II Simpósio Internacional de Onco-Hematologia

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Drug therapy in the patient with primary myelofibrosis: what are the options?

Cristiana Solza, MD, PhD
Associate Professor, Department of Internal Medicine
Universidade do Estado do Rio de Janeiro

Disclosures

According to the Resolution of the Federal Council of Medicine nº 1595/2000 and Resolution of the Collegiate Board of ANVISA nº 96/2008, I declare that:

Scientific presentations - As a speaker: Novartis and Jansen

I declare that I do not hold shares on the stock exchange of the aforementioned companies. My prerequisites for participating in these activities are scientific exchange, autonomy of scientific thinking, independence of opinion and freedom of expression, respected by Novartis.

MPNs – The diseases

Classic types of chronic myeloproliferative neoplasms (MPNs)

- Essential thrombocythemia (ET)
- **Primary myelofibrosis (PMF)**
- Polycythemia vera (PV)

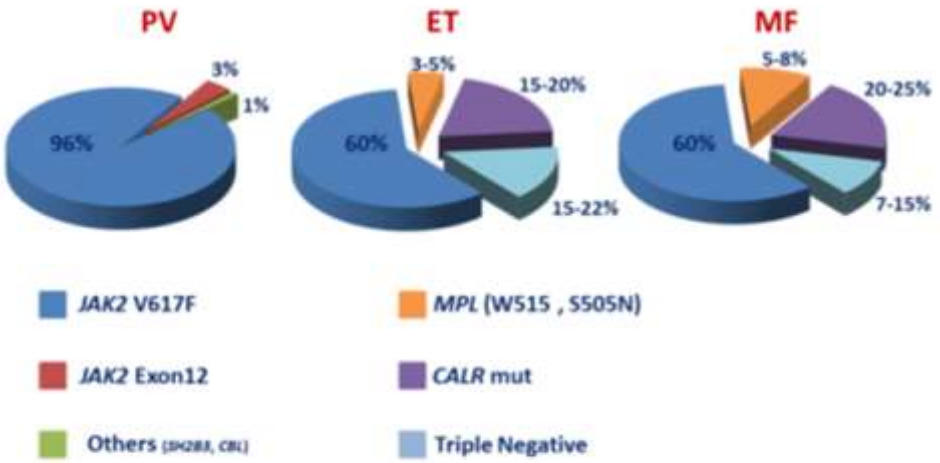
Clinical manifestations:

- Severe citopenias
- Marked splenomegaly
- Constitutional symptoms
- Thrombosis and bleeding

- Other types of MPNs
- Chronic myeloid leukemia
- Chonic neutrophilic leukemia
- Chronic eosinophilic leukemia (hypereosinophilia)
- Mastocytosis

Tefferi et al., JAMA Oncol. 2015 Apr;1(1):97-105
Mesa RA, et al. Cancer.2007;109: 68-76
Mesa RA. Blood.2009;113:5394-400

MPN: Somatic mutations



GENE	Mutational frequency
ASXL1	13%
TET2	17%
SRSF2	17%
TP53	4% / blast phase 27%
IDH1 e IDH2	4%
EZH2	7%
U2AF1	16%

ASXL1	*DDX41*	*IDH1*	*KRAS*	*PTPN11*	*TET2*
CALR	*DMNT3A*	*IDH2*	*MLL*	*RUNX1*	*TP53*
CBL	*EZH2*	*JAK2*	*MPL*	*SETBP1*	*U2AF1*
CEBPA	*FLT3*	*KDM6A*	*NPM1*	*SF3B1*	*WT1*
CSF3R	*GATA1*	*KIT*	*NRAS*	*SRSF2*	*ZRSR2*

Tefferi A. Am J Hematol.2018;93:1551-60
Nangalia J, et al.NEJM.2013;369 (25):2391-405

Risk Assessment and Prognosis in Myelof
Comparison between Scores

IPSS		
Risk category	N° risk factors	Median survival (years)
High	≥3	2,3
Intermediate 2	2	4,0
Intermediate 1	1	7,9
Low	0	11,3

VARIABLE	IPS
Age >65	√
Constitutional symptoms	√
Hemoglobin	√
WBC count	√
PB blasts	√
Platelet count	
Transfusion status	
karyotype	
	1 pt

TABLE 5 New prognostic models in primary myelofibrosis

	MIPSS70 (3-tiered)		MIPSS70+ version 2.0 (5-tiered)		GIPSS (4-tiered)
	Genetic variables *One HMR mutation* *(1 point)* *≥2 HMR mutations* *(2 points)* *Type 1/like CALR absent* *(1 point)*	Clinical variables *Hemoglobin < 10 g/dL* *(1 point)* *Leukocytes > 25 × 10(9)/L* *(2 points)* *Platelets < 100 × 10(9) /L* *(2 points)* *Circulating blasts ≥2%* *(1 point)* *Constitutional symptoms* *(1 point)* *Bone marrow fibrosis grade ≥2* *(1 point)*	Genetic variables *VHR karyotype* *(4 points)* *Unfavorable karyotype* *(3 points)* *≥2 HMR mutations* *(3 points)* *One HMR mutation* *(2 points)* *Type 1/like CALR absent* *(2 points)*	Clinical variables *Severe anemia* *(2 points)* *Moderate anemia* *(1 point)* *Circulating blasts ≥2%* *(1 point)* *Constitutional symptoms* *(2 points)*	Genetic variables *VHR karyotype* *(2 points)* *Unfavorable karyotype* *(1 point)* *Type 1/like CALR absent* *(1 point)* *ASXL1mutation* *(1 point)* *SRSF2 mutation* *(1 point)* *U2AF1Q157 mutation* *(1 point)*
Very low risk (median survival)			Zero points (*not reached*)		
Low risk (median survival)	0-1 points (*not reached*)		1-2 points (*16.4 years*)		Zero points (*26.4 years*)
Intermediate-1 risk (median survival)					One point (*8 years*)
Intermediate risk (median survival)	2-4 points (*6.3 years*)		3-4 points (*7.7 years*)		
Intermediate-2 risk (median survival)					Two points (*4.2 years*)
High risk (median survival)	≥5 points (*3.1 years*)		5-8 points (*4.1 years*)		≥3 points (*2 years*)
Very high risk (median survival)			≥9 points (*1.8 years*)		

Abbreviations: MIPSS70: mutation-enhanced international prognostic system for transplant-age patients (age ≤ 70 years) (*J Clin Oncol*. 2018;36:310); MIPSS70+ version 2.0: mutation and karyotype enhanced international prognostic system (*J Clin Oncol*. 2018. doi:10.1200/JCO.2018.78.9867). Survival quotes are for age ≤ 70 years; GIPSS: genetically inspired prognostic scoring system (*Leukemia*. 2018. doi:10.1038/s41375-018-0107-z). Survival quotes are for all age groups; HMR: high molecular risk mutations include ASXL1, SRSF2, EZH2, IDH1, IDH2 and, in addition, for GIPSS and MIPSS70+ version 2.0, U2AF1Q157; VHR: very high risk karyotype. Severe anemia: Hemoglobin <8 g/dL in women and < 9 g/dL in men. Moderate anemia: Hemoglobin 8-9.9 in women and 9-10.9 in men.

Passamonti F, et al. Blood. 2010;115(9):1703-17
Gangat N, et al. J Clin Oncol. 2011; 29(4):392-97

Tefferi A, et al. Am J Hematol.2018;93:1551-60
Guglielmelli P, et al.J Clin Oncol.2018;36:310-18
Tefferi A, et al. Leukemia. 2018;32:1631-42

Current treatment approach

Curative options	Control symptoms
• Allogenic SCT	JAK inhibitors

Symptomos	Intervención
Anemia	Steroids Danazol, Thalidomide
Esplenomegaly	Hydroxyurea Cladribine Esplenectomy
Extramedular hematopoyesis	Radiotherapy
Thrombosis	Aspirin

Barbui T, et al. J Clin Oncol. 2011;29(6):761-70
Tefferi A, et al. Blood 2011;117(13):3494-504

Allogeneic stem cell transplantation

haematologica
Journal of The Ferrata Storti Foundation

State-of-the-art review: allogeneic stem cell transplantation for myelofibrosis in 2019

by Donal P. McLornan, Ibrahim Yakoub-Agha, Marie Robin, Yves Chalandon, Claire N. Harrison, and Nicolaus Kroger

Haematologica 2019 [Epub ahead of print]

Citation: Donal P. McLornan, Ibrahim Yakoub-Agha, Marie Robin, Yves Chalandon, Claire N. Harrison, and Nicolaus Kroger. State-of-the-art review: allogeneic stem cell transplantation for myelofibrosis in 2019. Haematologica. 2019; 104:xxx doi:10.3324/haematol.2018.206151

Summary of outcomes in the main studies on reduced intensity and myeloablative conditioning in myelofibrosis.

Conditioning intensity	N.	Conditioning regimen	GvHD rates	Overall survival	Comments	Reference
RIC	66	Flu Mel (sibling) Flu Mel + ATG (URD)	Acute grade II-IV Sibling 38% URD 41%	75% sibling 32% URD	24% graft failure in the URD group	49
RIC	103	Flu Bu	Acute grade II-IV 26% Chronic L:24%; E:24%	67% at 5 years	Low rates of graft failure and timely engraftment	32
MAC	170 Sibling 117 MUD 33 Other	Various	Acute / Chronic 43% 40% 40% 32% 24% 26%	39% at 5 years 31% at 5 years 31% at 5 years	Heterogeneous cohort; disease-free survival long-term in approximately 1/3	35
Predominantly MAC	104	TBI based (n=15) Busulphan based (n=80) RIC (n=9)	Acute grade II-IV : 64% Chronic L+E: 84%	61% at 7 years	Improved survival with targeted busulfan dosing in BuCy	46
RIC	233	Flu Bu (38%) Flu Mel (28%) Flu TBI. (22%)	Acute grade II-IV : 37% Chronic at 1 year 42%	56% for MSD, 37% URD, 34% MMUD	Donor type most important determinant of outcome	77
RIC	66	Flu Bu FBM Flu Mel	Acute grade II-IV 47% 68% 68 %	Similar OS, NRM and relapse rates	100% donor chimerism was seen more frequently at day +30 and day +100 in patients who received FBM or Flu Mel than Flu Bu.	78
RIC	160	Flu Bu (105) Flu Mel (55)	Acute / Chronic 31% 62% 53 % 49%	7-year OS was 52% for the Flu Mel group and 59% for the Flu Bu group	Flu Mel regimen appears to induce more NRM than the Flu Bu regimen; but with augmented disease control; similar outcomes.	48
MAC RIC	760 1423	Common regimens BuCy or TBI based Flu Bu; Flu Mel	Acute grade I-IV / Chronic L/E 29% 23/27% 32% 20/32%	Median OS= 6.6 years Median OS =5.3 years	Primary analyses; full analysis in preparation No differences in NRM between MAC/RIC Worse outcome with MMUD and poor Performance Status	34

ATG: antithymocyte globulin; Bu: busulfan; Cy: cyclophosphamide; E: extensive; FBM: fludarabine, bis-chloroethyl-nitroso-urea/carmustine, melphalan; Flu: fludarabine; GvHD: graft-versus-host disease; L: limited; MAC: myeloablative conditioning; Mel: melphalan; MMUD: mismatched unrelated donor; MUD: matched unrelated donor; NRM: non-relapse mortality; OS: overall survival; RIC: reduced intensity conditioning; TBI: total body irradiation; URD: unrelated donor.

McLornan DP, et al. Haematologica.2019 (Epub ahead of print)

Rondelli D, et al. Blood. 2014;124(7):1183-91
Kroger N, et al. Blood.2009;114(26):5264-70
Ballen KK, et al. Biol Blood Marrow Transplant.2010;16(3):358-67
Kerbauy DM, et al. Biol Blood Marrow Transplant.2007;13(3):355-65
Gupta V, et al. Biol Blood Marrow Transplant. 2014;20(1):89-97
Jain T, et al. Bone Marrow Transplant.2019;54(2):204-11
Robin M, et al. Biol Blood Marrow Transplant.2016;22(7):1206-11
McLornan,et al. Annual EBMT meeting.2018;OS5-5

Ruxolitinib: a new drug for the management of MF patients

- JAK1/2 inhibitor
- Strikingly reduces spleen size
- Quickly leads to symptom relief
- Improves QoL, and
- Results in survival benefit for MF patients

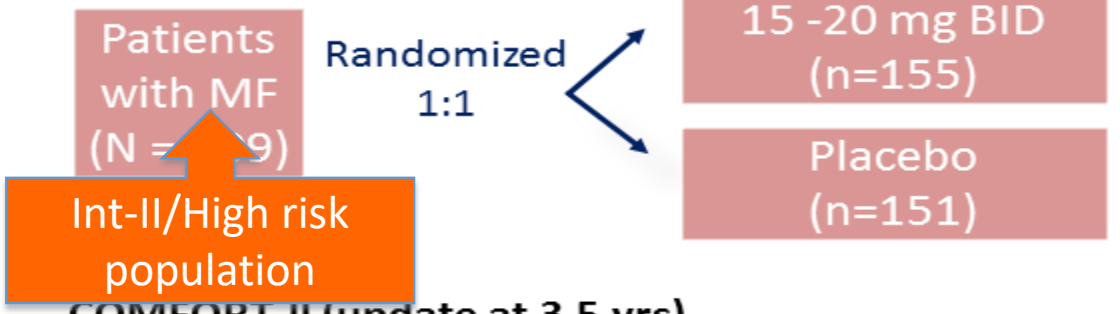
BUT...

- Do not reverse bone marrow fibrosis (improvement in 15,8% of patients in COMFORT II)
- Do not modify disease natural history (progression of disease and to AML)
- Do not effect on JAK2V617F allele burden (26 of 236 evaluable patients in COMFORT I achieved molecular PR or CR)

Plosker GL. Drugs. 2015 Feb;75(3):297-308
Verstovsek S et al., N Engl J Med, 2012; 366(9):799-807
Harrison C et al., N Engl J Med, 2012; 366(9):787-98

Ruxolitinib in Myelofibrosis: Phase III, Randomized COMFORT Trials

COMFORT-I (update at 3 yrs)



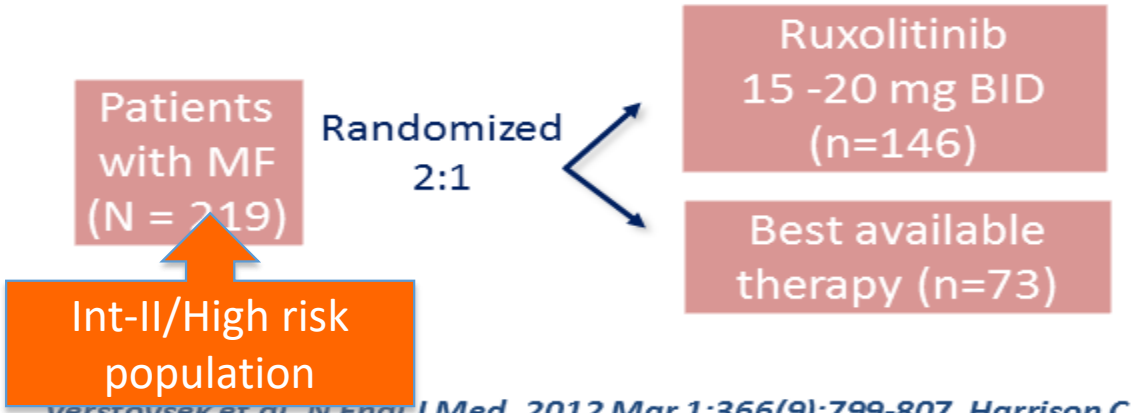
Primary Endpoint

- 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)

COMFORT-II (update at 3.5 yrs)



Primary Endpoint

- Number of subjects achieving ≥ 35% reduction in spleen volume from baseline to week 48

Secondar/Exploratory endpoints

- Changes in functioning and symptoms

Verstovsek et al. N Engl J Med. 2012 Mar 1;366(9):799-807, Harrison C, et al. N Engl J Med. 2012 Mar 1;366(9):787-98

Ruxolitinib: spleen reduction and symptom improvement

Overview of key Ruxolitinib trials in MF: Efficacy[1-6]

Clinical trial (n=number of patients treated with Ruxolitinib)	Spleen response at Week 24	Definition of spleen response	Symptom response at Week 24	Definition of symptom response
Intermediate-2 and High-risk patients:				
COMFORT-I (155)	41.9%	≥35% volume reduction (MRI)	45.9%	2013 IWG-MRT criteria (≥50% TSS reduction from baseline)
COMFORT-II (146)	32%	≥35% volume reduction (MRI)	n/a	Improvement in different scales
Intermediate-1 risk patients:				
JUMP (163)	63.8%	≥50% length reduction*	n/a	Improvement in different scales
UK ROBUST (14)	50%†	≥50% length reduction*	21.4%†	2013 IWG-MRT criteria (≥50% TSS reduction from baseline)
Italian study (70)	54.7%	2013 IWG-MRT criteria*	80%	2013 IWG-MRT criteria (≥50% TSS reduction from baseline)

COMFORT-I: a double-blind, Phase 3, placebo-controlled study; COMFORT-II: a randomised, Phase 3, multicenter study vs best available therapy; JUMP: a Phase 3b expanded access trial; UK ROBUST: an open-label, Phase 2 study; Italian study: an independent study in Italian and German haematology centers.

1. Palandri F, et al. [Supplementary Appendix.] *Oncotarget*. 2017. doi:10.18632/oncotarget.18674. **2.** Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807. **3.** Harrison C, et al. *N Engl J Med*. 2012;366(9):787-798. **4.** Al-Ali HK, et al. *Haematologica*. 2016;101(9):1065-1073. **5.** Mead AJ, et al. *Br J Haematol*. 2015;170(1):29-39. **6.** Palandri F, et al. *Hematol Oncol*. 2017;1-6.

Adverse Events

COMFORT 1

- Anemia (98% all grades; 45% grades 3-4)
- Thrombocytopenia (69% all grades; 13% grades 3-4)
- Herpes zoster infections (10,3%)
- Pneumonia (16,4%)
- AEs= 33% discontinuation of treatment

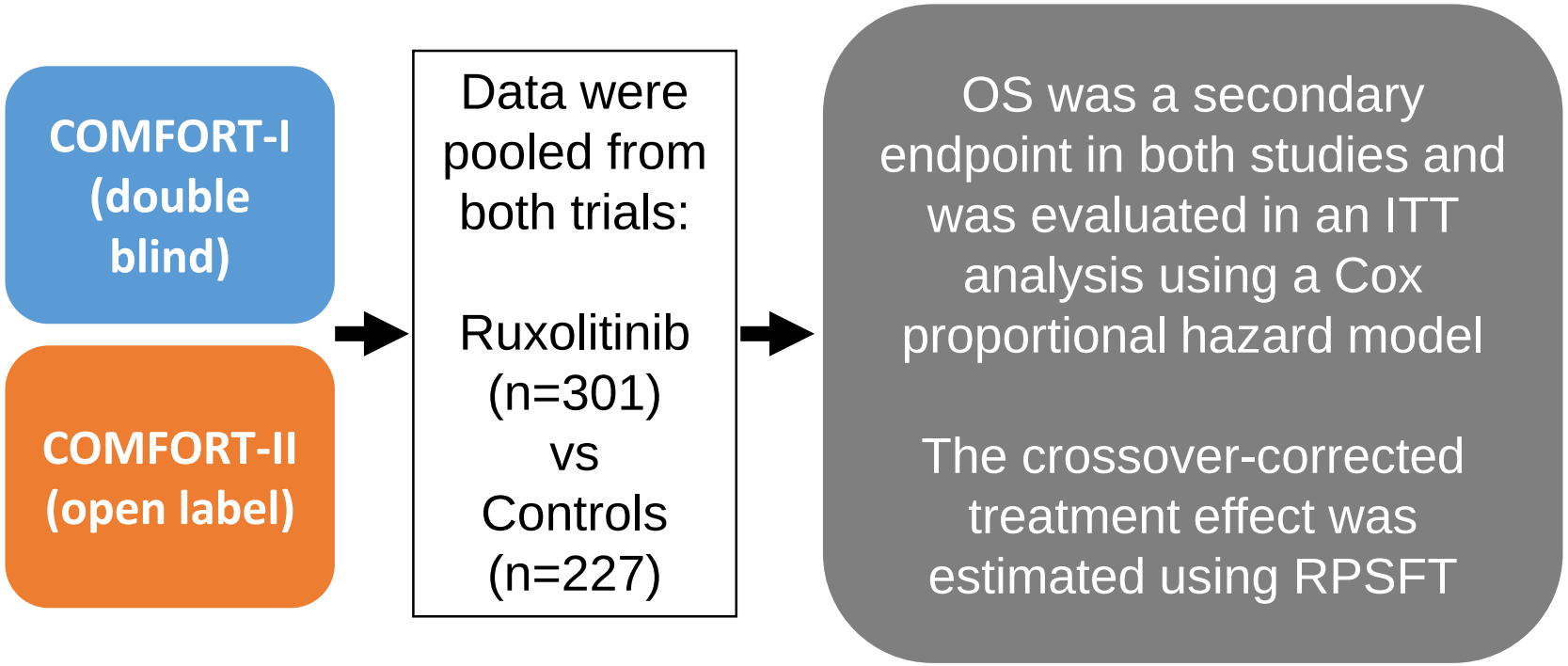
COMFORT 2

- Anemia= 22,5% (grade 3/4)
- Thrombocytopenia= 15,2% (grade 3/4)
- Pneumonia (15%)
- H.zoster (11,3%)
- Urinary tract infections (24,6%)
- Aes= 25% discontinuation of treatment

Verstovsec et al.NEJM.2012;366(9):799-807
Harrison C, et al.NEJM.2012;366(9):787-98

POOLED COMFORT-I AND –II: 5-YEAR OVERALL SURVIVAL

STUDY DESIGN

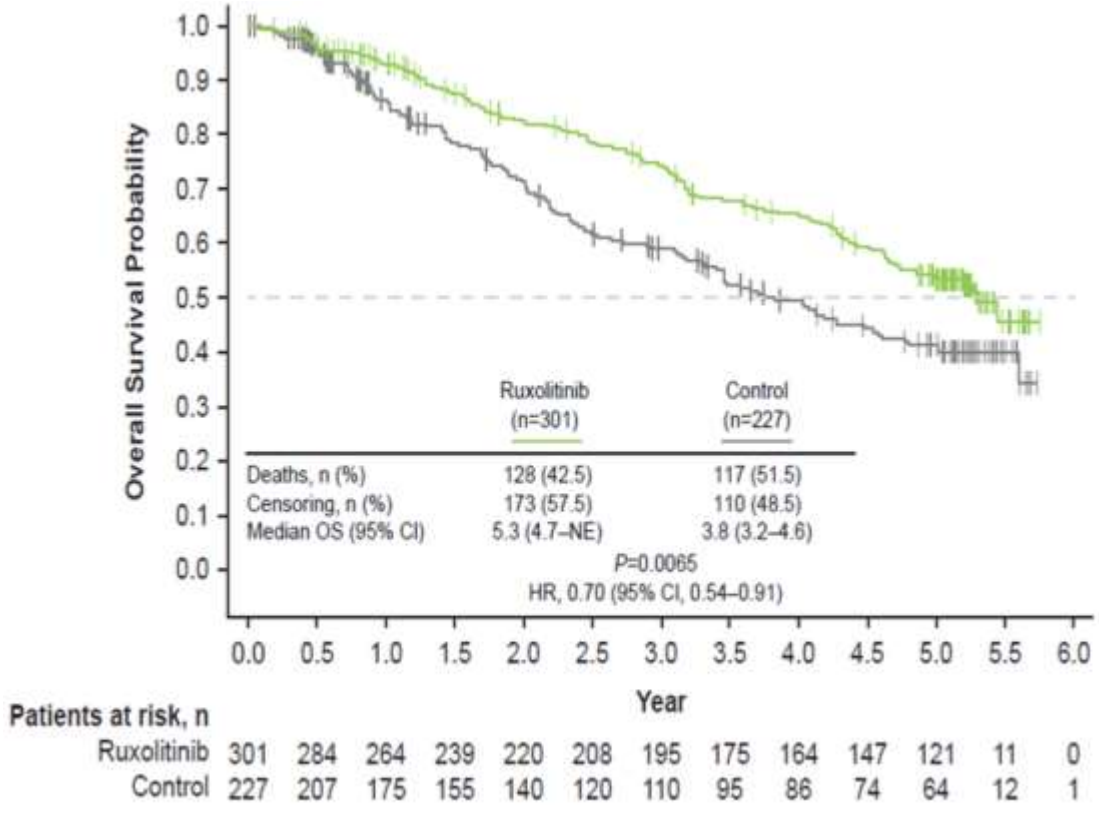


Verstovsek et al. Poster presentation at ASH 2016. Session 634. Abstract 3110.

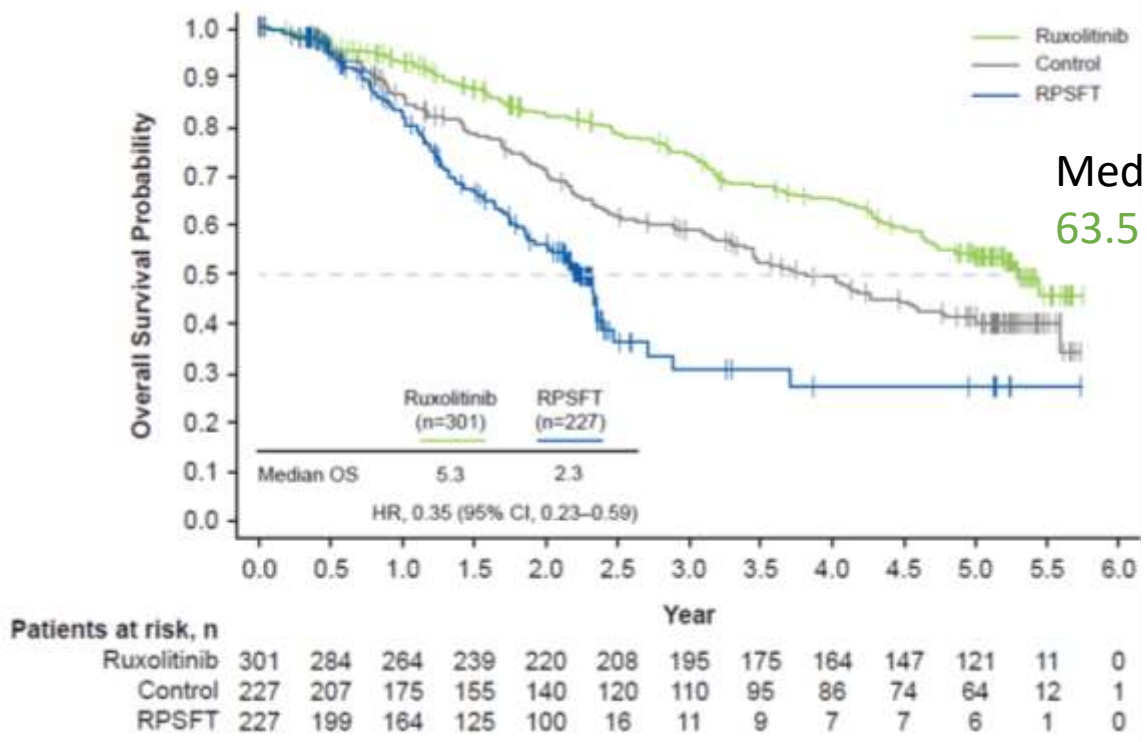
ITT, intent-to-treat; RPSFT, rank preserving structural failure time.

POOLED COMFORT-I AND –II: 5-YEAR OVERALL SURVIVAL

OVERALL SURVIVAL IN THE ITT POPULATION



OVERALL SURVIVAL CORRECTED FOR CROSSOVER WITH THE RPSFT MODEL



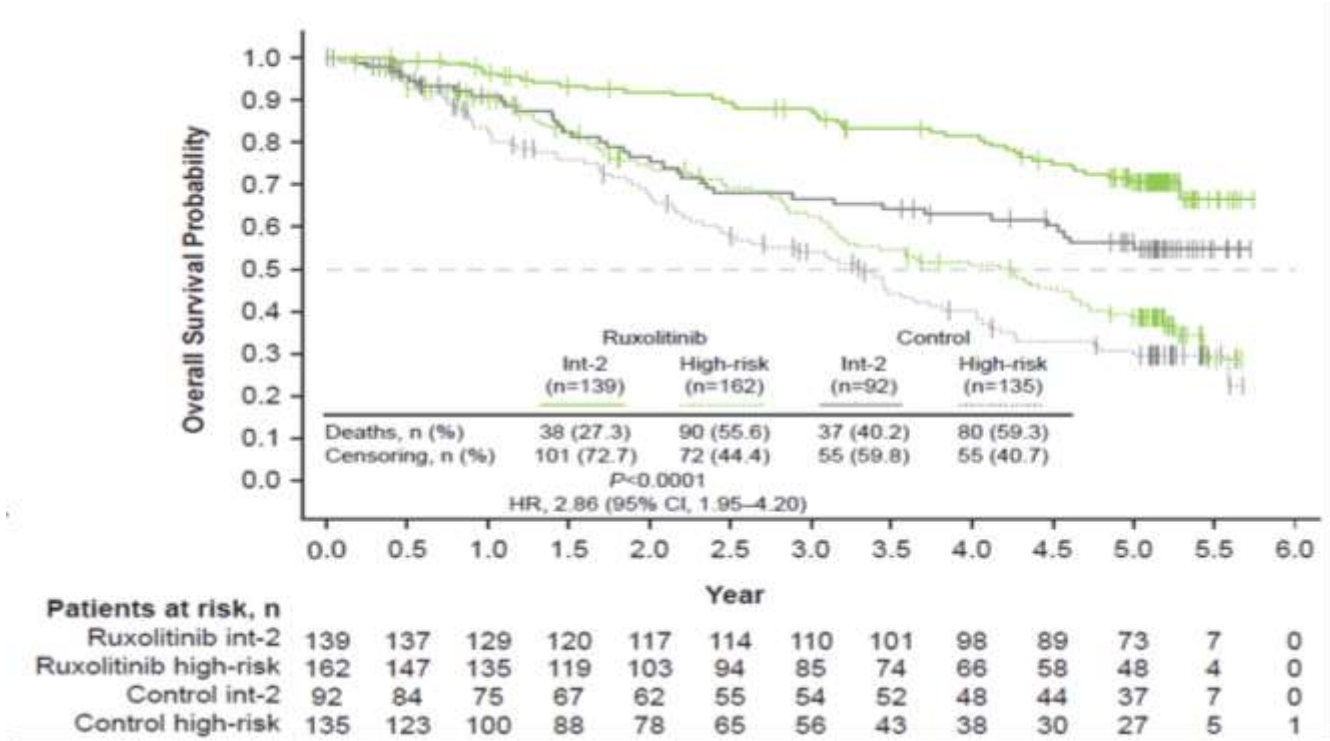
Median OS:
63.5 m x 27 m

Verstovsek et al. Poster presentation at ASH 2016. Session 634. Abstract 3110.

CI, confidence interval; HR, hazard ratio; NE, not evaluable.

POOLED COMFORT-I AND –II: 5-YEAR OVERALL SURVIVAL

OVERALL SURVIVAL BY IPSS STATUS AMONG PATIENTS TREATED WITH RUXOLITINIB



Median OS

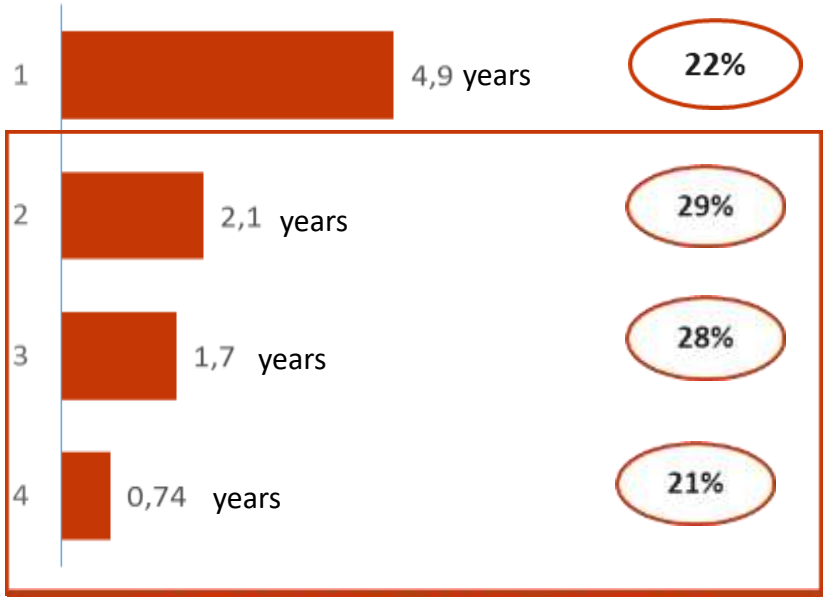
Int-2 risk NR [est. 102 months]	High risk 50 months	HR 2.86 (95% CI, 1.95–4.20; P<0.0001)

Verstovsek et al. Poster presentation at ASH 2016. Session 634. Abstract 3110.

Despite Ruxolitinib, MF patients progress in their disease; especially in intermediate and high-risk MF

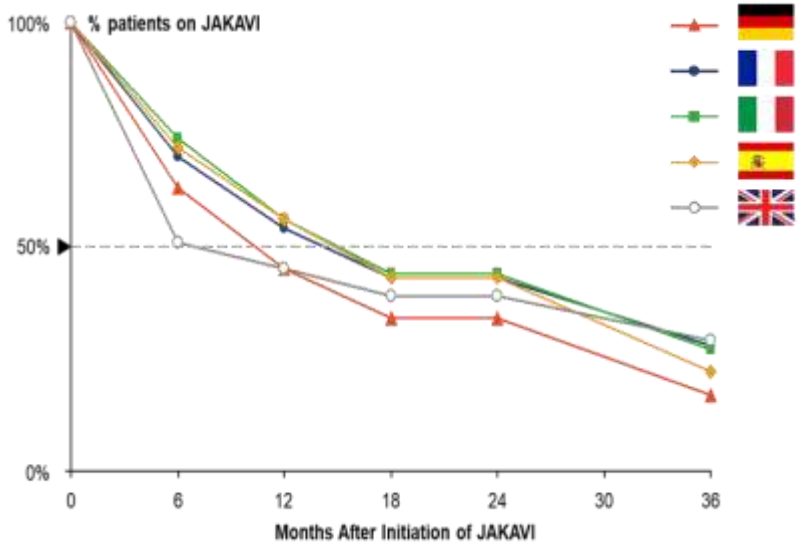
Median time to progression by risk group (years)

Percentage of MF patients per risk group



Intermediate- and high-risk patients (78% of MF) progress in 2 years

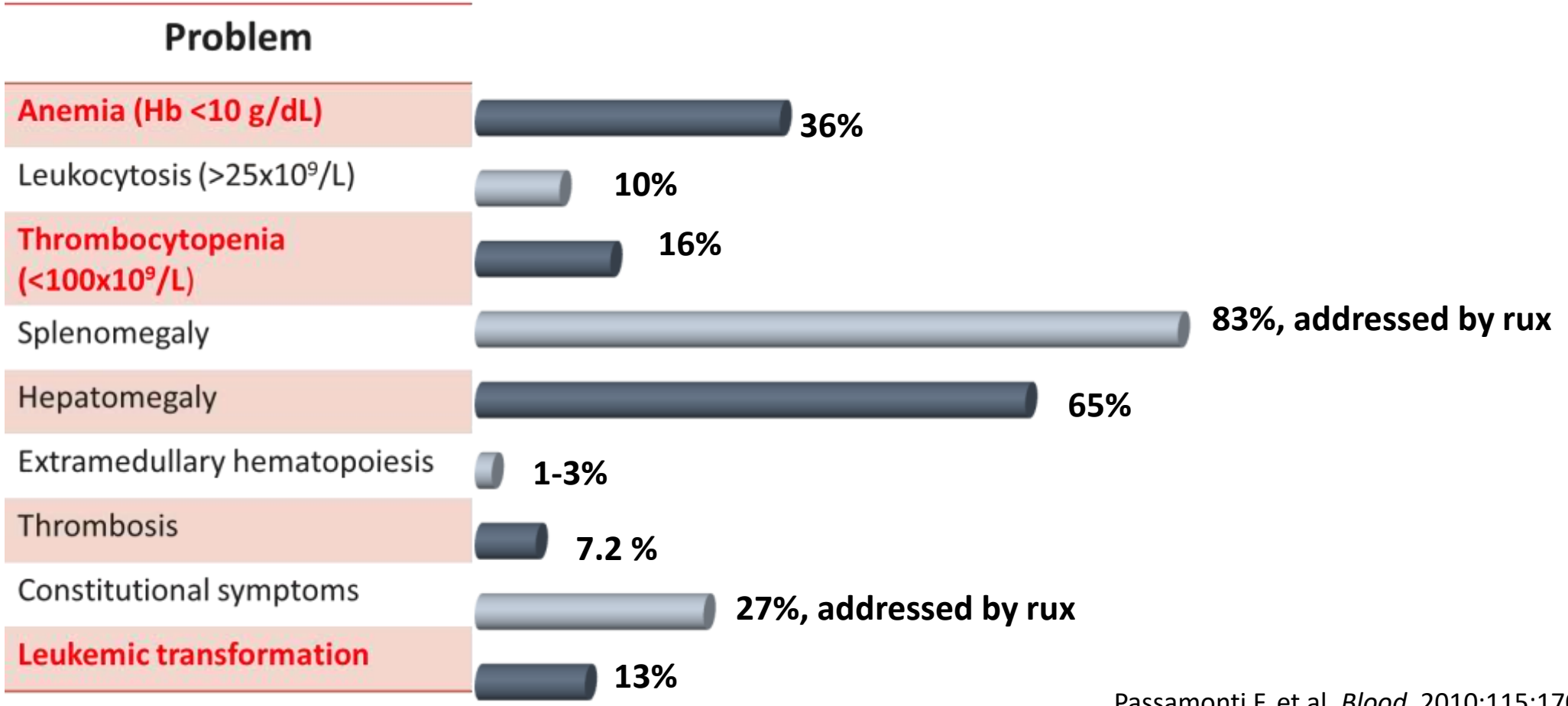
Ruxolitinib discontinuation rate in real life



Half of Ruxolitinib initiated patients have discontinued treatment in 1 year

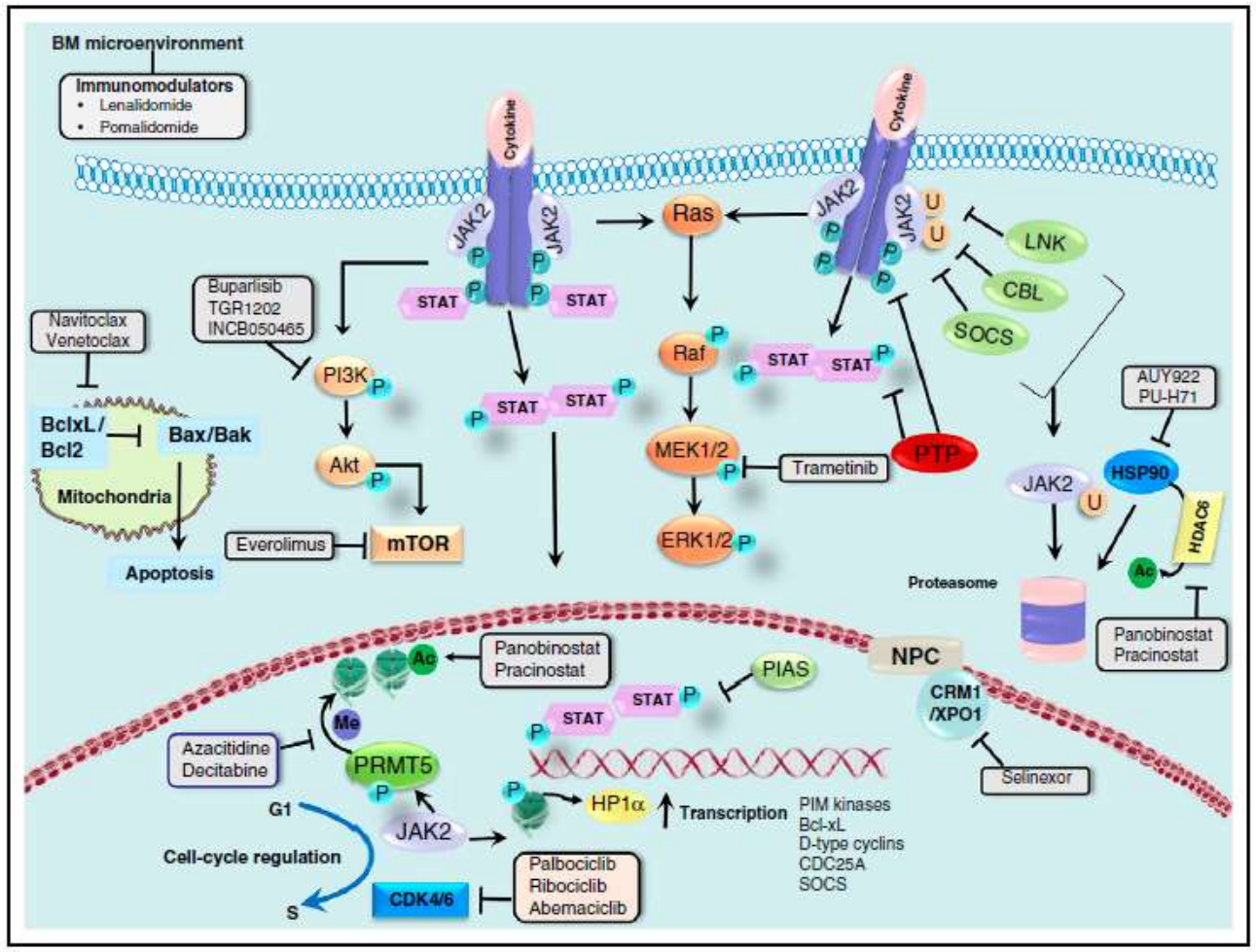
Mughal TI, et al. *Int J Gen Med*. 2014;7:89-101.

Remaining Clinical Problems in PMF



Passamonti F, et al. *Blood.* 2010;115:1703-8;
Barbui T, et al. *Blood*. 2010; 115;778-82;
Passamonti F, et al. *Blood.* 2010; 116:2857-8

New potential therapeutic targets for MPNs



JAK inhibitors

- Pacritinib ?
- fedratinib
- Momelotinib
- NS-018
- INCB039110

Telomerase inhibitor

- Imetelstat

Ruxolitinib-based combinations

- with talidomide
- Azacitidine #
- Inhibithors of histone deacetylase (HDAC)#
- PRM 151#

Bose P, et al.Blood.2017; 130(2):118-25
Tefferi A, et al. NEJM. 2015;373 (10):908-19
Masarova L, et al. Blood. 2018; 132(16);1664-74
TefferiA, et al. Blood Cancer Journal. 2018.;8:29-33

Tefferi et al. *Blood Cancer Journal* (2018)8:29
DOI 10.1038/s41408-018-0067-6

Blood Cancer Journal

ARTICLE Open Access

Momelotinib therapy for myelofibrosis: a 7-year follow-up

Ayalew Tefferi[1], Daniela Barraco[1], Terra L. Lasho[1], Sahrish Shah[1], Kebede H. Begna[1], Aref Al-Kali[1], William J. Hogan[1], Mark R. Litzow[1], Curtis A. Hanson[2], Rhett P. Ketterling[3], Naseema Gangat[1] and Animesh Pardanani[1]

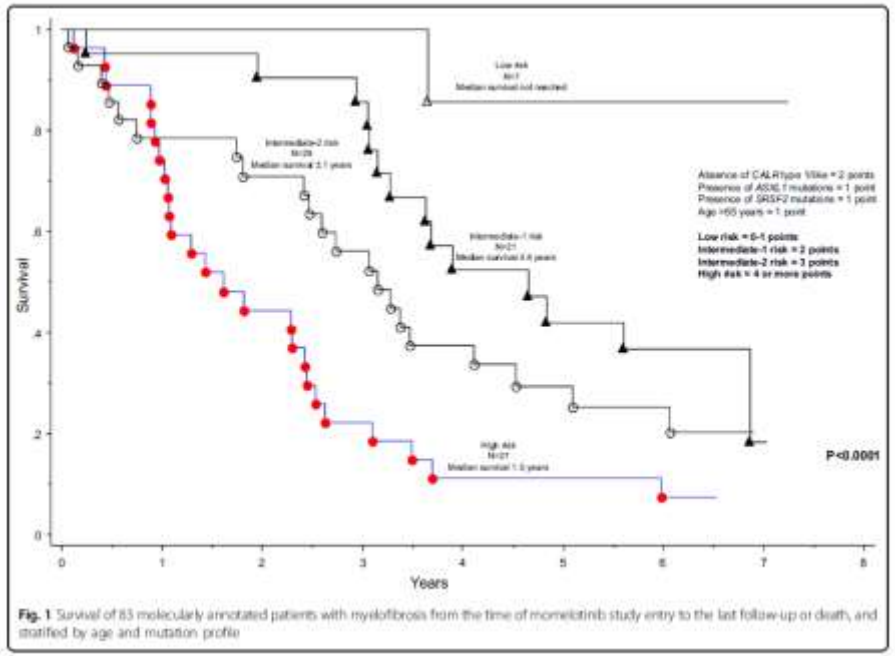


Fig. 1 Survival of 83 molecularly annotated patients with myelofibrosis from the time of momelotinib study entry to the last follow-up or death, and stratified by age and mutation profile

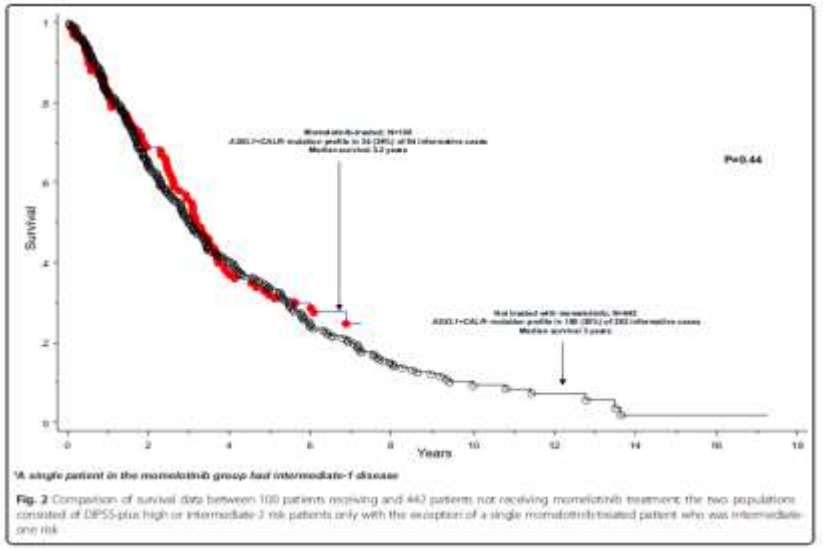


Fig. 2 Comparison of survival data between 100 patients receiving and 442 patients not receiving momelotinib treatment, the two populations consisted of DIPSS-plus high or intermediate-2 risk patients only with the exception of a single momelotinib-treated patient who was intermediate-one risk

-SIMPLIFY1 and 2
-relief from symptomatic splenomegaly and constitutionals symptoms
-anemia response: 44%
-better responses: CALR+, ASXL1- and

ORIGINAL ARTICLE

A Pilot Study of the Telomerase Inhibitor Imetelstat for Myelofibrosis

Ayalew Tefferi, M.D., Terra L. Lasho, Ph.D., Kebede H. Begna, M.D., Mrinal M. Patnaik, M.D., Darci L. Zblewski, C.N.P., Christy M. Finke, B.Sc., Rebecca R. Laborde, Ph.D., Emnet Wassie, M.D., Lauren Schimek, B.S., Curtis A. Hanson, M.D., Naseema Gangat, M.D., Xiaolin Wang, Ph.D., and Animesh Pardanani, M.D., Ph.D.

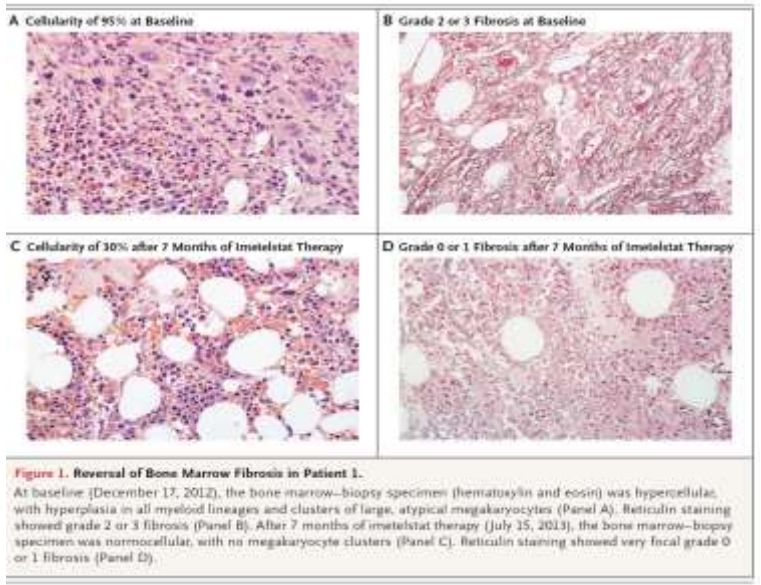


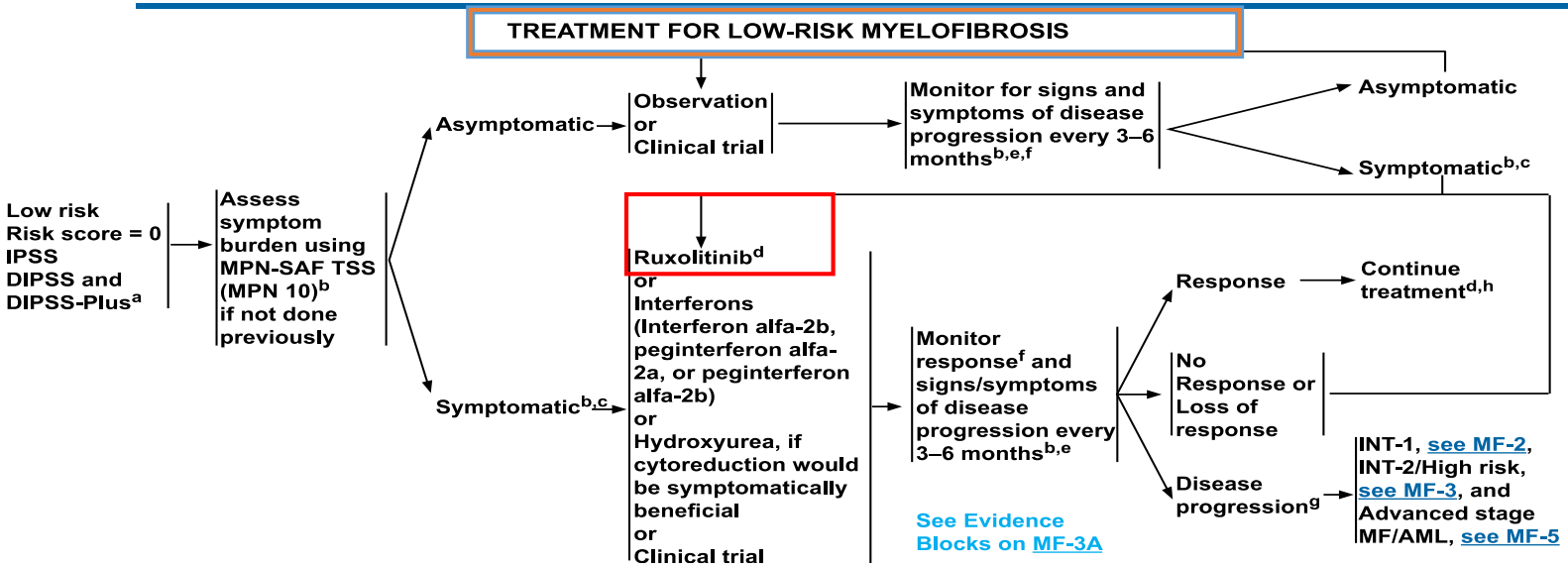
Figure 1. Reversal of Bone Marrow Fibrosis in Patient 1.
At baseline (December 17, 2012), the bone marrow–biopsy specimen (hematoxylin and eosin) was hypercellular, with hyperplasia in all myeloid lineages and clusters of large, atypical megakaryocytes (Panel A). Reticulin staining showed grade 2 or 3 fibrosis (Panel B). After 7 months of imetelstat therapy (July 15, 2013), the bone marrow–biopsy specimen was normocellular, with no megakaryocyte clusters (Panel C). Reticulin staining showed very focal grade 0 or 1 fibrosis (Panel D).

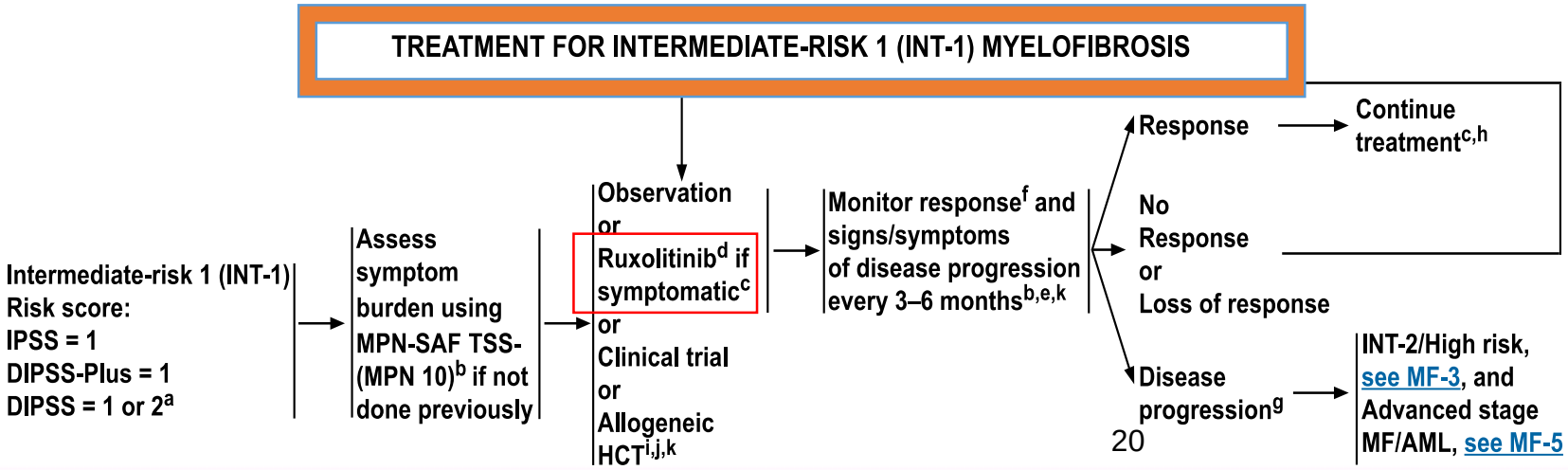
Table 2. Baseline Clinical and Laboratory Characteristics, including Mutational Status, of the Seven Patients Who Had a Complete or Partial Remission after Treatment with Imetelstat.*

Patient No.	Dosing Group†	Best Response	Age and Sex	Type of MF	Risk Status‡	Palpable Spleen Size	Hemoglobin	White-Cell Count	Platelet Count	Karyotype	*JAK2*, *CALR*, or *MPL*	*ASXL1*	*IDH1* or *IDH2*	*U2AF1*, *SF3B1*, or *SRSF2*
							g/dl	$\times 10^{-9}$/liter						
1	A	CR	73-yr-old man	Primary	Intermediate-2	Spleen edge palpable	Transfusion-dependent	5.5	153	Normal	*JAK2* Mut	WT	WT	*U2AF1* Q157P
2	A	CR	53-yr-old woman	Post-PV	Intermediate-2	7 cm	12.5	12.1	848	Normal	*JAK2* Mut	WT	WT	WT
3	A	CR	73-yr-old man	Primary	Intermediate-2	Spleen edge palpable	Transfusion-dependent	9.6	286	Normal	*JAK2* Mut	WT	WT	*U2AF1* Q157-Y158insYE
4	B	CR	79-yr-old man	Post-ET	High	10 cm	10.2	26.3	585	Loss of Y chromosome	*JAK2* Mut	WT	WT	*SF3B1* K666E
5	A	PR	76-yr-old man	Primary	High	5 cm	Transfusion-dependent	15.1	337	Normal	*JAK2* Mut	WT	WT	*SRSF2* 283–306de
6	B	PR	67-yr-old man	Primary	Intermediate-2	Not palpable	9.0	12.8	2525	Del(9)(q13q22) +9	*JAK2* Mut	WT	WT	WT
7	B	PR	69-yr-old man	Primary	High	8 cm	11.3	32.9	766	Normal	*JAK2* Mut	WT	WT	WT

- 33 patients
- 21% RC+ RP
- JAK2+; ASXL1- and U2AF1+
- 3 patients: molecular response
- Aes: myelossuppression grade 3 and 4

TefferiA, et al. NEJM.2015; 373 (10):908-19



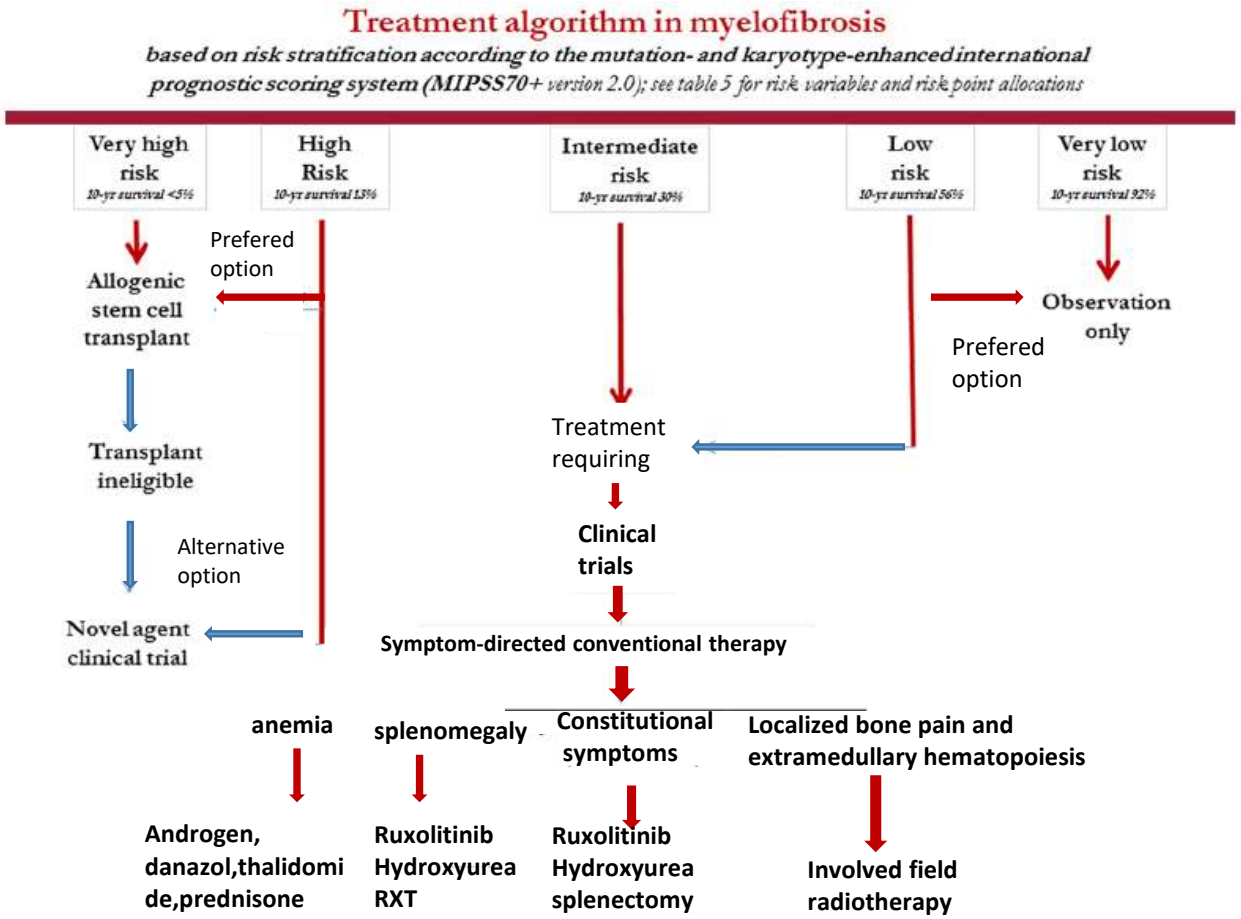


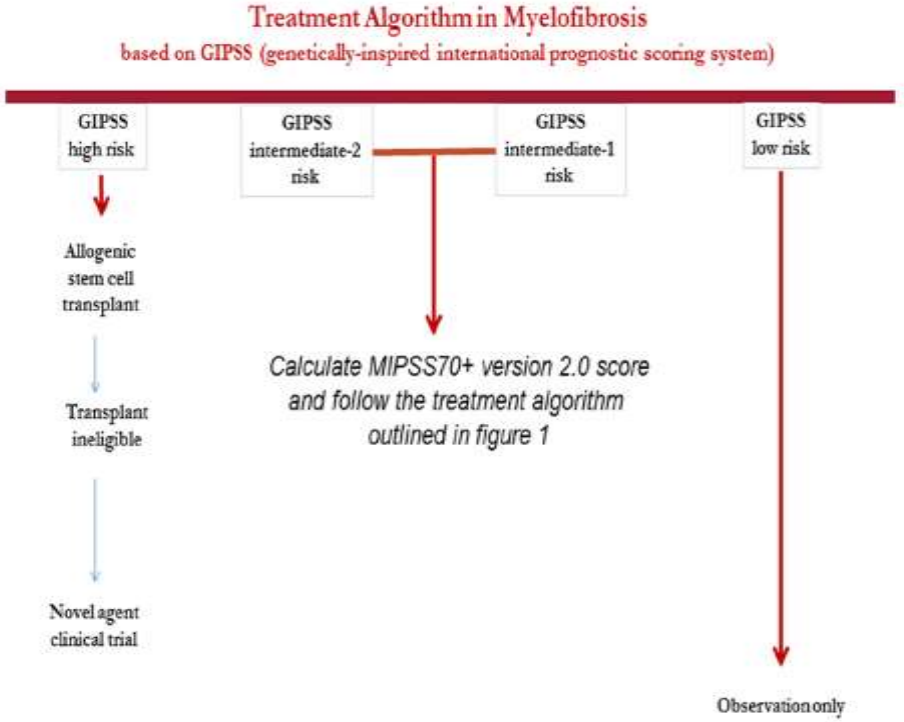
- TREATMENT FOR INTERMEDIATE 2 AND HIGH RISK MYELOFIBROSIS

- Transplant candidate = allogeneic HCT

- Not a transplant candidate:
  - >50 000 plt: ruxolitinib or clinical trial
  - ≤ 50,000 plt: clinical trial

Risk adapted therapy





Tefferi A. Am J Hematol.2018;93:1551-60.

Conclusions I: Treatment of MF – Remaining Medical Need

- MF patients are very different upon clinical presentation
  - Some may not **appear to** need treatment for several years
  - Others are very unwell at diagnosis and need treatment straight away
  - Therefore, treatment needs to be tailored **to the individual patient**
- **Allogeneic stem cell transplantation is the only potentially *curative* therapy – only few pts eligible**
- **Treatment goal in vast majority of MF patients remains to be**
  - **1) extend survival and/or PFS,**
  - **2) improve symptoms/QoL and**
  - **3) reduce spleen size**

Jain et al. Biol Blood Marrow Transplant. 2017 Sep;23(9):1429-1436
Samuelson BT et al. Biol Blood Marrow Transplant.2017

Conclusions II: Treatment of MF – Remaining Medical Need

- Genetic markers in PMF have also proven to be primary determinants of survival
- They are part of formal prognostic systems: MIPSS 70, MIPSS70+ and GIPSS
- There is also emerging evidence for genetic predition of treatment response (momelotinib and imetelstat)

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Lab Resource: Stem Cell Line

Generation and characterization of a human induced pluripotent stem (iPS) cell line derived from an acute myeloid leukemia patient evolving from primary myelofibrosis carrying the *CALR* 52 bp deletion and the *ASXL1* p.R693X mutation

Cintia E. Gomez Limia [a], Sylvie Devalle [b], Marcelo Reis [b], Jaroslaw Sochacki [b], Mayra Carneiro [a], Rodrigo Madeiro da Costa [b], Mariana D'Andrea [d], Telma Padilha [d], Ilana R. Zalcberg [d], Cristiana Solza [e], Adelmo Daumas [f], Stevens Rehen [b,c], Bárbara Monte-Mór [d,**], Martín H. Bonamino [a,g,*]

[a] Molecular Carcinogenesis Program, Research Coordination, Brazilian National Cancer Institute (INCA), Rua André Cavalcante 37, Rio de Janeiro 20230-240, Brazil
[b] D'Or Institute for Research and Education (IDOR), Rua Diniz Cordeiro 30, Rio de Janeiro 22281-100, Brazil
[c] Institute of Biomedical Sciences, Federal University of Rio de Janeiro (UFRJ), Avenida Carlos Chagas 373, Rio de Janeiro 21941-590, Brazil
[d] Laboratory of Molecular Biology, Bone Marrow Transplant Center (CEMO), Brazilian National Cancer Institute (INCA), Praça Cruz Vermelha, 23, Rio de Janeiro 20230-130, Brazil
[e] Pedro Ernesto University Hospital (HUPE), University of the State of Rio de Janeiro (UERJ), Boulevard 28 de Setembro, 77, Rio de Janeiro 20551-030, Brazil
[f] Antônio Pedro University Hospital (HUAP), Fluminense Federal University (UFF), Rua Marques de Paraná, 303, Niterói 24033-900, Brazil
[g] FIOCRUZ - Oswaldo Cruz Foundation Institute, Avenida Brasil 4365 - Manguinhos, Rio de Janeiro 21040-360, Brazil

Bonamino MH, et al. Stem Cell Research.2017;24:16-20.

Stem Cell Research 33 (2018) 130–134

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Lab resource: Stem Cell Line

Characterization of a human induced Pluripotent Stem (iPS) cell line (INCABRi002-A) derived from a primary myelofibrosis patient harboring the 5-bp insertion in *CALR* and the p.W146X mutation in *TP53*

Cintia E. Gomez Limia[a], Sylvie Devalle[b], Marcelo Reis[b], Jaroslaw Sochacki[b,1], Rodrigo Madeiro da Costa[b], Mariana D'Andrea[d], Telma Padilha[d], Ilana R. Zalcberg[d], Cristiana Solza[e], Adelmo Daumas[f], Stevens Rehen[b,c], Martín H. Bonamino[a,g,**], Bárbara Monte-Mór[d,*]

[a] Molecular Carcinogenesis Program, Research Coordination, Brazilian National Cancer Institute (INCA), Rua André Cavalcante 37, Rio de Janeiro 20230-240, Brazil
[b] D'Or Institute for Research and Education (IDOR), Rua Diniz Cordeiro 30, Rio de Janeiro 222281-100, Brazil
[c] Institute of Biomedical Sciences, Federal University of Rio de Janeiro (UFRJ), Avenida Carlos Chagas 373, Rio de Janeiro 21941-590, Brazil
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Monte-Mor B, et al. Stem Cell Research.2018;33:130-34.

INCA –Laboratório de Biologia Molecular
Ilana Zalcberg
Martim Bonamino
Barbara Monte-Mor
UERJ
Andrea Soares
Maria Christina maioli
Flavia Bandeira
Renata Lyrio
Jussara Medeiros
Carolina Leite
Ana Carolina Araujo
Luciana Souza
Karina Mello

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6 a 9 de novembro de 2019 - Rio de Janeiro/RJ/Brasil

Thank you!
csolza@hotmail.com
(21) 98157-9068