Which pre transplant therapy for myelofibrosis patients?

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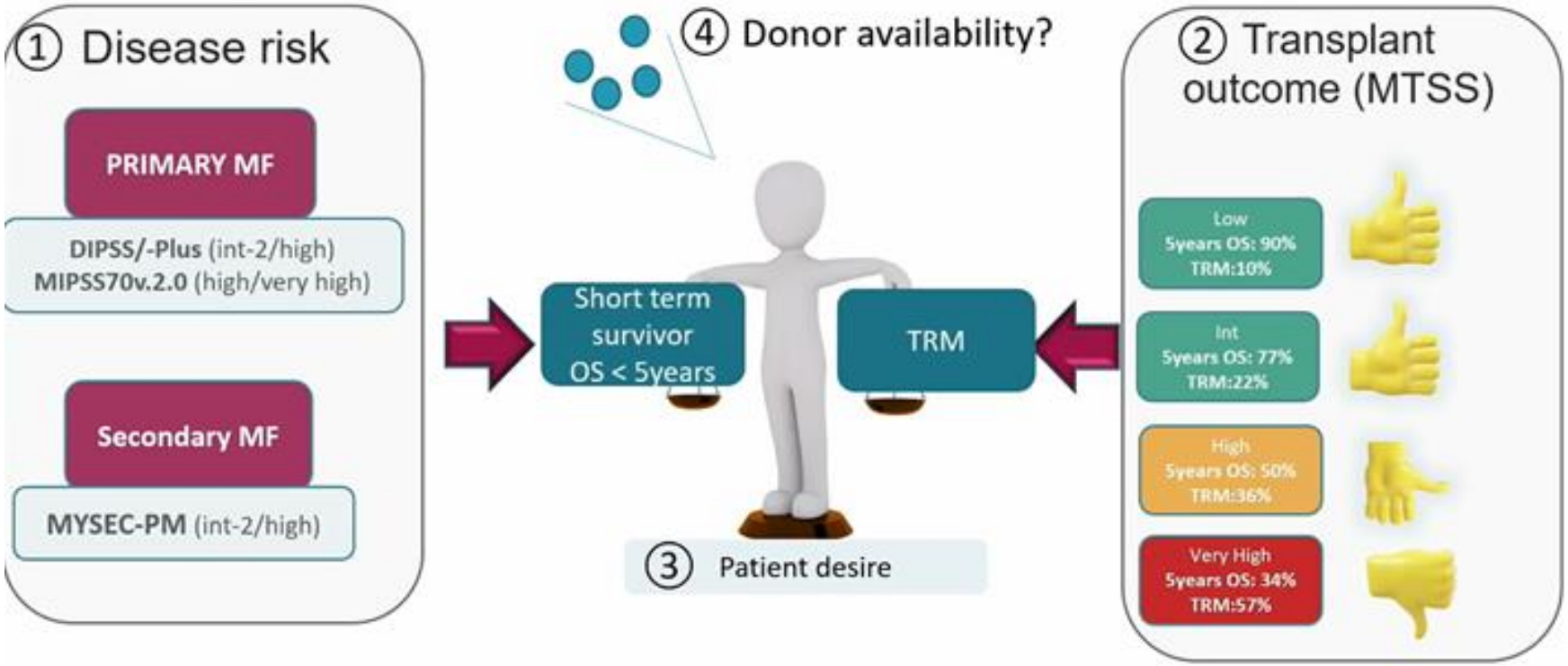
Disclosures

Honoraria : Abbvie, Alexion, Astra Zeneca, BMS Celgene, Gilead, GSK, Iqone, Incyte, Janssen, Kartos, Medac, Morphosys, Novartis, Pfizer, Sandoz, Sanofi, Sobi, Takeda, Telios

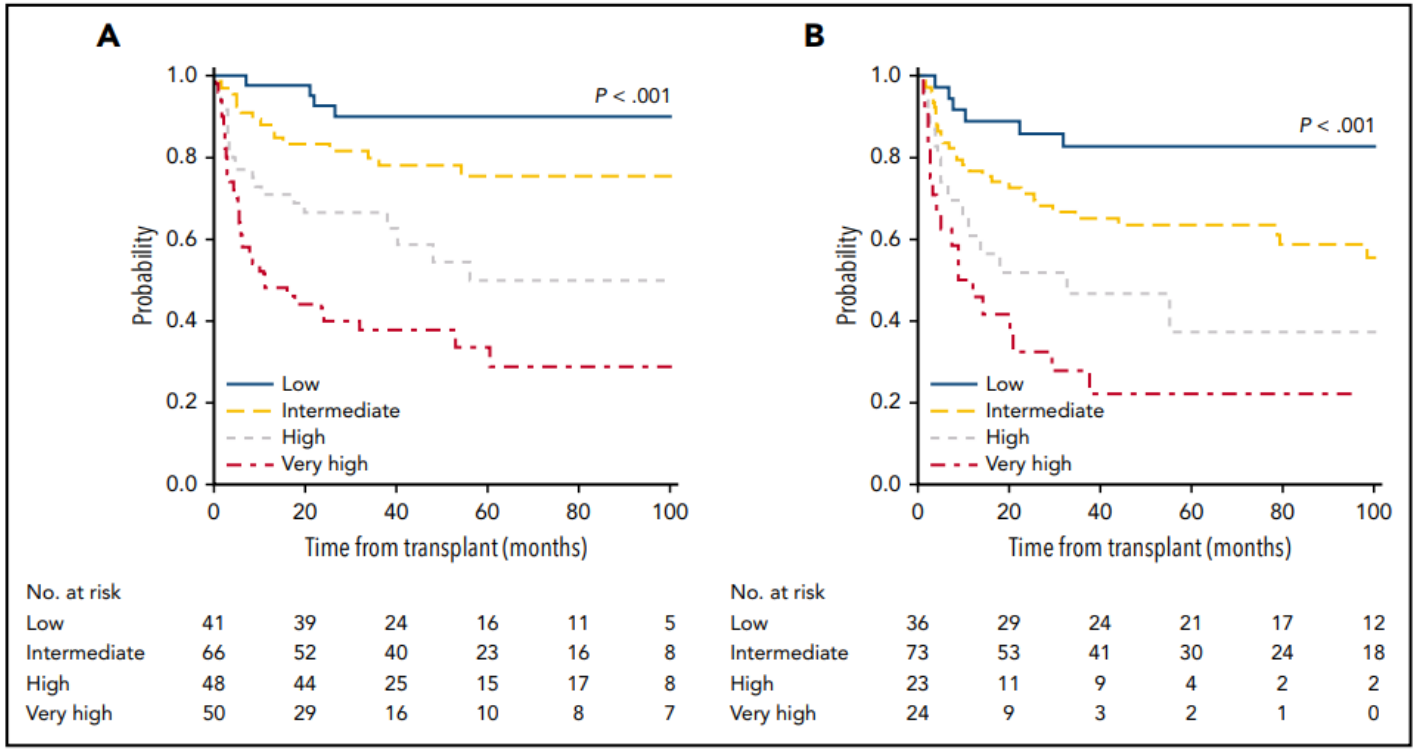
Predicting outcome (primary AND sMF)



Sockel, EBMT 2023

Predicting outcome after transplantation (primary AND sMF)

- Most recent : MTSS
  - Leukocytes > 25G/L
  - Platelets<150G/L
  - *CALR* absence
  - Karnofsky<90%
  - Age≥57yo
  - MMUD
  - *ASXL1* mut



Variable	Platelets <150 x 10^9/L	Leukocytes >25 x 10^9/L	Karnofsky performance status <90%	Age ≥57 years	Non-*CALR*/*MPL* driver mutation genotype	*ASXL1* mutation	HLA-mismatched unrelated donor
HR	1.67	1.57	1.50	1.65	2.40	1.42	2.08
Score	1	1	1	1	2	1	2

Gagelmann et al., Blood 2019

Prognostic factors

Variable	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Leukocyte count >25 × 10⁹/L	1.62 (1.10-2.41)	.015	1.57 (1.16-2.41)	.007
Platelet count <150 × 10⁹/L	1.89 (1.17-3.05)	.009	1.67 (1.16-2.40)	.006
Peripheral blasts >1%	1.03 (0.63-1.66)	.918		
Peripheral blasts (continuous)	1.02 (0.93-1.11)	.696		
Hemoglobin <10 g/dL	1.13 (0.70-1.84)	.617		
KPS <90%	1.47 (1.05-2.06)	.026	1.50 (1.06-2.13)	.021
Constitutional symptoms	1.35 (0.95-1.92)	.092		
Transfusion dependence	1.15 (0.81-1.64)	.423		
BM fibrosis grade >1	1.00 (0.66-1.53)	.999		
Driver mutation				
CALR type 1	Reference			
CALR type 2	1.05 (0.38-2.92)	.929		
MPL	0.52 (0.07-4.17)	.540		
JAK2	2.67 (1.26-5.60)	.010		
Triple negative	3.02 (1.19-7.67)	.020		
CALR* or *MPL				
Present	Reference			
Absent	2.97 (1.48-6.01)	.002	2.40 (1.30-4.71)	.012
Age ≥57 y	2.69 (1.59-4.56)	<.001	1.65 (1.15-2.36)	.006
HLA-mismatched unrelated	1.99 (1.40-2.82)	<.001	2.08 (1.45-2.97)	<.001
HLA-match				
Matched related	Reference			
Matched unrelated	1.24 (0.75-1.93)	.303		
Mismatched related	1.08 (0.15-7.91)	.943		
Mismatched unrelated	2.41 (1.51-3.84)	<.001		
ASXL1	1.50 (1.13-2.25)	.018	1.42 (1.01-2.01)	.041
*U2AF1**	1.48 (0.70-3.07)	.309		
DNMT3A†	1.58 (0.90-2.61)	.100		
TP53‡	1.02 (0.14-7.35)	.985		
Number of mutations >3	1.52 (0.92-2.57)	.098		
High molecular risk¶	1.49 (0.89-2.48)	.129		

Prognostic factors

Score, %	State of Health
100	Healthy, no symptoms or signs of disease
90	Capable of normal activity, few symptoms or signs of disease
80	Normal activity with some difficulty, some symptoms or signs
70	Caring for self, not capable of normal activity or work
60	Requiring some help, can take care of most personal requirements
50	Requires help often, requires frequent medical care
40	Disabled, requires special care and help
30	Severely disabled, hospital admission indicated but no risk of death
20	Very ill, urgently requiring admission, requires supportive measures or treatment

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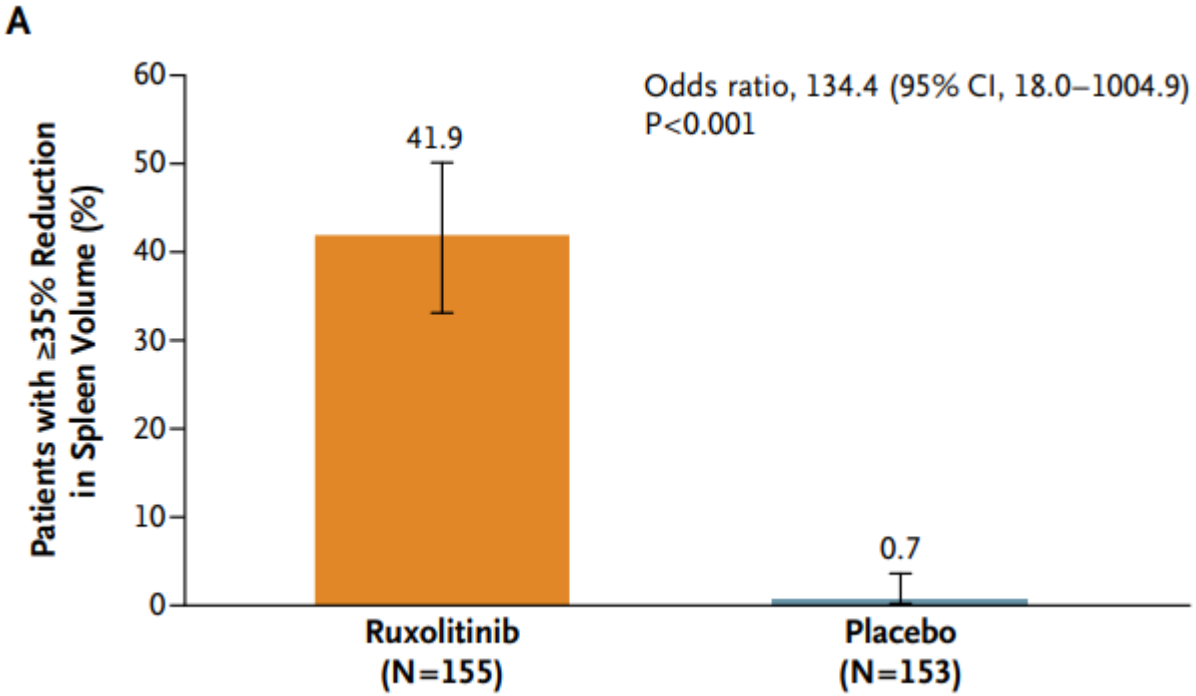
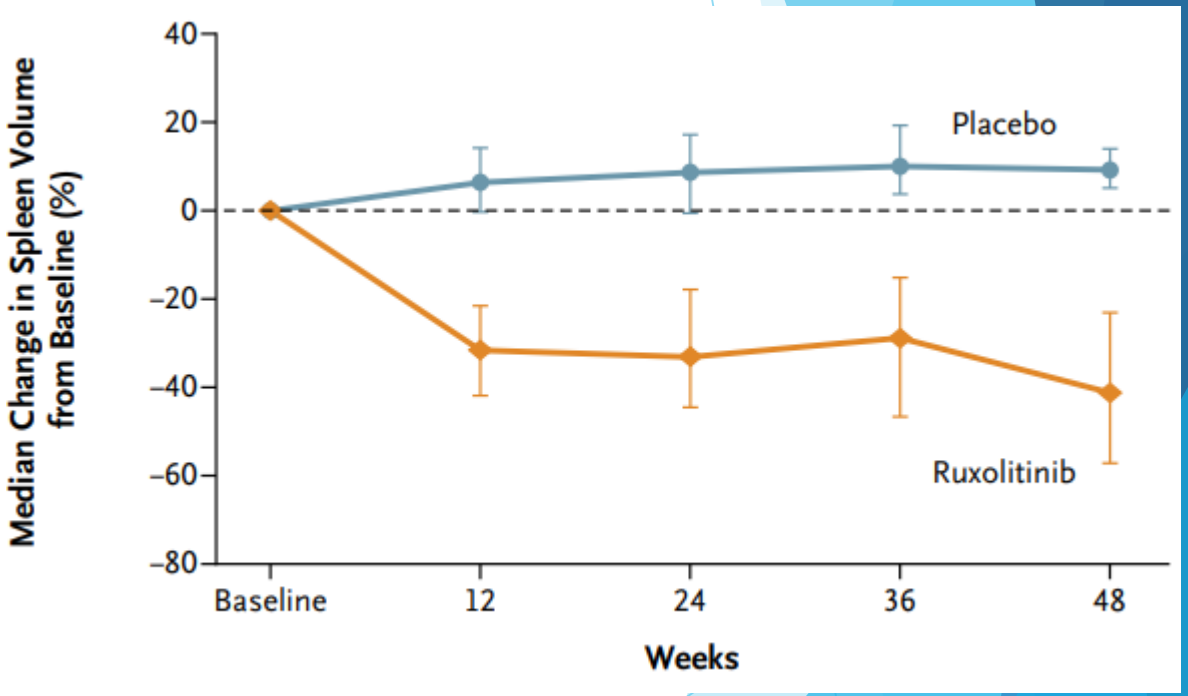
Which therapeutic options before HSCT?

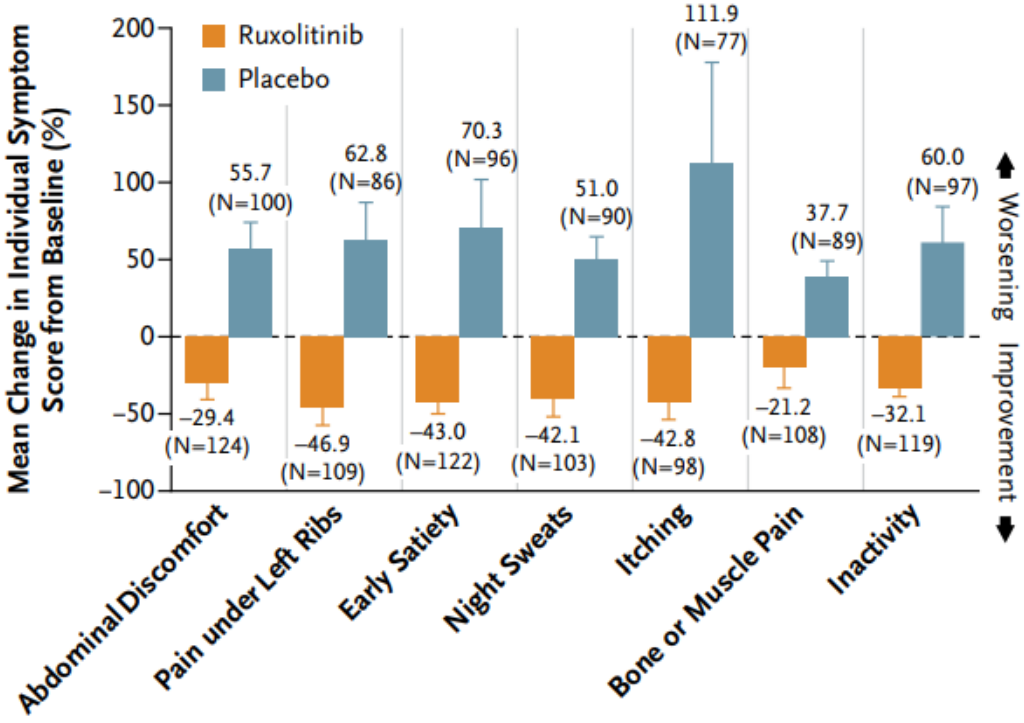
Ruxolitinib – spleen size - COMFORT

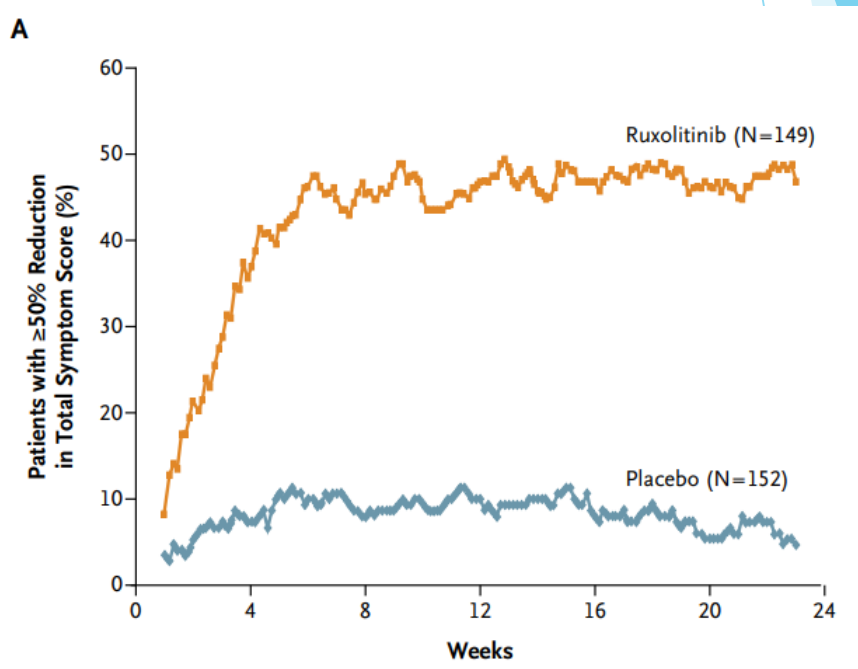




Verstovsek et al. NEJM 2012

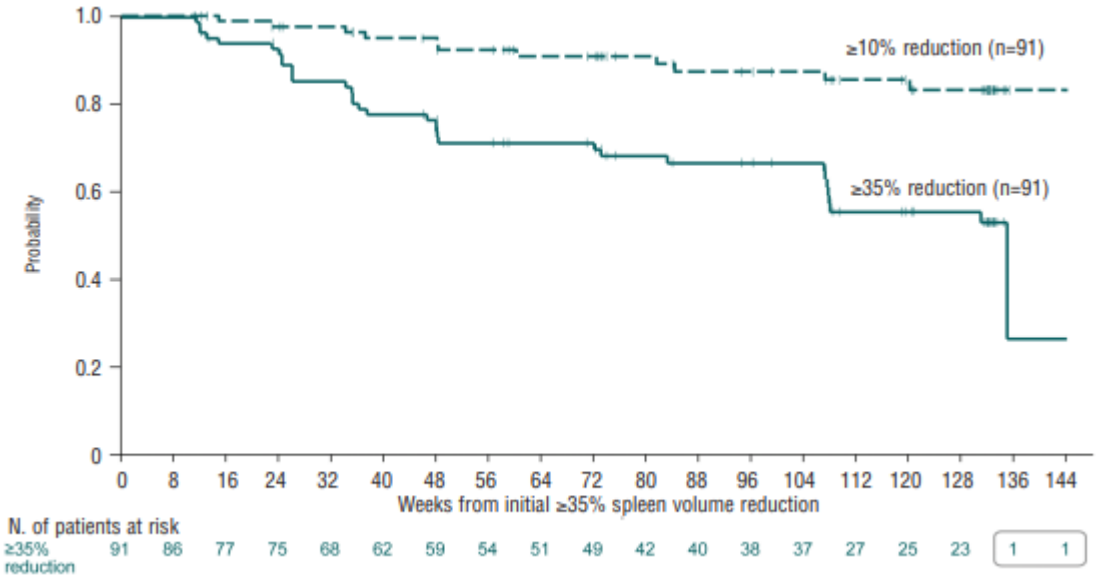
Ruxolitinib – Symptoms

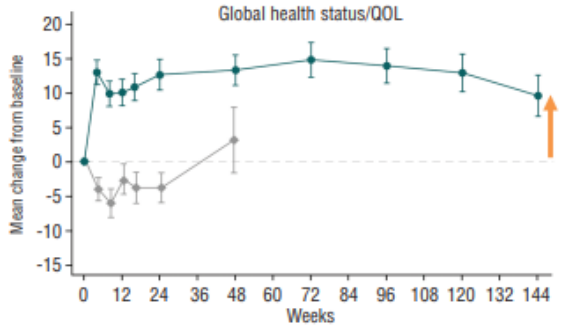


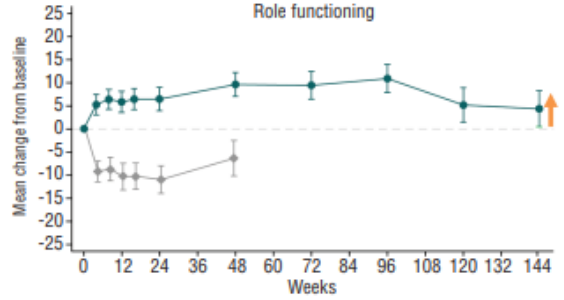


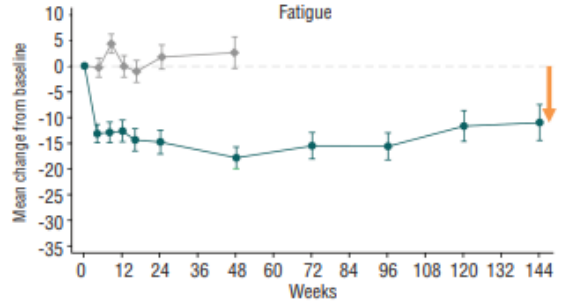
Verstovsek et al. NEJM 2012

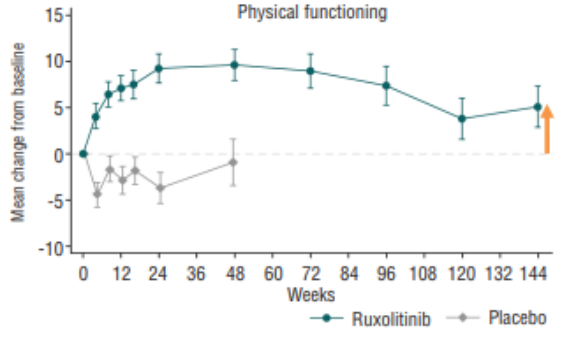
COMFORT-I – 3 years follow up











Verstovsek et al. NEJM 2012

HSCT and ruxolitinib

- Retrospective study
- Multicenter EBMT study
- Inclusion criteria :
  - Patients with PMF or myelofibrosis post polycythemia vera or essential thrombocythemia
  - HSCT from related or unrelated donor matched or mismatched donor
  - Between 2012 and 2016
  - with or without RUX treatment prior to transplantation
  - aged 18–75 years
- Objectives :
  - impact of pretreatment RUX on :
    - spleen size
    - engraftment
    - NRM
    - GVHD
    - relapse incidence (RI)
    - 2-year event-free and OS
- Spleen reduction = reduction ≥ 25% spleen size
- 551 patients who received HSCT
- Without (n = 274) or with (n = 277) ruxolitinib pre transplant

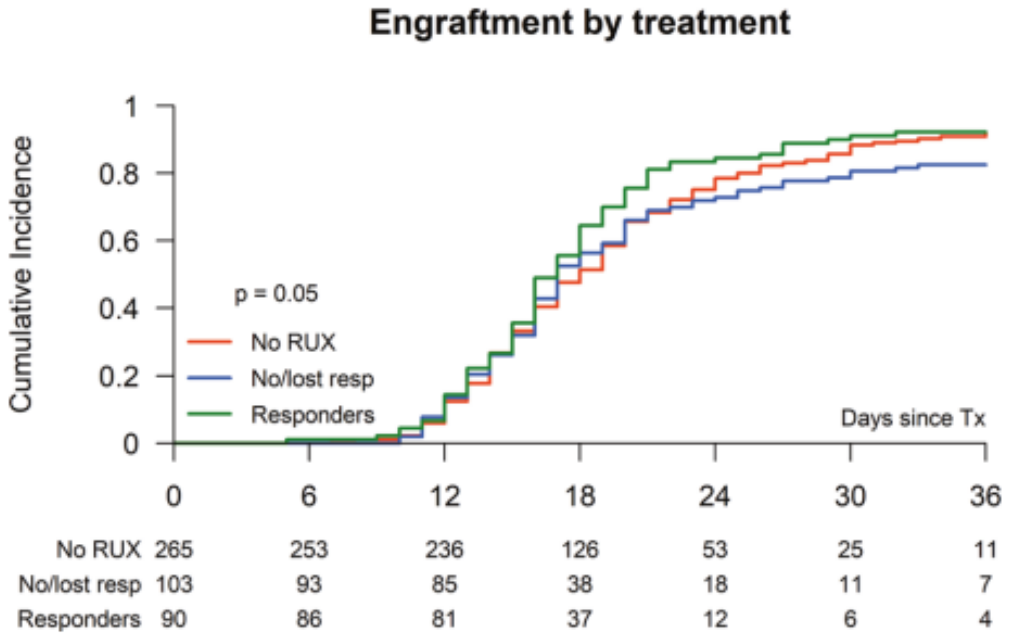
Table 1 Patients characteristics at study entry ($n = 551$).

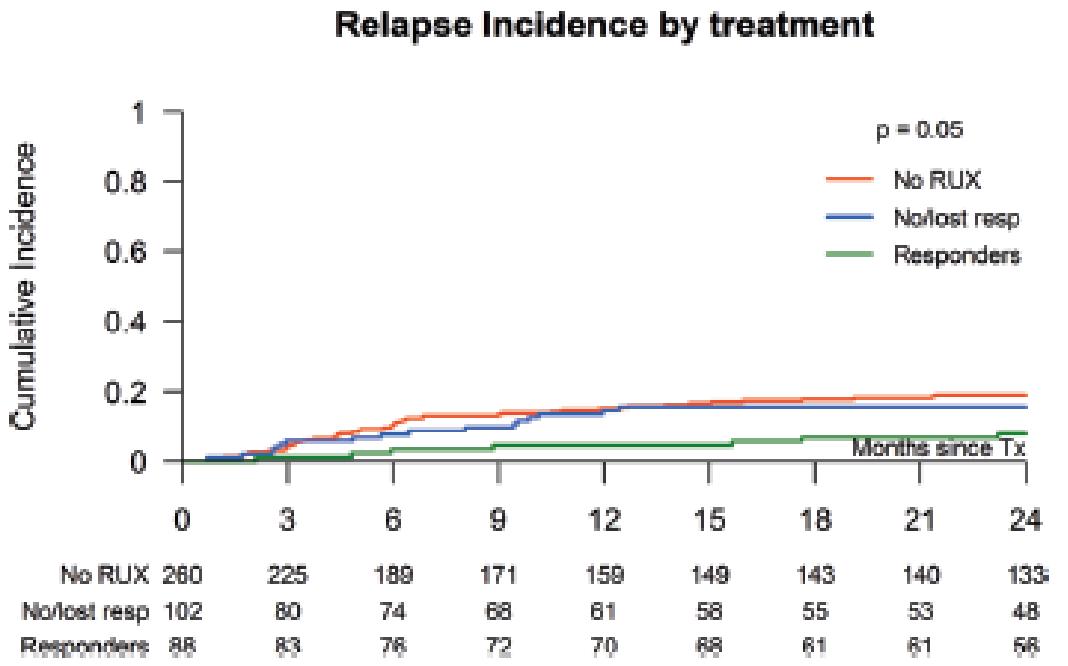
	Prior RUX	No RUX	p = value
Number of patients	$n = 277$ (50.3%)	$n = 274$ (49.7%)	
Median age (range)	58 (30–75)	58 (29–75)	$p = 0.4$
Patients gender ($n = 551$)			
Male	$n = 175$ (63%)	$n = 173$ (63%)	$p = 0.9$
Female	$n = 102$ (37%)	$n = 101$ (37%)	
DIPSS at transplant ($n = 421$, 76%)			
Low	$n = 2$ (1%)	$n = 11$ (6%)	$p < 0.01$
Intermediate-1	$n = 48$ (21%)	$n = 69$ (35%)	
Intermediate-2	$n = 125$ (56%)	$n = 76$ (39%)	
High risk	$n = 49$ (22%)	$n = 41$ (20%)	
JAK ($n = 354$, 64%)			
Positive	$n = 154$ (79%)	$n = 134$ (86%)	$p = 0.05$
Negative	$n = 44$ (21%)	$n = 22$ (14%)	
Donor ($n = 551$, 100%)			
MRD	$n = 66$ (24%)	$n = 100$ (36%)	$p = 0.003$
MUD	$n = 192$ (69%)	$n = 150$ (55%)	
MMUD/MMRD	$n = 19$ (7%)	$n = 26$ (9%)	
CMV status ($n = 533$, 97%)			
+/+	$n = 113$ (41%)	$n = 108$ (41%)	$p = 0.56$
+/−	$n = 46$ (20%)	$n = 55$ (21%)	
−/−	$n = 90$ (33%)	$n = 75$ (29%)	
−/+	$n = 23$ (9%)	$n = 23$ (9%)	
Disease ($n = 551$, 100%)			
Primary myelofibrosis	$n = 185$ (67%)	$n = 199$ (73%)	$p = 0.1$
Post-ET/-PV	$n = 92$ (33%)	$n = 75$ (27%)	
Median follow-up (months)	44 (6–87)	49 (2–91)	$p < 0.01$
Conditioning regimen ($n = 548$, 99%)			
RIC	$n = 187$ (67%)	$n = 164$ (60%)	$p = 0.08$
MAC	$n = 90$ (33%)	$n = 107$ (40%)	
Spleen size at transplant (palpable in cm) ($n = 305$)	10 (1–30)	8 (1–30)	$p = 0.4$
Constitutional symptoms at transplant ($n = 297$, 55%)	$n = 159$ (68%)	$n = 138$ (61%)	$p = 0.1$
Donor source ($n = 551$, 100%)			
BM	$n = 21$ (8%)	$n = 23$ (7.6%)	$p = 0.9$
PB	$n = 255$ (91.6%)	$n = 250$ (91%)	
CB	$n = 1$ (0.4%)	$n = 1$ (0.4%)	
Karnofsky at transplant ($n = 537$, 97%)			
≤80	$n = 113$ (42%)	$n = 89$ (33%)	$p = 0.03$
≥90	$n = 154$ (58%)	$n = 181$ (67%)	
Interval from diagnosis to transplant (months)	68 (2–430)	32 (2–527)	$p < 0.01$

Kroger et al., Leukemia 2021

HSCT and ruxolitinib

- Results
- No difference in aGVHD incidence (despite more unrelated donors in the RUX treated group)



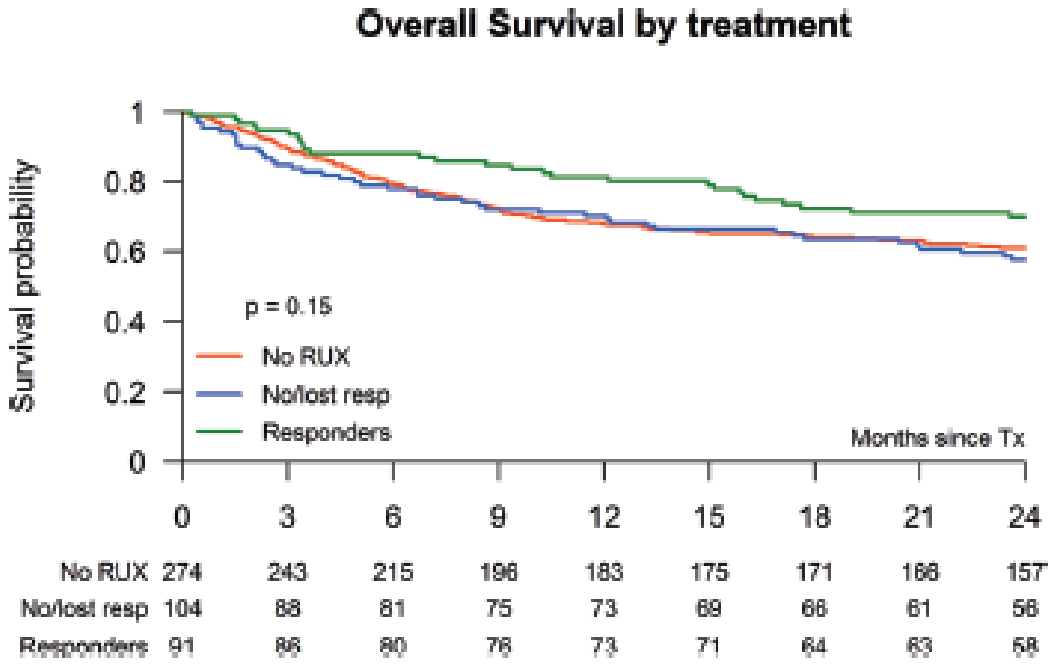


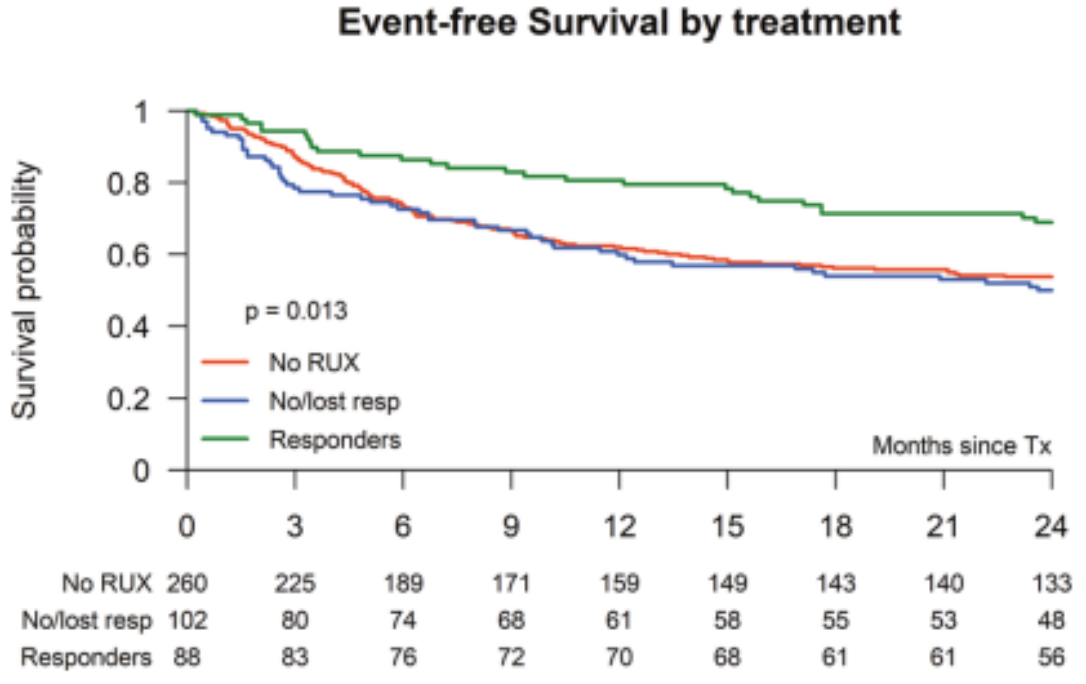
Ongoing vs. no/lost spleen response	0.41 (0.15–1.09)	0.073
Ongoing spleen response vs. No RUX	0.34 (0.12–0.95)	0.039
No/lost response vs. No RUX	0.83 (0.51–1.34)	0.449
Age: ≥58 vs. <58	1.34 (0.91–1.96)	0.133
DIPSS: High vs. Other	1.06 (0.66–1.70)	0.809
DIPSS: Missing vs. Other	0.71 (0.38–1.31)	0.273
Unrelated vs. matched donor	0.84 (0.42–1.66)	0.615
Mismatched vs. matched donor	0.62 (0.16–2.44)	0.495

Kroger et al., Leukemia 2021

HSCT and ruxolitinib

- Results



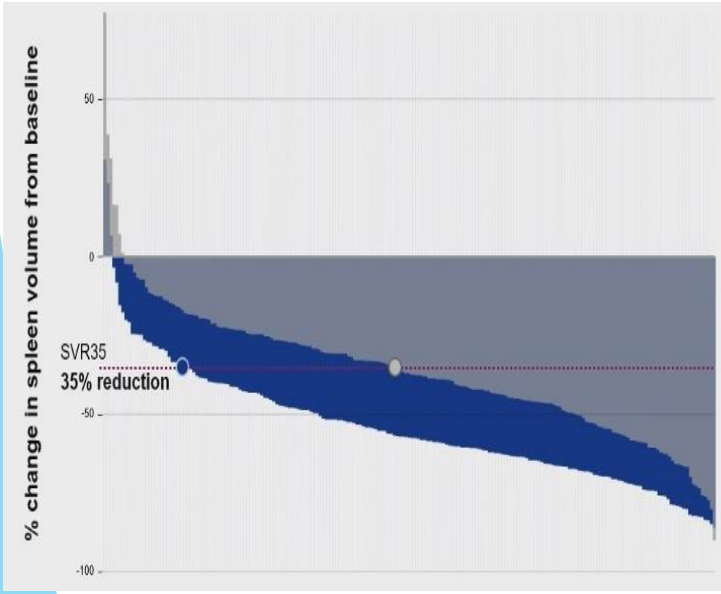


Ongoing vs. no/lost spleen response	0.55 (0.37–0.81)	0.003
Ongoing spleen response vs. No RUX	0.61 (0.40–0.91)	0.016
No/lost response vs. No RUX	1.11 (0.69–1.77)	0.676
Age: ≥58 vs. <58	1.48 (1.12–1.97)	0.006
DIPSS: High vs. Other	1.00 (0.70–1.44)	0.982
DIPSS: Missing vs. Other	1.08 (0.79–1.47)	0.635
Unrelated vs. matched donor	1.16 (0.76–1.77)	0.493
Mismatched vs. matched donor	1.87 (1.06–3.28)	0.030
Interval Diagnosis-Transplant: +1 month	1.00 (1.00–1.00)	0.983

Kroger et al., Leukemia 2021

Better than Rux mono?

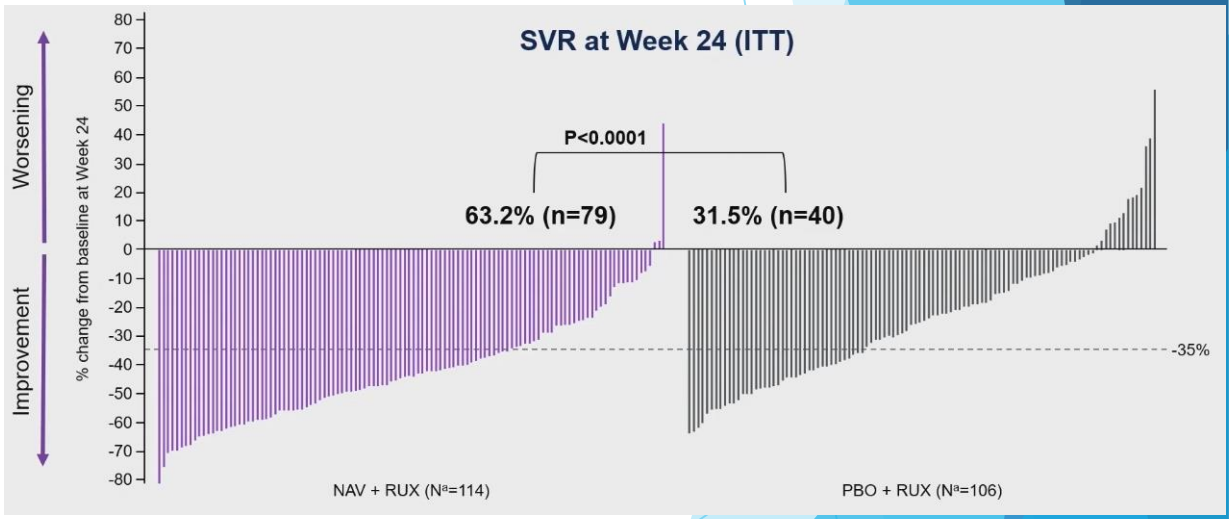
Ruxolitinib + Pelabresib
Manifest 2



ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	p-value
SVR35 at Week 24	65.9%	35.2%	
Difference† (95% CI)	30.4 (21.6, 39.3)		<0.001
Mean % change in spleen volume at Week 24‡	-50.6 (n=171)	-30.6 (n=183)	
95% CI	-53.2, -48	-33.7, -27.5	

Ruxolitinib + Navitoclax
Transform 1

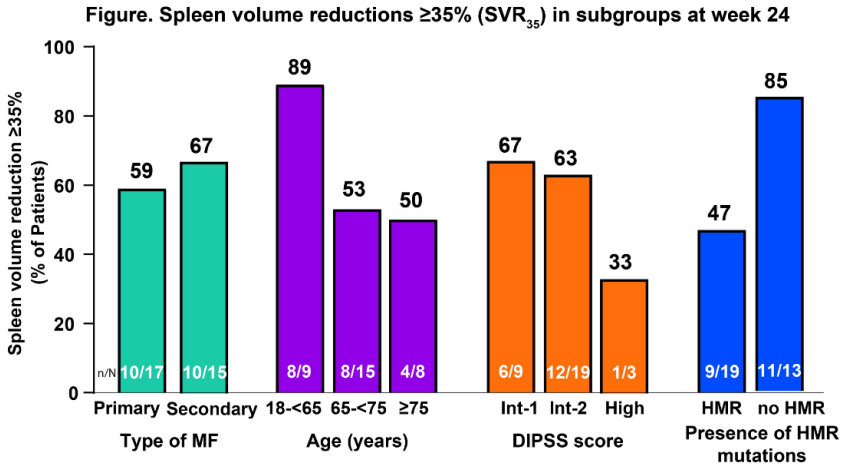


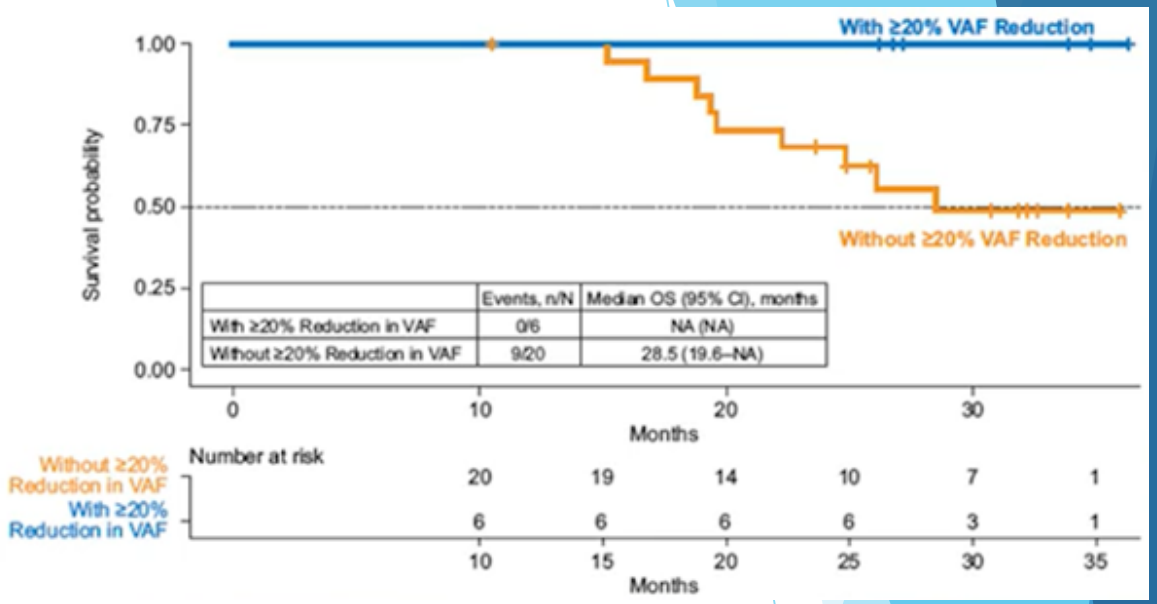
Rampal et al., Pemmaraju et al., ASH 2023

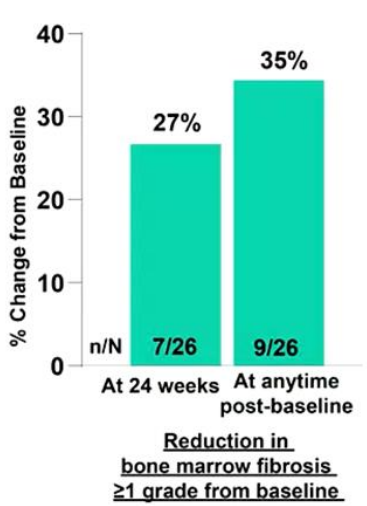
Navitoclax

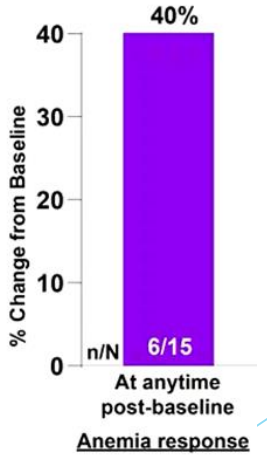
Navitoclax: orally bioavailable small molecule inhibitor of BCL-2 family members BCL-xL, BCL-2, and BCL-w

- REFINE trial
- Phase II trial to assess safety and efficacy of navitoclax alone or in combination with ruxolitinb
- Adult patients w/ DIPSS int 2 or high
- Ruxolitinib naive or R/R
- Measurable splenomegaly







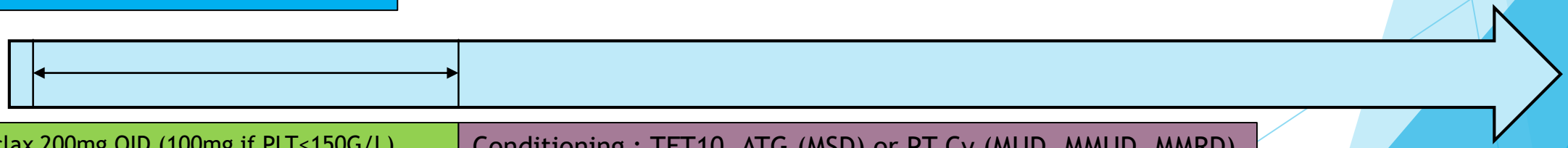


Pemmaraju, AACR 2022, Passamonti et al. ASH 2022, Harrison JCO 2022

Navallo trial

- Primary endpoint:
- NRM at 1 year
- Secondary endpoint:
  - aGVHD grade III-IV incidence
  - DFS at 1 year
  - OS at 1 year
  - Graft failure at 6 months
  - cGVHD incidence
  - Spleen volume
  - QoL
  - JAK2/MPL/CALR VAF
  - BM fibrosis

Primary or secondary MF :
- MIPSS 70+ v2.0 : high, very high
- MYSEC : int 2 or high
- Platelets≥100G/L



Navitoclax 200mg QID (100mg if PLT<150G/L)
+ruxolitinib 10mg BID : 6 months

Conditioning : TFT10, ATG (MSD) or PT Cy (MUD, MMUD, MMRD)
Stop navitoclax
Progressive taper of rux, stop at D0
MSD, MUD, MMUD, MMRD

Conclusion

- Available options are currently limited : rux quiet disappointing when given as monotherapy
- Futur looks bright to better reduce the tumor burden before transplantation :
  - Navitoclax
  - BETi
  - Imetelstat
  - Bomedemstat
  - Selinexor
  - PIM-1i
  - Navtemadlin…..
- One size fits all? Design the right combo for the right patient
- Clonal evolution before transplantation?
- Design clinical trials

Thank you for your attention