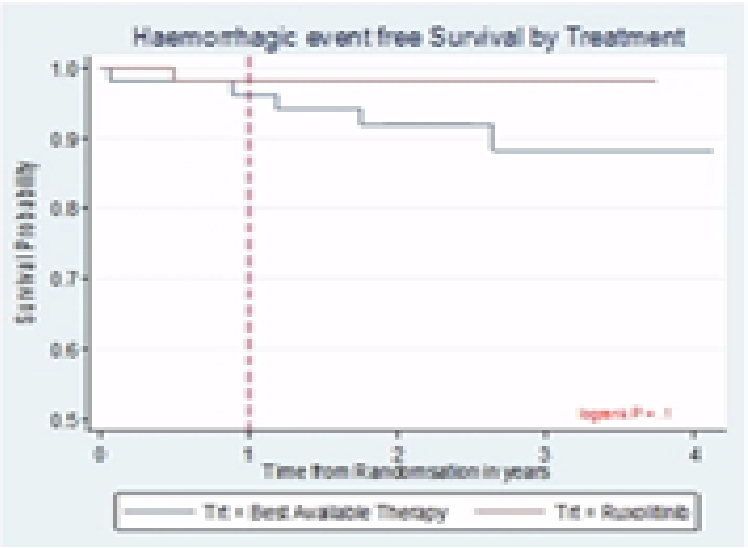


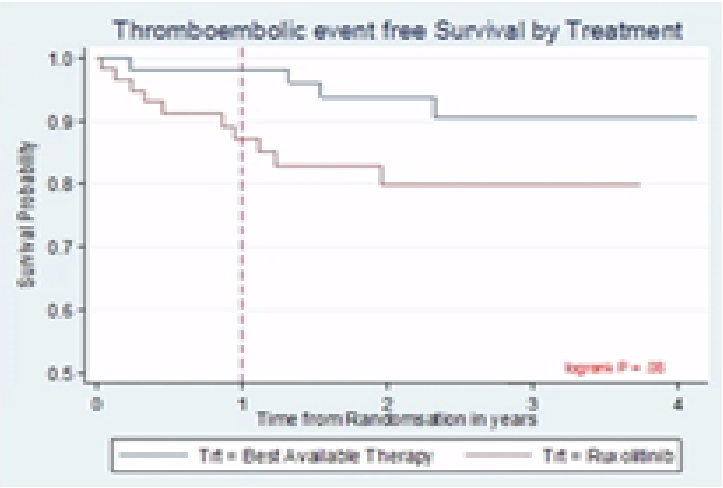
TREATMENT DISCONTINUATION

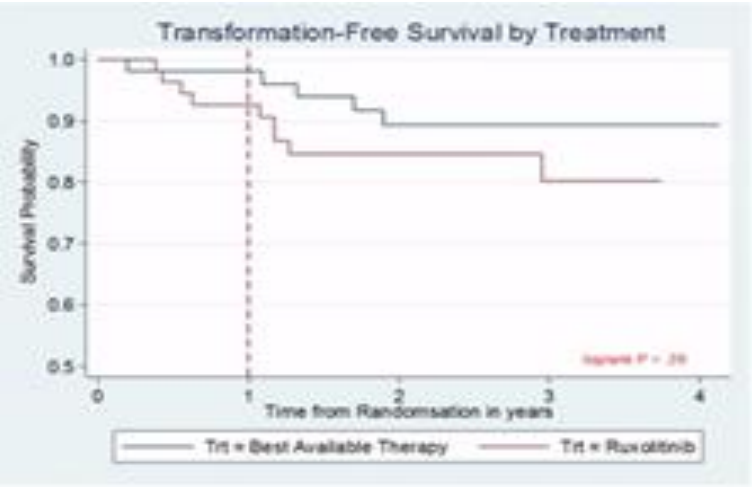
	Rux	BAT	Total
Lack of efficacy	15	1	16
Transformation	9	3	12
Toxicity	6	1	7
Other	3	3	6
Consent	1	0	1
Death*	1	2	3
Total	35	10	45

MAJIC ET trial: survival curves









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- MPD RC 112 trial
- PROUD PV

??

PV/ET treatment: what role for IFN and ruxolitinib?

Useful in about 10 – 15% of patients

- Response-2
- MAJIC ET

??

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WHO 2016 MPN classification: “hot” topics

ASSOCIATION WITH ESA?

ELDERLY PATIENTS?

STARTING WITH LOW DOSES?

MPN and prognosis: the simpler the better?

PILLS FROM “REAL-LIFE”

INFECTIVE COMPLICATIONS?

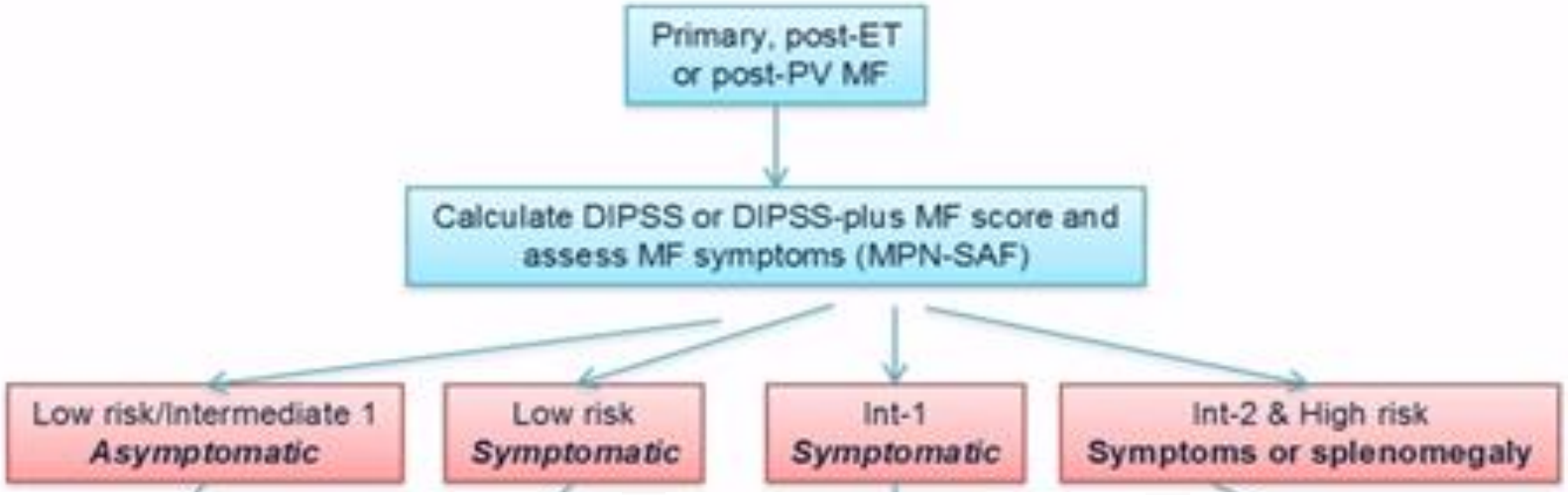
TREATMENT OF LOW-RISK PATIENTS?

PV/ET treatment: what role for IFN and ruxolitinib?

PMF treatment: the ruxolitinib “empire”

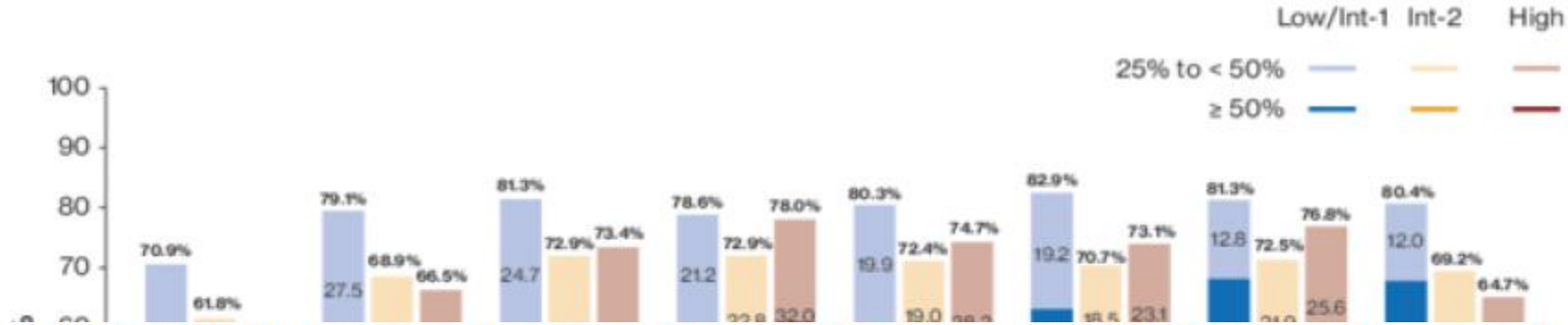
PMF treatment: there is something beyond ruxolitinib?

Ruxolitinib in PMF: therapeutic landscape in 2017

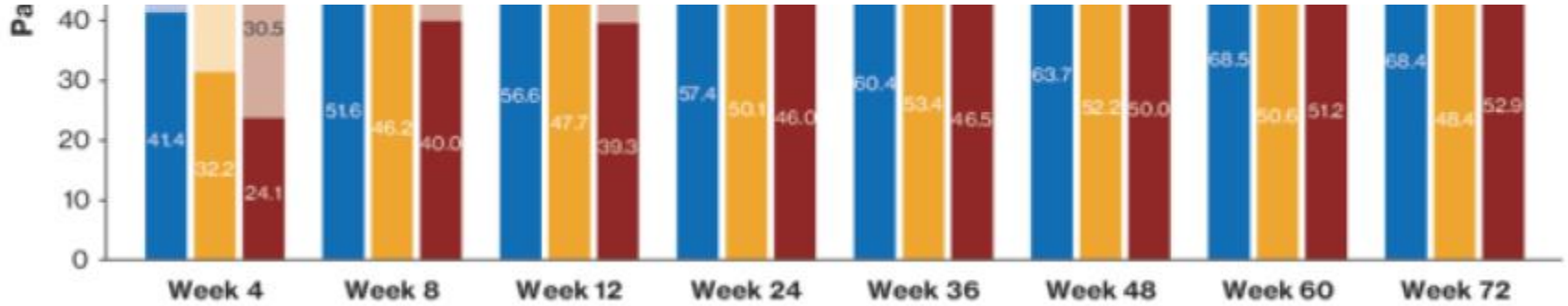


Is ruxolitinib effective and safe in low risk DIPSS patients?

1800 patients with PMF enrolled in the JUMP study



- Overall, findings from our study suggest that ruxolitinib is safe in DIPSS lower-risk patients and that earlier ruxolitinib treatment may lead to greater benefits in patients with MF

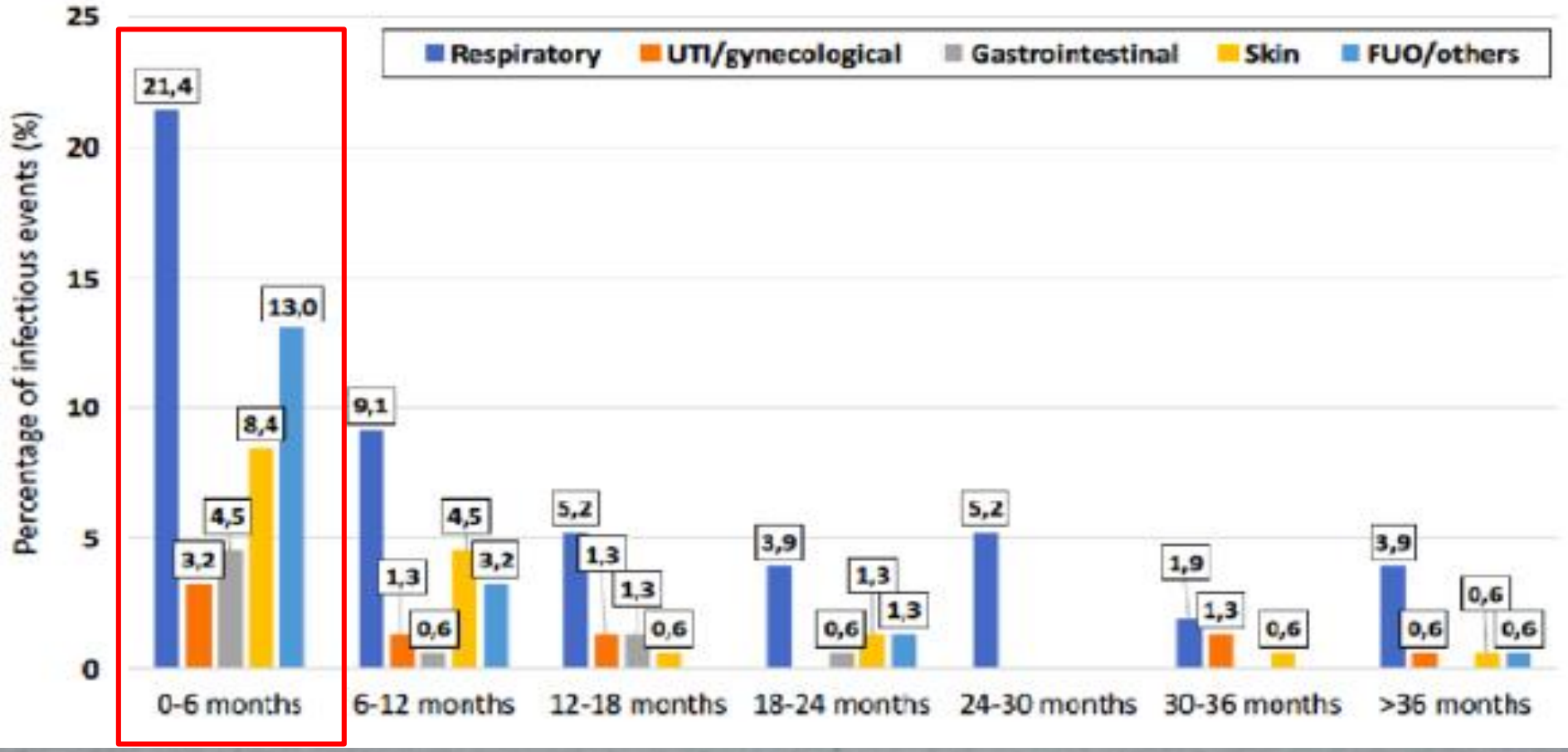


Low/Int-1, n =	833	779	692	575	437	355	305	266
Int-2, n =	695	634	572	403	311	232	178	159
High, n =	174	155	135	100	71	52	43	34

Passamonti F, et al. Poster 705

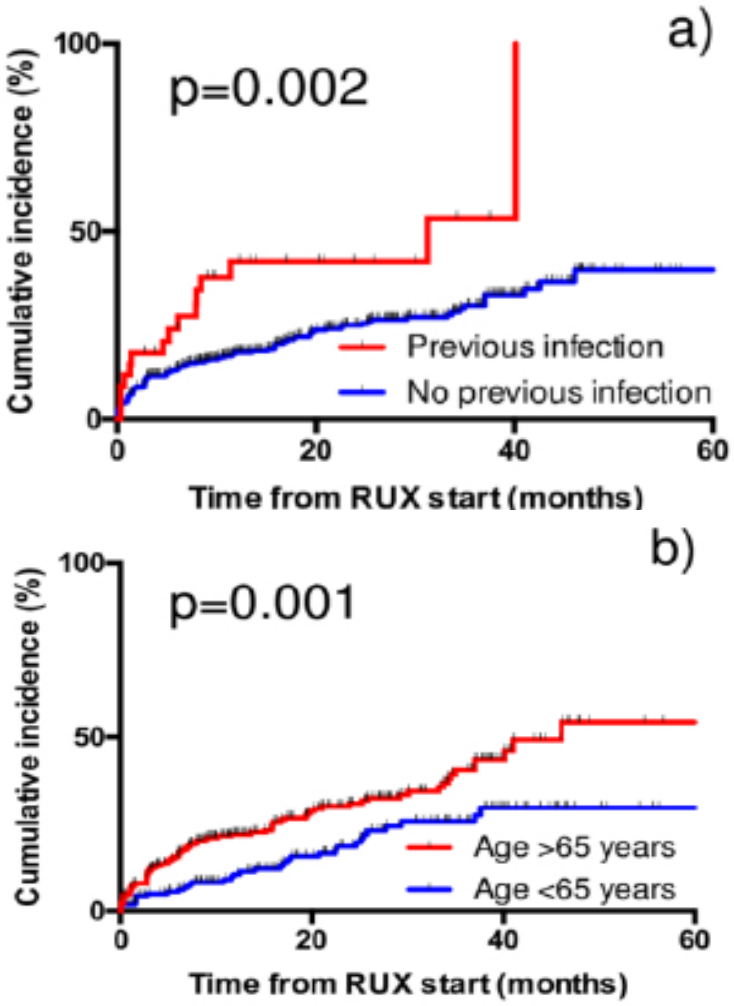
Incidence of infective complications during ruxolitinib treatment

446 patients with PMF treated with RUX in 22 European Centers



Polverelli N, et al. Poster 705

Incidence of infective complications during ruxolitinib treatment



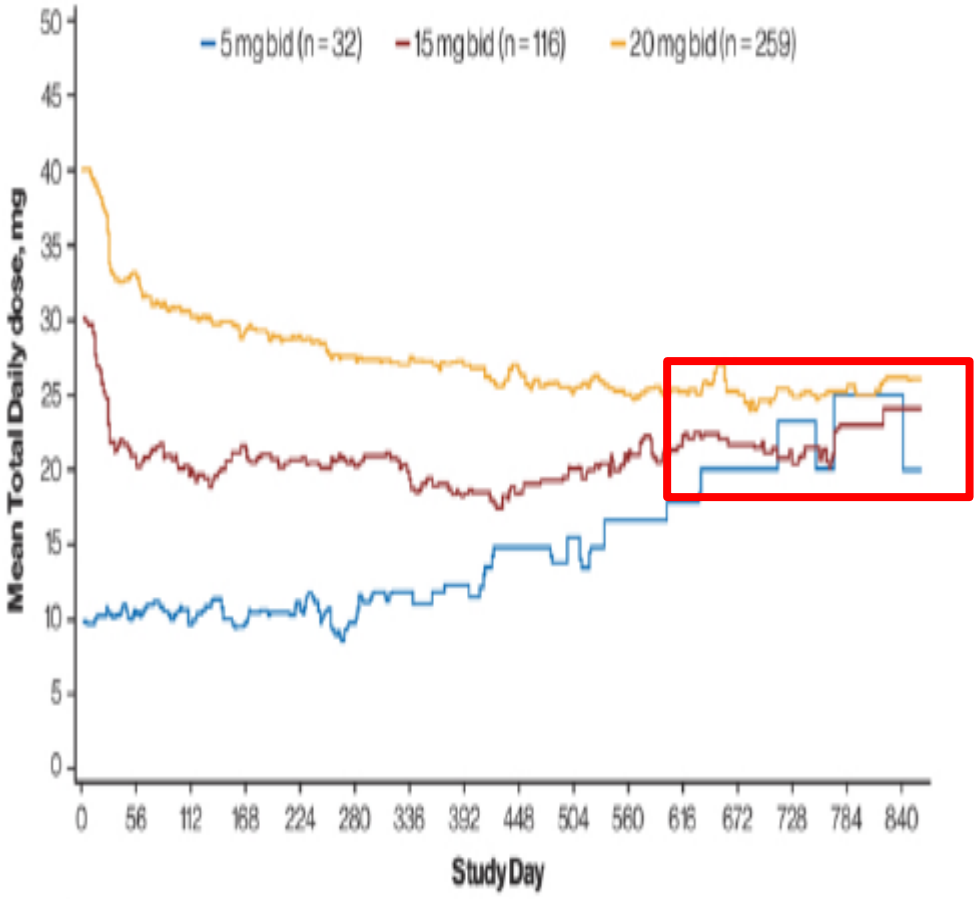
Previous infection (HR 2.03, CI95% 1.06-4.50

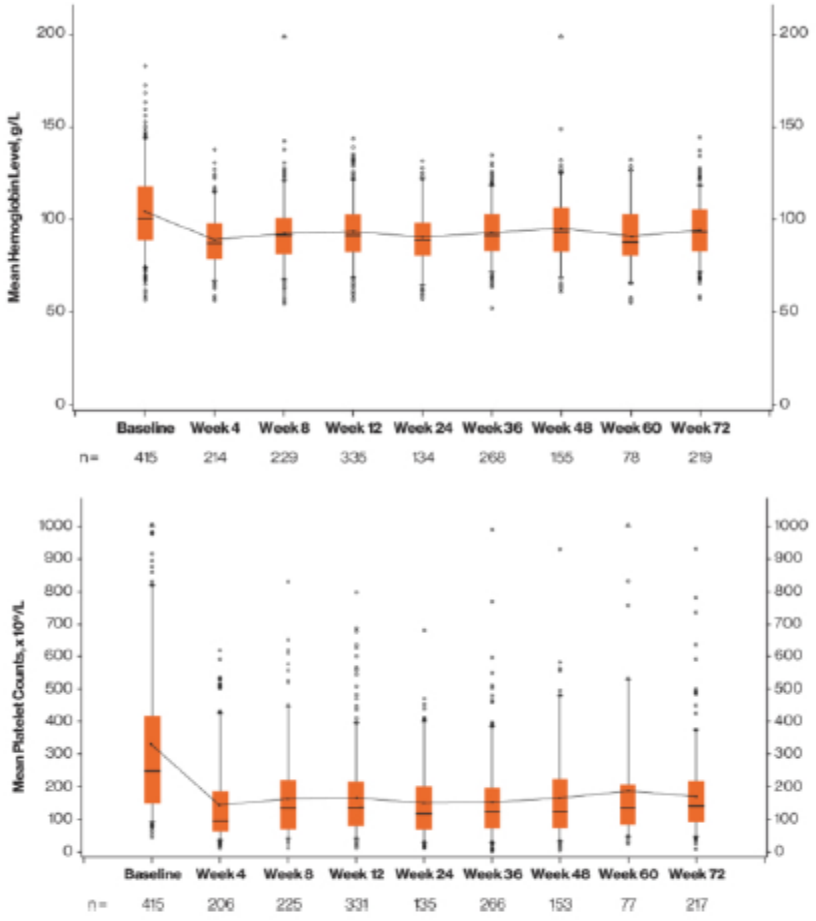
Age ≥ 65 years (HR 2.23, CI95% 1.27-3.92

Polverelli N, et al. Poster 705

Is ruxolitinib safe and effective in elderly patients?

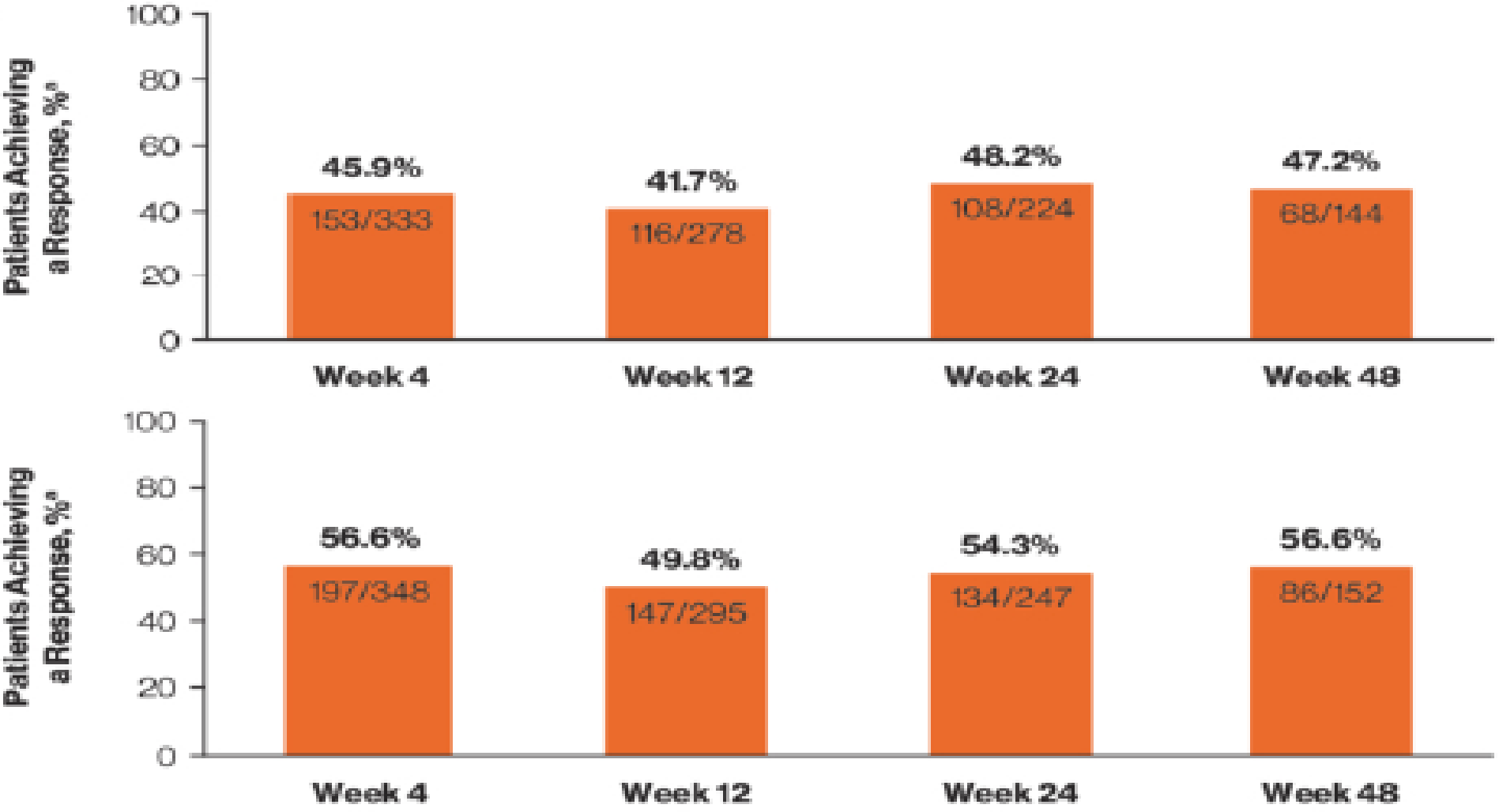
416 patients ≥ 75 years with PMF enrolled in the JUMP study





Raanani P, et al. Poster 702

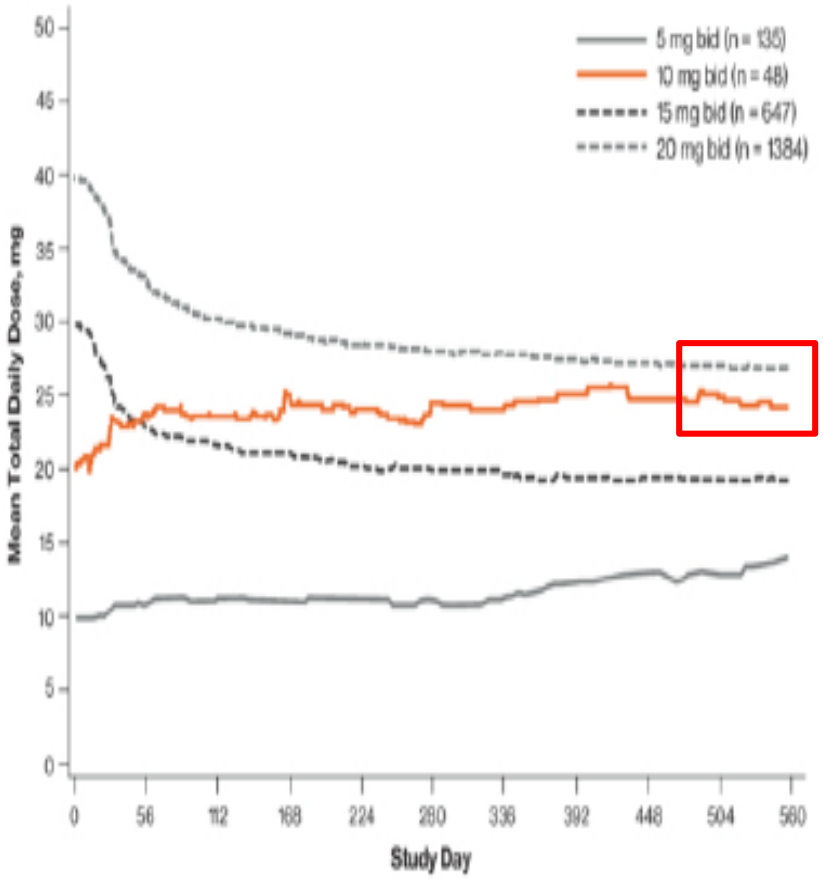
Is ruxolitinib safe and effective in elderly patients?

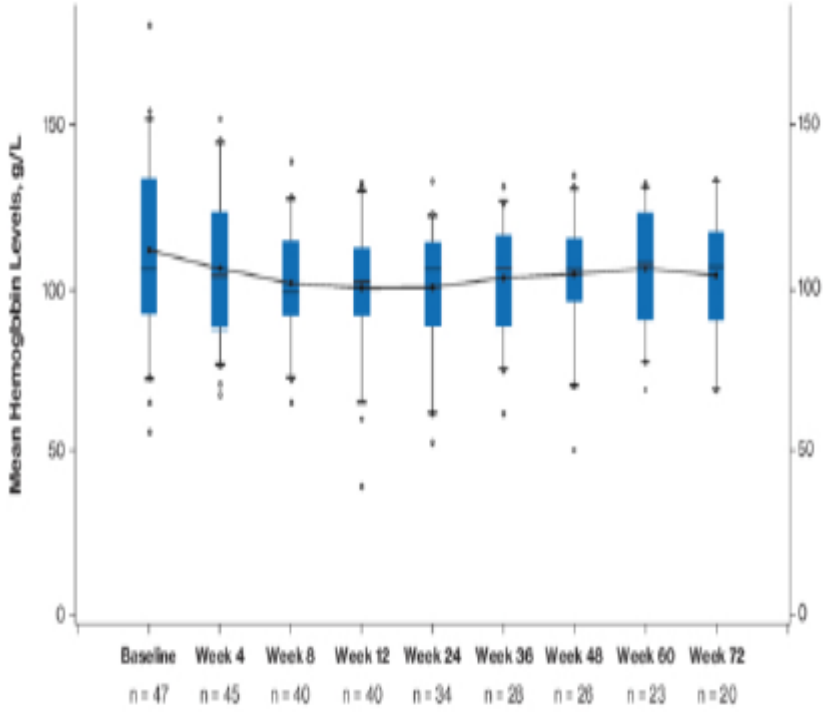


Raanani P, et al. Poster 702

Some surprise from low-dose ruxolitinib….

48 patients with PMF enrolled in the JUMP study who started low-dose ruxolitinib (10 mg bid)

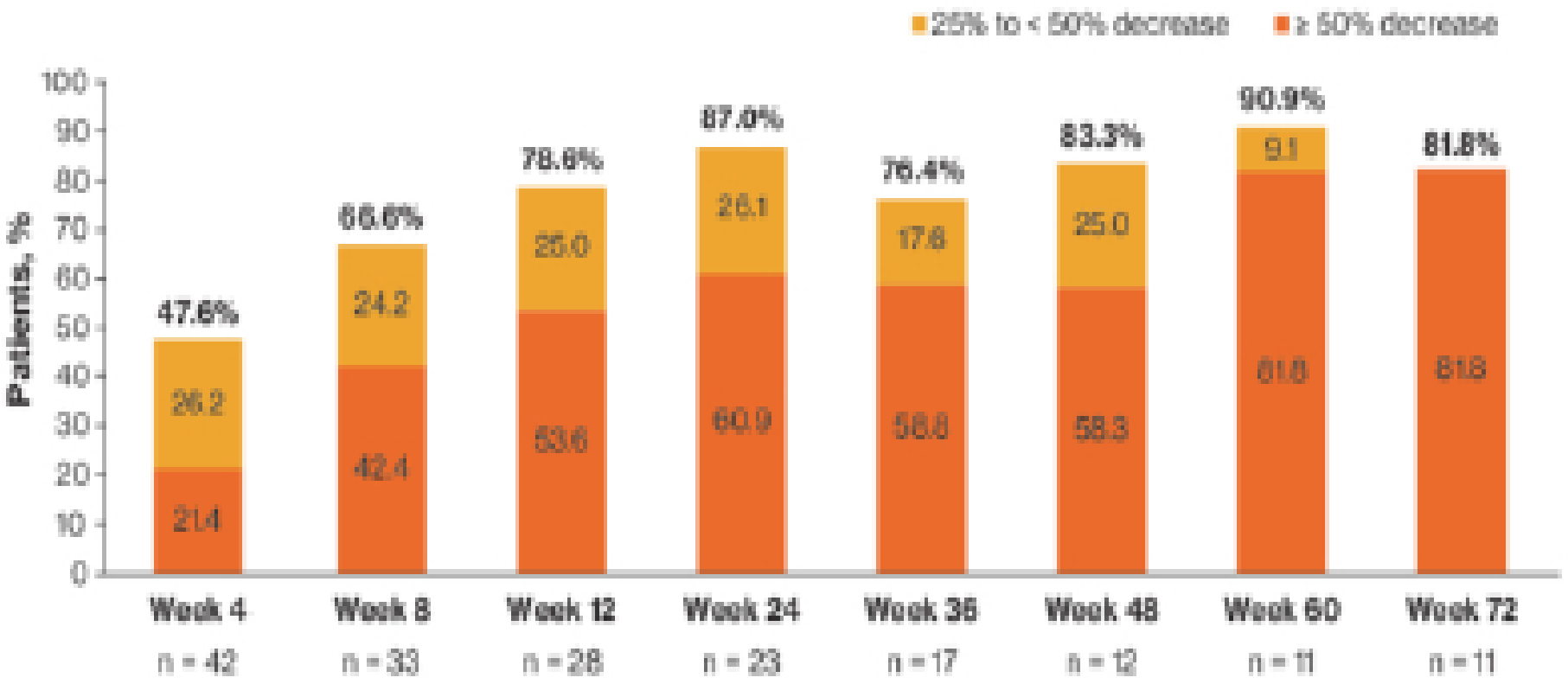




Grade 3-4 anemia 27%
(vs all JUMP cohort 34%)

Foltz L, et al. Poster e1334

Some surprise from low-dose ruxolitinib….



Spleen lenght reduction ≥ 50% at any time by week 72: 64.3%

Foltz L, et al. Poster e1334

How to face with anemia during ruxolitinib treatment? Association of ESA

32 patients treated with ESA during ruxolitinib therapy

TYPE OF ESA

EPO alpha	59%	40,000 UI/week
EPO zeta	13%	40,000 UI/week
Darbepoietin	28%	→ 150 µg/week

MEDIAN Hb AT BASELINE 8.0 g/dl (range 6.2 – 10.0)

MEDIANA ENDOGENOUS EPO 58.0 UI/l (range 8 – 146)

OVERALL ERYTHROID RESPONSE 87.6% → major erythroid response 68.8%

MEDIAN TIME TO RESPONSE 4 months

MEDIAN RESPONSE DURATION 31 months

Crisà E, et al. Poster e1332

Highlights from EHA 2017: some points to address today

WHO 2016 MPN classification: “hot” topics

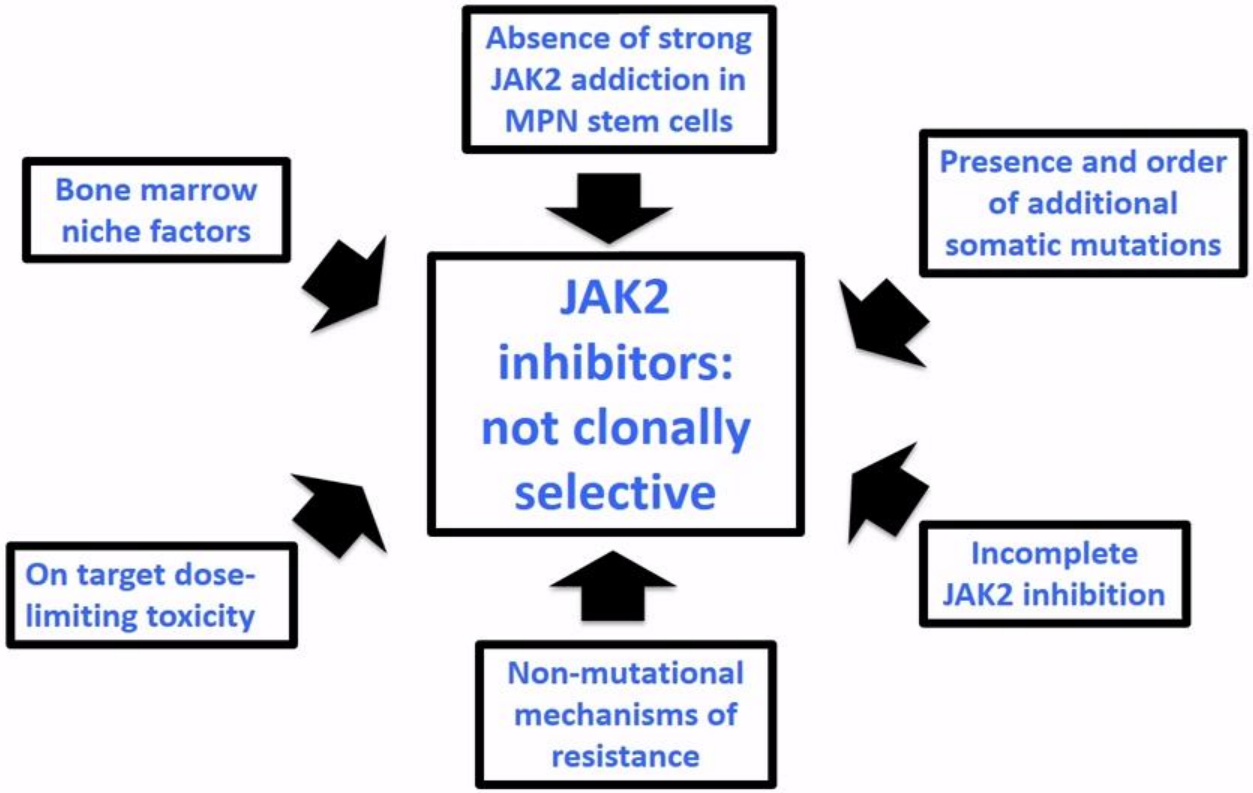
MPN and prognosis: the simpler the better?

PV/ET treatment: what role for IFN and ruxolitinib?

PMF treatment: the ruxolitinib “empire”

PMF treatment: there is something beyond ruxolitinib?

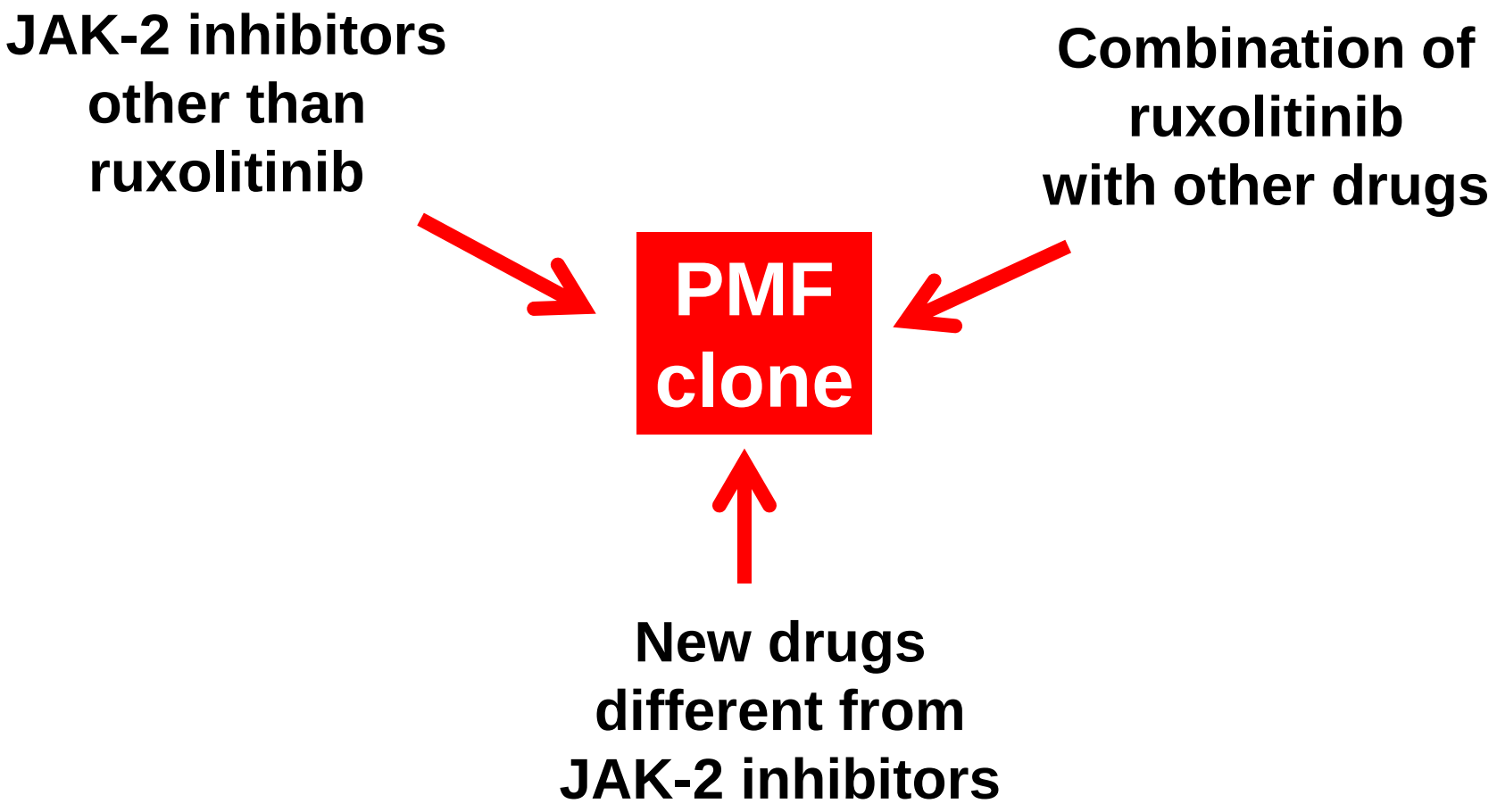
Biological limitations of ruxolitinib in PMF



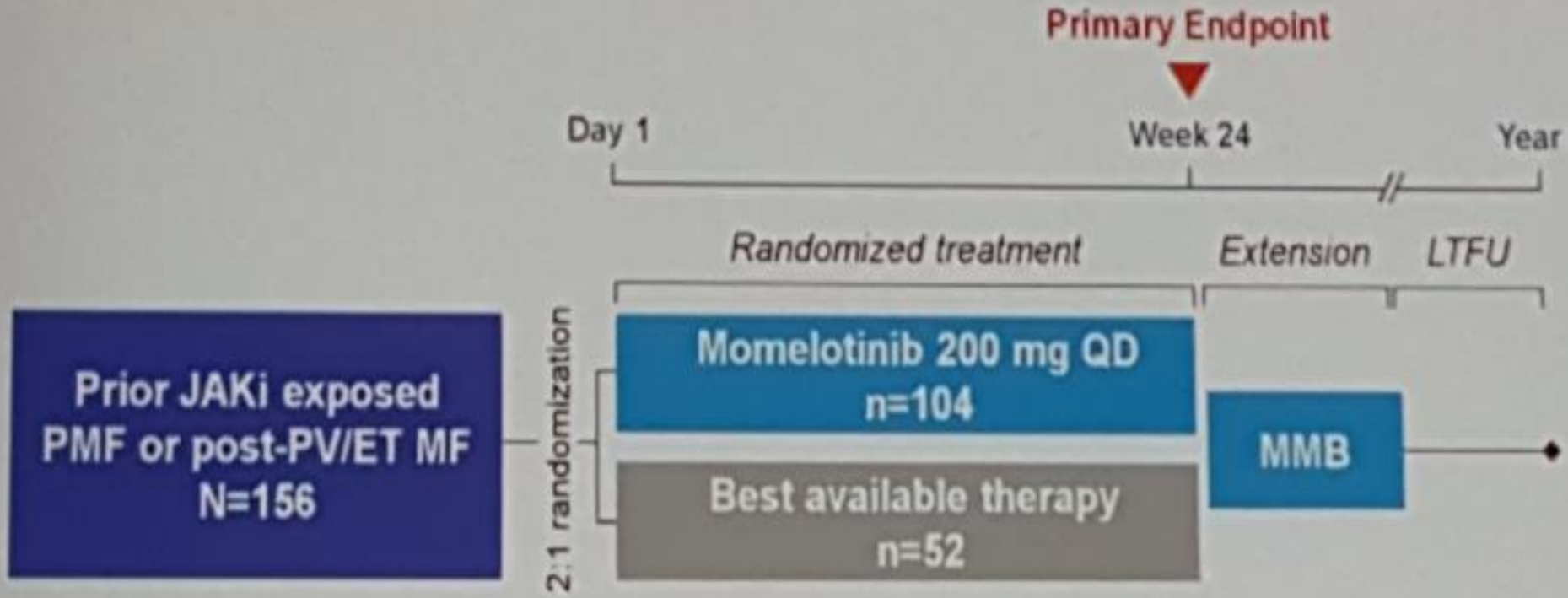
Clinical limitations of ruxolitinib in PMF

- Response criteria a challenge in trials and real life practice
- Criteria for loss of response heterogeneous in trials & do not exist for standard practice
- Mechanism of resistance undefined
- Anaemia and thrombocytopenia can limit effective dosing
- Infections may be problematic
- Some potential signal for cancer – skin SCC in RESPONSE study (PV patients often heavily pre-treated with HU)
- Lack of current credible benefit intervention in asymptomatic low-risk patients
- Median duration of response 3-4 years in clinical trials

How to overcome these clinical limitations of ruxolitinib in PMF?



Results of the phase III Simplify-2 trial (momelotinib vs BAT in PMF previously treated with ruxolitinib)

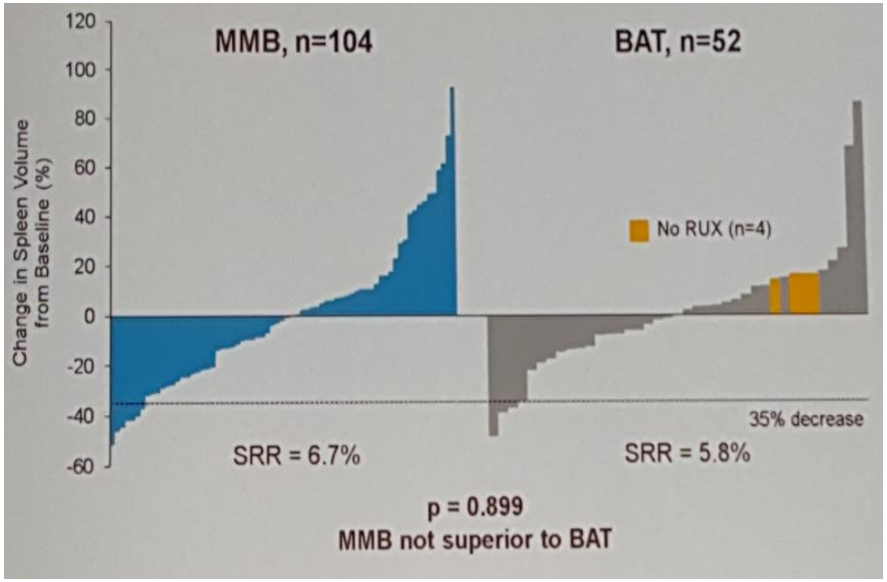


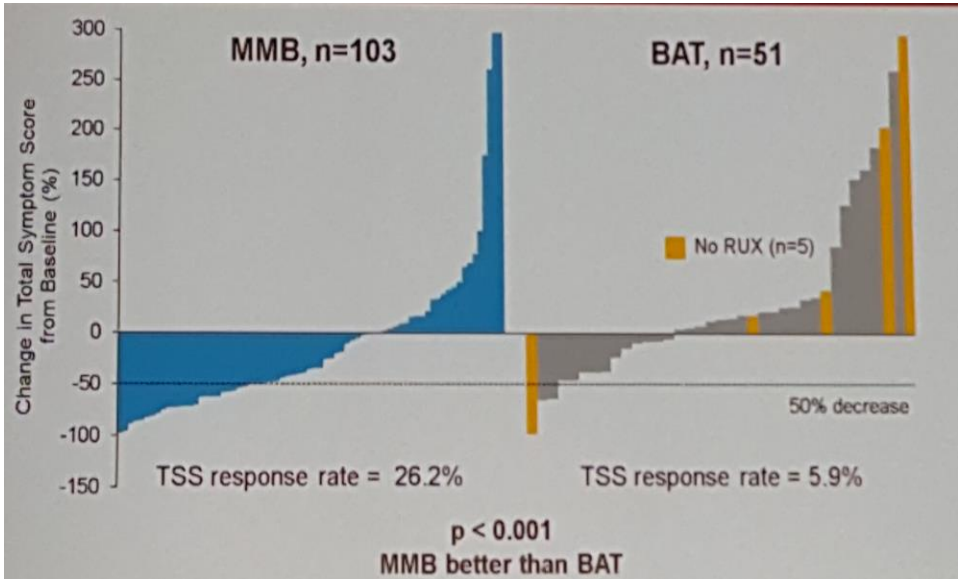
- Phase 3, randomized, open-label, multicenter trial
- Stratification: RBC transfusion dependence (Yes vs No) and TSS (<18, ≥18)
- Best available therapy could include ruxolitinib or no MF therapy

Harrison C, et al. S786

Results of the phase III Simplify-2 trial (momelotinib vs BAT in PMF previously treated with ruxolitinib)

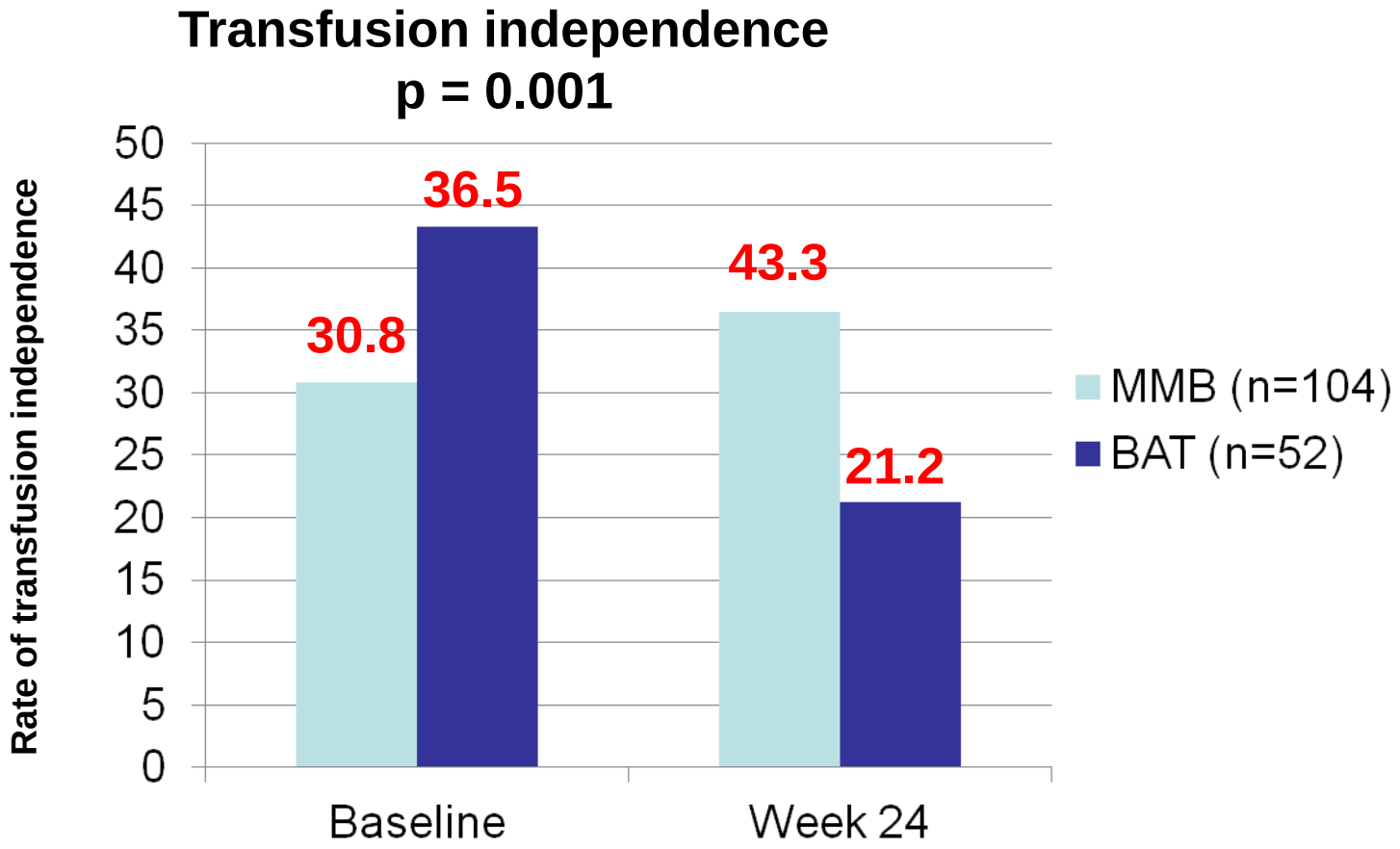
Endpoint	MMB	BAT	*p*-value
Spleen response rate, %	6.7	5.8	0.89
Total Symptom Score Response Rate, %	26.2	5.9	**< 0.001**
Transfusion rate (units/month), median	0.5	1.2	0.39
Transfusion Independence rate, %	43.3	21.2	**0.001**
Transfusion Dependence rate, %	50.0	63.5	0.10





Harrison C, et al. S786

Results of the phase III Simplify-2 trial (momelotinib vs BAT in PMF previously treated with ruxolitinib)

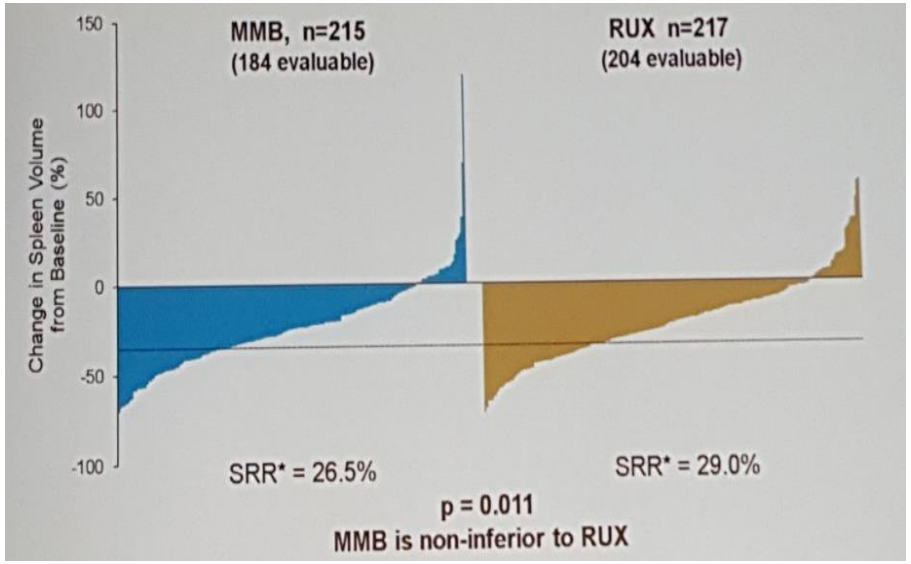


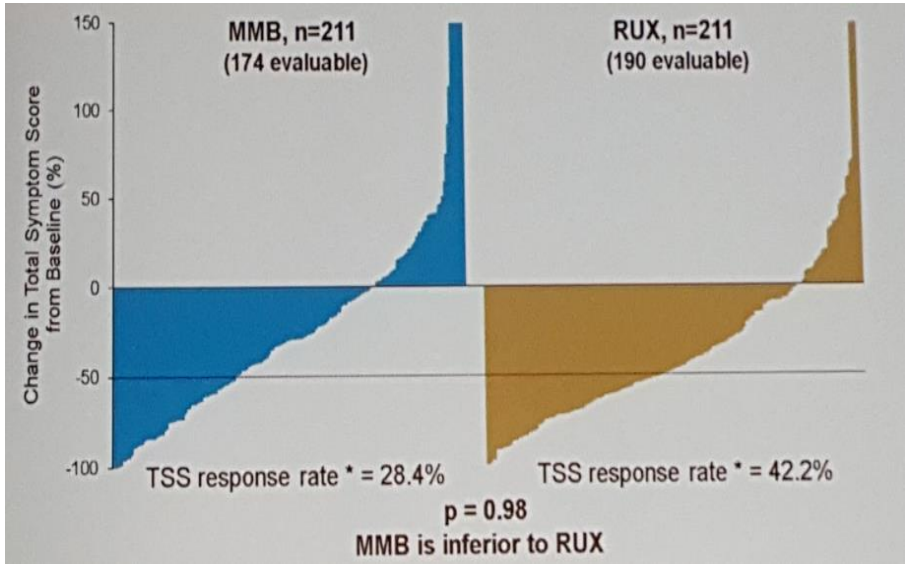
Incidence of peripheral neuropathy in MMB arm = 11%

Harrison C, et al. S786

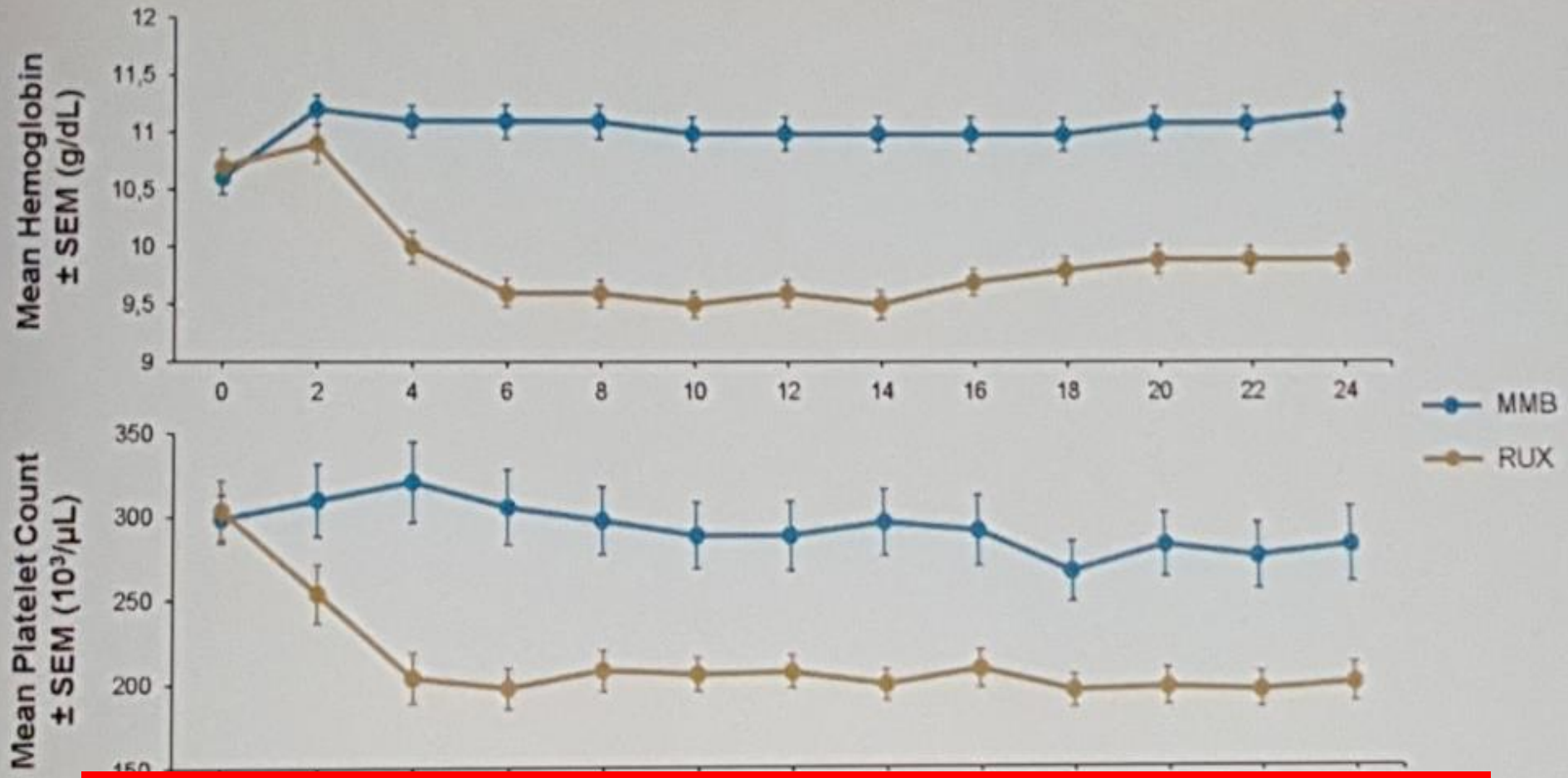
Results of the phase III Simplify-1 trial (momelotinib vs ruxolitinib in JAK inhibitor naïve PMF)

Endpoint	MMB	RUX	*p*-value
Spleen response rate, %	26.5	29.0	**0.011**
Total Symptom Score Response Rate, %	28.4	42.2	0.98
Transfusion rate (units/month), median	0.0	0.4	**<0.001**
Transfusion Independence rate, %	66.5	49.3	**<0.001**
Transfusion Dependence rate, %	30.2	40.1	**0.019**





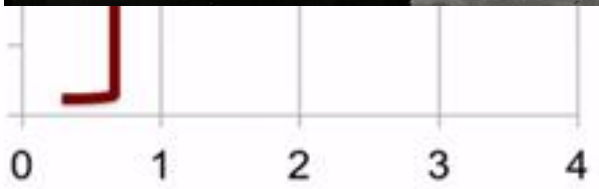
Results of the phase III Simplify-1 trial (momelotinib vs ruxolitinib in JAK inhibitor naïve PMF)



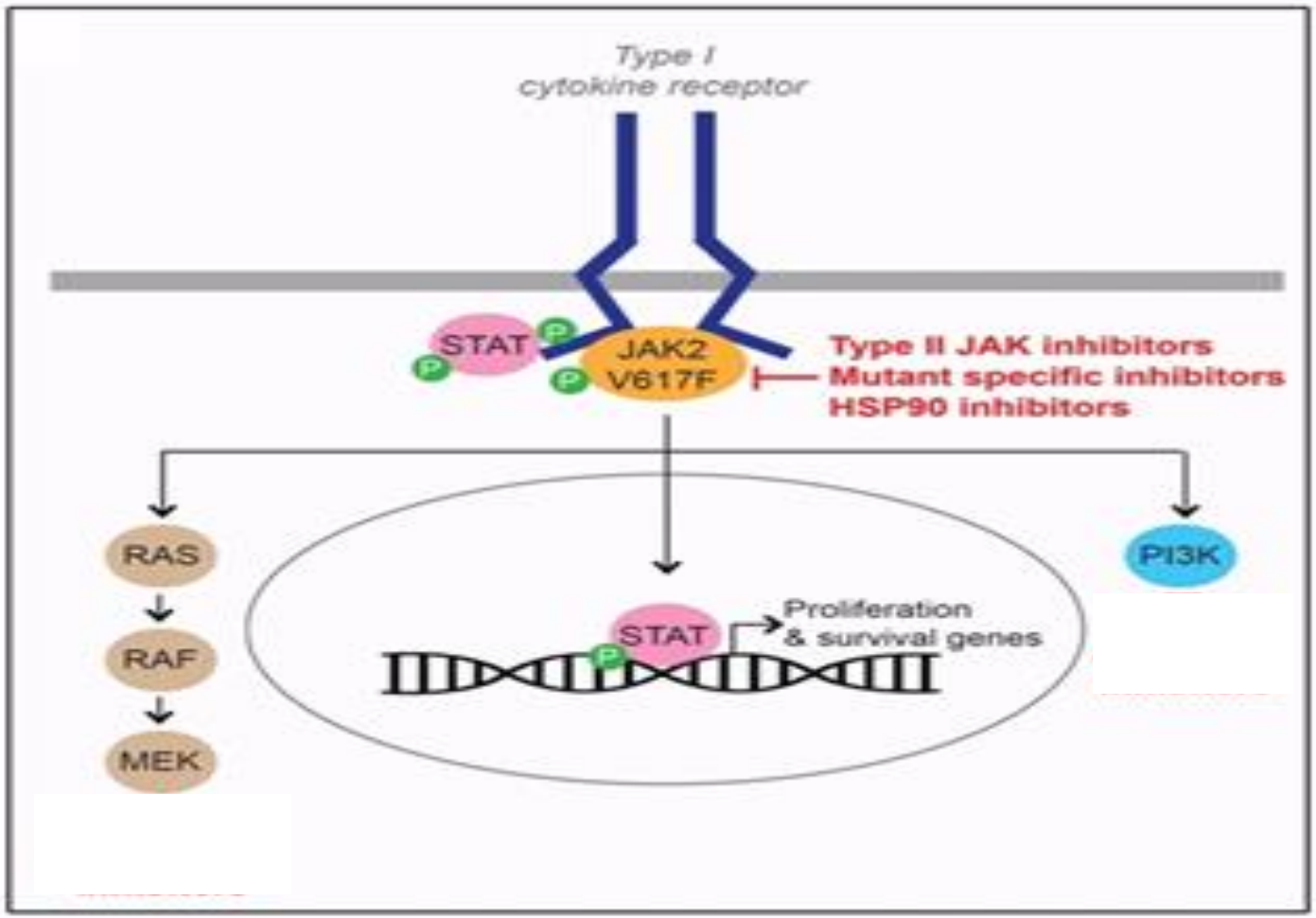
Incidence of peripheral neuropathy in MMB arm = 10%

Gotlib JR, et al. S785

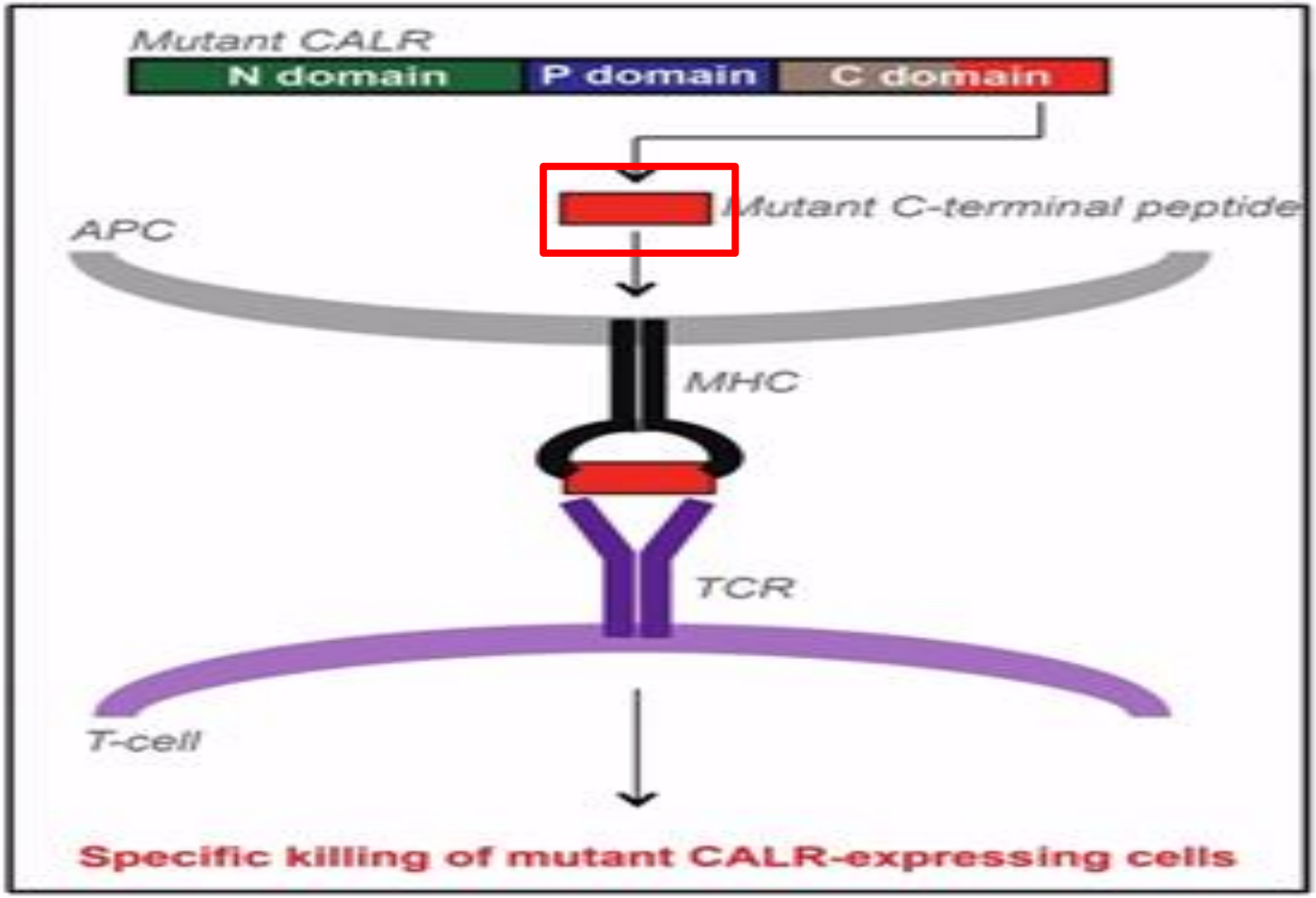
The JAK-2 inhibitors “natural selection”



Are some new strategies reasonable in JAK-2 mutated patients?

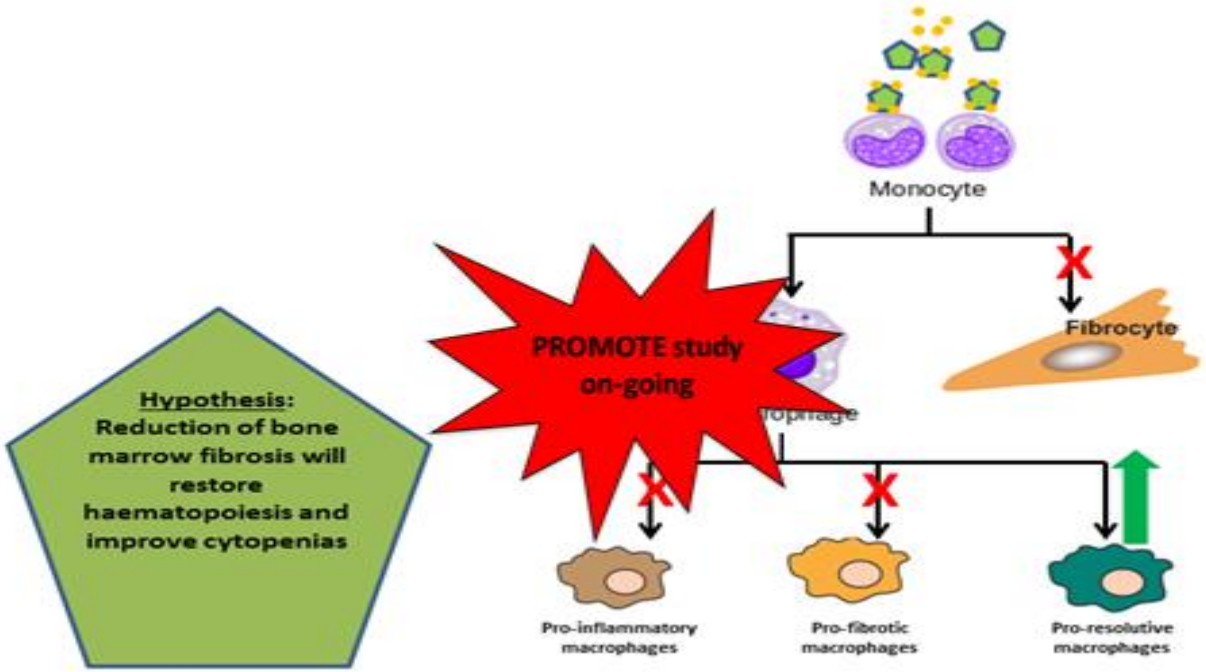


Are some new strategies reasonable in CALR mutated patients?



A possible future in MPN: pentraxin in the treatment of PMF patients

- PTX-2 (⬟) is an endogenous regulator of tissue repair
- PTX-2 binds to damaged tissue (●) and monocytes/macrophages
- PTX-2 prevents and reverses fibrosis in preclinical models
- PTX-2 levels are low in MF patients
  - Also low in patients with renal, pulmonary, and liver fibrosis

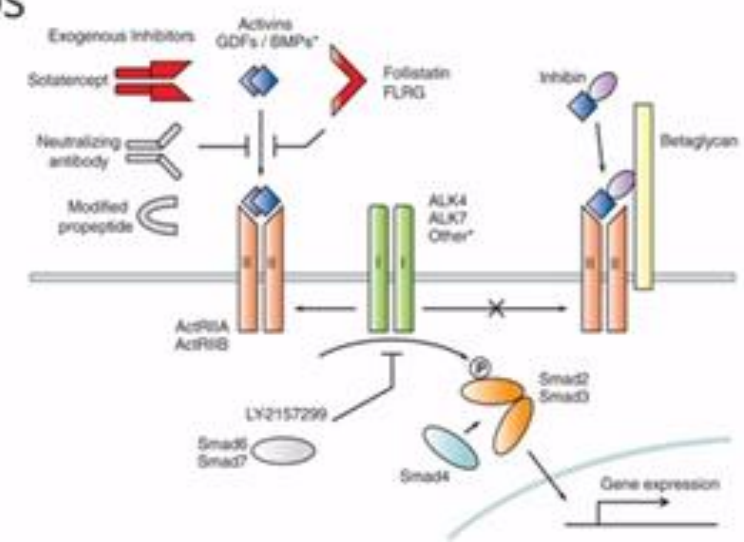


A possible future in MPN: sotatercept and luspatercept in the treatment of anemia

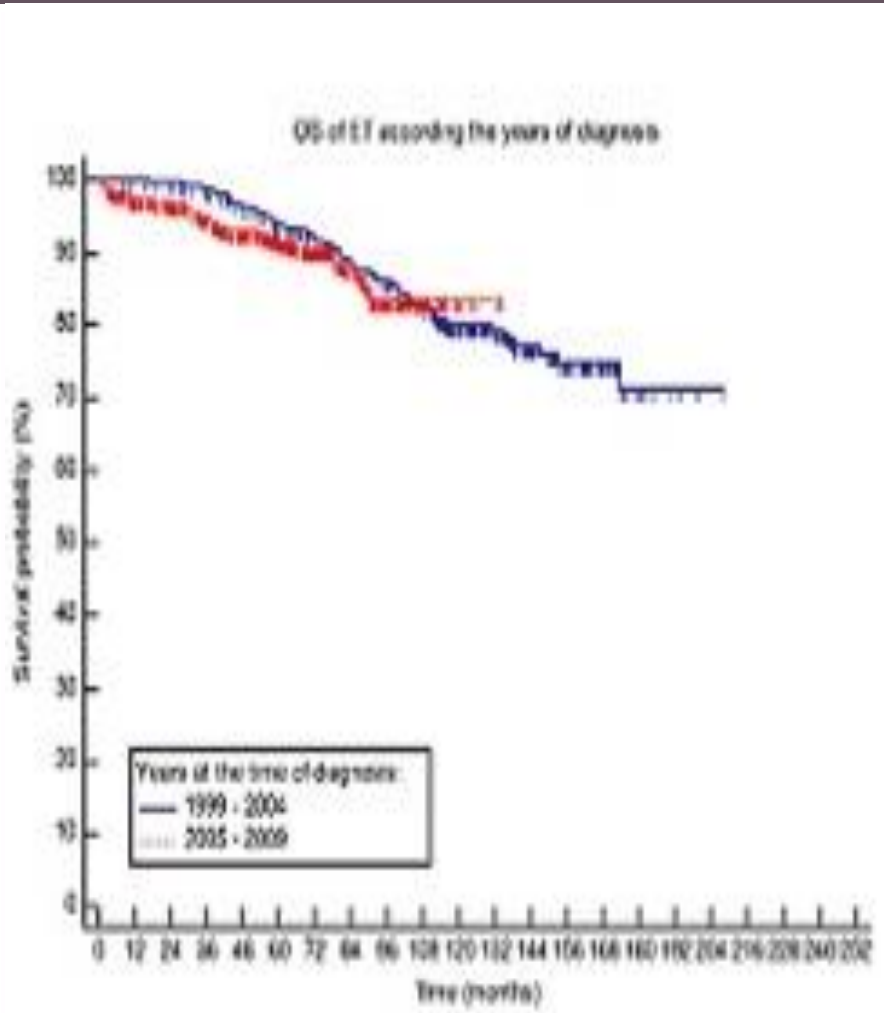
Soluble receptor fusion protein (activin receptor type IIA linked to Fc of human IgG1) that "traps" ligands that bind to ActIIRA, relieves blockade of terminal erythropoiesis

Preclinically in thalassemia, Diamond-Blackfan anemia, hepcidin transgenic mice; clinically in patients with ß-thalassemia and MDS

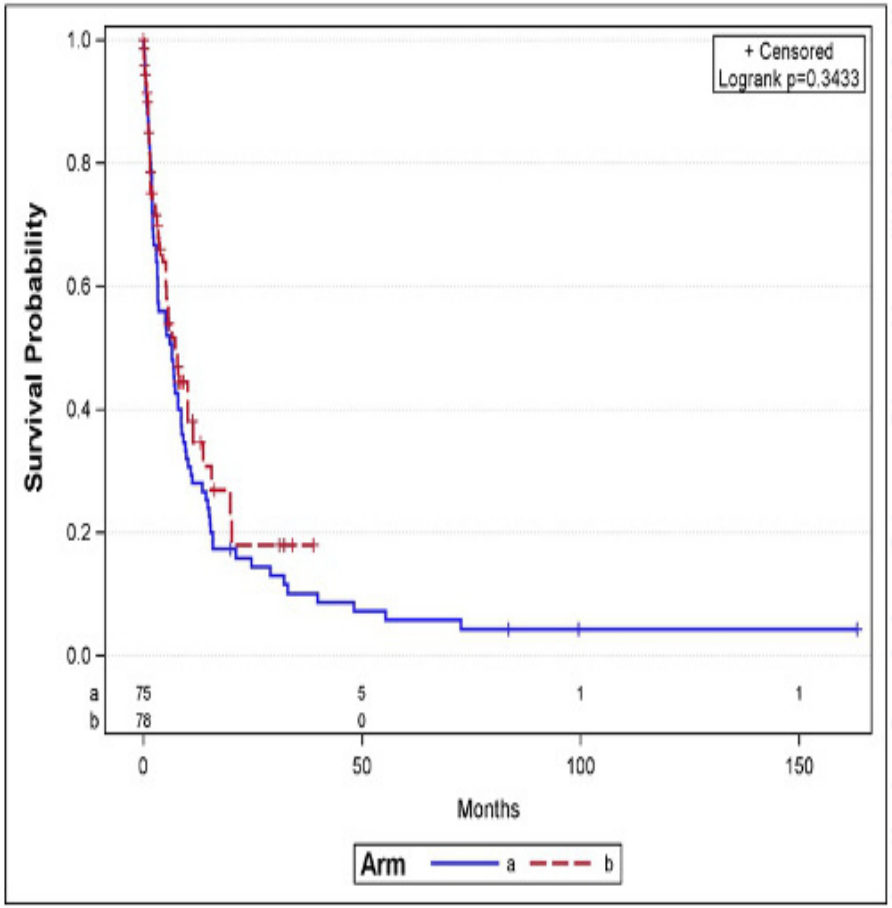
Study planned for the autumn



Is the survival of MPN patients improved in the recent period?



…nor in AF/BF!



Andriani A, et al. ePoster

McNamara C, et al. Poster 708

Some issues to discuss….

- Triple negative MPN: how to face with them in the diagnosis and treatment?

- Are IFN and ruxolitinib really the future in the PV/ET treatment?

- Is there something beyond ruxolitinib in the treatment of PFM?

It’s a long way to….Stockolm!