The Evolving Role of Transplantation for MPN

(PMF, PV, ET)

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MPN should be excellent indications for transplantation:

- Proliferating cells are typically sensitive to cytotoxic therapy
- The extensive “scar” formation, reticulin fibrosis, collagen fibrosis and osteosclerosis, is completely reversible

Risk Factors Included

- **Anemia**
- **WBC > 25,000**
- **Myeloblasts in blood**
- **Age (> 65 years)**
- **Symptoms**

DIPSS

- **Abnormal chromosomes**
- **Low platelet count**
- **Requiring transfusions**

DIPSS plus

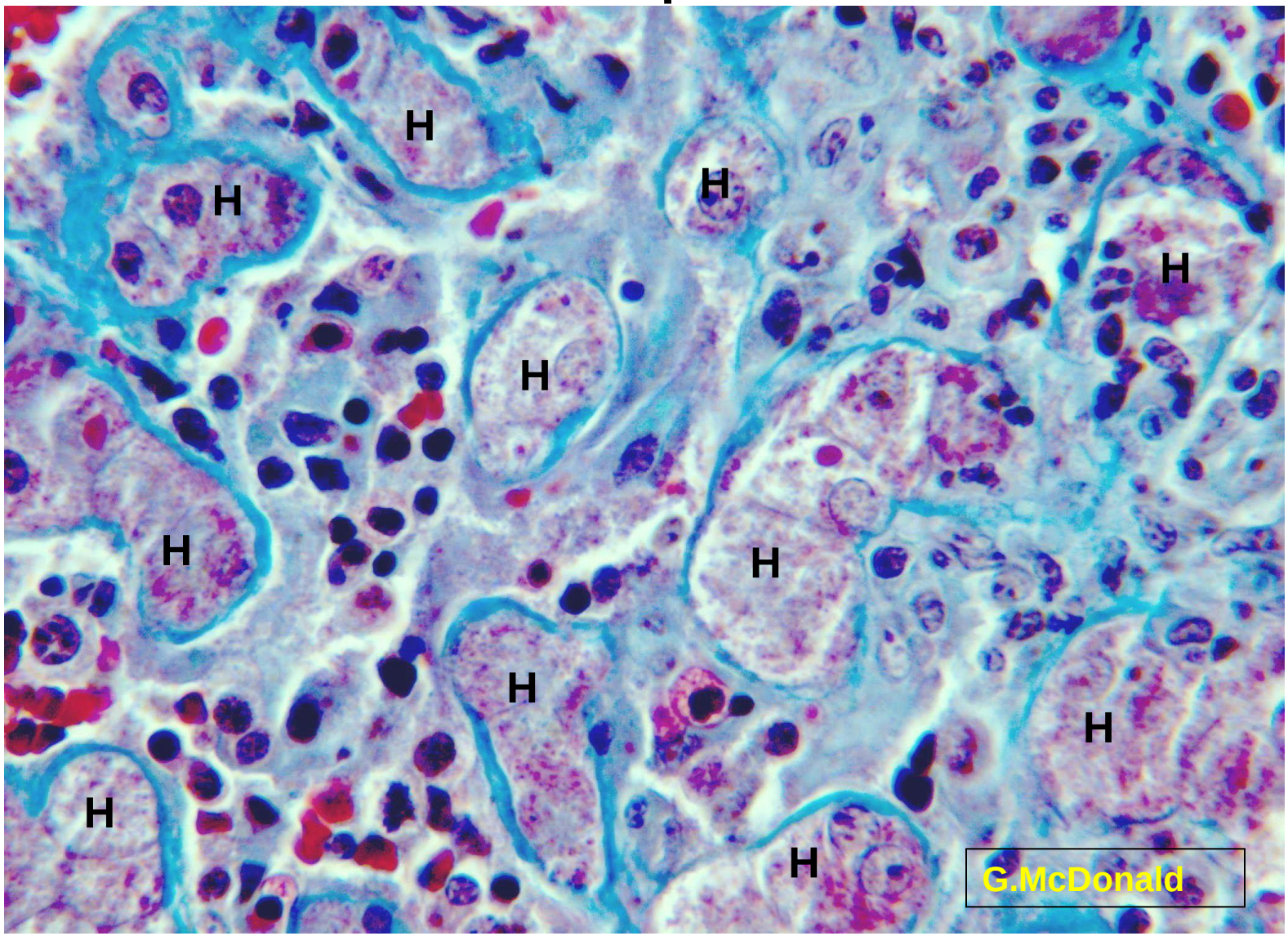
- **Mutations**
  - ***JAK2, MPL1, CALR***
  - ***ASXL1, p53, etc***

MIPSS

However

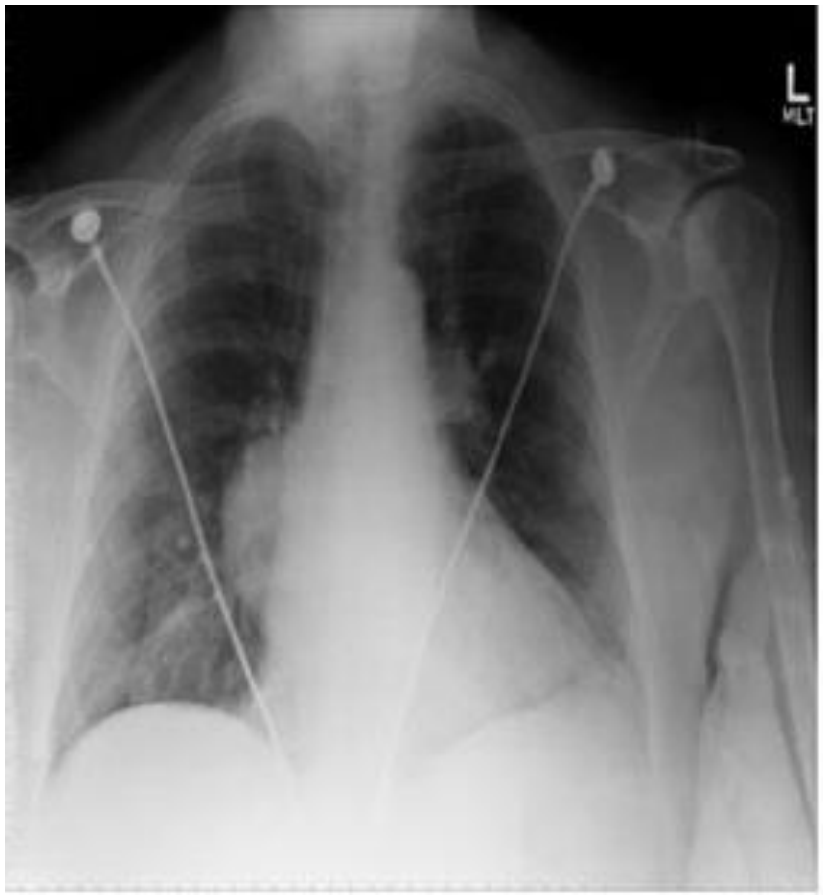
- *Extramedullary disease*, *portal or pulmonary hypertension*, *not included in current risk classification schemes*, increase the risk of non-relapse morbidity and mortality after transplantation

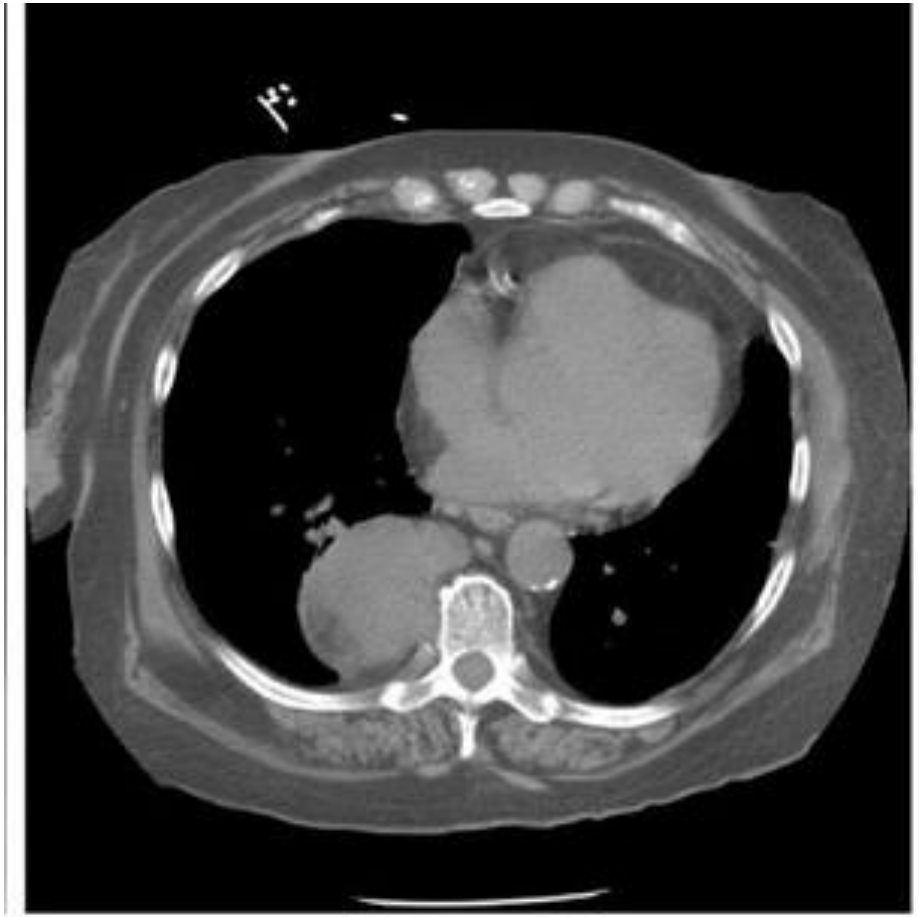
Liver: Sinusoidal fibrosis associated with extramedullary hematopoiesis



H = hepatocytes. Extensive EMH and collagen deposition (blue) in sinusoids.

“Bone marrow” in the Lung



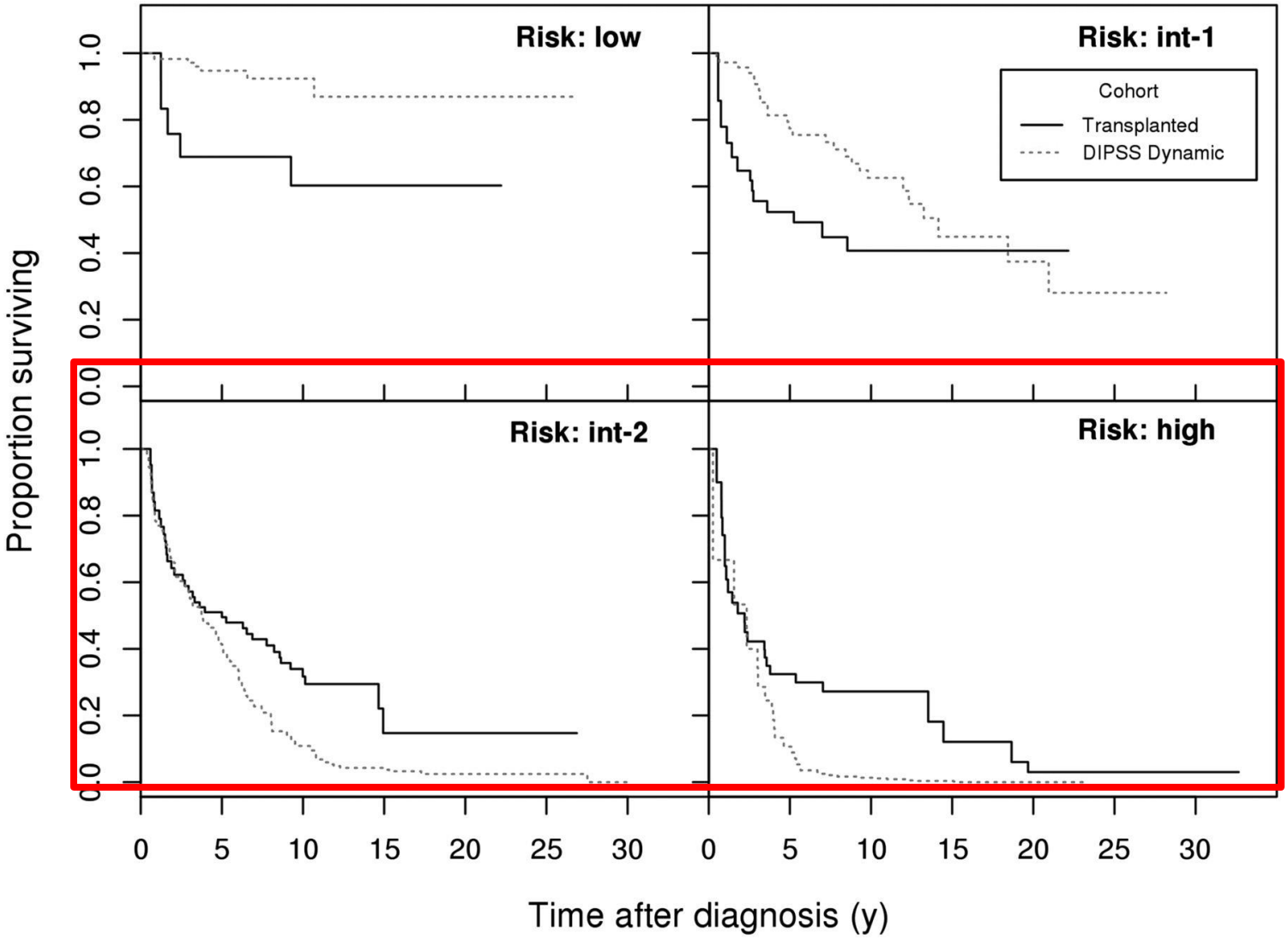


J.Wang & D.I.Kuperman, Ann.Hematol. 92: 1559, 2013

The basic question:

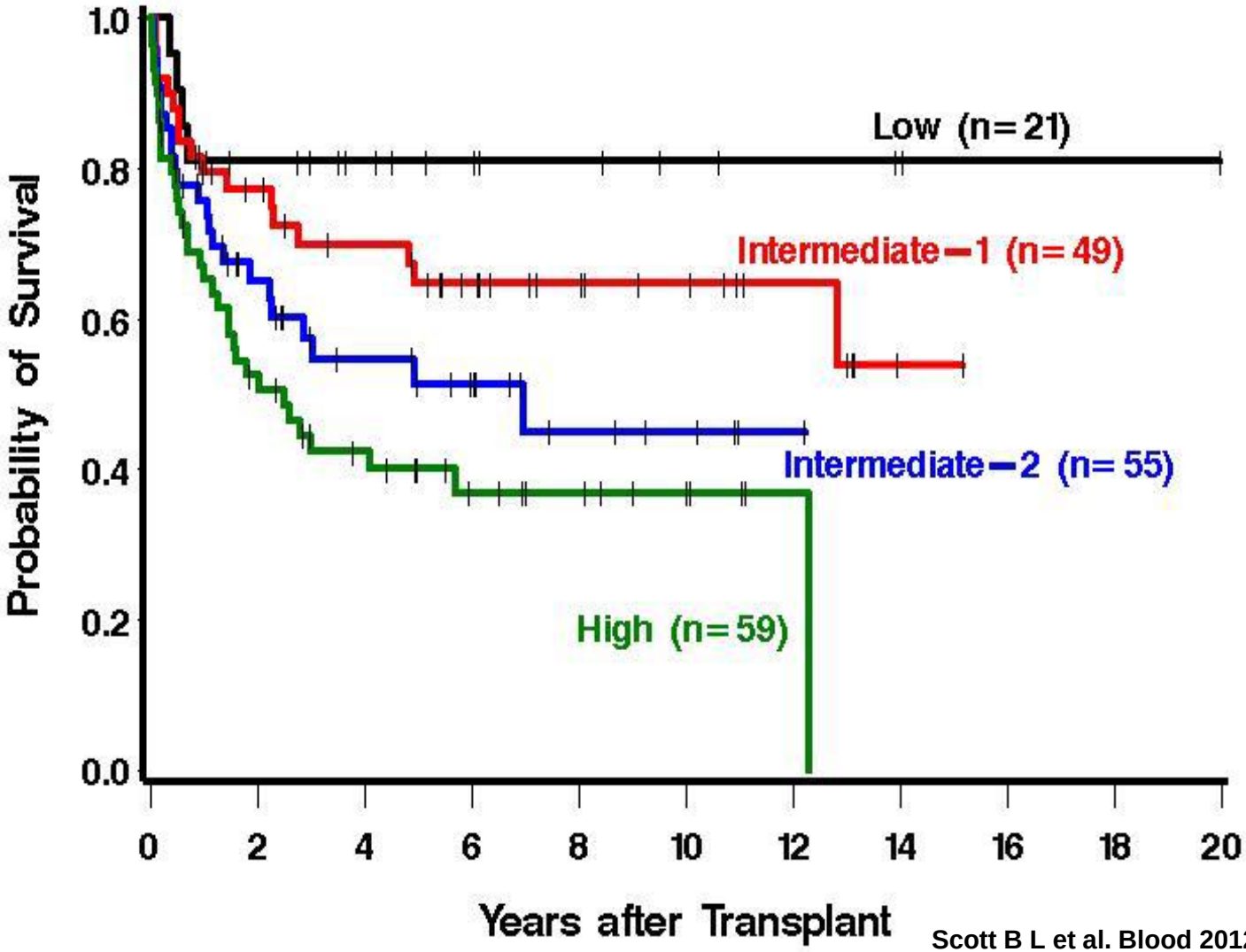
Transplantation: *no – or when?*

(by DIPSS risk)



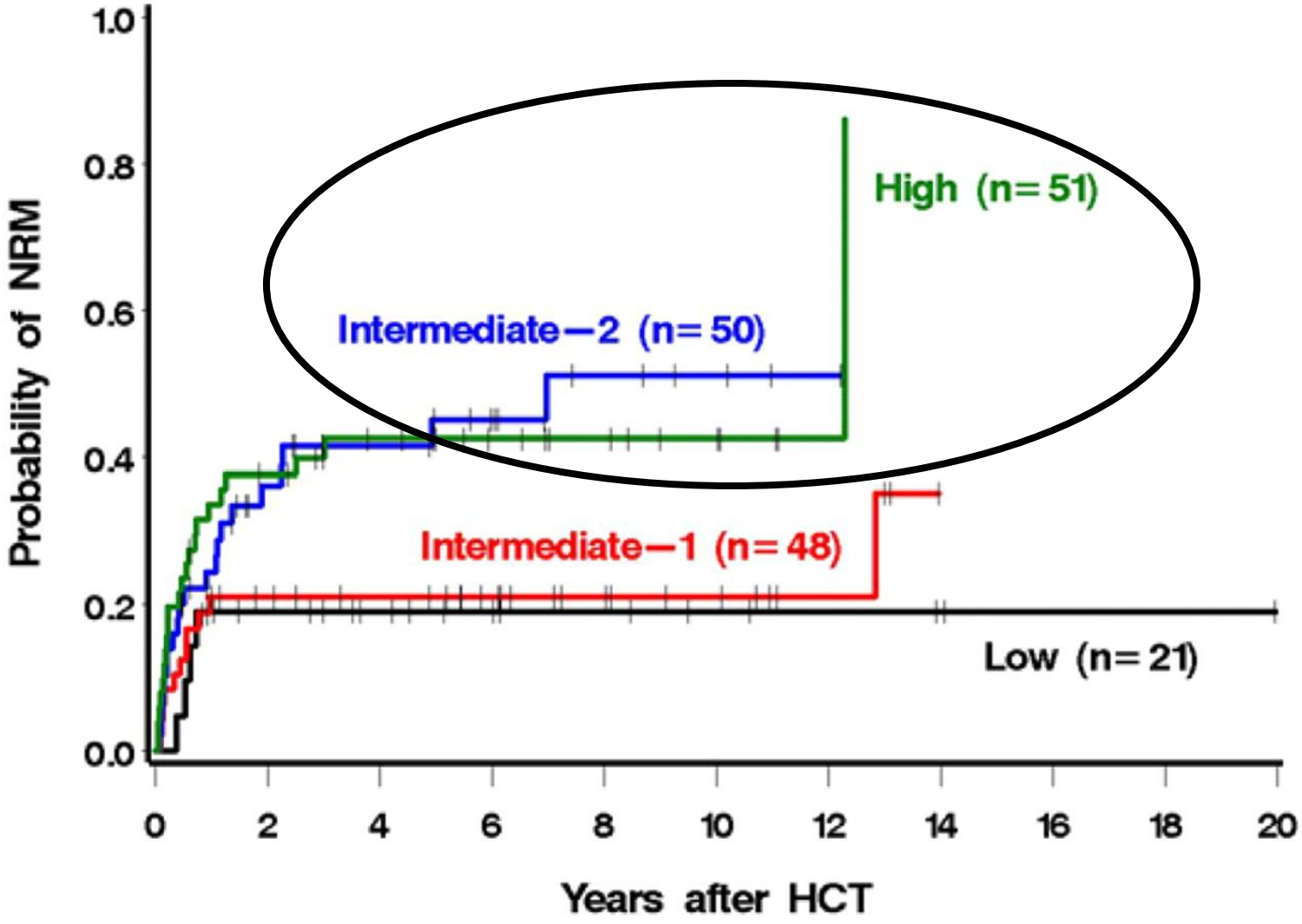
N. Kroeger et al, Blood 125: 3347, 2015

Post-HCT Survival (by DIPSS risk)
(High intensity conditioning)



Scott B L et al. Blood 2012;119:2657-2664

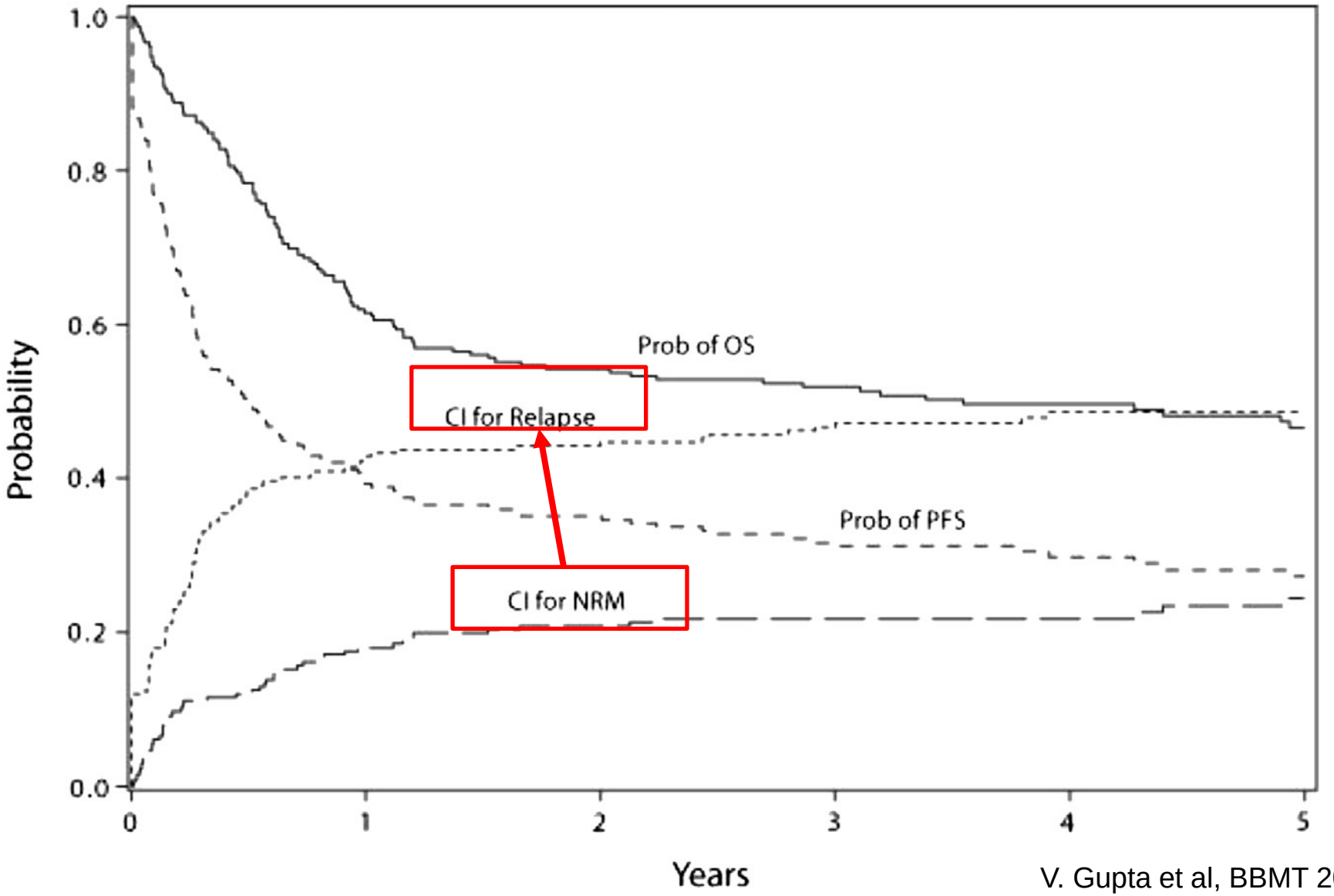
Non-Relapse Mortality (by DIPSS)



Scott B L et al. Blood 2012;119:2657-2664

Are we doing better with *Reduced Intensity* Conditioning (RIC) Transplantation?

RIC for PMF – OS, PFS and Relapse



V. Gupta et al, BBMT 2014

Is there a place for JAK inhibitors in transplantation?

Potential benefits of JAK inhibitors in transplant protocols

- **Engraftment?**
  - **Reduced Spleen size – faster engraftment**
- **Performance status?**
  - **Suppression of cytokines – Better QoL**
- **GVHD?**
  - **Decreased cytokine levels may reduce the risk of severe GVHD**
- **TRM?**
  - **Better performance status prior to HCT may yield improved outcomes**

Hypothesis

- Treatment with a JAK inhibitor before allogeneic HCT will reduce non-relapse mortality *without increasing* the risk of *relapse*

Three options:

- #1. If clinical improvement or stable disease on JAK inhibitor therapy—Proceed to Transplant
- #2. Delay HCT as long as patient “benefits”from JAK inhibitor therapy. Consider HCT if
- #3. Wait until progression to leukemia

Adapted from Shavanas & Gupta, Best Pract Res Clin Haematol. 2014; 27:165-74.

Limitations to the Use of Ruxolitinib
(with respect to HCT)

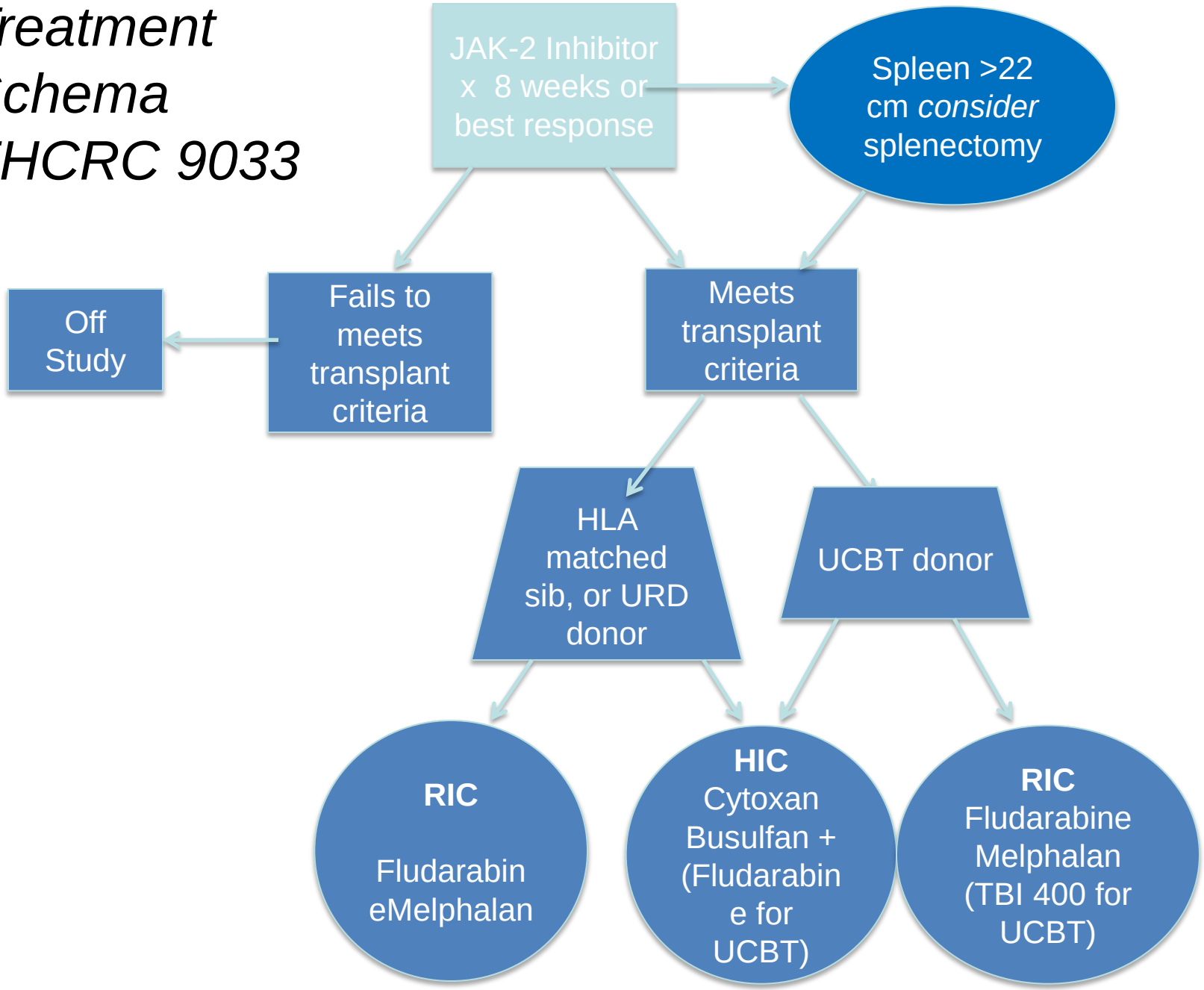
- Disease persistence
- Lack of improvement or worsening of cytopenias
- Atypical infections
  - Mycobacterial, hepatitis reactivation etc
- No decrease in the risk of Leukemic Transformation

Experience with JAK inhibitors in transplant protocols

Study	No	Study Design	Results	Conclusions
Jaekel et al BMT 2014	14	Retrospective	GF, 1/14 Treatment related sepsis, 1/14	Tapering Rux. until conditioning did not result in unexpected SAE
Shanavas, et al, BMT 2014	6	Retrospective	No adverse impact on early post HCT outcomes	As above
Stubig et al, Leukemia, 2014	22	Retrospective	1-year OS of 100% in those good resp. to Rux. vs. 60% others	Continuing Rux. until conditioning without taper – No unexpected SAEs
Lebon et al, ASH abstract 2013	11	Retrospective	Good engraftment rates	Differing schedules of tapering

Jaekel N et al. BMT 2014;49:179-84.; Shanavas M et al. BMT 2014;49:1162-69.; Stubig T et al. Leukemia 2014;28:1736-38.; Lebon D et al. ASH 2013, abstract 2111

Treatment Schema FHCRC 9033



Other Factors

DIPSS *plus*

Clinical Feature	Points
DIPSS-Low	0
DIPSS-Int-1	1
DIPSS-Int-2	2
DIPSS-High	3
PLUS	
Unfavorable Karyotype[2]	1
Transfusion Dependence	1
Platelet <100,000/ul	1

Prognostic Category	Points	Median Survival (mo)
Low	0	185
Intermediate-1	1	78
Intermediate-2	2-3	35
High	4-6	16

Patient and Disease Characteristics

Characteristic	Value
No. of patients	233
Age range, y (median)	12.9 – 78.9 (54.1)
Sex, male/female, no (%) of patients	133 (57)/100 (43)
Months from diagnosis to HSCT, range (median)	0.7-313.7 (15.5)
Type of myelofibrosis, no. (%)	
Primary	139 (60)
Secondary	94 (40)
Essential thrombocythemia	56 (24)
Polycythemia vera	28 (12)
Other/uncertain	10 (4)
Cytogenetic classification, no. (%)	
Favorable	183 (79)
Unfavorable	44 (19)
Undetermined	6 (3)
Mutational status, no. (%)	
JAK2-V617F mutant	64 (27)
CALR mutant	18 (4)
MPL	1 (0.4)
Triple negative	13 (5)
N/D	137 (59)
DIPPSPlus score, no. (%)	
Low	10 (4)
Intermediate-1	25 (11)
Intermediate-2	107 (46)
High	91 (39)

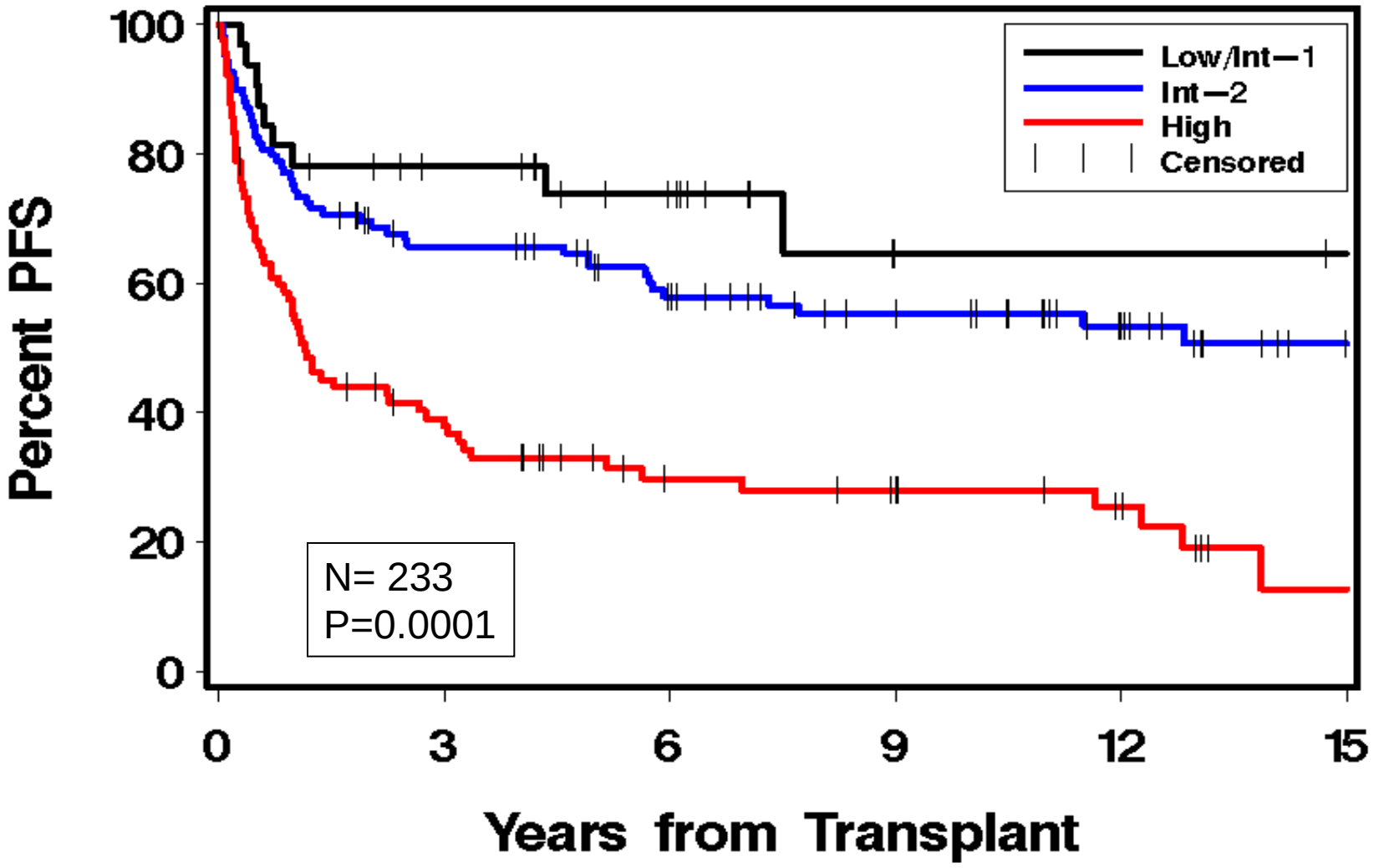
Samuelson, Salit et al

Transplant Characteristics

Characteristic	N (%)
Donor type, no. (%)	
Syngeneic	3 (1)
Allogeneic	230 (99)
Related donor	102 (46)
HLA-matched	101 (99)
HLA-mismatched	1 (1)
Unrelated donor	127 (57)
HLA-matched	106 (83)
HLA-mismatched	21 (17)
Conditioning	
Bu 16 mg/kg oral + Cy 120mg/kg	128 (55)
Bu 16mg/kg oral + Cy 120mg/kg + ATG	15 (6)
Cy 120mg/kg + Bu 16mg/kg IV	18 (8)
Flu 120mg/m2 + Bu 16 mg/kg oral	3 (1)
Flu 250 mg/m2+ Bu 16mg/kg IV + ATG	3 (1)
Flu 120 mg/m2 + Bu 12.8 mg/kg IV + ATG	5 (2)
Bu 7mg/kg oral + TBI 12Gy	10 (4)
Cy 120 mg/kg + TBI 12-14 Gy	5 (2)
Flu 150mg/m2 + Melphalan 140mg/kg	3 (1)
Other	7 (3)
Flu 90mg/m2 + TBI 2Gy	36 (15)
Source of stem cells	
Bone marrow	47 (21)
Peripheral blood	185 (79)
Cord blood	1

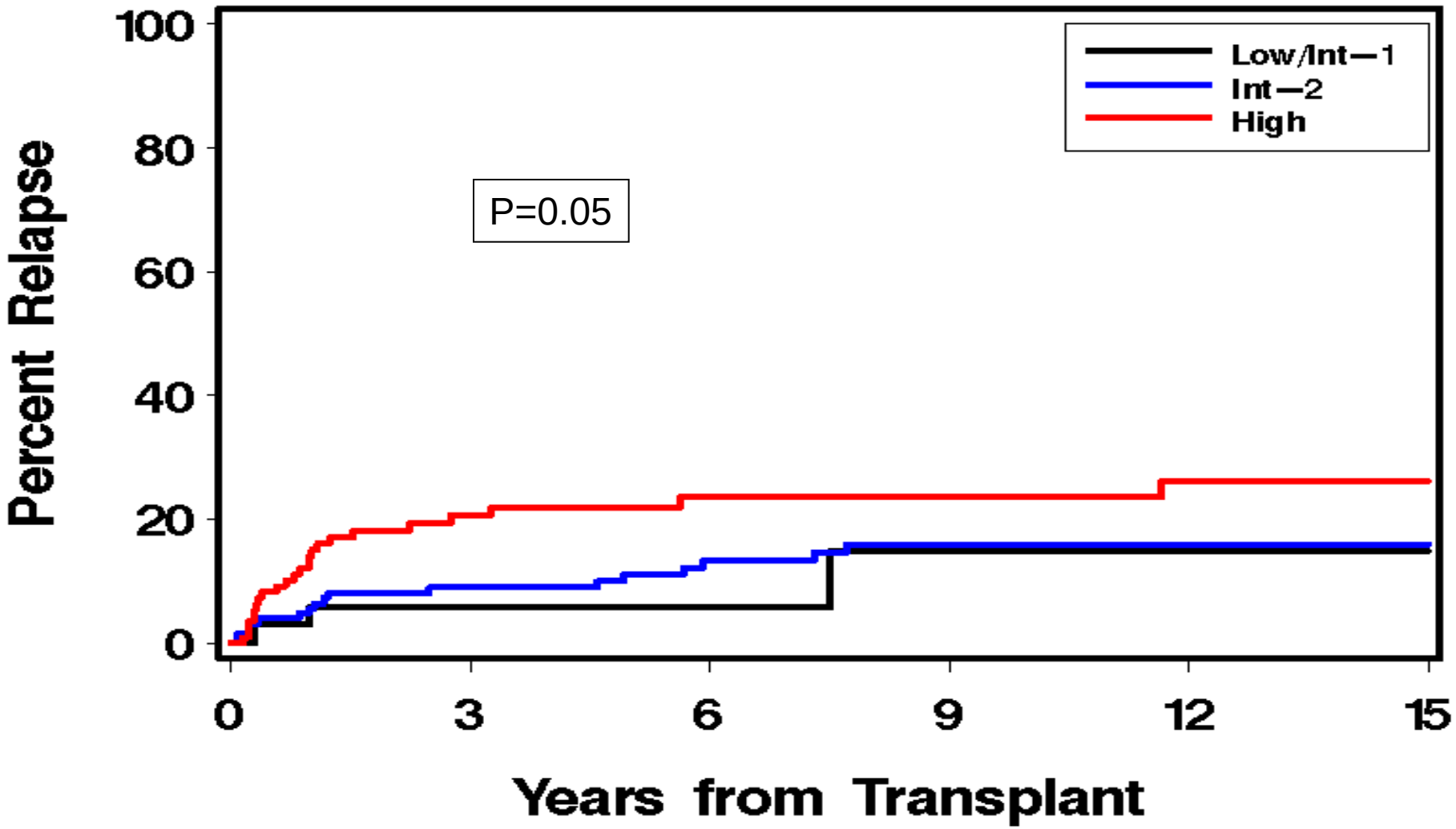
Samuelson, Salit et al

Progression-free survival by DIPSS *plus*



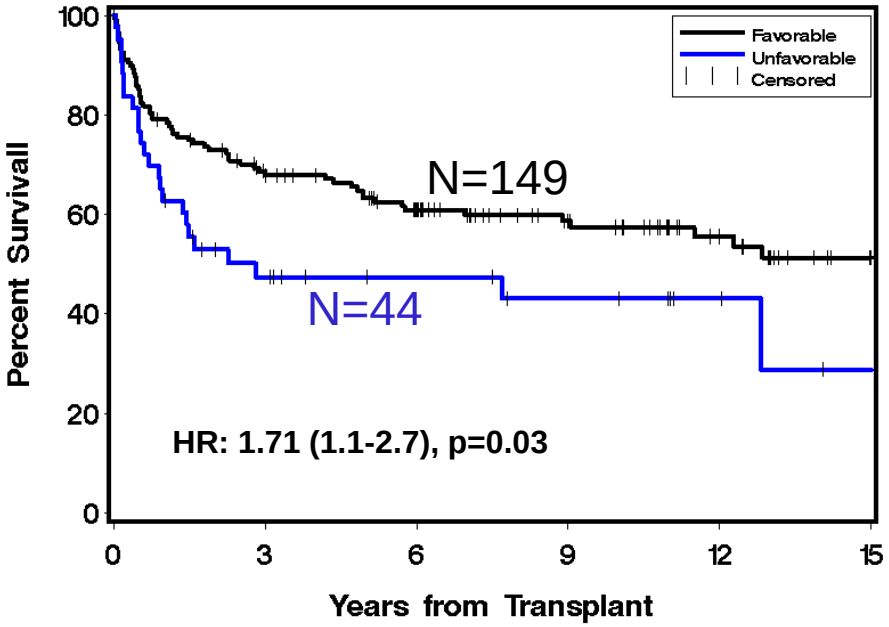
Samuelson B, Salit R et al…Unpublished

Relapse by DIPSS plus (adjusted)

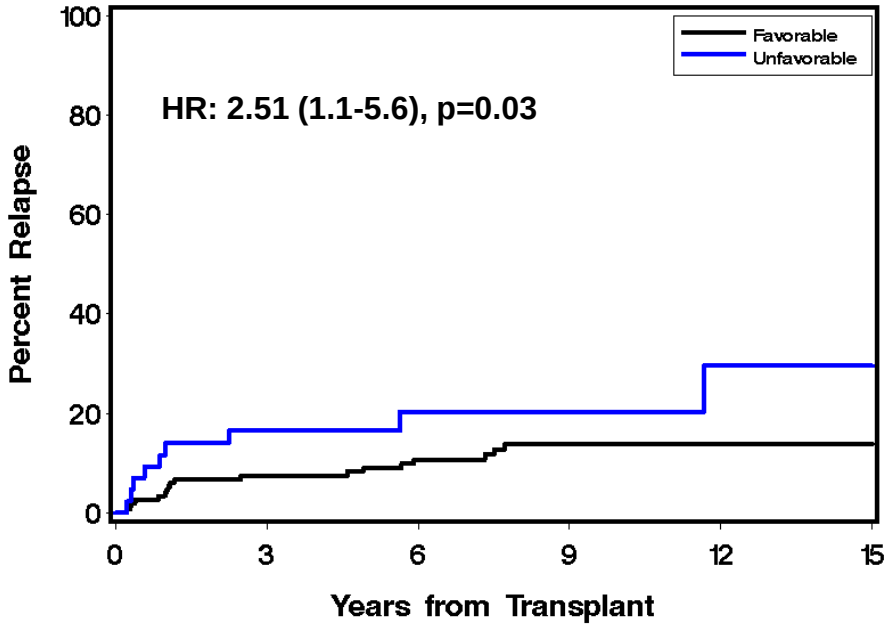


Cytogenetics and Outcome

Survival



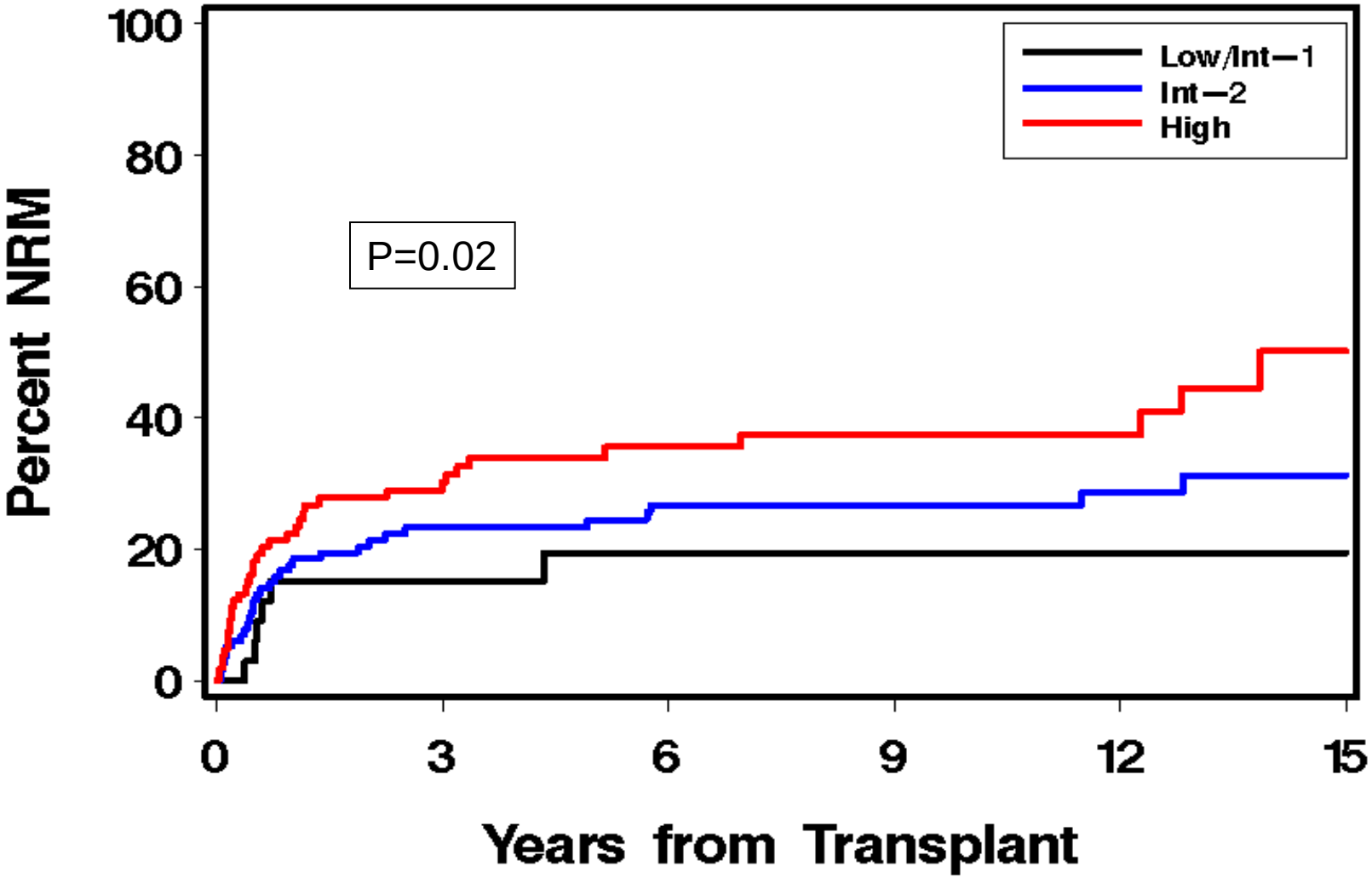
Relapse



Unfavorable: +8, -7/7q-, i17q, inv3, -5/5q-, 12p-, 11q23, or ≥ 3 abnml

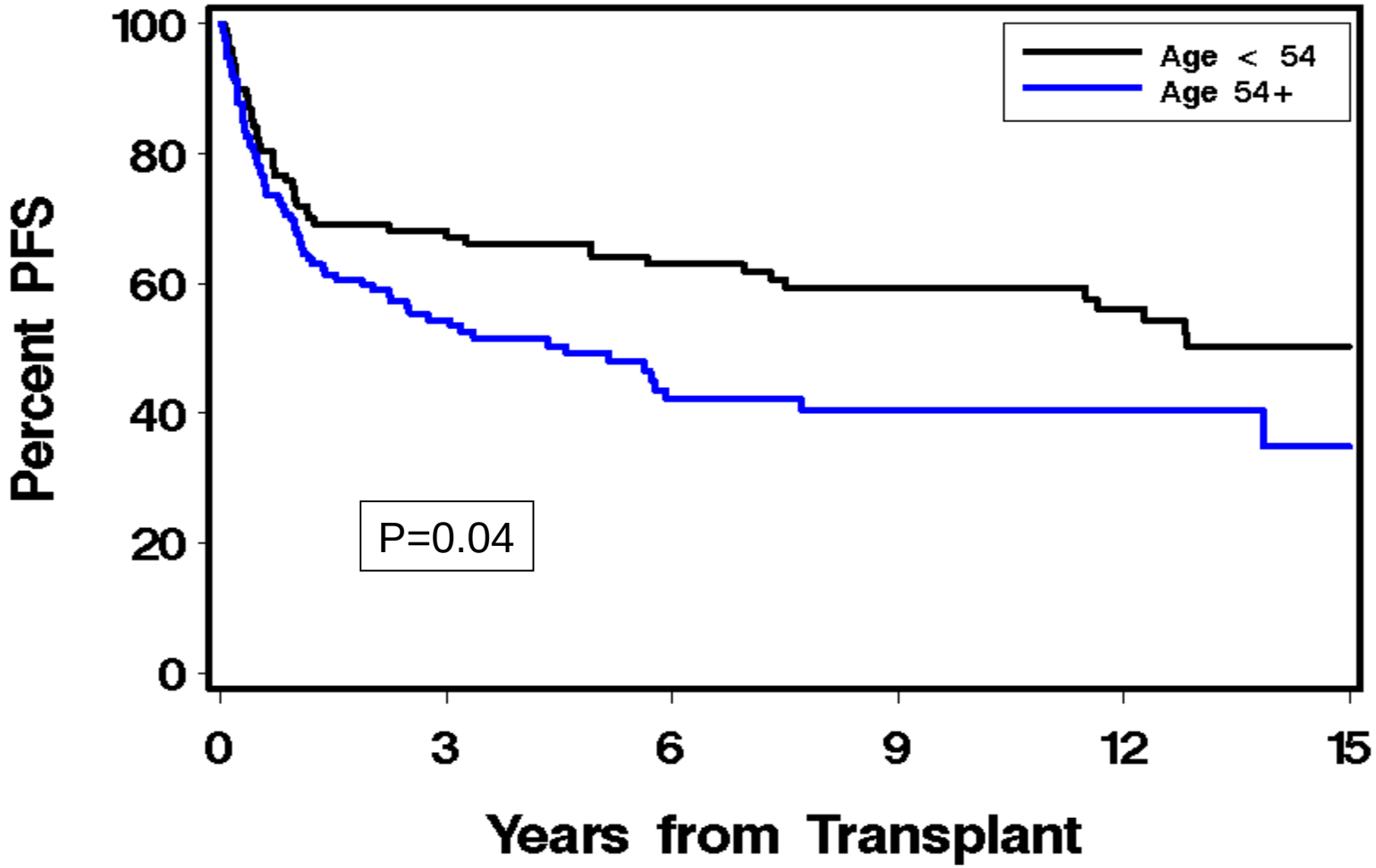
FHCRC, Unpublshed

Non-Relapse Mortality (adjusted)



FHCRC, Unpublshed

Age and Survival



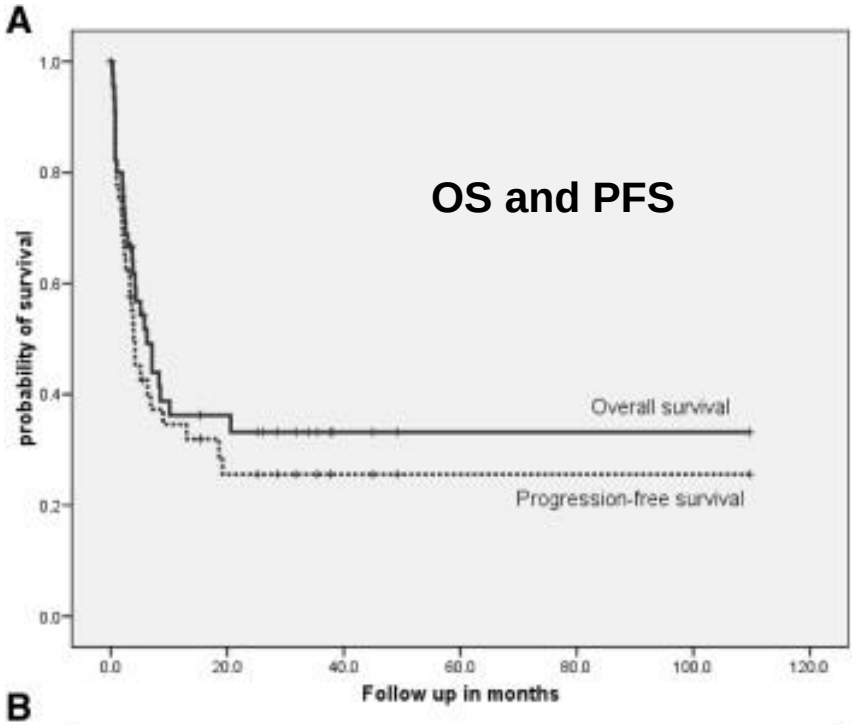
FHCRC, Unpublshed

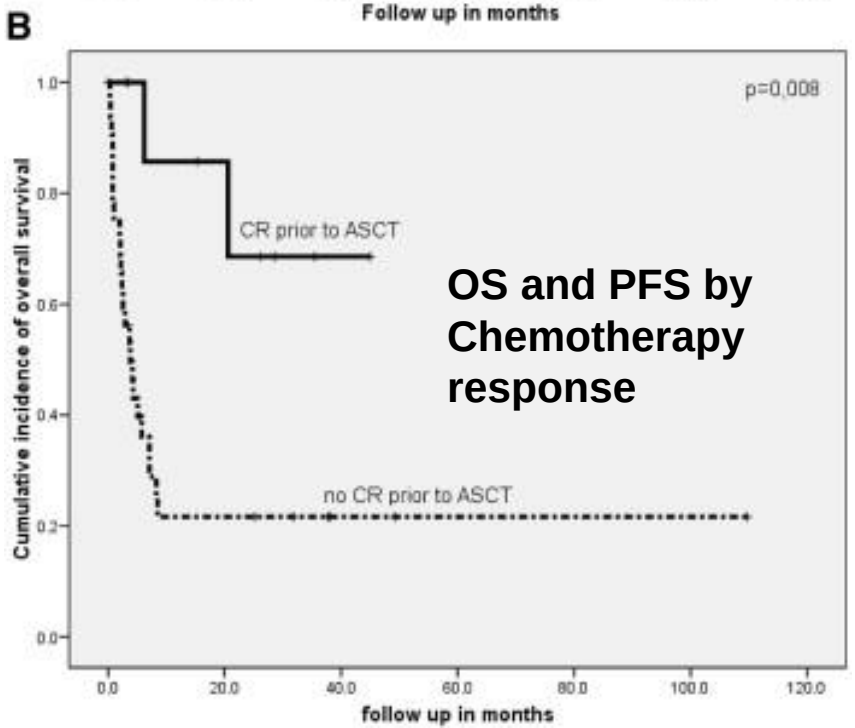
Progression to Leukemia

Risk Factors for Leukemic Transformation

- Severe thrombocytopenia (Plt <41)
- Higher blasts in peripheral blood (>2%)
- High risk cytogenetics (monosomal karyotype, inversion 3, or isochrome 17)
- Refractory transfusion-requiring anemia
- Triple negative (JAK2, CALR, MPL) or high molecular risk

Transplantation for Myelofibrosis with Leukemic Transformation



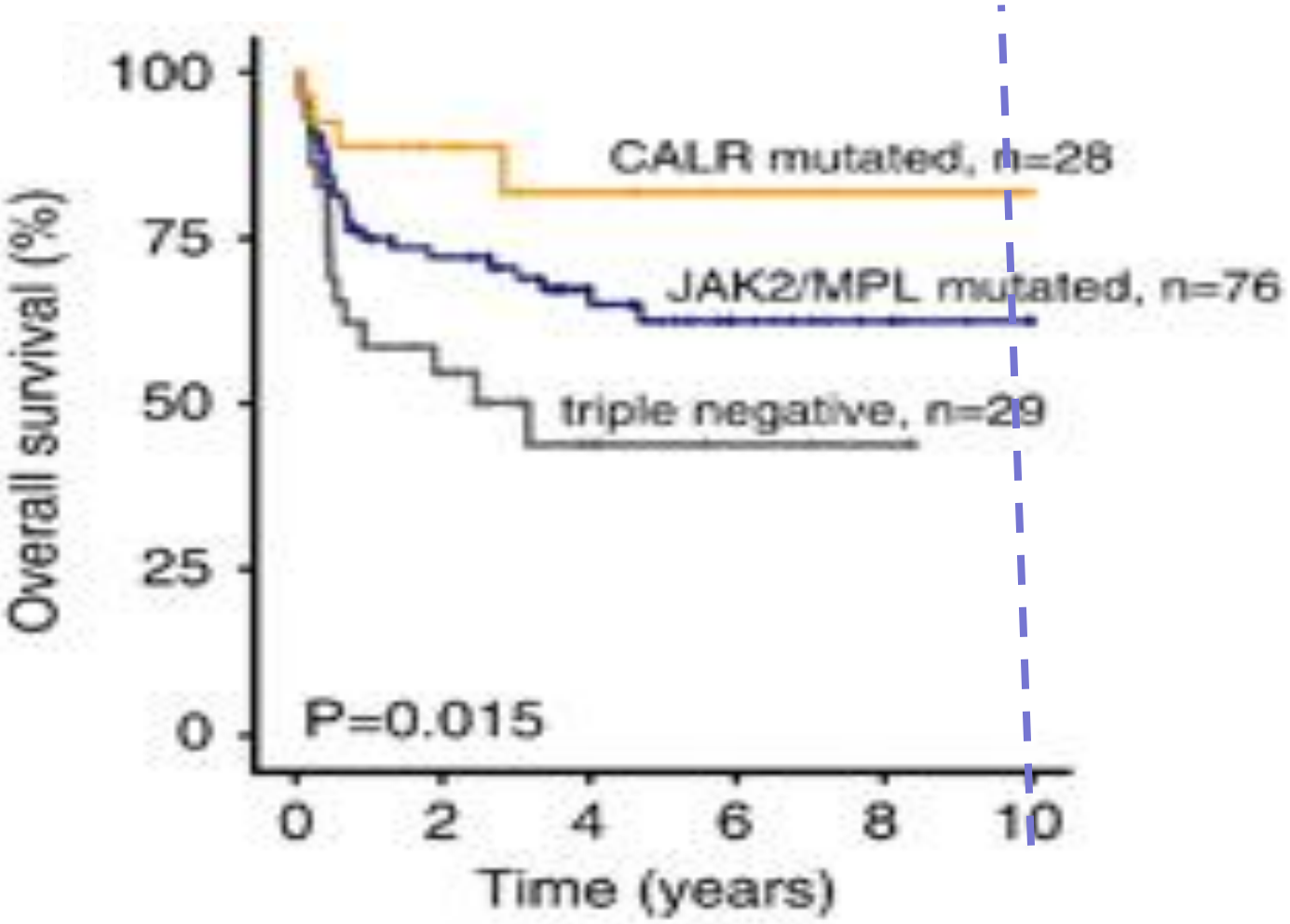


H. Alchalby et al ,, ….. 2014

And Mutations?

Mutations and transplant outcome

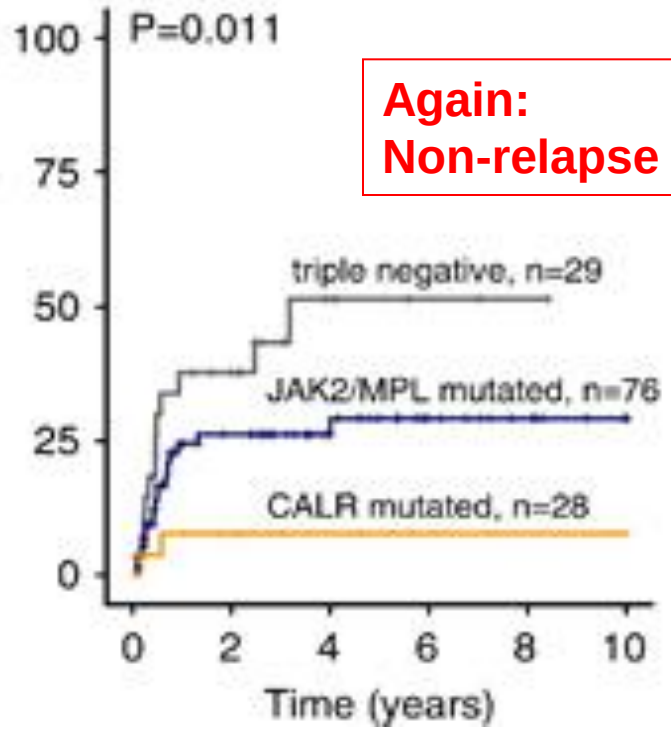
-Survival-



V. Panagiota et al, Leukemia 28:1552, 2014

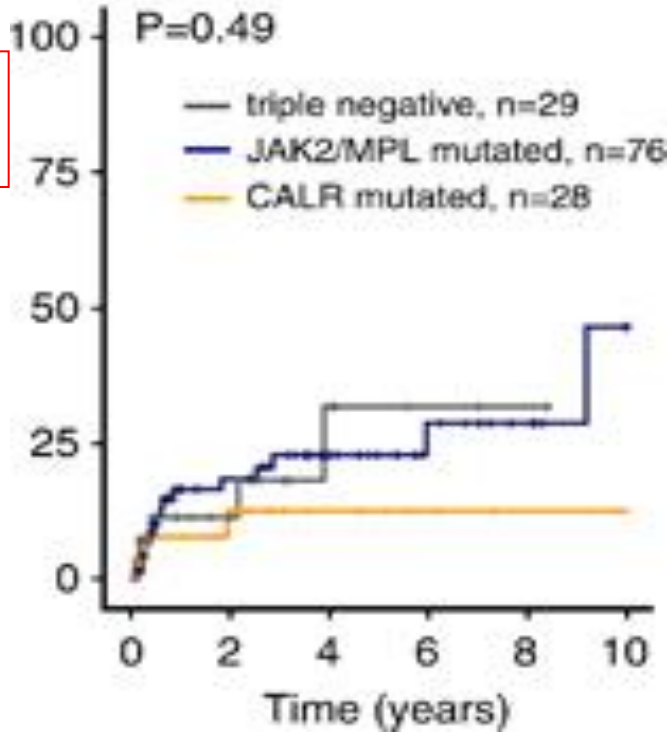
Mutations and transplant outcome

Non-Relapse Mortality



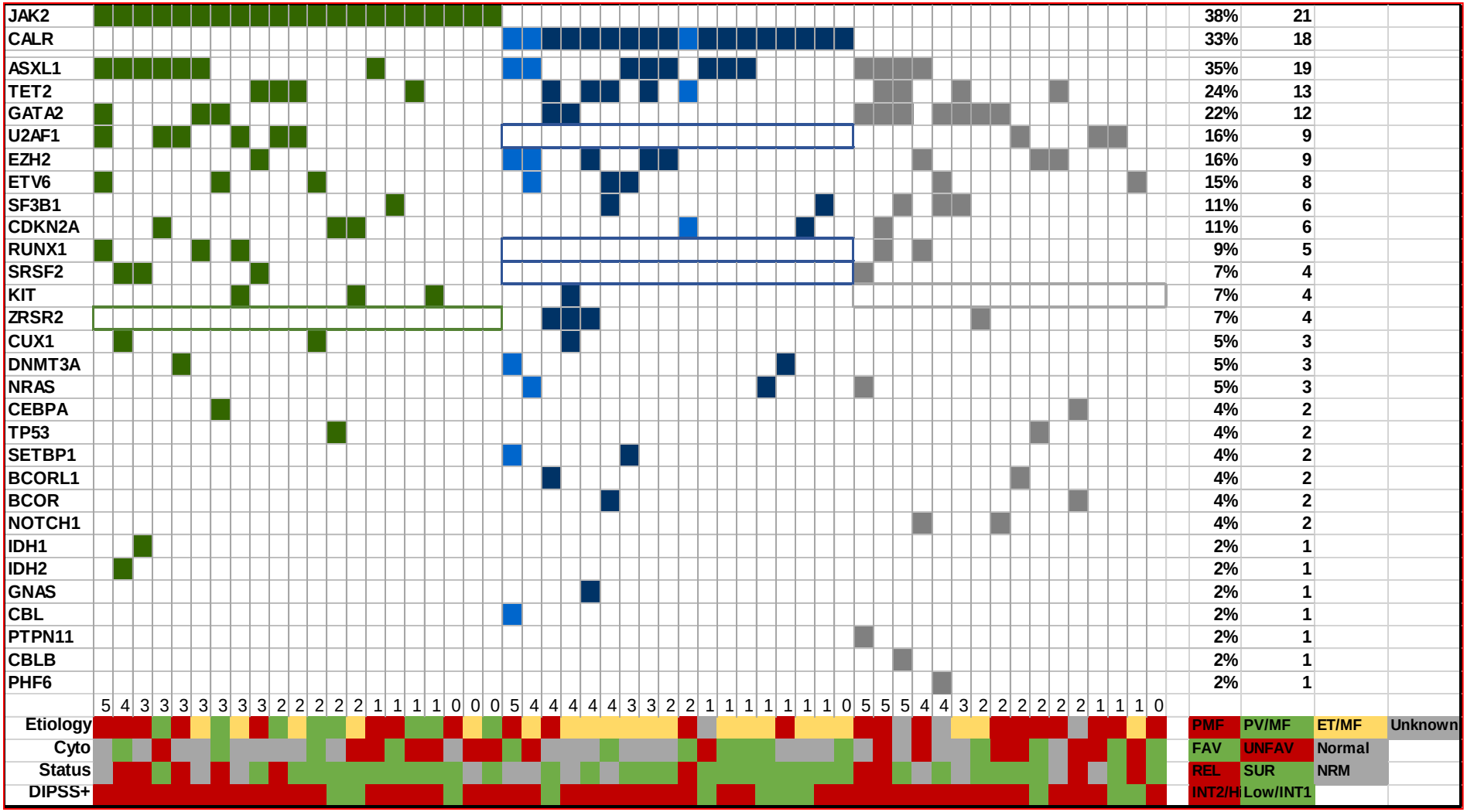
Again:
Non-relapse mortality !

Relapse



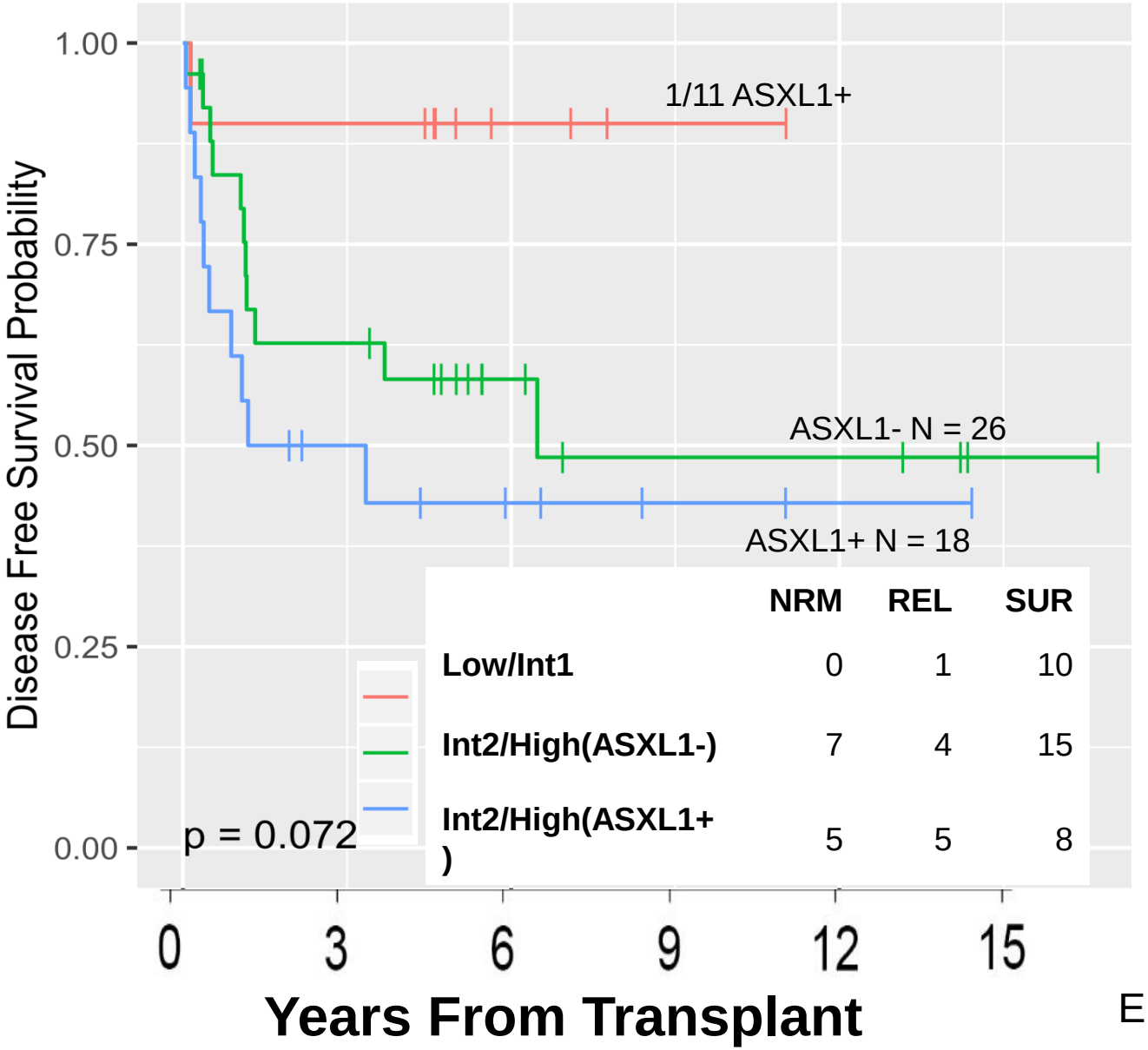
V. Panagiota et al, Leukemia 28:1552, 2014

Mutation Patterns and Outcome



98% ≥1 mutation (ave 2.3/pt)
PV/MF JAK2+
CALR+ rare Unfav Cyto

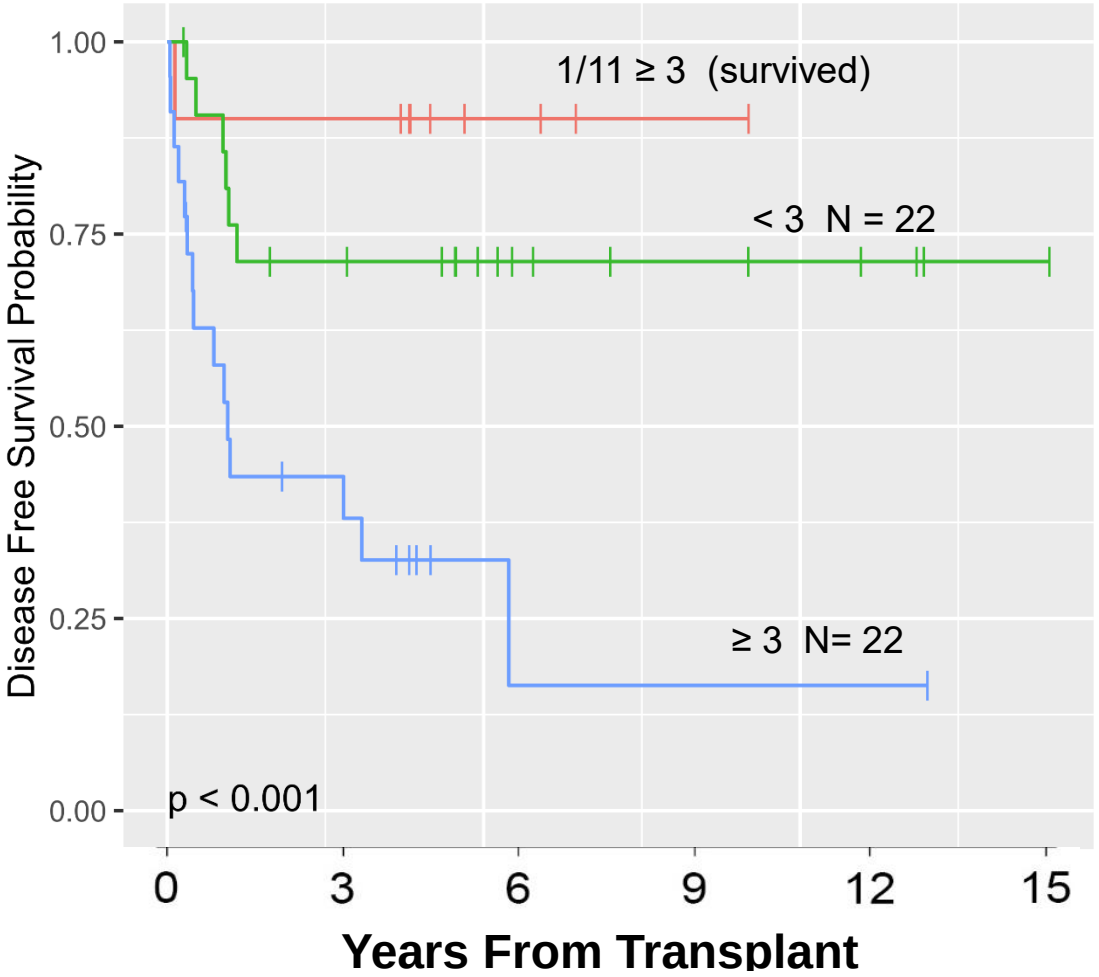
Disease-Free Survival by ASXL1



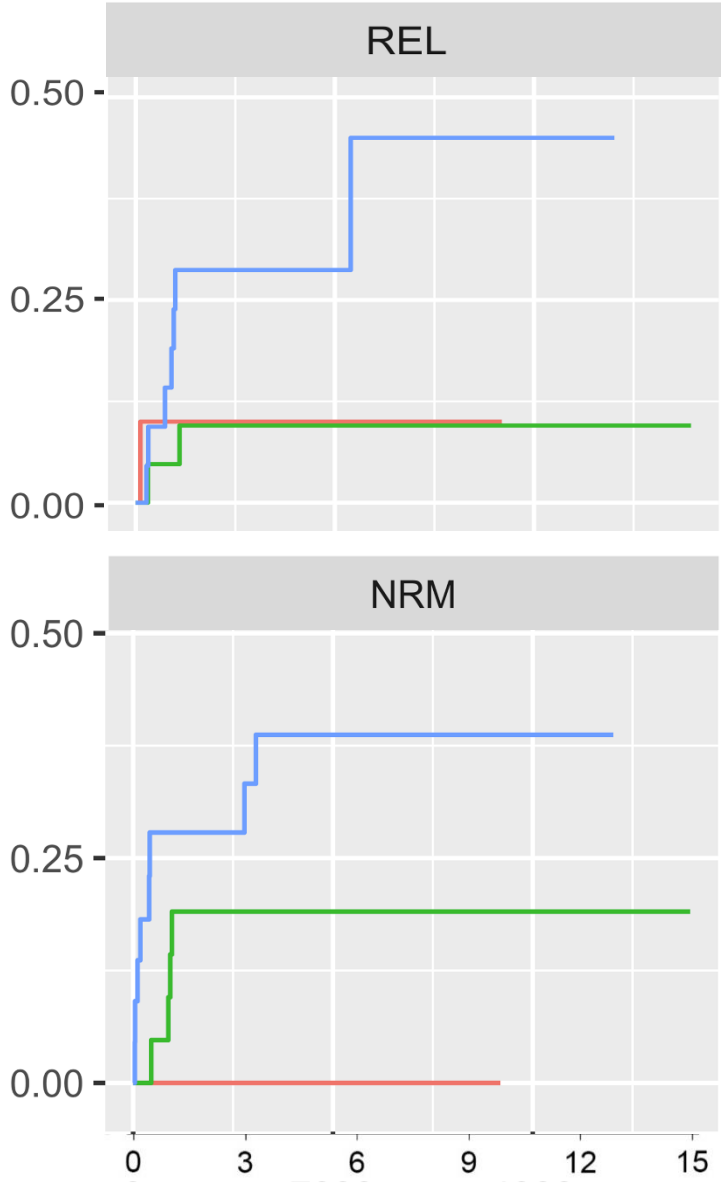
	NRM	REL	SUR
Low/Int1	0	1	10
Int2/High(ASXL1-)	7	4	15
Int2/High(ASXL1+)	5	5	8

E.Stevens, unpublished

Relapse-Free Survival by Mutation



	NRM	REL	SUR
Low/Int1	0	1	10
Int2/High(<3)	4	2	16
Int2/High(>3)	8	7	7



Association of Mutations with Other Variables

	Total (n = 55)	ASXL1^{-} (n = 36)	ASXL1^{+} (n = 19)	*p*	Adjusted *p*
DIPSS+ Var				**<0.001**	**0.0068**
Low/Int1	20% (11)	28% (10)	5% (1)		
Int2/High(<3)	40% (22)	47% (17)	26% (5)		
Int2/High(≥3)	40% (22)	25%(9)	69% (13)		
Peripheral Blasts				**<0.001**	**0.0062**
No	55% (30)	72% (26)	21% (4)		
Yes	44% (24)	28% (10)	74% (14)		

E.Stevens, unpublished

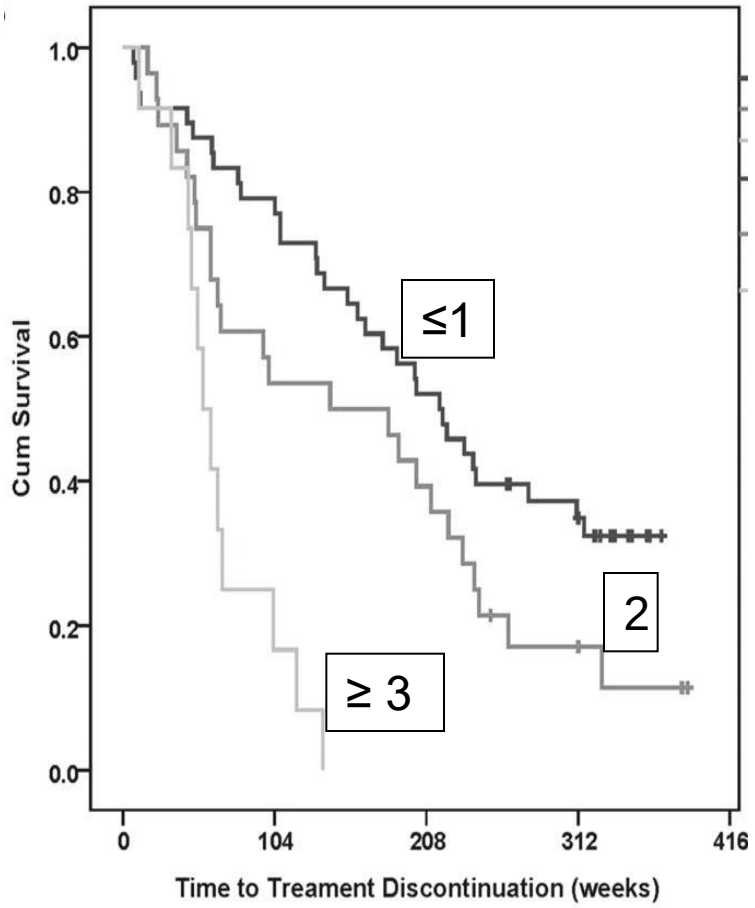
“Additional” Mutations and Transplant Outcome
(48 patients)

	≤2 mutations	≥3 mutations
Survived >1 year after Transplantation	79%	41%
Death from Non-Relapse Causes	13%	35%
Relapse	8%	24%

E. Stevens et al, unpublished

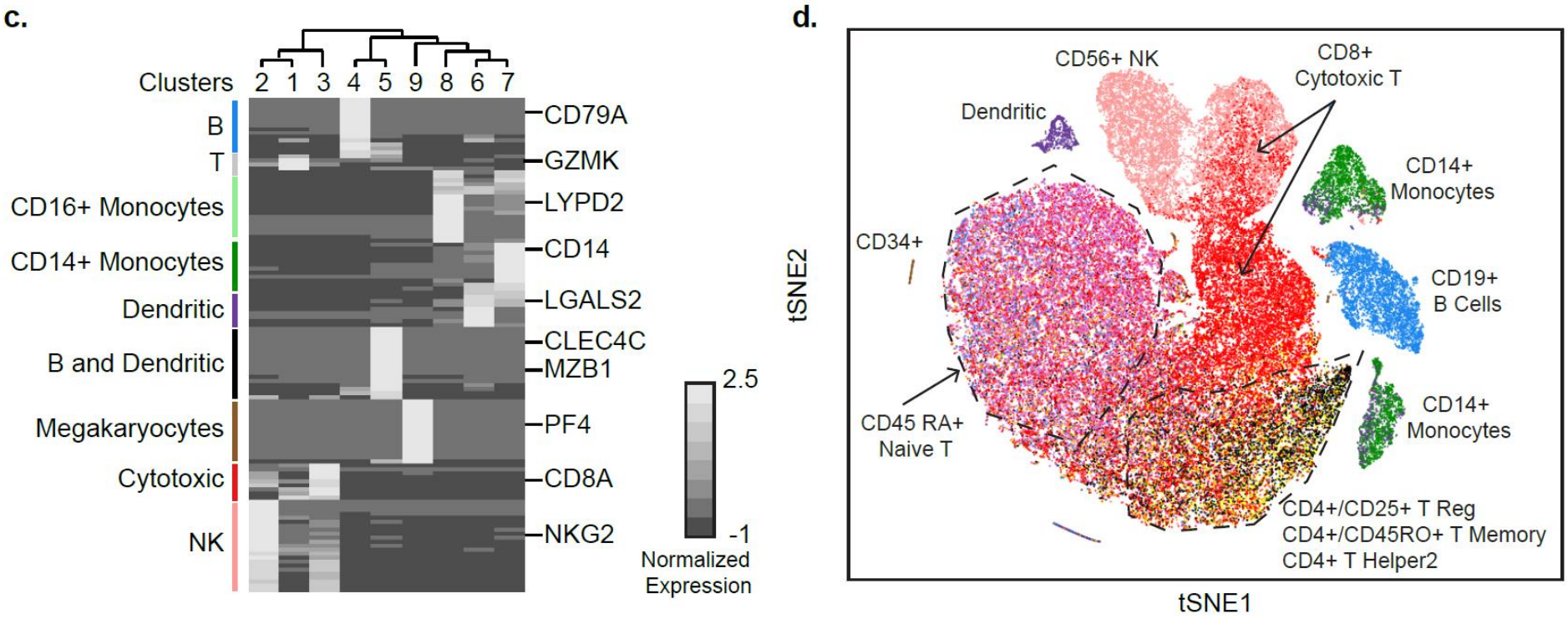
Mutations and response to Ruxolitinib

- Spleen response (≥50% reduction) inversely correlated with the number of mutations.
  - ≤2 mutations : 9-fold higher odds of spleen response than those with ≥3 mutations
- With ≥3 mutations: shorter time to treatment discontinuation and shorter survival



Patel et al., Blood 2015;126:790-797

10x Genomics 3’ Single Cell RNAseq



Gu et al. 2017. Nature Communications

Summary and Conclusions

- **HCT has highly *curative* potential for MF**
- **Improved *safety* - day 100 mortality <5%**
- **Results with HLA-matched *unrelated* donors equal to those with sibling donors**
- **Appropriate for many patients with *advanced* MF and *some* patients *with early* stage disease**
- **DIPSS plus > DIPSS discriminates risk for post-HCT outcome**

Summary and Conclusions

- ***Comorbid conditions* have to be considered**
- **Ruxolitinib may alter HCT course**
  - **Is effective to *treat* GVHD**
- **Mutational load impacts transplant outcome**
  - **Relapse**
  - **Non-relapse mortality**
- **Availability of new drugs must be planned into the overall treatment strategy**

Thank you

- Barry Storer
- Bart Scott
- Jerry Radich
- Emily Stevens
- Rachel Salit
- Bethany Samuelson
- Janghee Woo

- ….and all of our patients

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