

Transplantation for MPN

(PMF, PV, ET)

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You are doing well

- No symptoms
- Blood counts are good, no need for transfusions
- Your spleen is not bothering you



No treatment needed

You are doing well

- But you have some night sweats
- Your spleen is large and you can't sleep on your left side
- But your blood counts are ok



Treatment with Jakafi®
(or possibly other drugs)

You are doing “ok”

- But you need transfusions
- Your symptoms have not improved with Jakafi
- Your spleen has not shrunk



Other drugs? Transplantation?

You are doing *not so well*

- Symptoms have not improved/have returned on Jakafi (or other Jak inhibitors)
- Your blood counts are low
- “Blasts” are increasing in (blood or marrow)



Transplantation is probably
the most promising option

PMF - Risk Classification

- Anemia (2)
- WBC > 25,000 (1)
- Myeloblasts in blood (1)
- Age > 65 years (1)
- Symptoms (1)

DIPSS

DIPSS plus

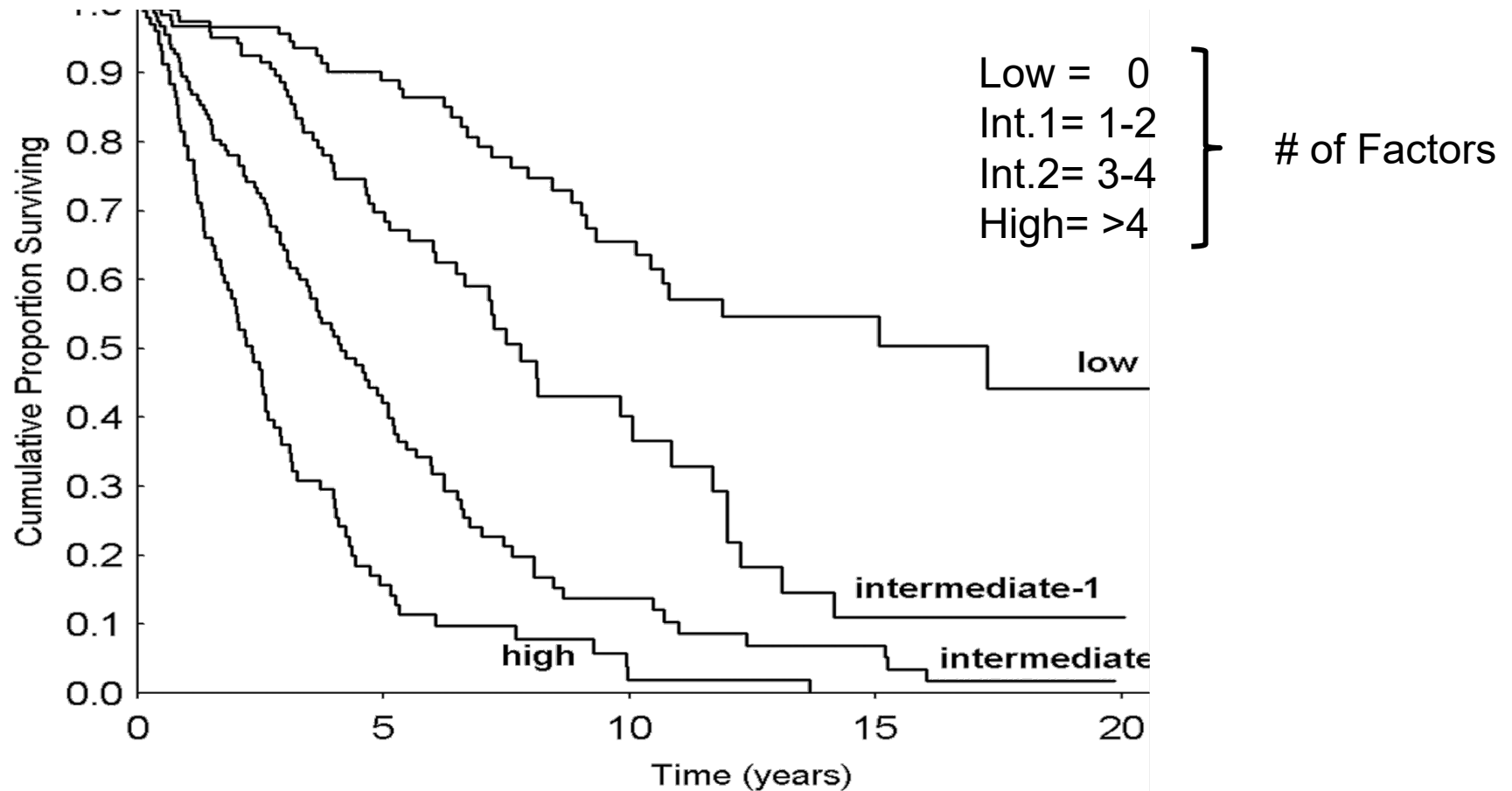
MIPSS70(plus)

- Adverse karyotype
- Low platelet count
- Needing RBC transfusions

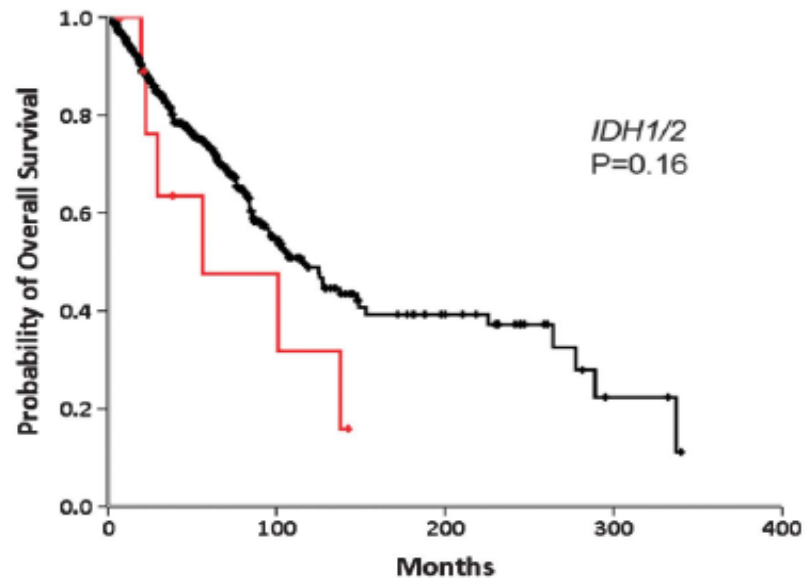
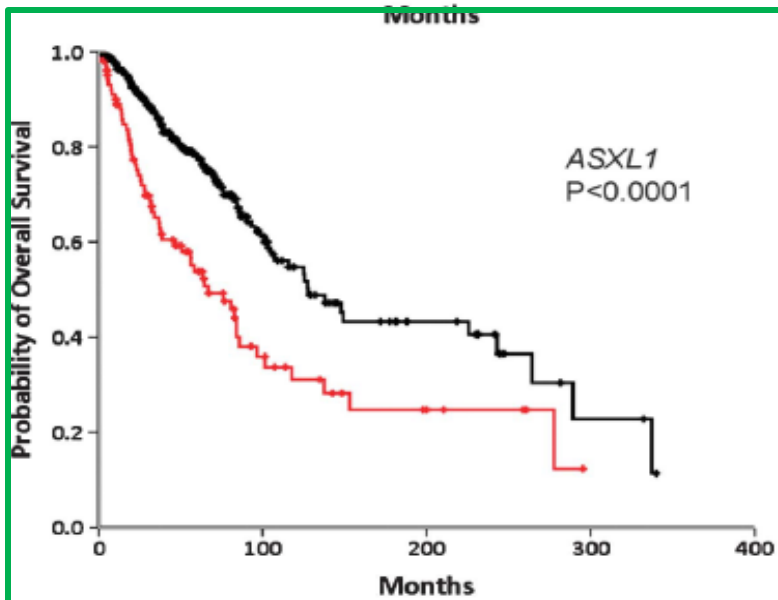
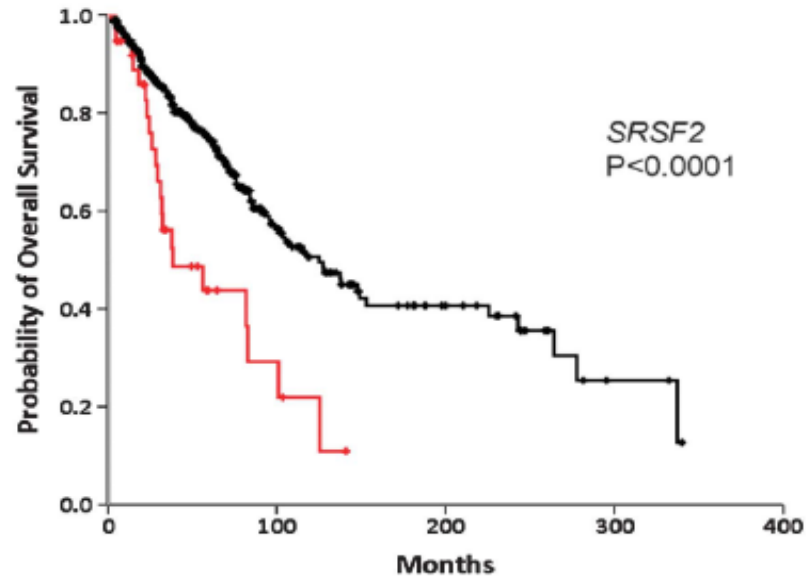
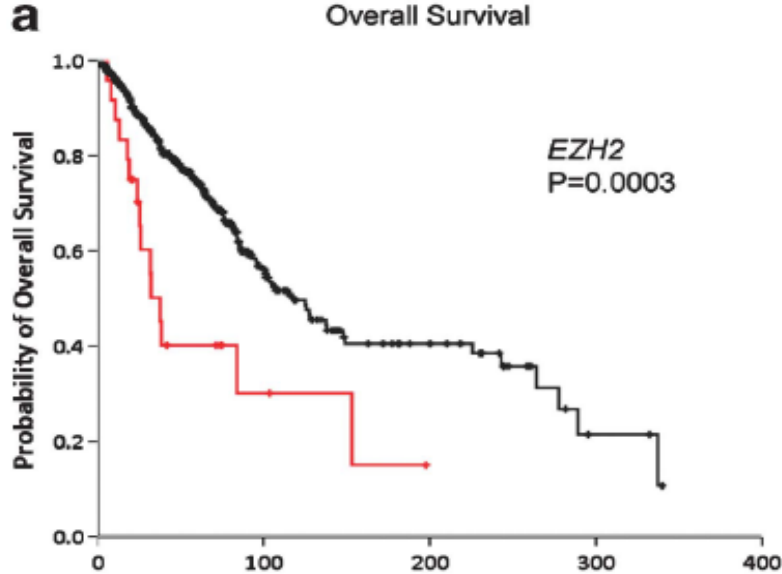
- Absence of CALR
- High risk mutations
- Marrow fibrosis

DIPSS and Survival

(no transplant – *without* JAK2 inhibitors)



Overall Survival by Mutation



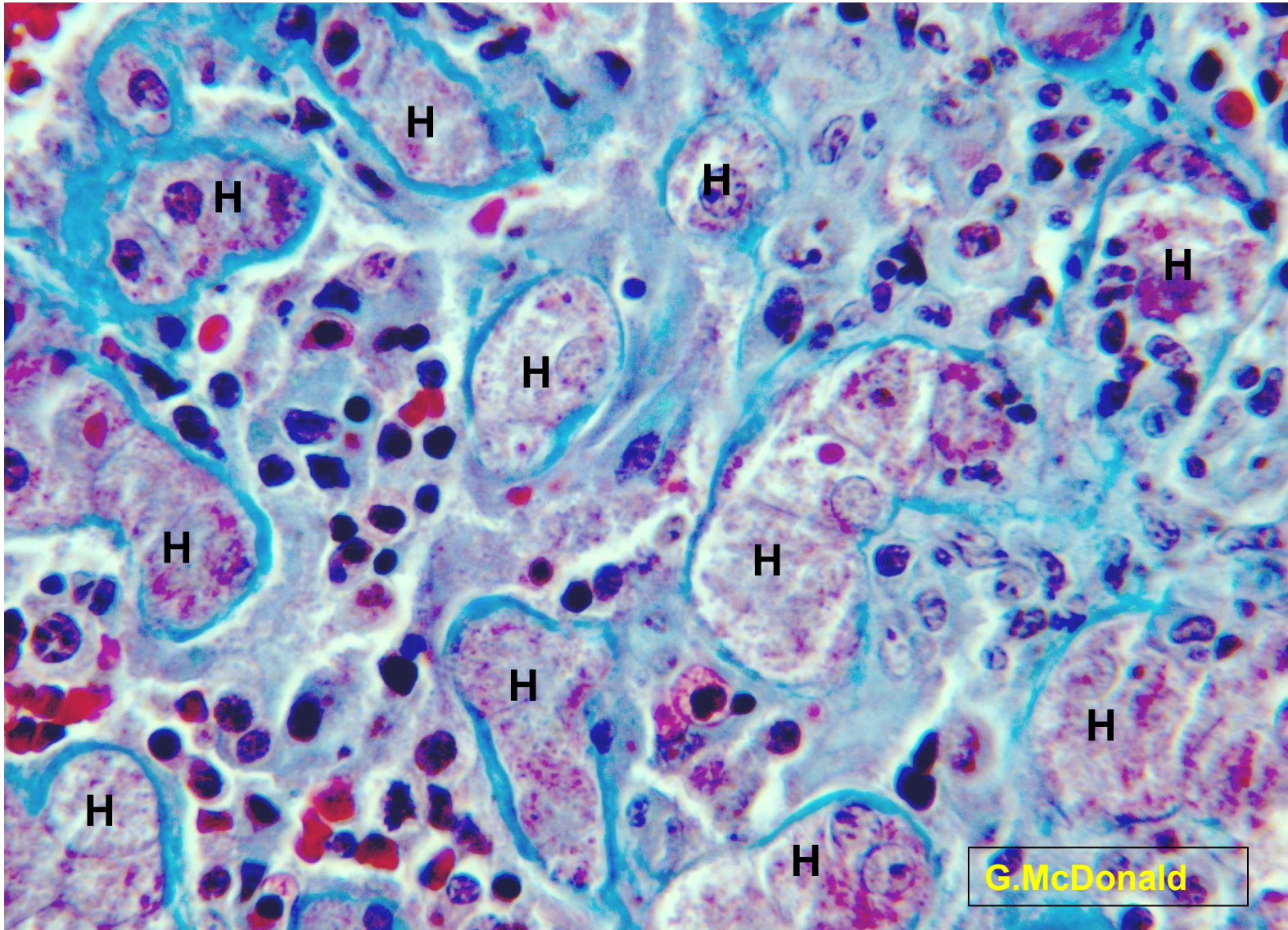
If Transplantation is medically indicated...

- *Who is a candidate?*
- *When should it be done?*
- *And how?*

Important for Transplantation:

- *Extramedullary disease, portal or pulmonary hypertension* increase the risk associated with transplantation

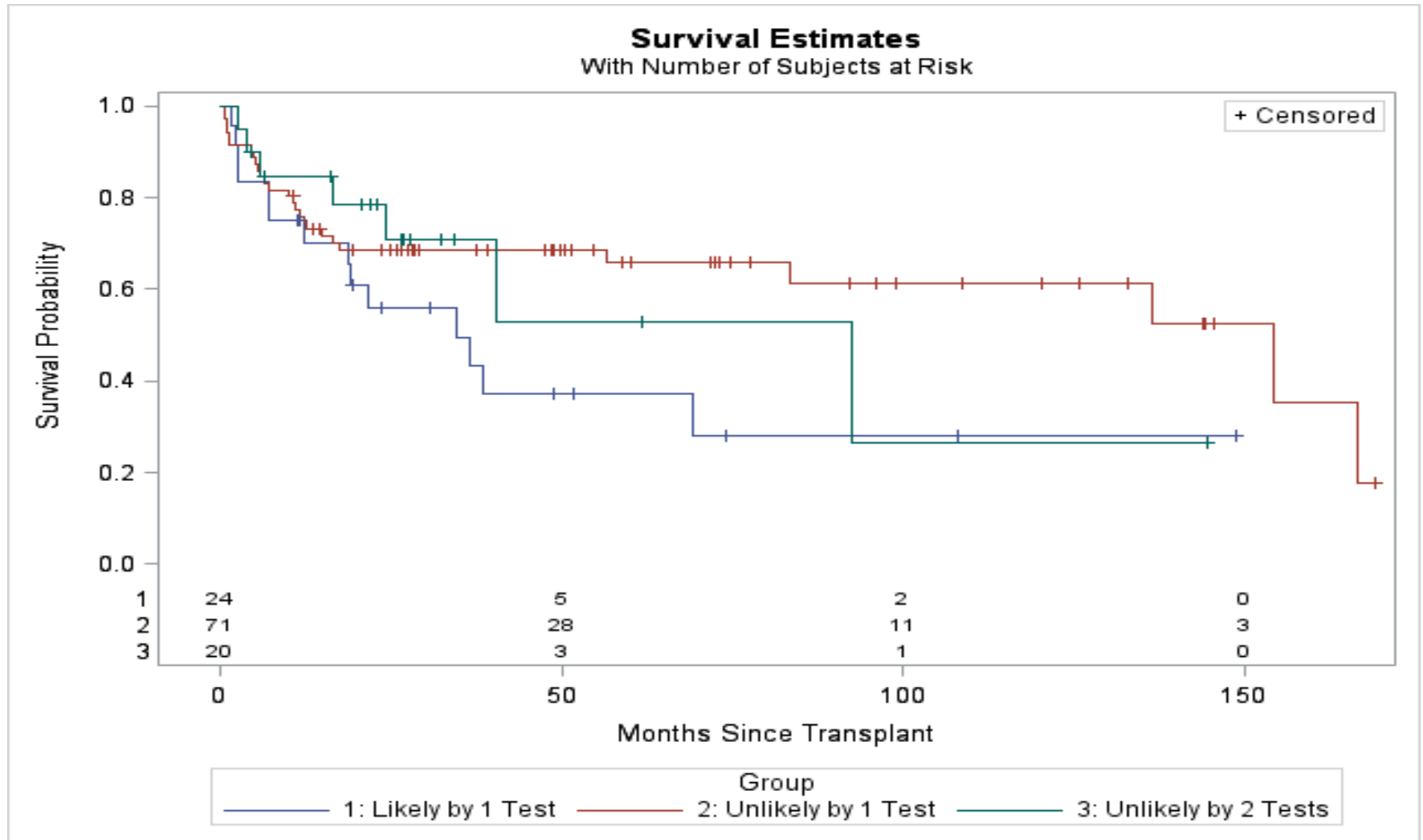
Liver: Sinusoidal fibrosis associated with extramedullary hematopoiesis



G.McDonald

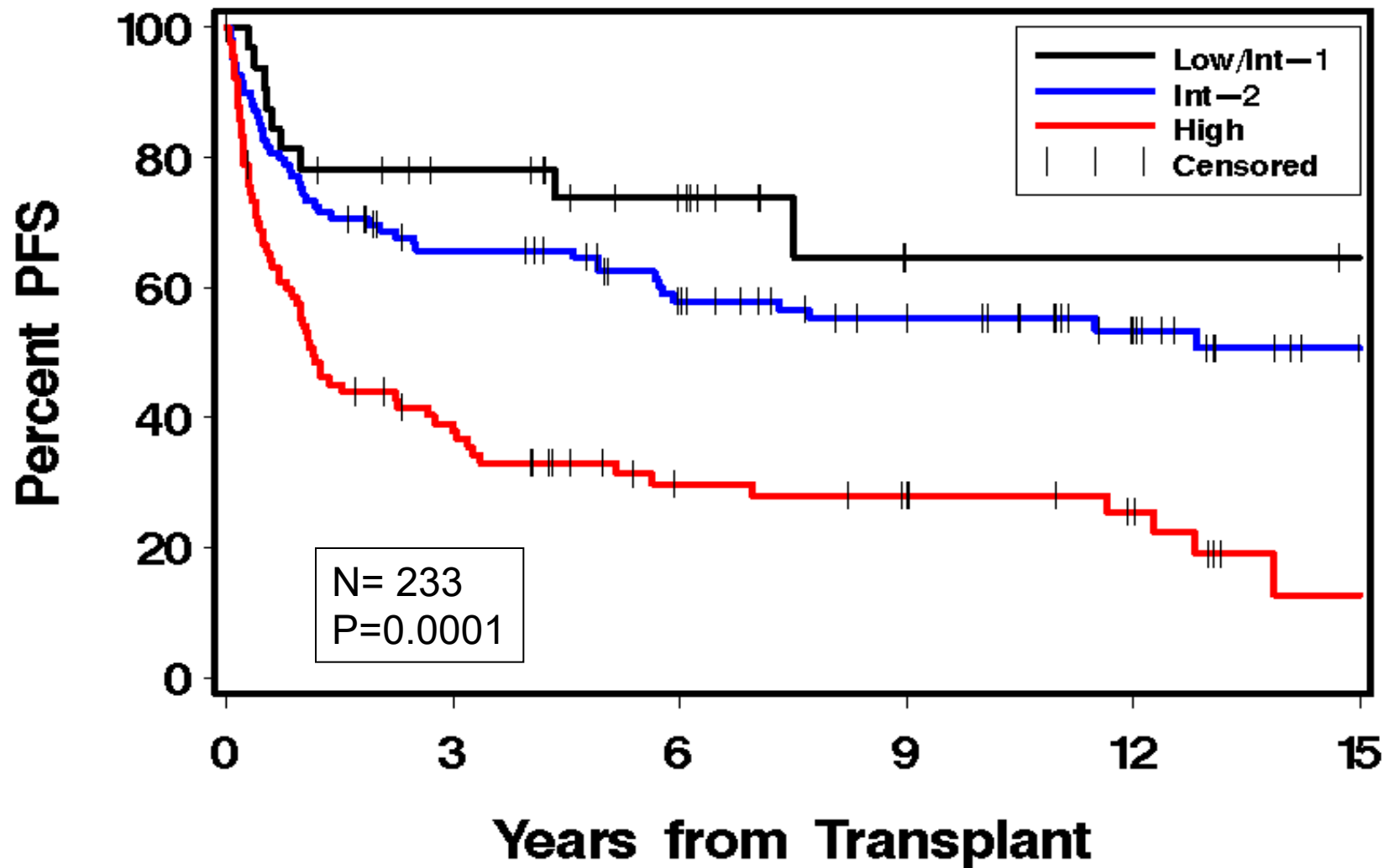
H = hepatocytes. Extensive EMH and collagen deposition (blue) in sinusoids.

Pulmonary Hypertension

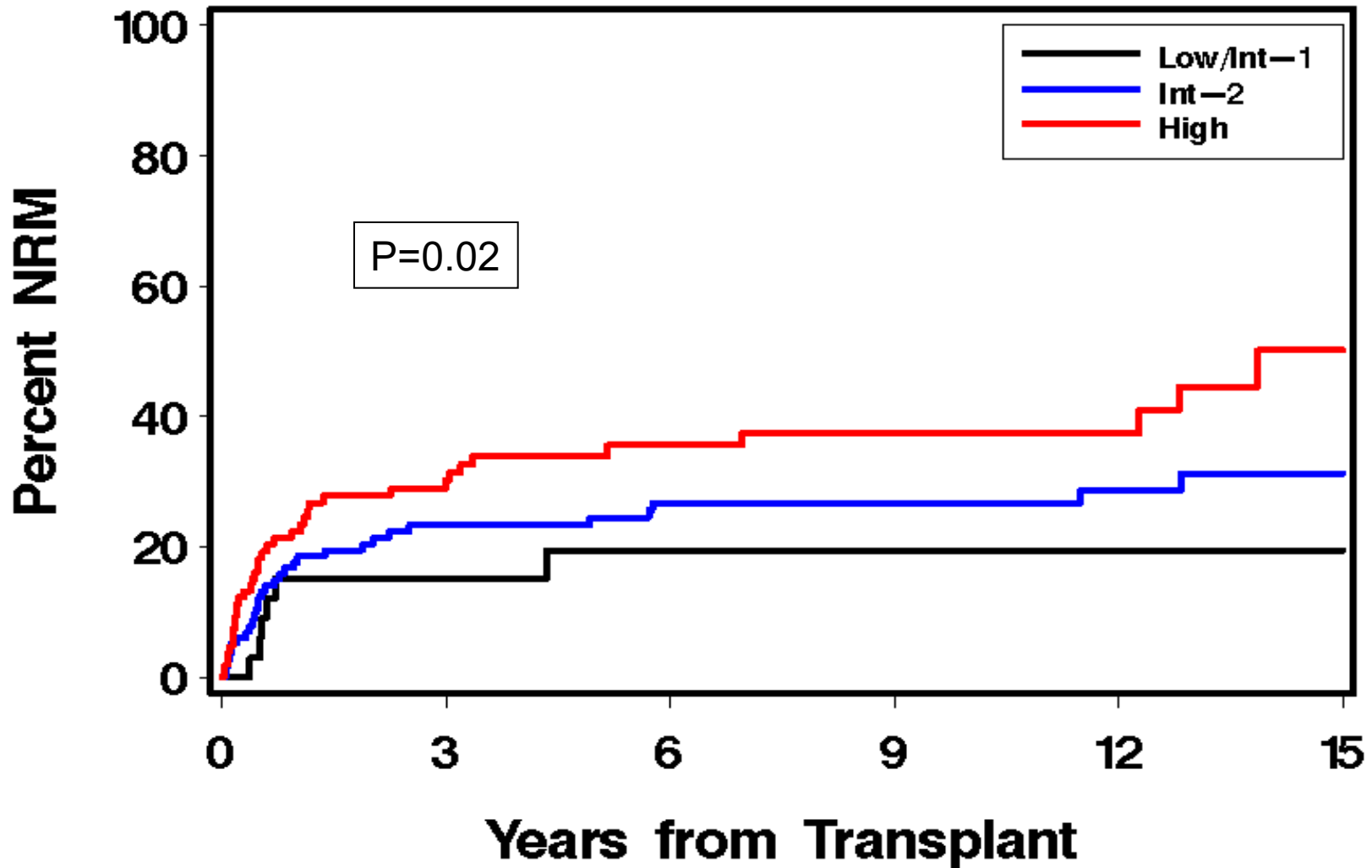


Transplantation ***before* Leukemic Transformation**

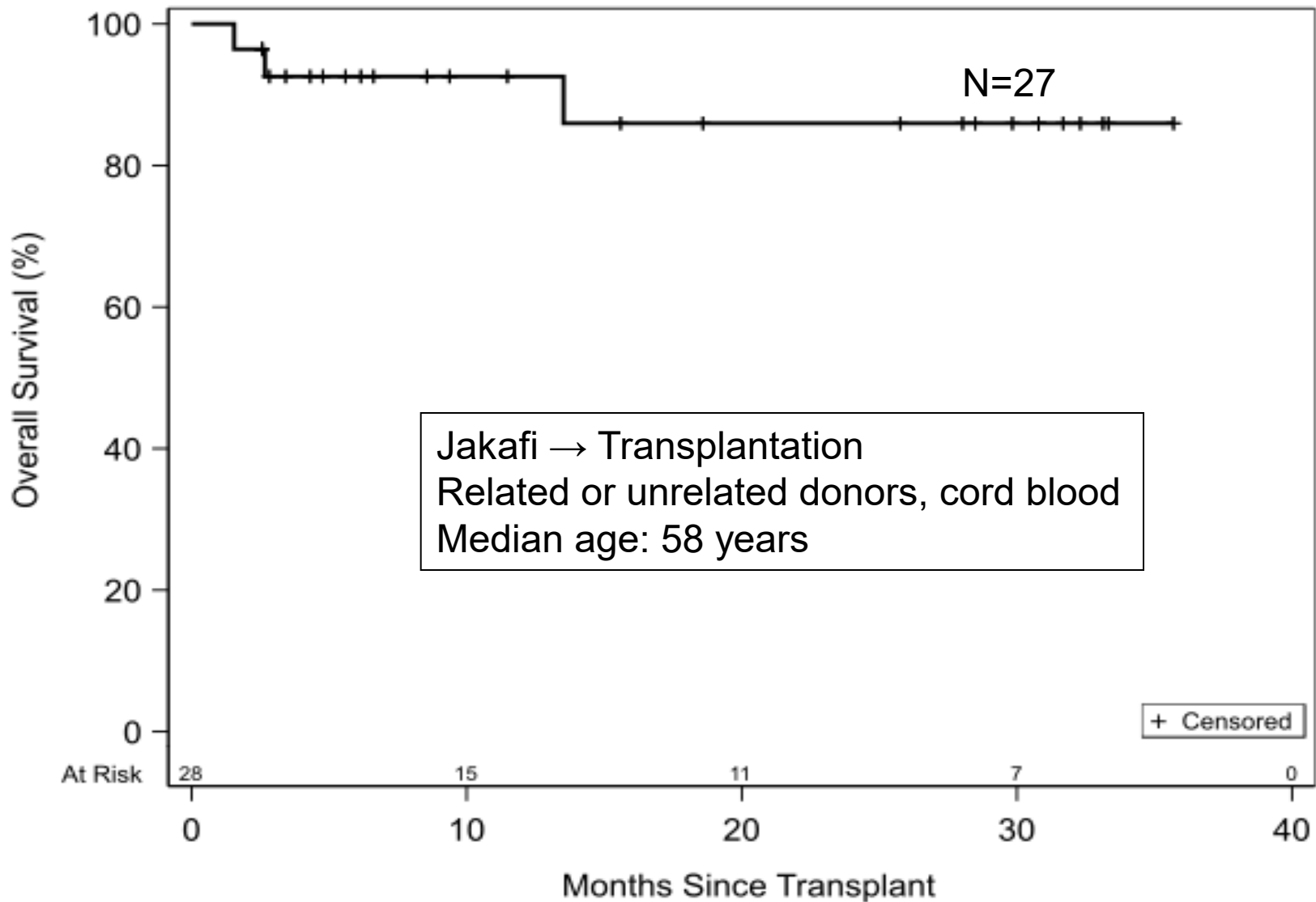
Relapse-free Survival (DIPSS *plus*)



Non-Relapse Mortality (adjusted)



Ruxolitinib before Transplant

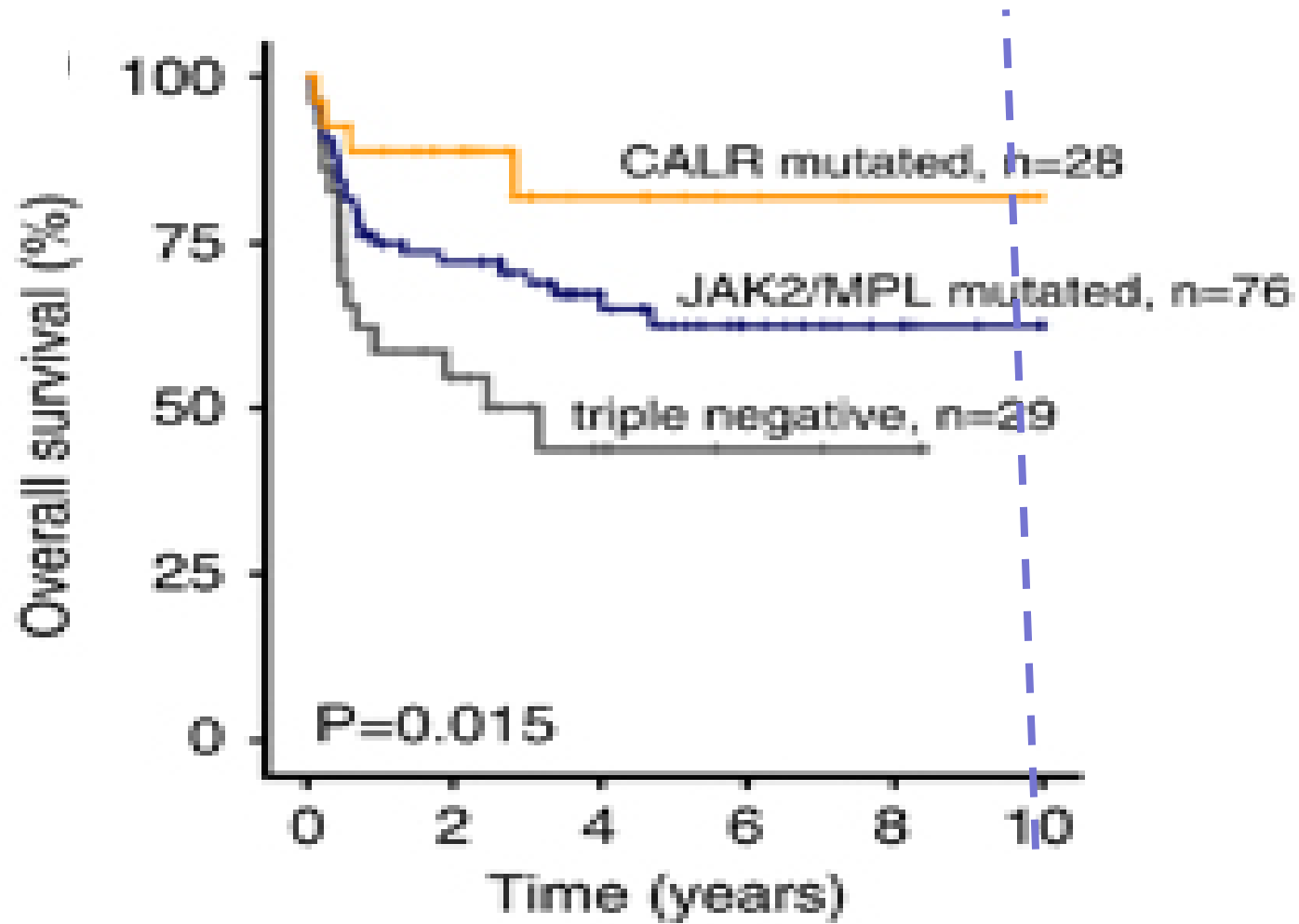


Mutations

- **Driver mutations**
 - JAK2, MPL1, **CALR** (type1 and type 2)
- **Other mutations**
 - *ASXL1, SRSF2, EZH1, IDH1/2, p53*
 - *other*

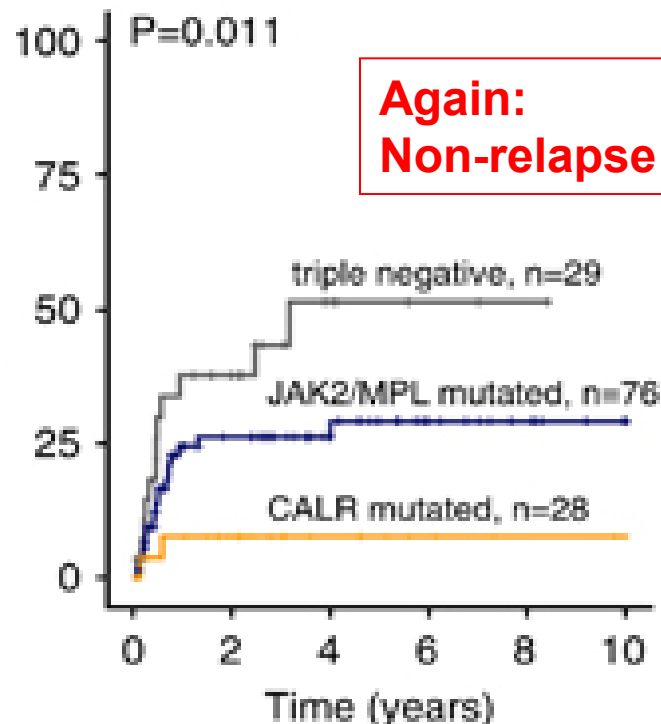
Mutations and transplant outcome

-Survival-

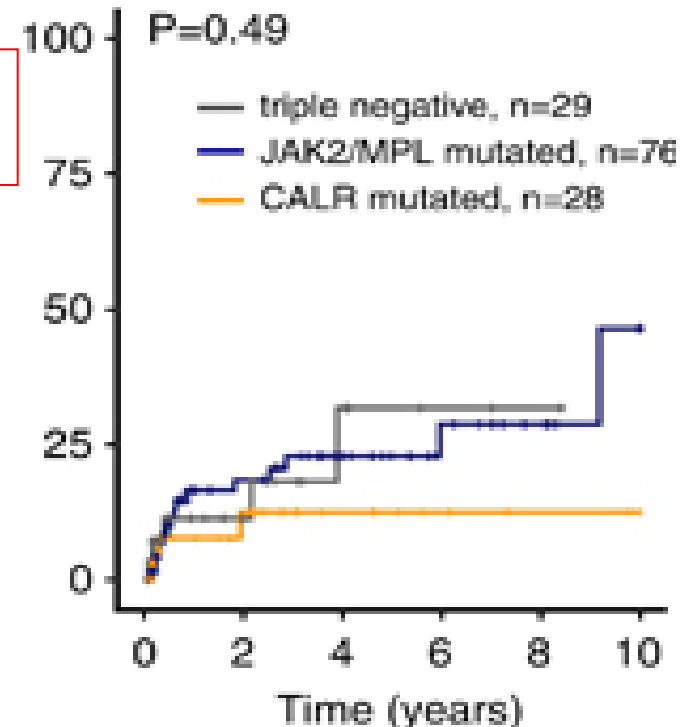


Mutations and transplant outcome

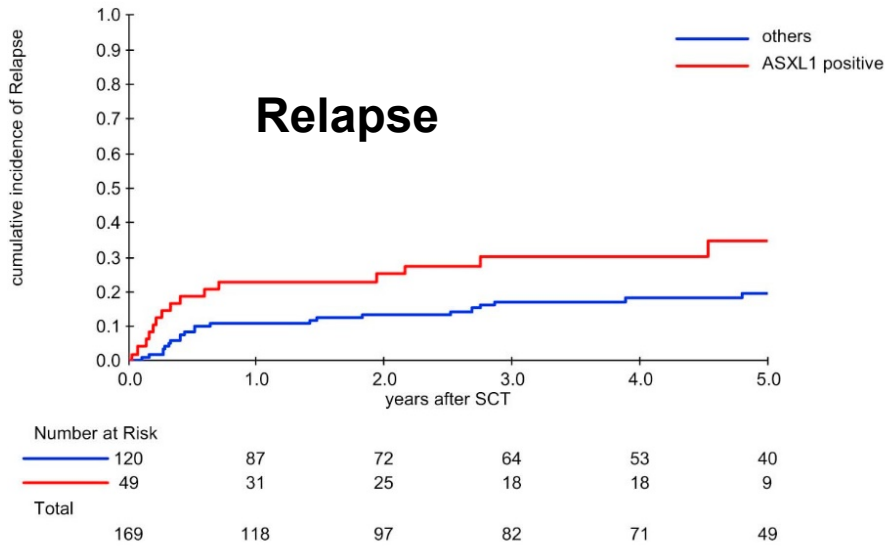
Non-Relapse Mortality



Relapse

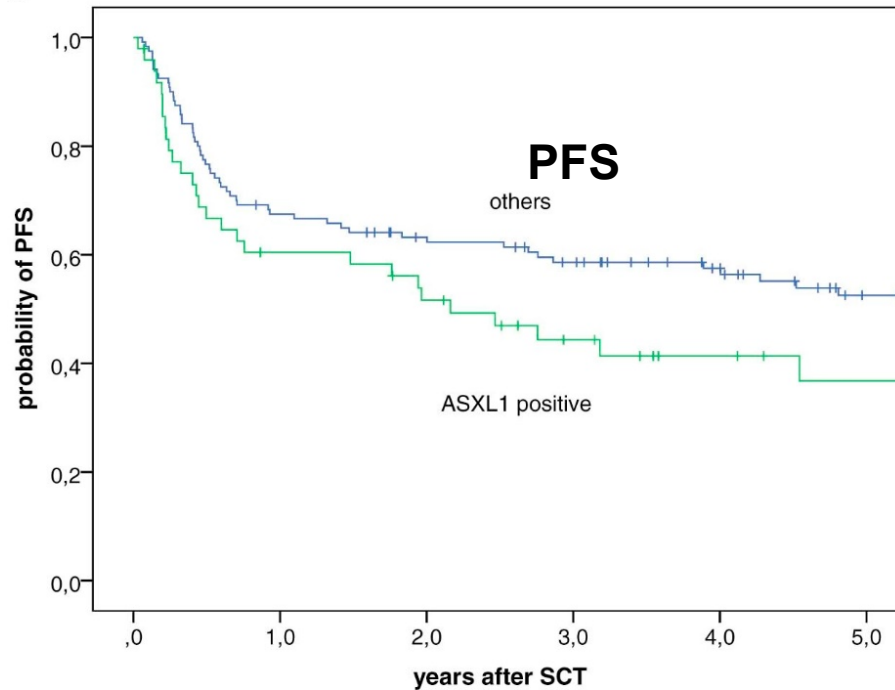


A



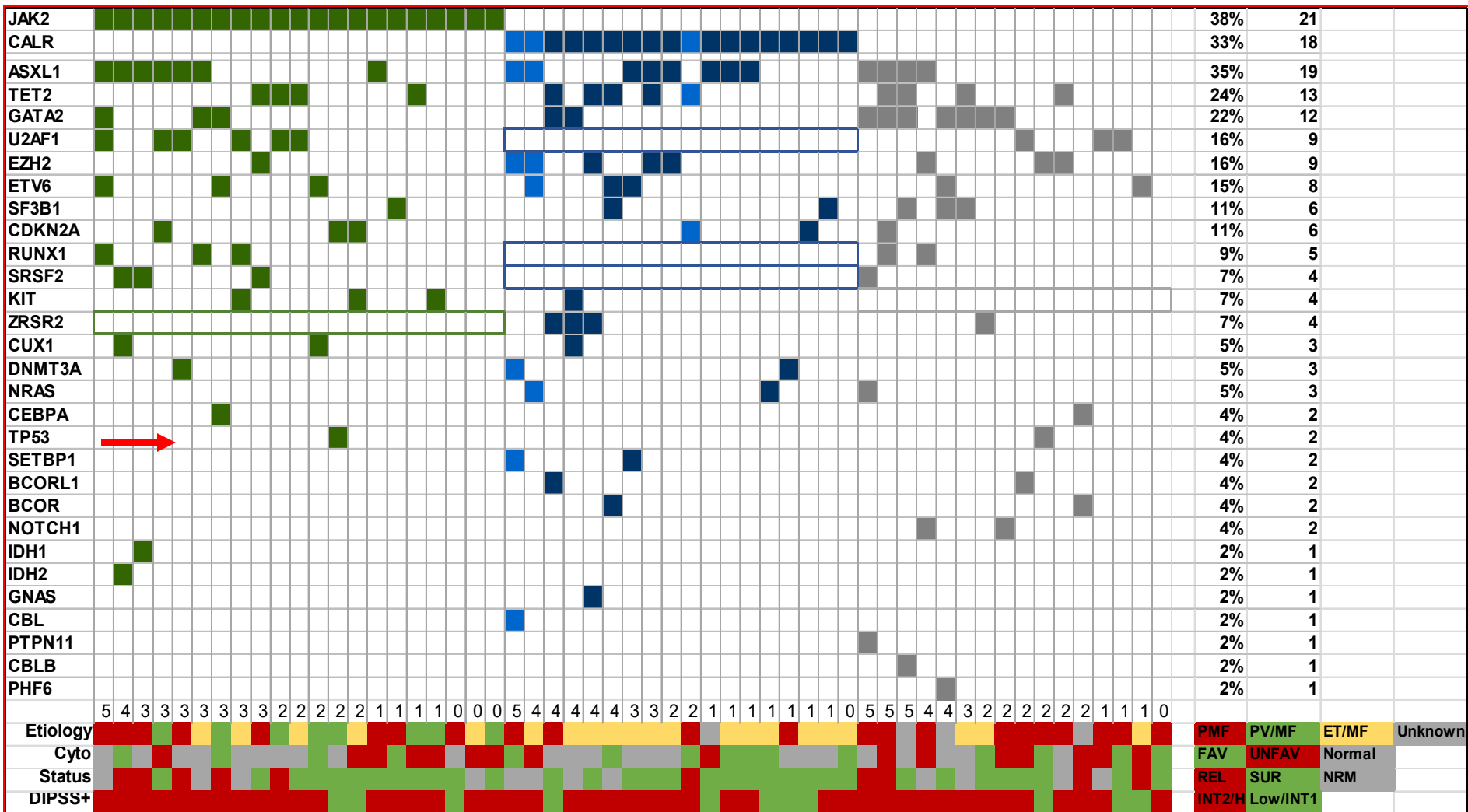
ASXL1 mutations: Relapse and PFS

B



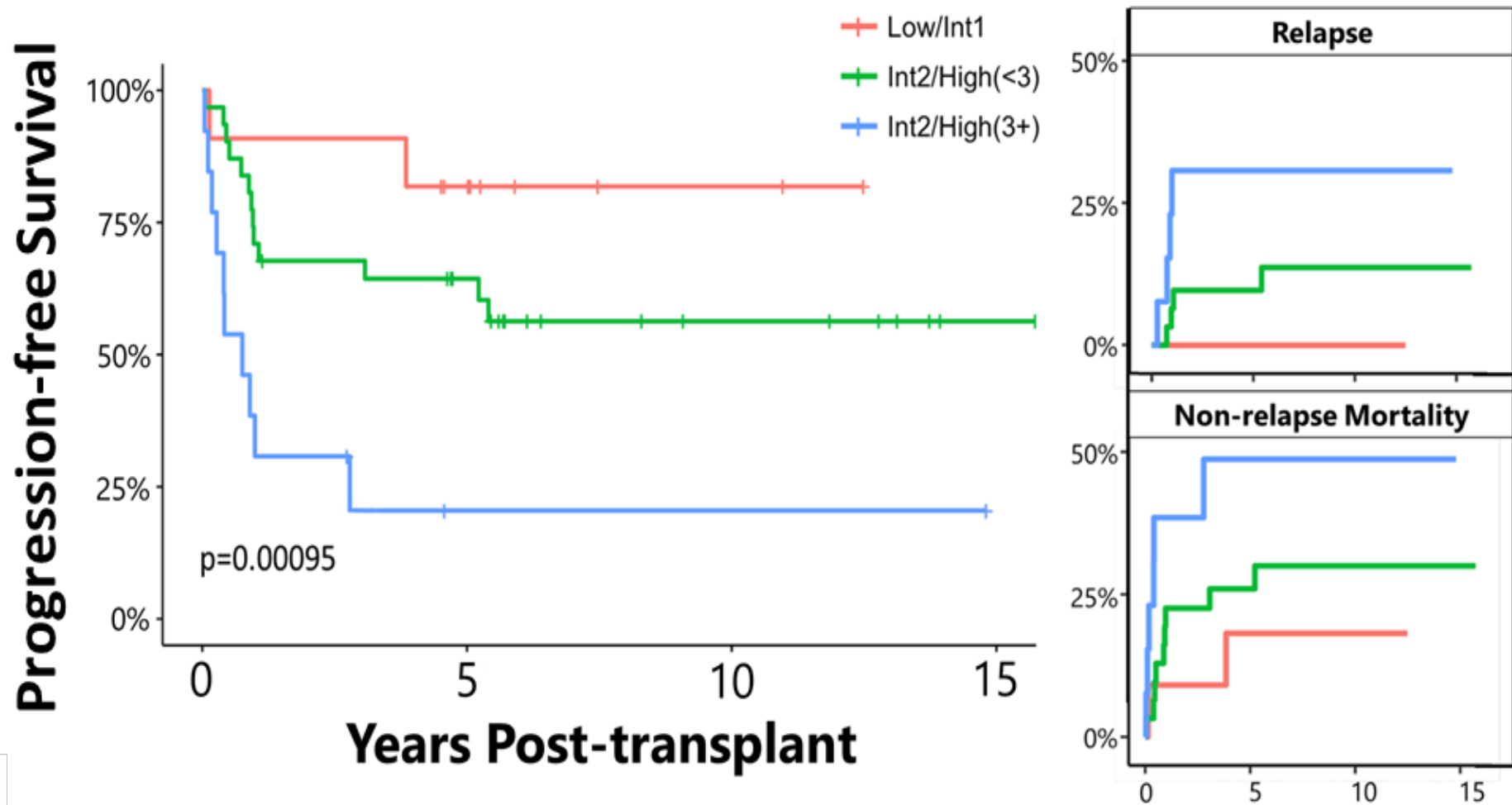
N. Kroeger et al, BBMT 23: 1095, 2017

Mutation *Patterns* and Outcome



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

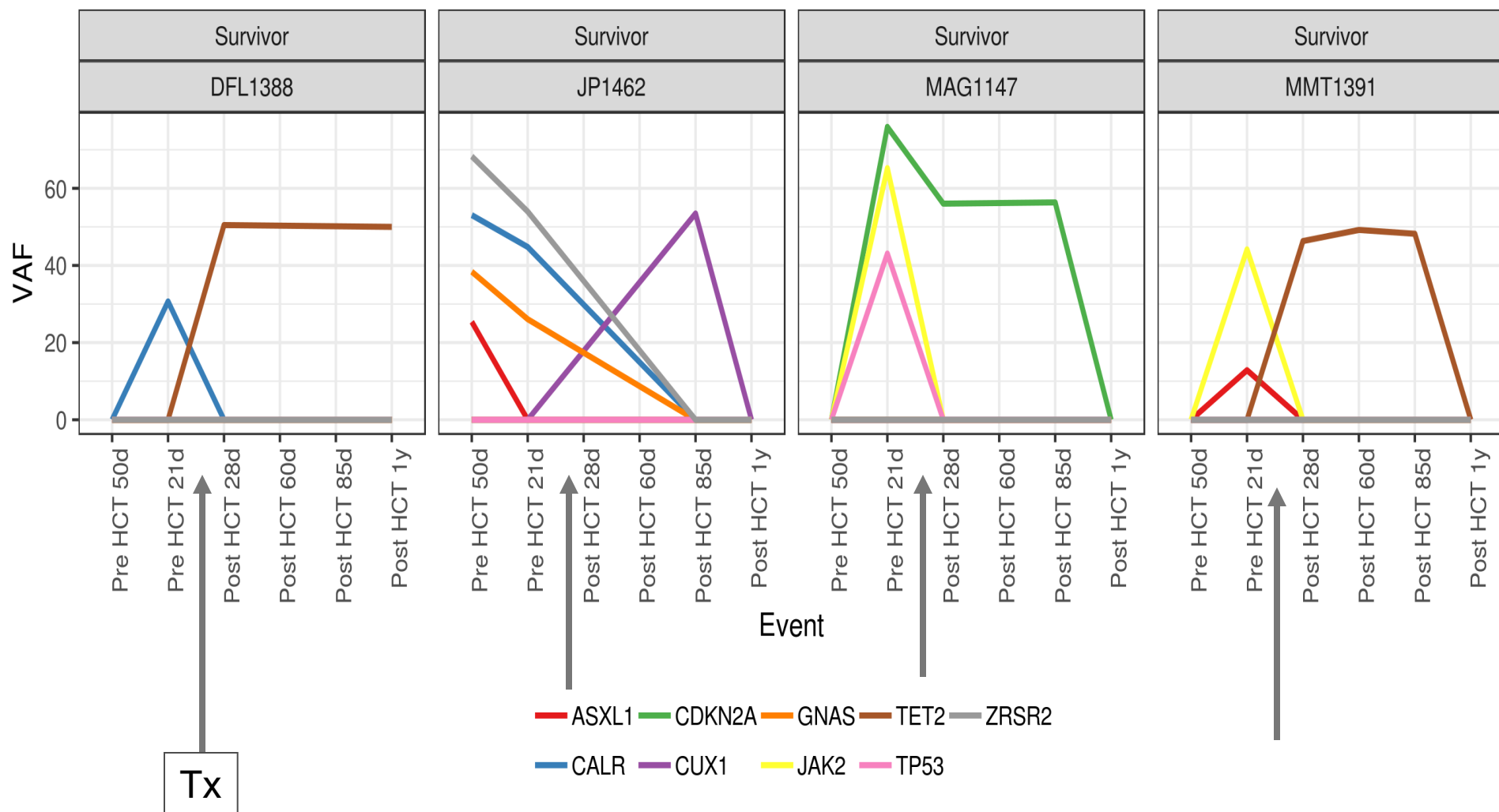
The *Number* of mutations matters



DIPSS plus, Mutations and PFS

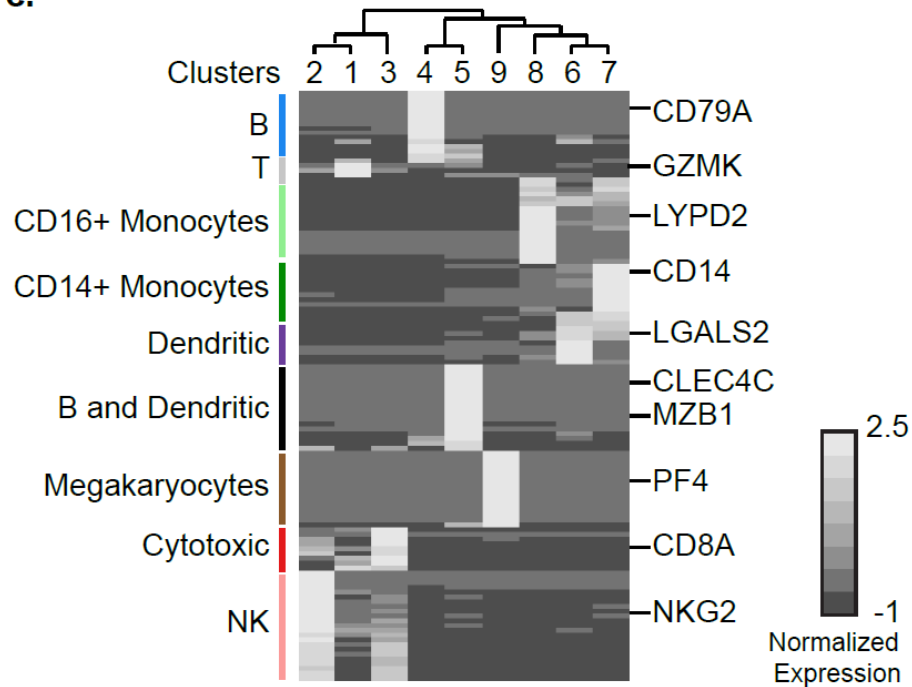
Parameter	Comparison	HR (95% CI)	P=
Driver	CALR vs TN	0.40 (0.14, 1.10)	0.076
	JAK2 vs TN	0.55 (0.22, 1.39)	0.205
	JAK2 vs CALR	1.38 (0.52, 3.62)	0.517
Nr. of mutations	≥3 vs <3	4.03 (1.77, 9.16)	<0.001
ASXL1	Yes vs No	1.48 (0.67, 3.30)	0.335
DIPSS plus	Int2/High vs Low/Int1	3.58 (0.84, 15.23)	0.084
	Int2/High<3 vs Low/Int1<3	2.52 (0.57, 11.19)	0.224
	Int2/High≥3 vs Low/Int1<3	8.45 (1.83, 39.12)	0.006
	Int2/High ASXL1- vs Low/Int1ASXL1-	5.38 (0.71, 40.94)	0.104
	Int2/High ASXL1 + vs Low/Int1ASXL1-	6.42 (0.81, 50.74)	0.078

Transplantation and Mutation Kinetics

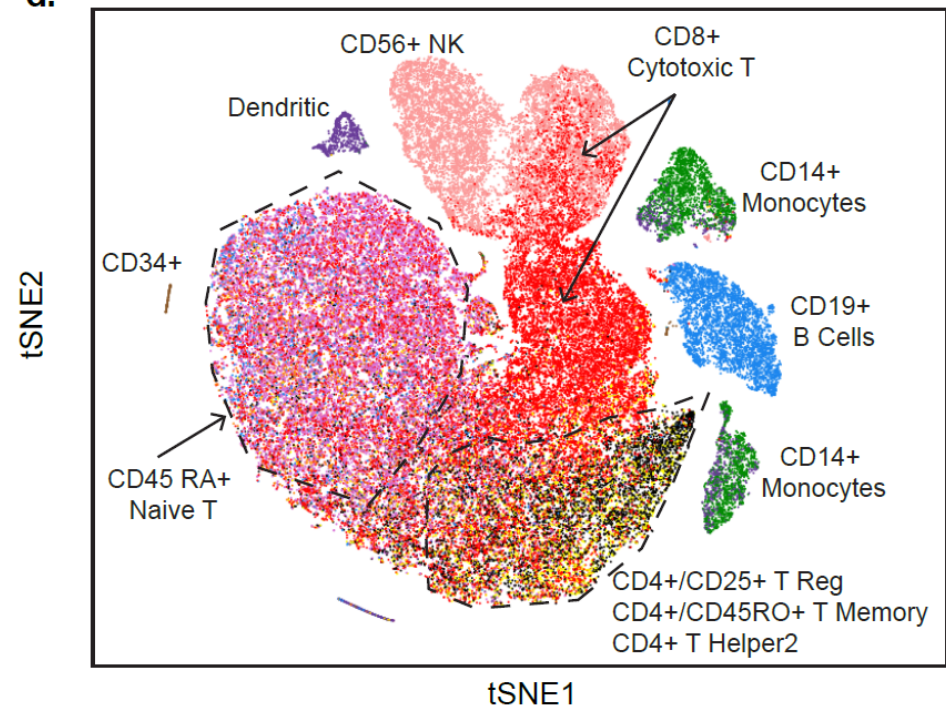


10x Genomics 3' Single Cell RNAseq

c.

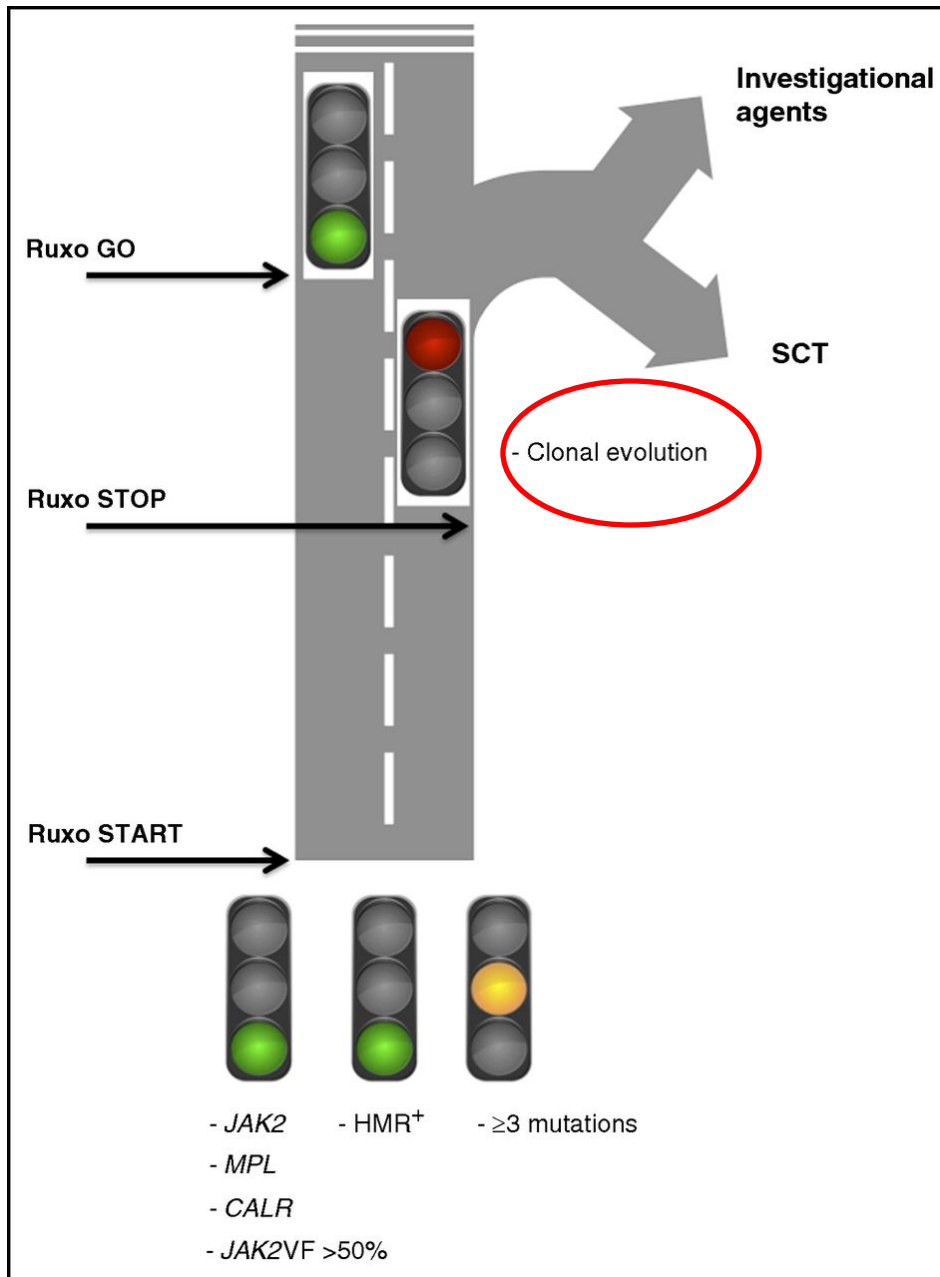


d.



Impact of Ruxolitinib

Mutations and decisions before and during ruxolitinib therapy

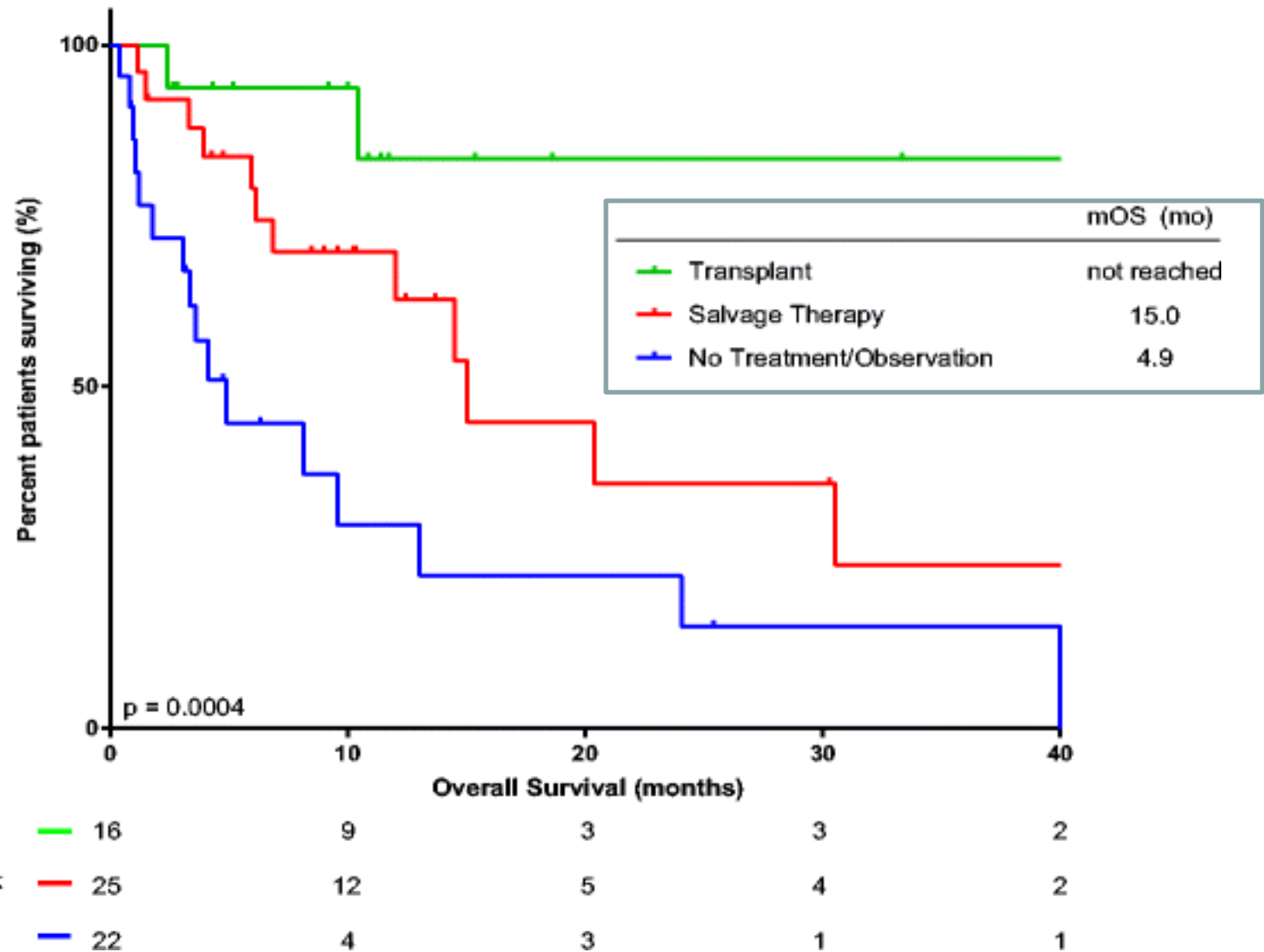


Alessandro M. Vannucchi, and
Paola Guglielmelli, *Blood* 2017;130:1075-
1077

HMR = high-molecular-risk mutation; Ruxo = ruxolitinib (Jakafi)

Salvage after Ruxolitinib

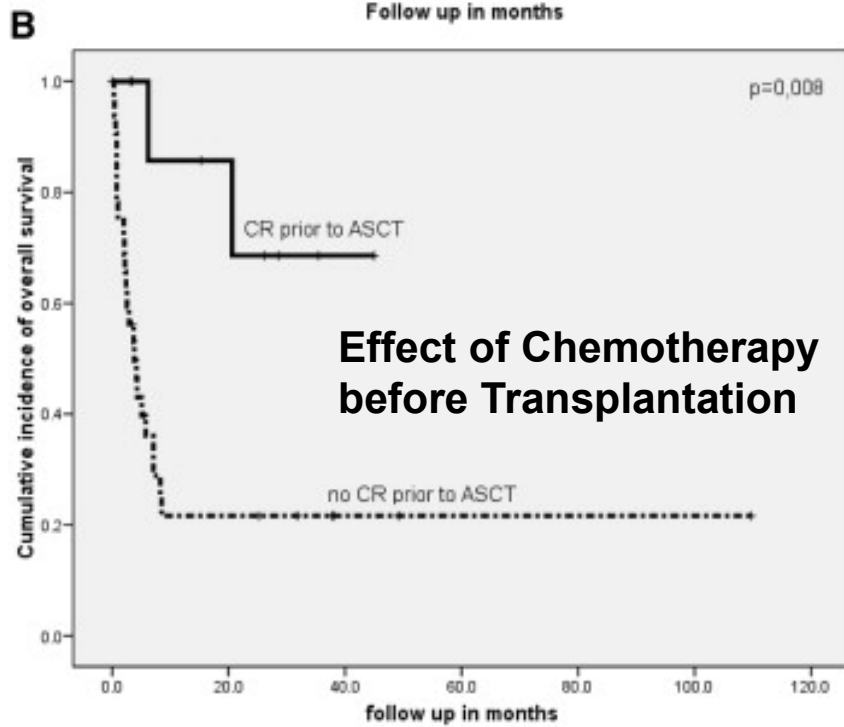
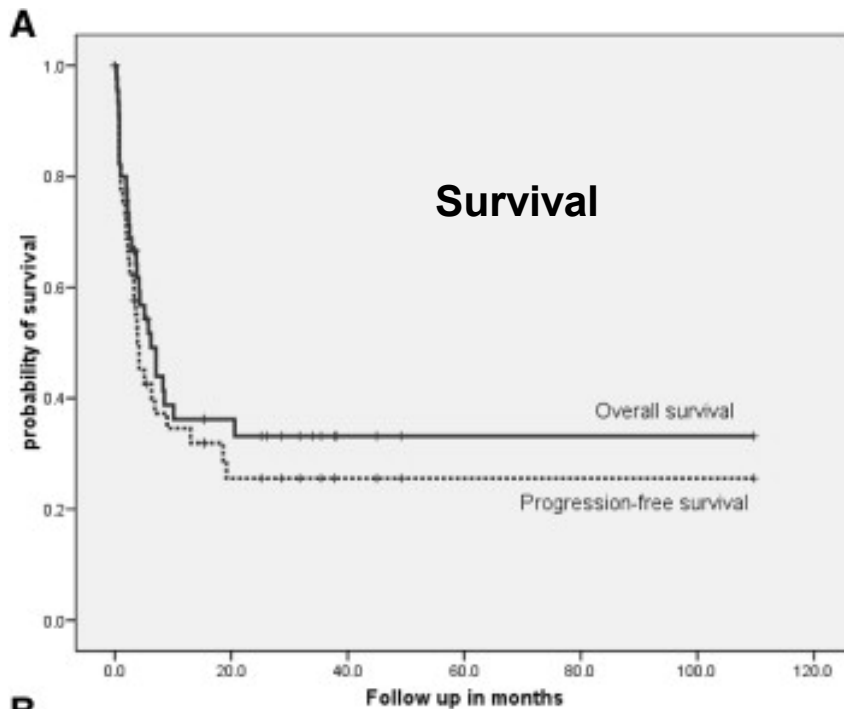
Overall Survival after Ruxolitinib Discontinuation



**Transplantation *after*
progression/leukemic
transformation**

Transplantation after *Leukemic Transformation*

TP53



Whom to Transplant?

- **Age:** No strict age limit. However, careful selection among patients older than 65 or 70 years (biological age).
- **Comorbidities:** Use reduced intensity conditioning (or no transplant).
- **Symptoms:** Quality of life? Need of transfusions? Response to Jakafi?

When to Transplant?

- **Disease characteristics:**
 - DIPSS int.1 – some patients will benefit
 - DIPSS int.2/high – HCT generally advised
 - DIPSS *plus* int.1/int.2/high – generally accepted as indication for HCT
 - Disease progression – HCT the only real option
 - Loss of response to JAK inhibitor

Consider Mutations?

- **Mutations – consider HCT for the following:**
 - Triple negative disease (no mutations of *JAK2*, *MPL1*, *CALR*)
 - Absence of *CALR* mutation (type 1)
 - Two or more high risk mutations
 - (*Any* high risk mutation)
- Molecular HCT risk score

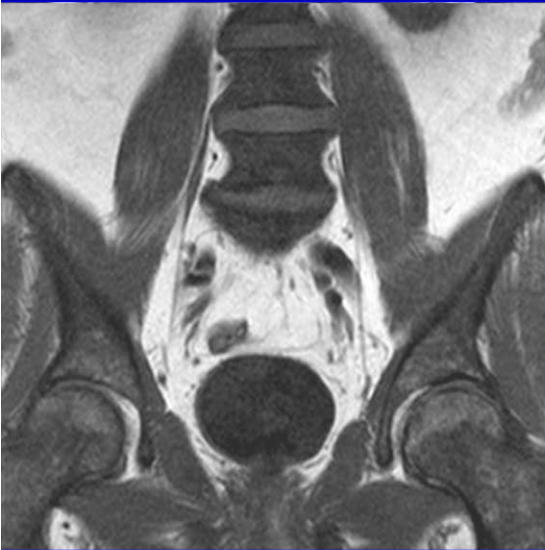
How to Transplant?

- Conditioning adjusted to
 - Patient co-morbidities/age; Disease stage; Mutation status; Stem cell source
- GVHD prophylaxis
 - Drug combinations; Post HCT Cytosan; Jak1(2) inhibitors
- “Adjuvant” therapy
 - Pre- or post-HCT
- **We need “improved” HCT regimens**

Summary and Conclusions

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

EA: Coronal T1 Spin Echo Femurs



9-23-02



12-27-02



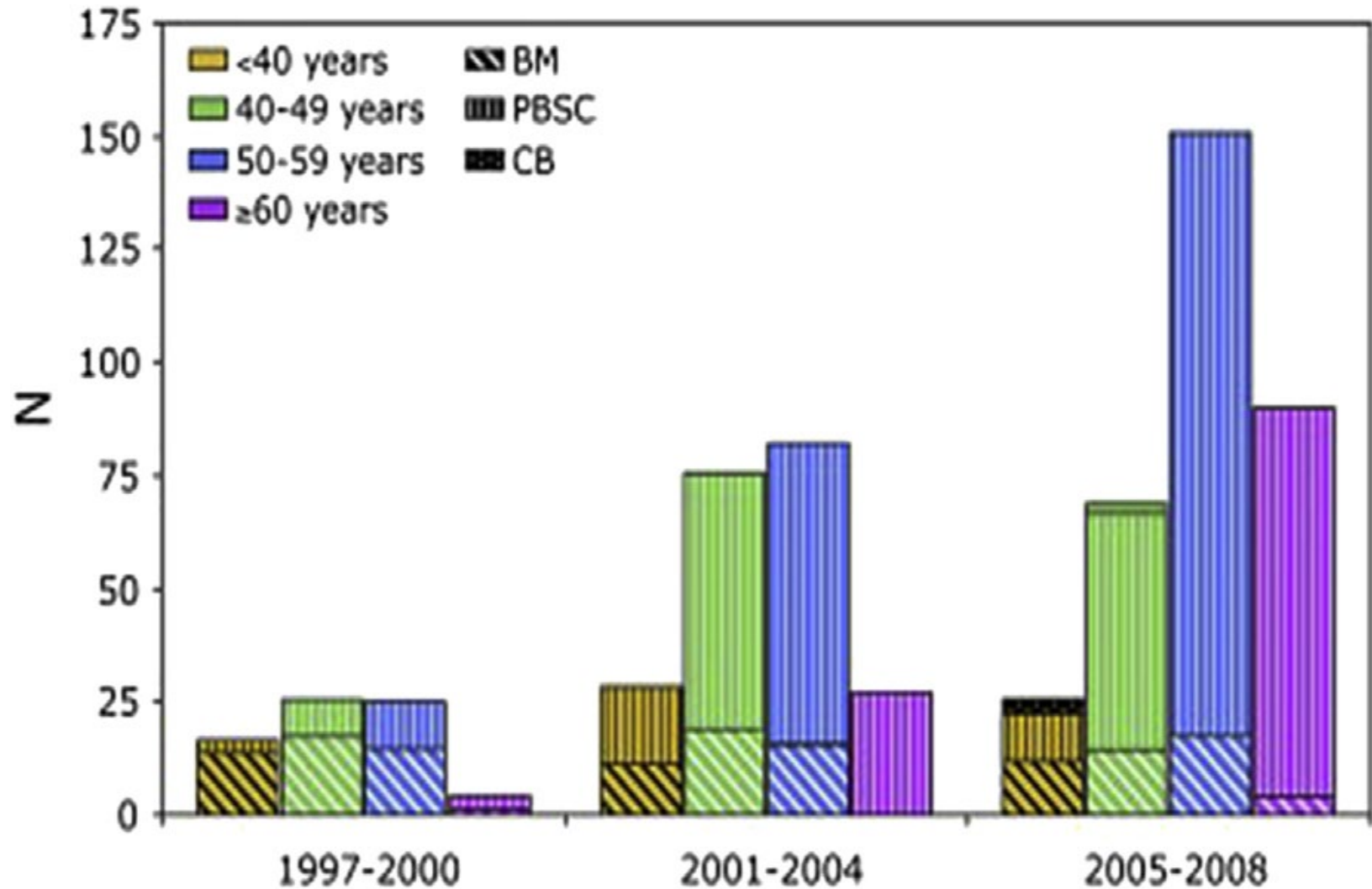
12-16-03

Thank you

- Barry Storer
- Rachel Salit
- Bart Scott
- Jerry Radich
- Emily Stevens
- Anna Halpern
- Janghee Woo
-and all of our patients

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ideeg@fhcrc.org

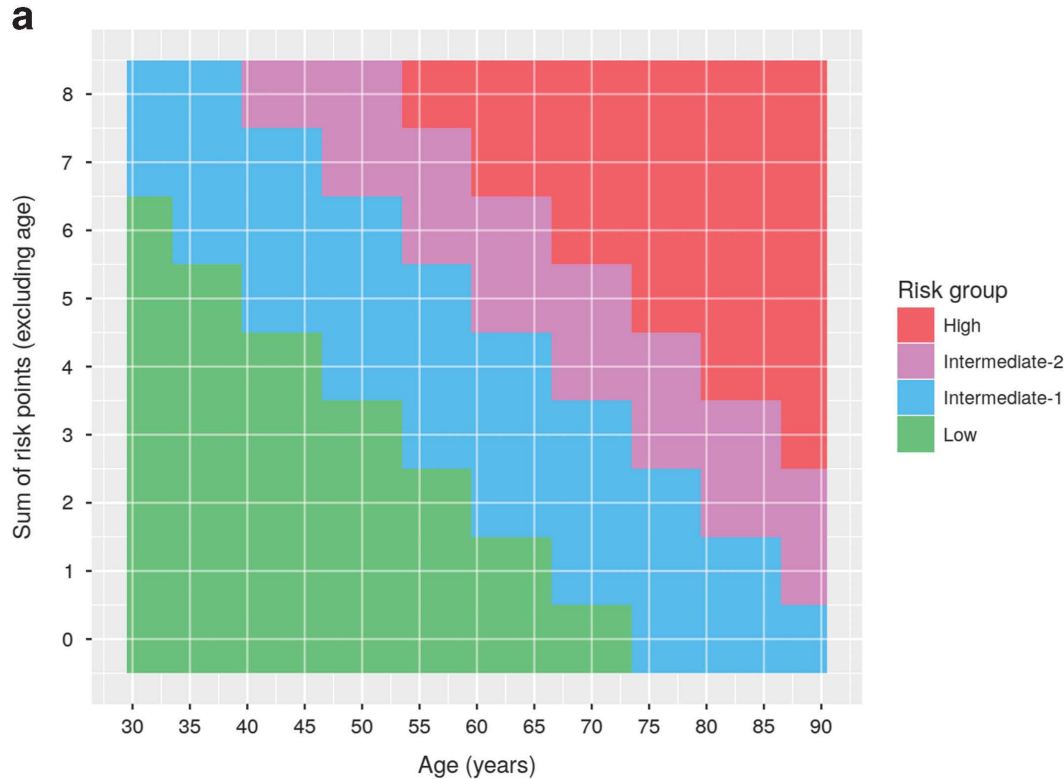
Age and Transplantation



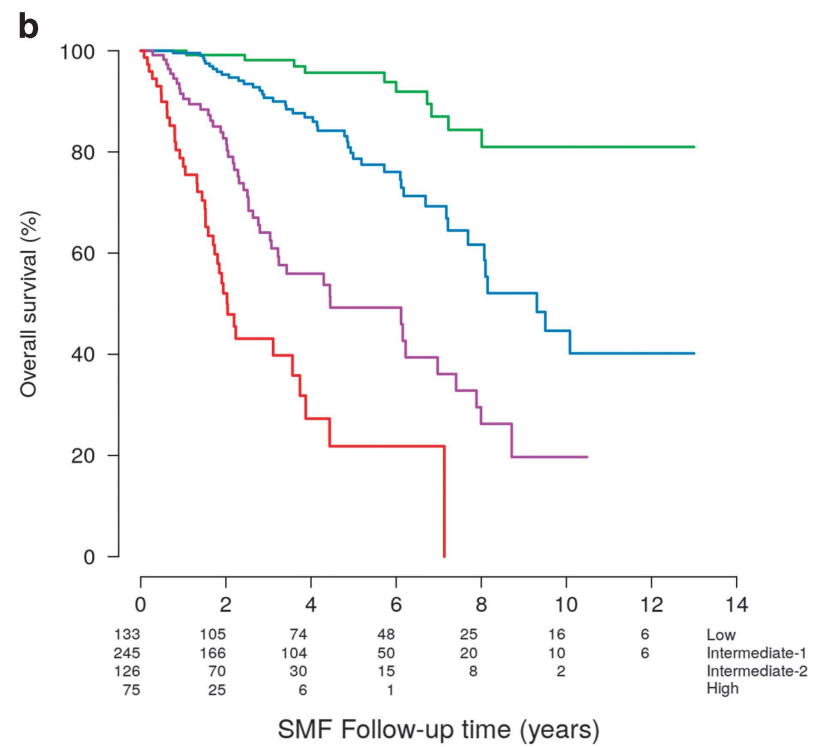
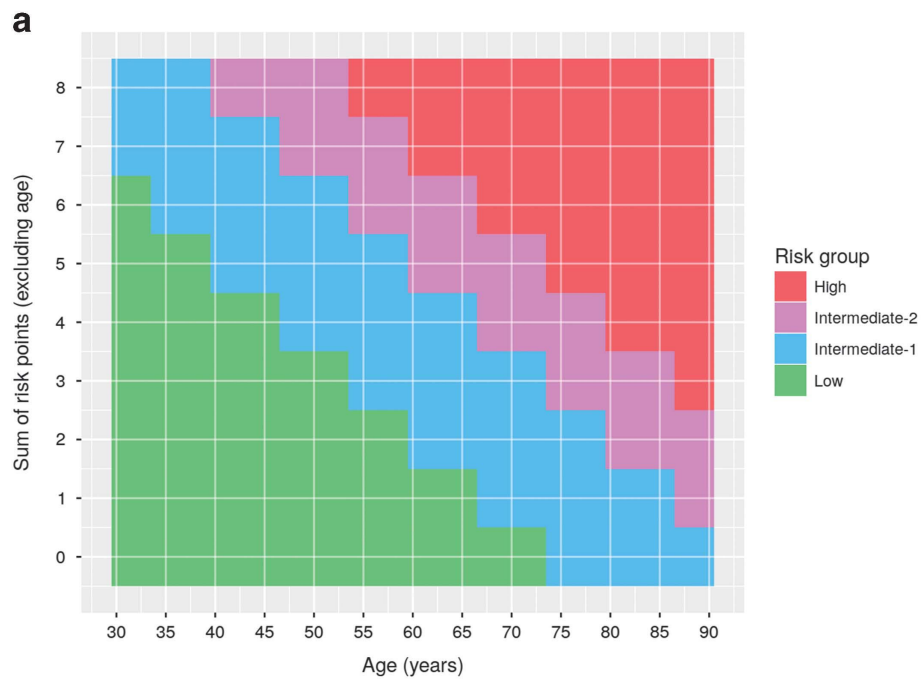
“Simplified” MIPSS70 and MIPSS70 plus

- **MIPSS70- Adds:**
 - Marrow fibrosis grade ≥ 2
 - Absence of **CALR (type 1)**
 - High-risk mutations
 - ≥ 2 High-risk mutations
- **MIPSS70 plus –Adds:**
 - Absence of **CALR (type 1)**
 - High-risk mutations
 - ≥ 2 High-risk mutations
 - *Adverse cytogenetics*

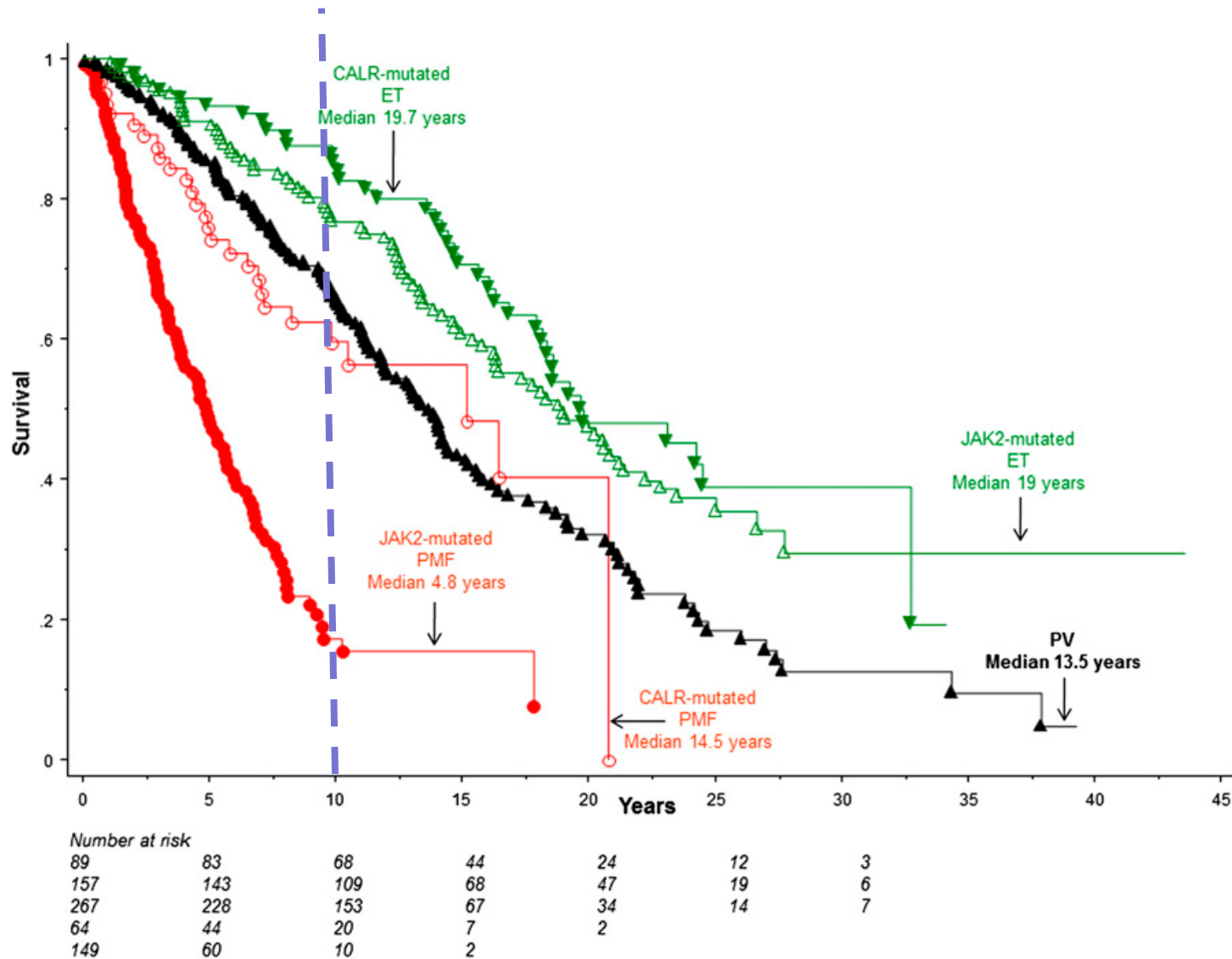
Post PV – ET Myelofibrosis



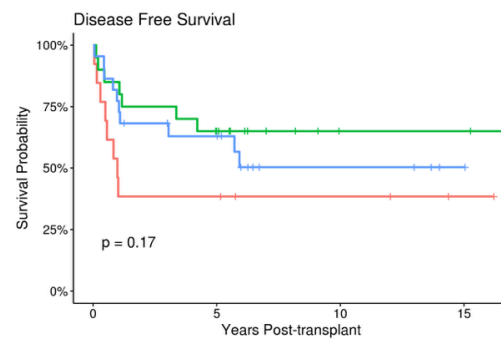
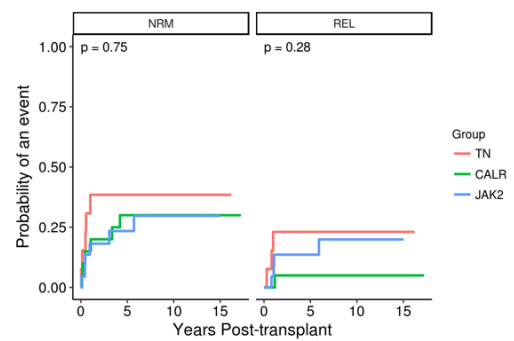
Passamonti et al Leukemia 31: 2726, 1917



Mutations and survival



Parameter	Comparison	Hazard Ratio (95%CI)	p
Driver	CALR vs TN	0.40 (0.14, 1.10)	0.0759
Driver	JAK2 vs TN	0.55 (0.22, 1.39)	0.2048
Driver	JAK2 vs CALR	1.38 (0.52, 3.62)	0.5168
Mutation-3	≥3 mutations vs <3 mutations	4.03 (1.77, 9.16)	<0.00 1
ASXL1	Yes vs No	1.48 (0.67, 3.30)	0.3351
DIPSSPlus	Int2/High vs Low/Int1	3.58 (0.84, 15.23)	0.0840
DIPSSPlus-3	Int2/High(<3) vs Low/Int1(<3)	2.52 (0.57, 11.19)	0.2243
DIPSSPlus-3	Int2/High(3+) vs Low/Int1(<3)	8.45 (1.83, 39.12)	0.0063
DIPSSPlus-A	Int2/High(ASXL1-) vs Low/Int1(ASXL1-)	5.38 (0.71, 40.94)	0.1043
DIPSSPlus-A	Int2/High(ASXL1+) vs Low/Int1(ASXL1-)	6.42 (0.81, 50.74)	0.0780



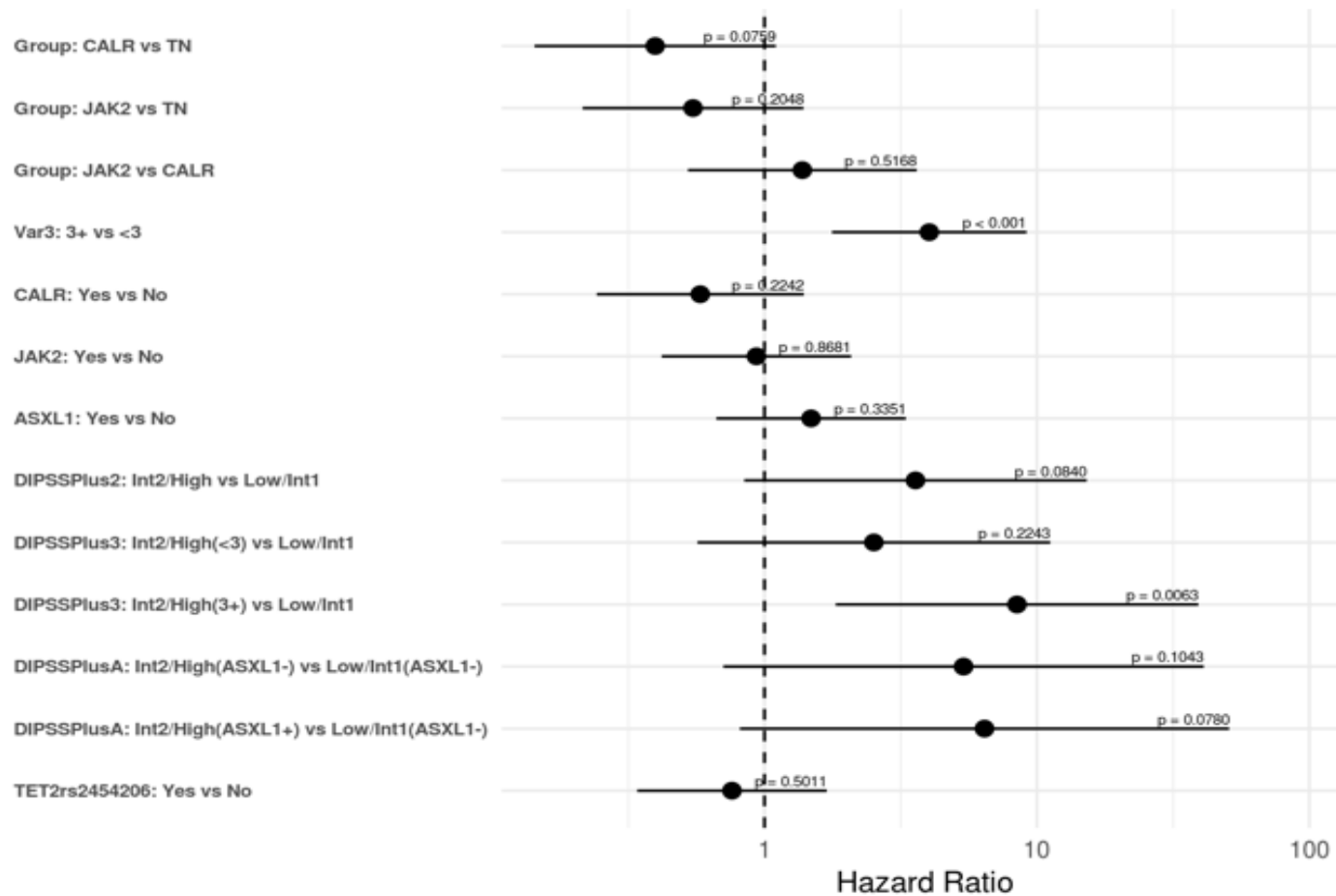


Figure 1: Progression-free survival, Relapse, and NRM by DIPSS plus classification (low/intermediate-1 vs. Intermediate-2/high).

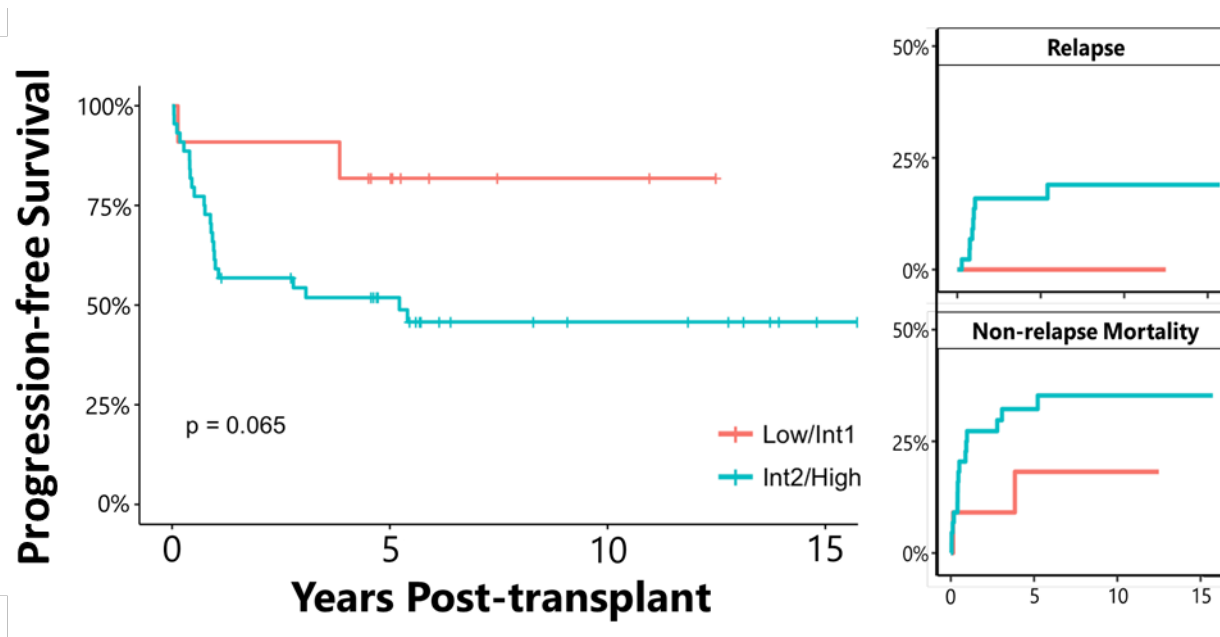
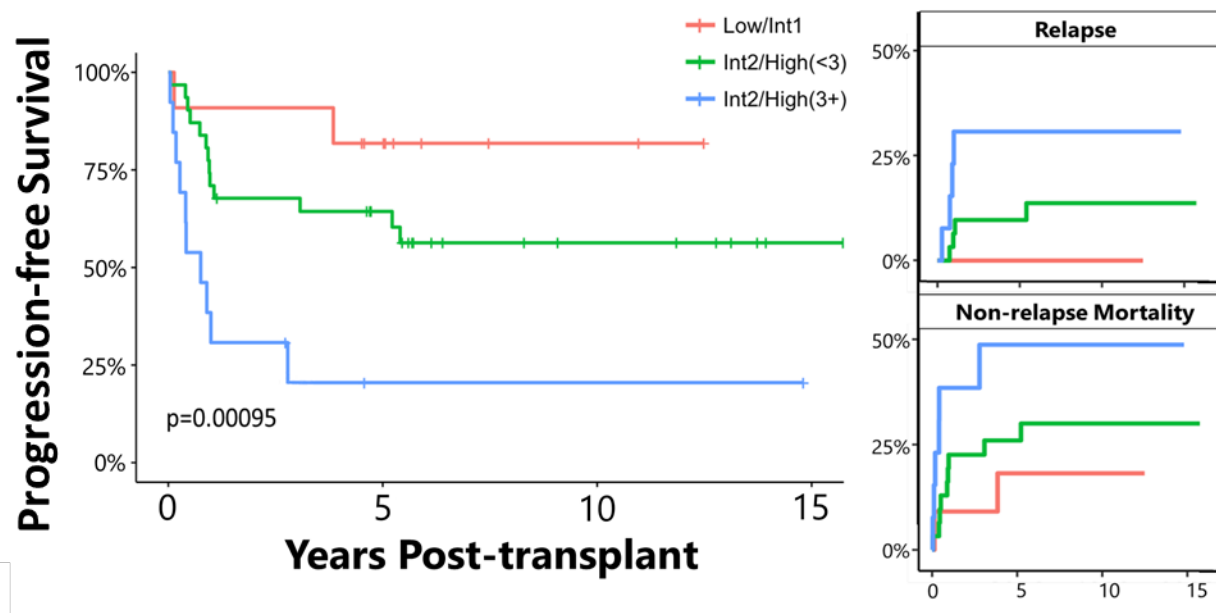
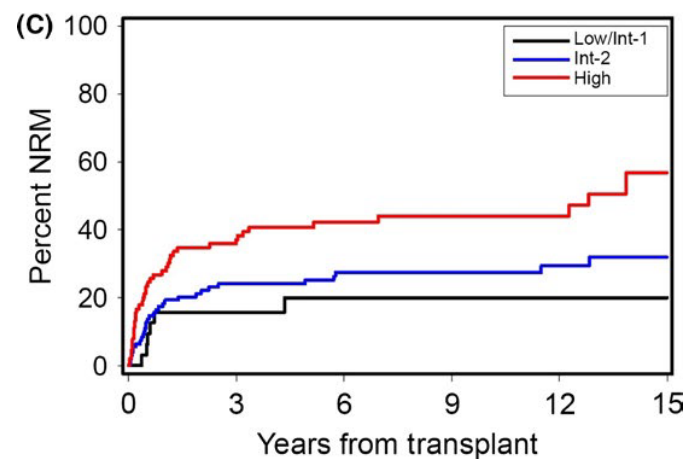
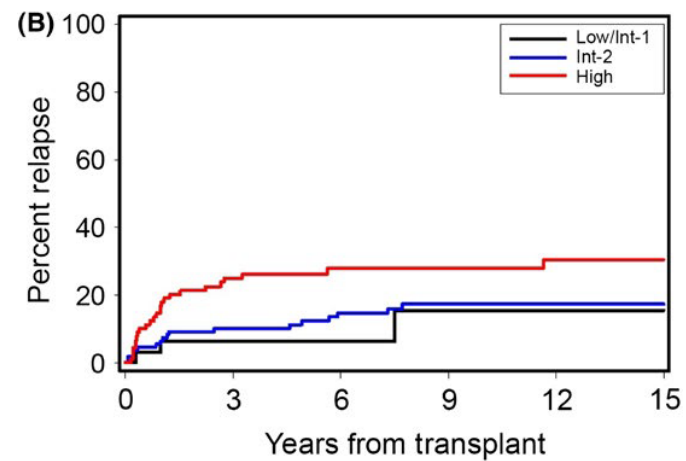
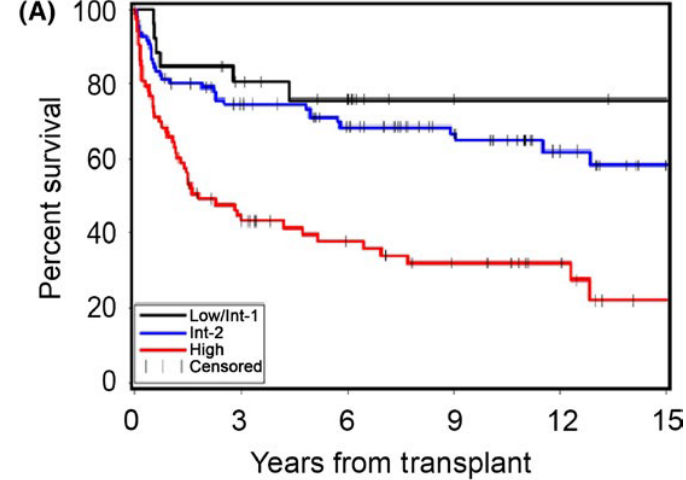


Figure 3: Progression-free survival, Relapse, and NRM by DIPSS plus classification and variant number (low/intermediate-1 vs. Intermediate-2/high <3 vs. Intermediate-2/high ≥ 3).





Current Recommendations to Consider Transplantation
Based on baseline characteristics

- DIPSS/DIPSS plus:
- Intermediate-2 and high risk
- Intermediate-1/low risk—dependent on mutations, patient age, response to JAK2 inhibitor therapy (see below)
- Transfusion dependence
- Leukemic transformation, if responsive to induction therapy
- Patients without excessive comorbidity (HCT-specific comorbidity index < 4)
- Up to eighth decade of life

Based on disease course

- Disease progression
- Increasing DIPSS/DIPSS plus scores
- Loss of response to *JAK2* inhibitor therapy
- Clonal evolution on *JAK2* therapy

Based on mutational characteristics*

- Triple negative
- *ASXL1* (In PMF)
- *SRSF2*
- *IDH1/2*
- *TP53*
- *SF3B1* + *IDH*

* As discussed in the text, data on additional mutations are evolving, and decisions will need to be reassessed on an ongoing basis.

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

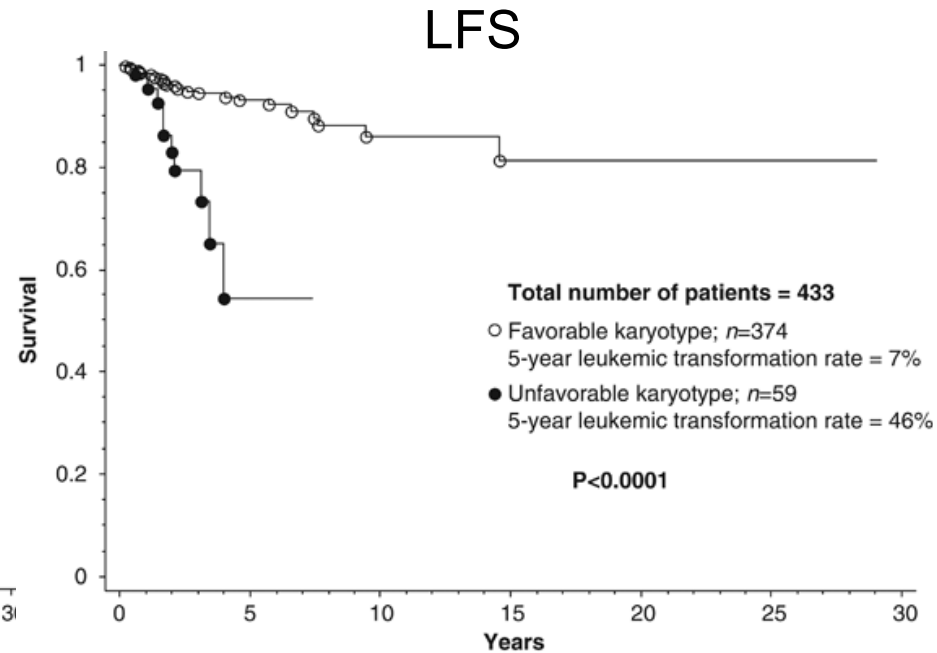
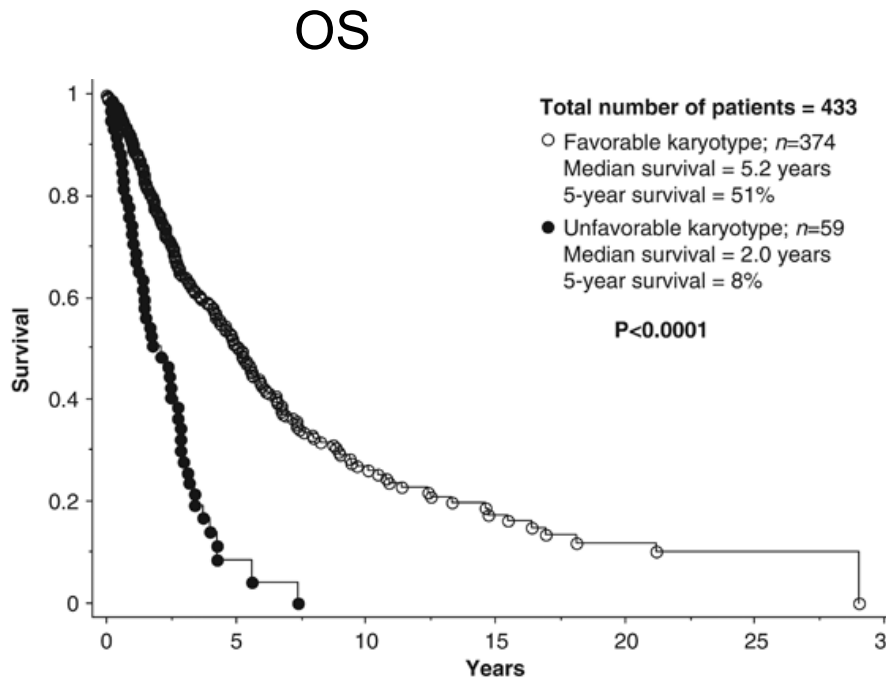
Risk Factors Included

- 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**
-
- ```
graph LR; A[Anemia] --- DIPSS; B[WBC > 25,000] --- DIPSS; C[Myeloblasts in blood] --- DIPSS; D[Age > 65 years] --- DIPSS; E[Symptoms] --- DIPSS; F[Abnormal chromosomes] --- DIPSS_plus; G[Low platelet count] --- DIPSS_plus; H[Requiring transfusions] --- DIPSS_plus; I[Mutations] --- MIPSS; J["- JAK2, MPL1, CALR"] --- MIPSS; K["- ASXL1, p53, etc"] --- MIPSS; DIPSS --- DIPSS_plus; DIPSS_plus --- 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

# Cytogenetics and Survival in MF



Unfavorable: +8, -7/7q-, i17q, inv3, -5/5q-, 12p-, 11q232, or  $\geq 3$  abnml

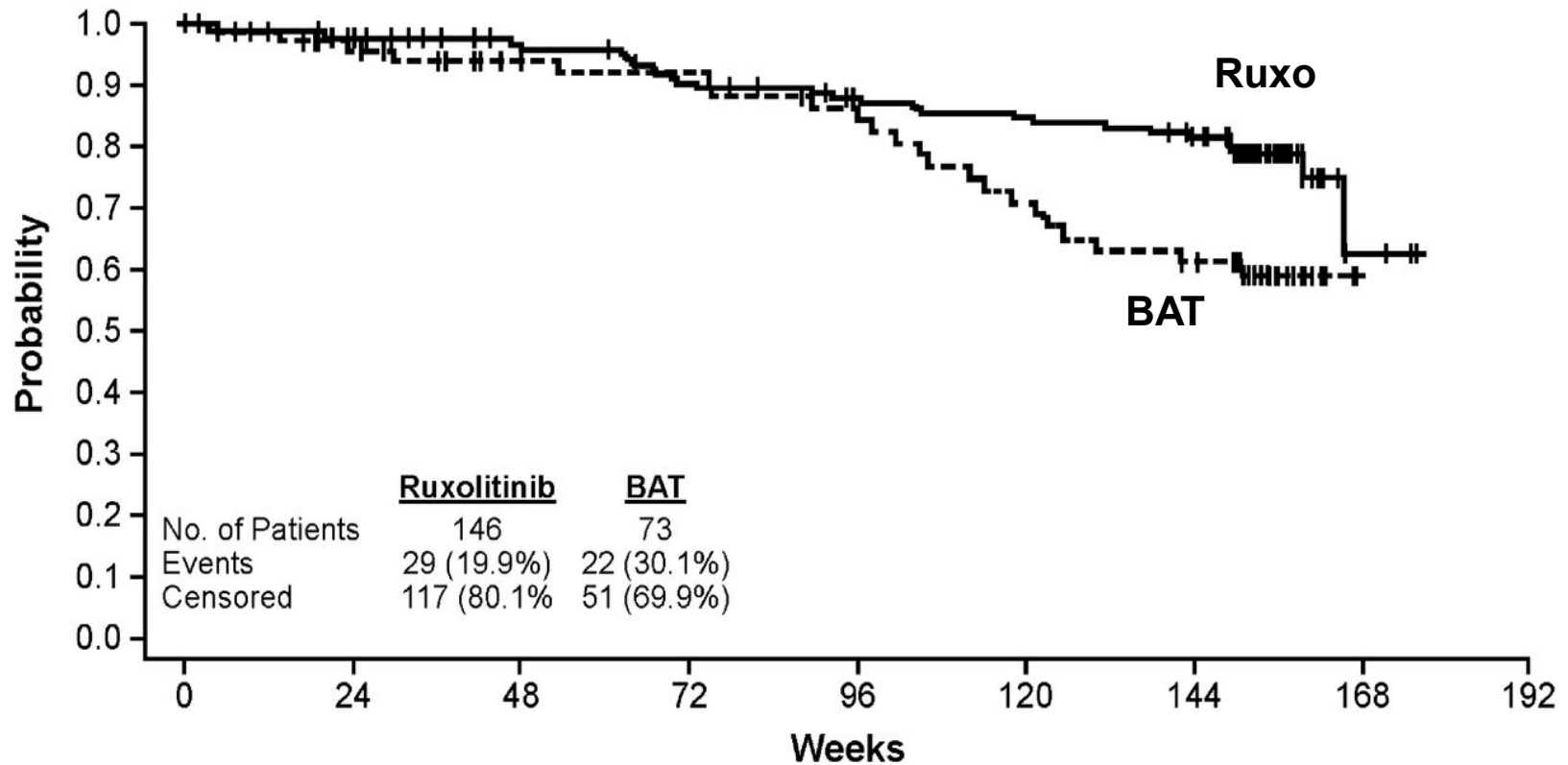
# Mutations

- **JAK2, MPL1, CALR** (type1 and type 2)
- ASXL1, TET2,
- SRSF2, U2AF1
- IDH1, IDH2, TP53, DNMT3a, IKZF1, LNK
- Other

# **JAK2 Inhibitors**

## **Benefits**

# Overall survival (COMFORT-II Trial)



**Patient feels better,  
Spleen shrinks,  
May live longer**

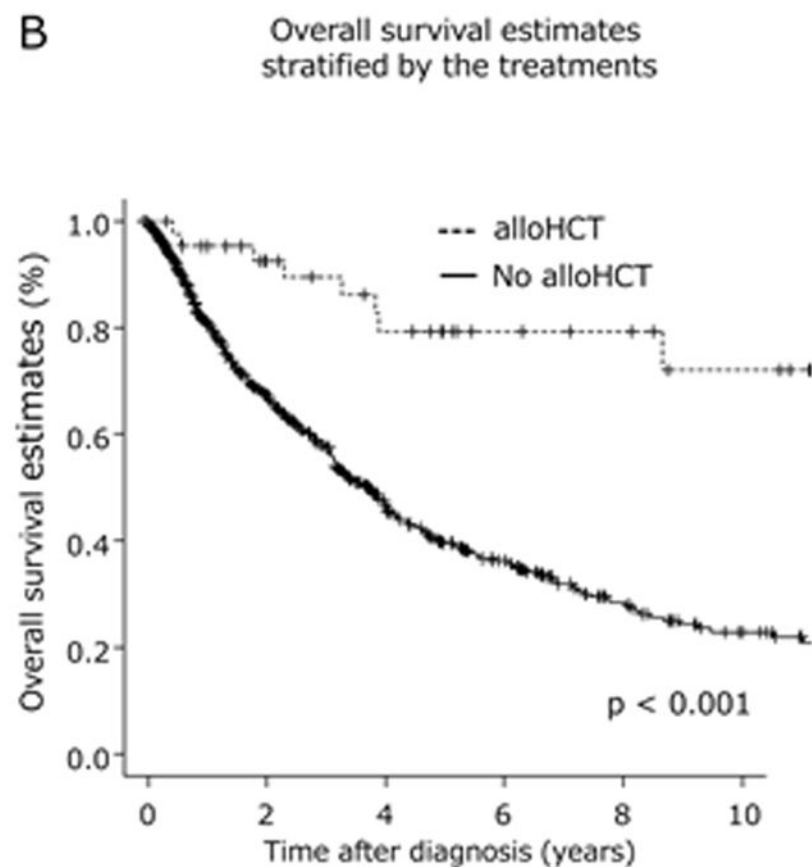
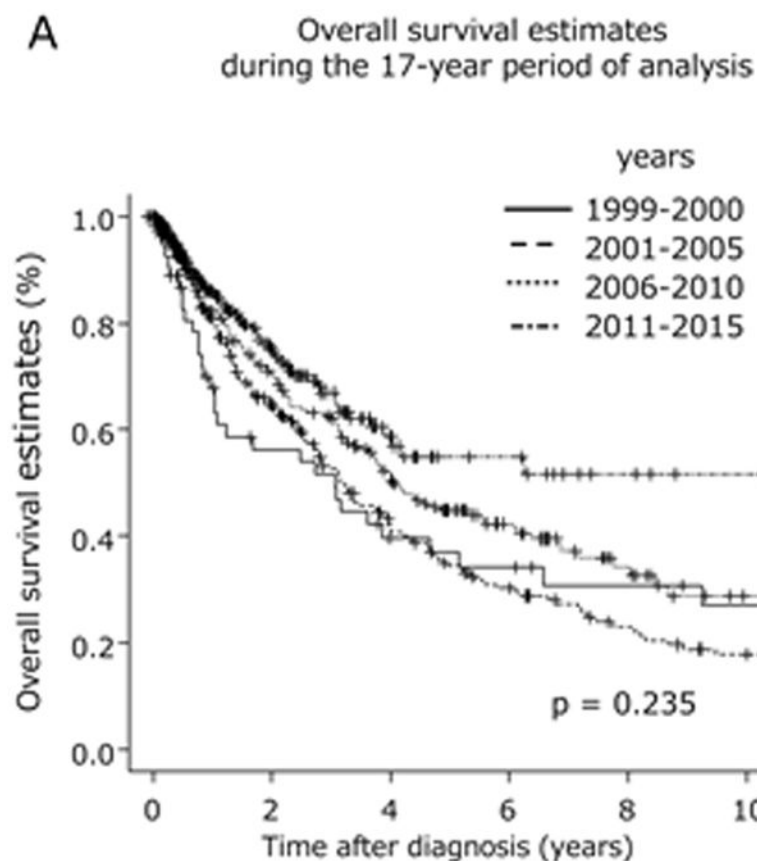
**JAK2 inhibitors**

**Potential *Risks***

# Transplantation

# **Factors not considered in classification *but important for transplantation***

- **Fibrosis in liver, lung, other organs**
- **Duration of the disease**
- **Big spleen/Portal hypertension**
- (Mutations
  - JAK2, MPL1, CALR
  - ASXL1, TP53 etc)



Katsuto Takenaka et al. Blood 2016;128:3126

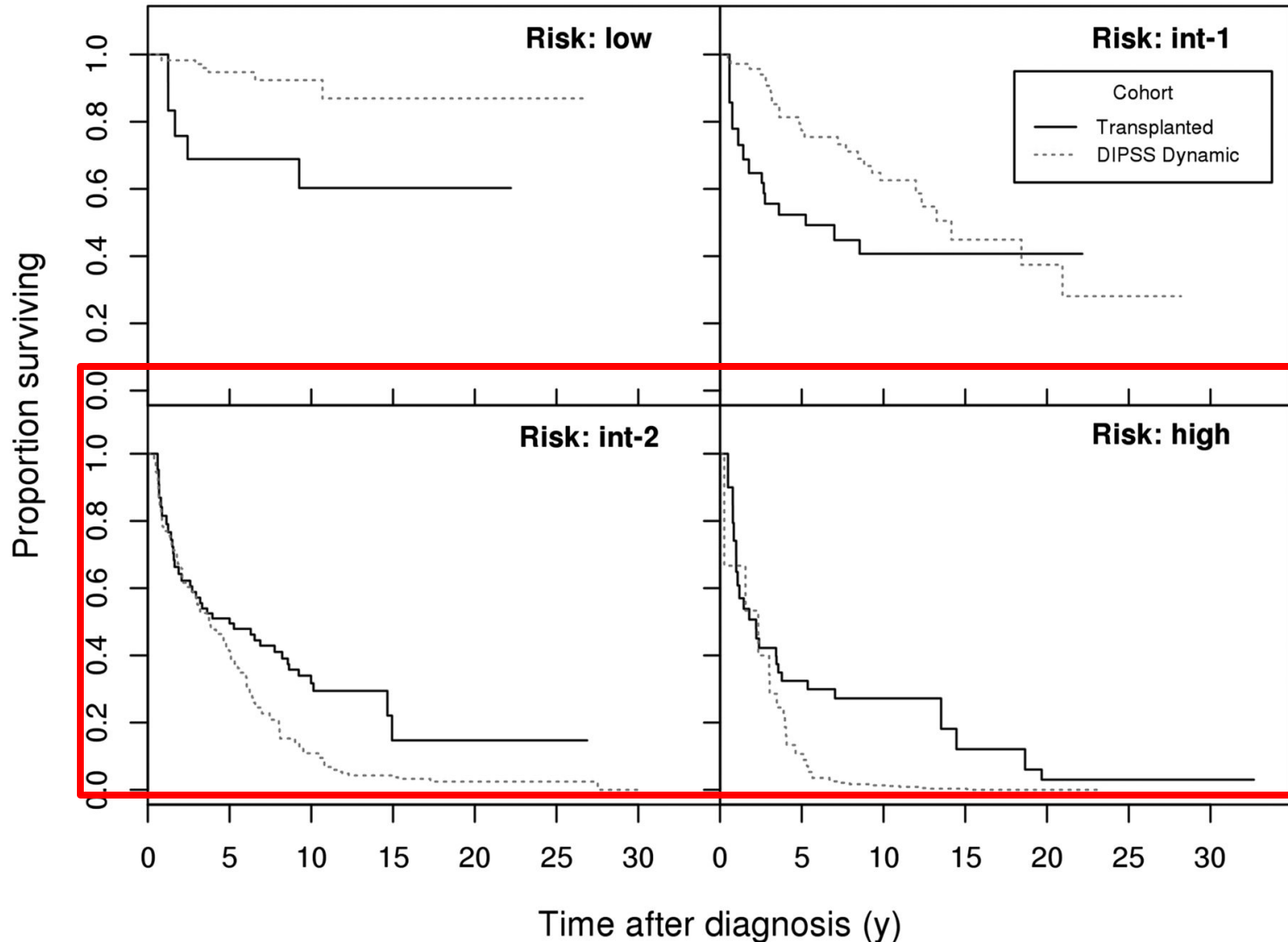
# “Bone marrow” in the Lung



**The basic question:**

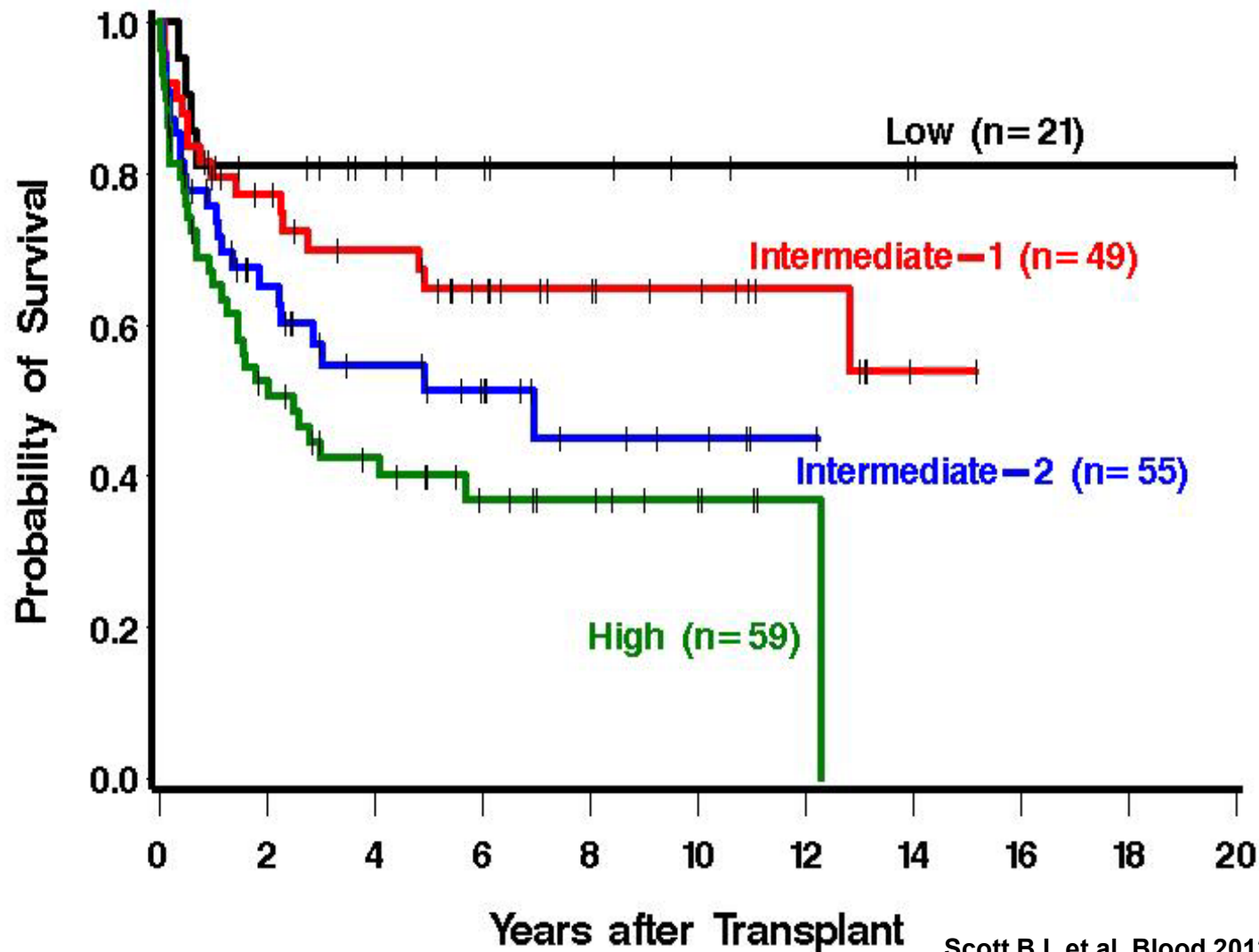
# Transplantation: *no – or when?*

(by DIPSS risk)

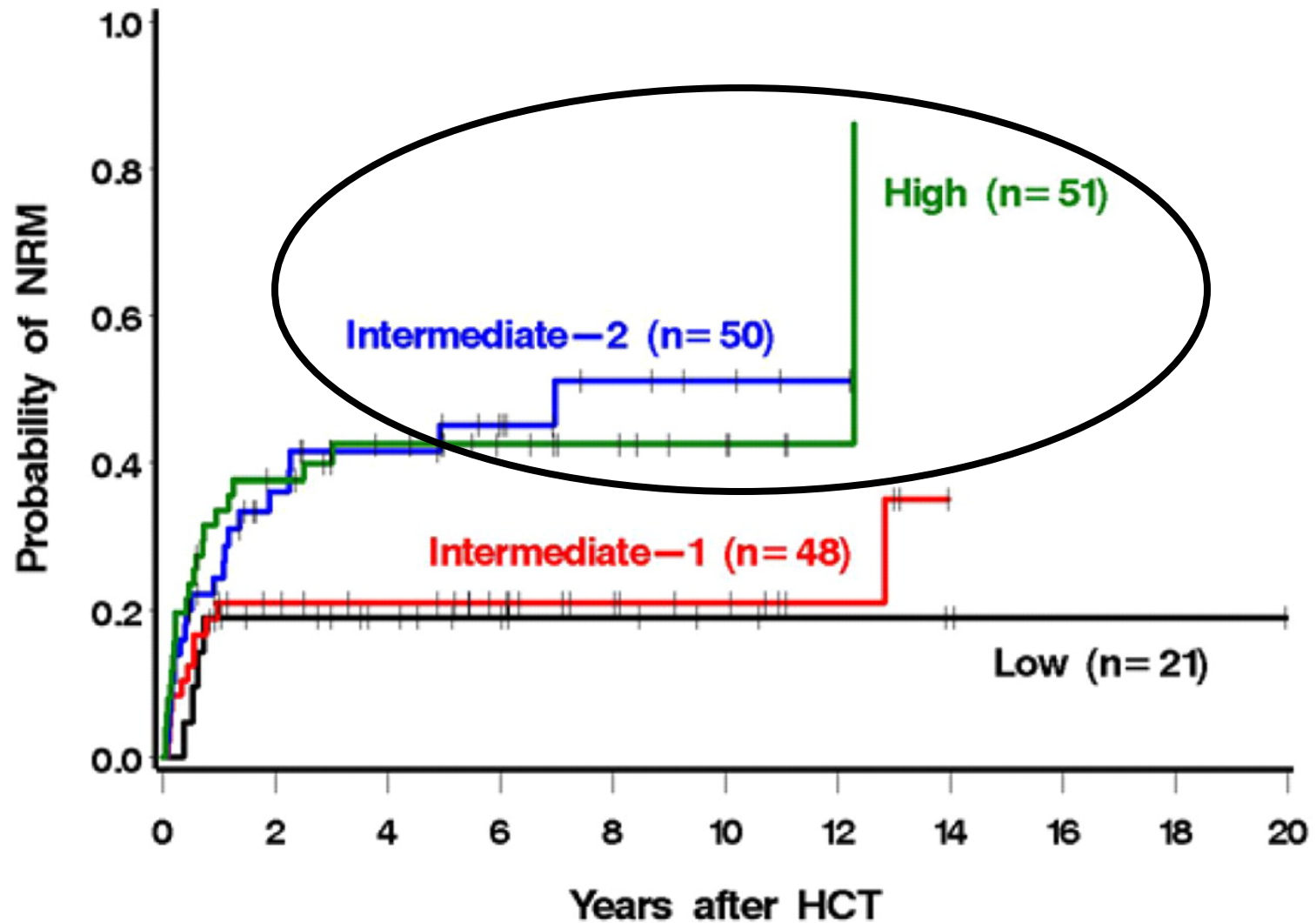


# Post-HCT Survival (by DIPSS risk)

(High intensity conditioning)

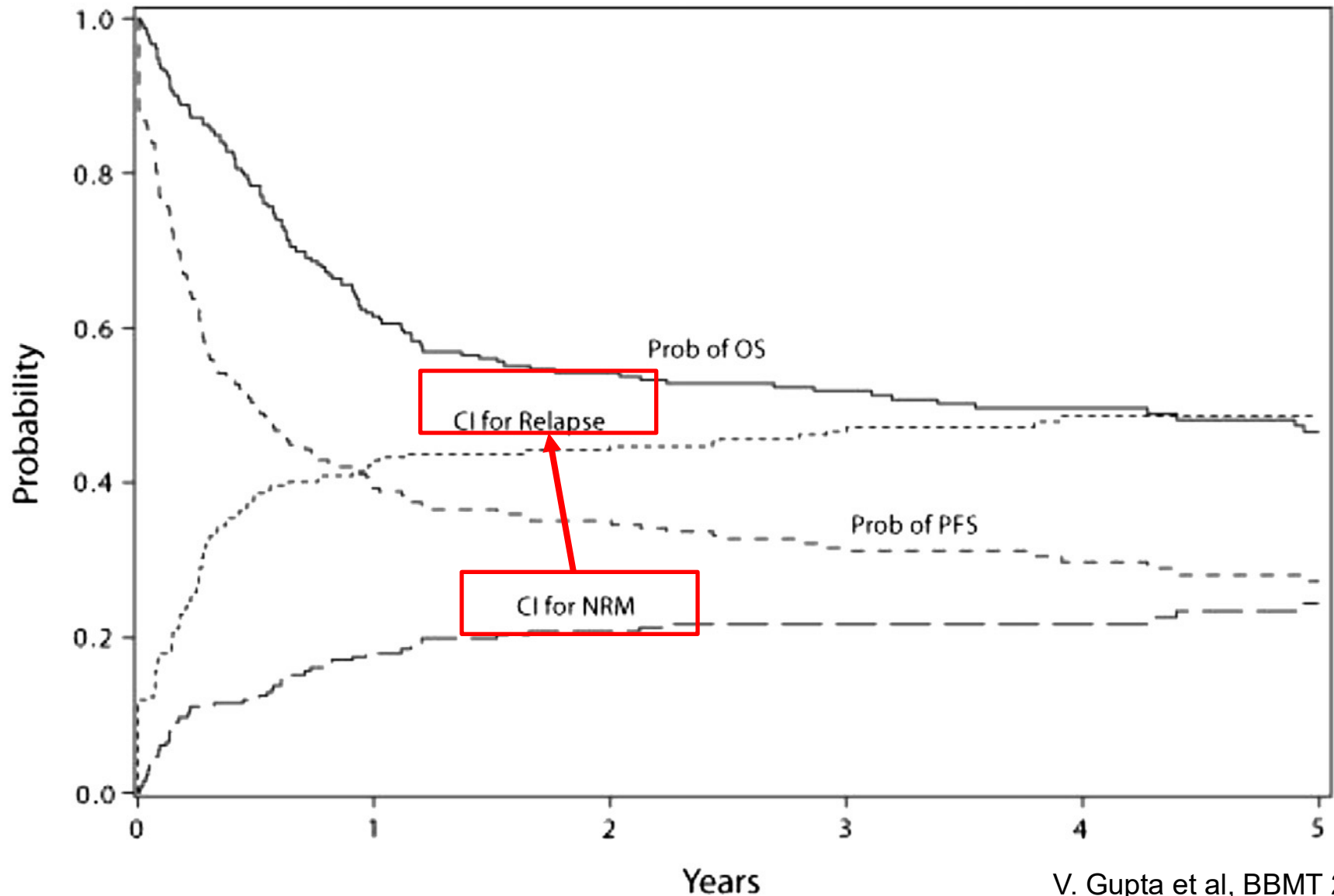


# *Non-Relapse Mortality (by DIPSS)*



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

# ***RIC for PMF – OS, PFS and Relapse***



**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

# Limitations to the Use of Ruxolitinib

## ( with respect to HCT)

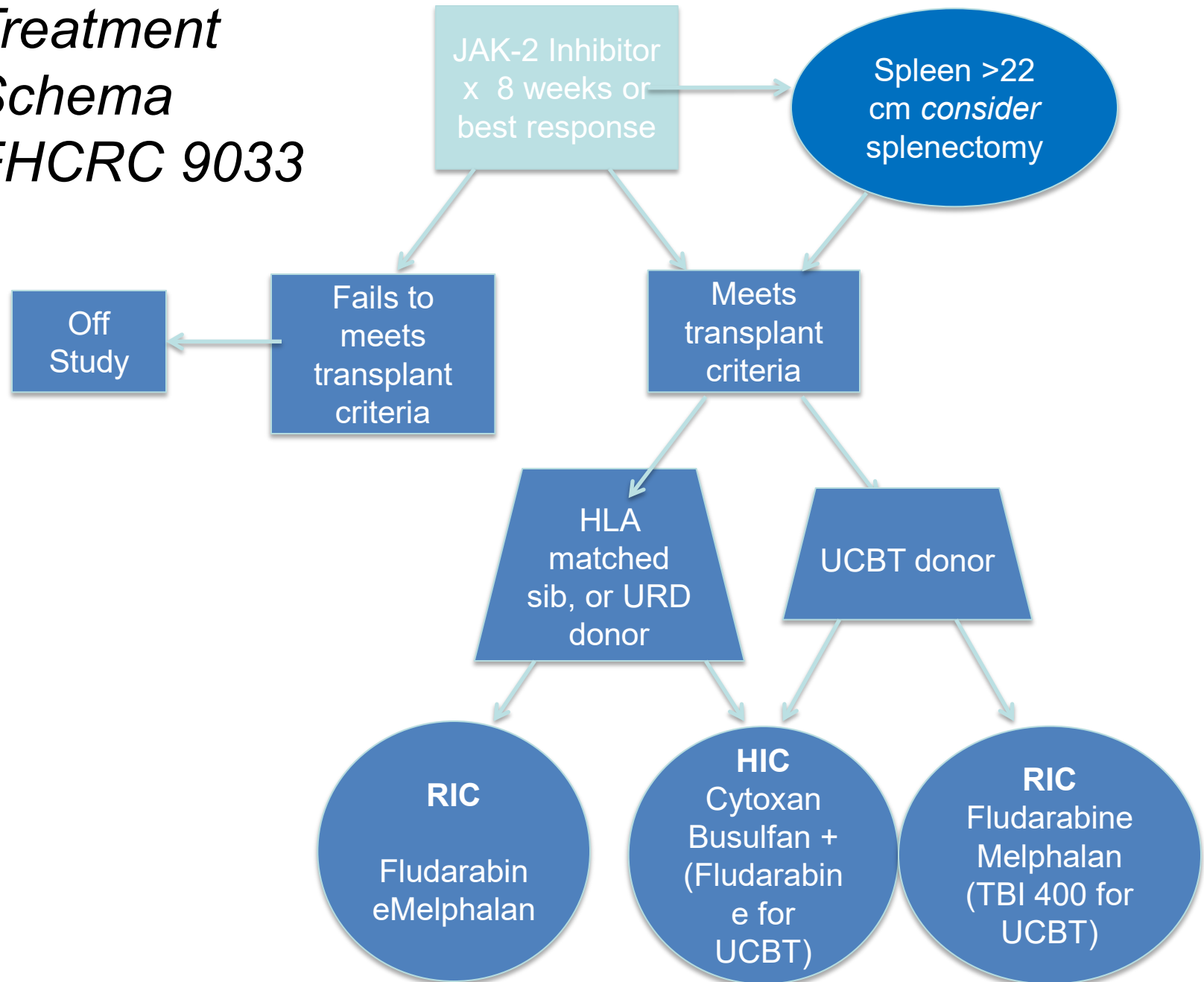
- Disease persistence
- Lack of improvement or worsening of cytopenias
- Atypical infections
  - Mycobacterial, hepatitis reactivation etc
- No decrease in the risk of Leukemic Transformation

# Experience with JAK inhibitors in transplant protocols

| Study                          | No | Study Design  | Results                                                      | Conclusions                                                           |
|--------------------------------|----|---------------|--------------------------------------------------------------|-----------------------------------------------------------------------|
| Jaekel et al BMT 2014          | 14 | Retrospective | GF, 1/14<br>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      |

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

## PLUS

|                                    |   |
|------------------------------------|---|
| Unfavorable Karyotype <sup>2</sup> | 1 |
| Transfusion Dependence             | 1 |
| Platelet <100,000/ul               | 1 |

| 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)            |

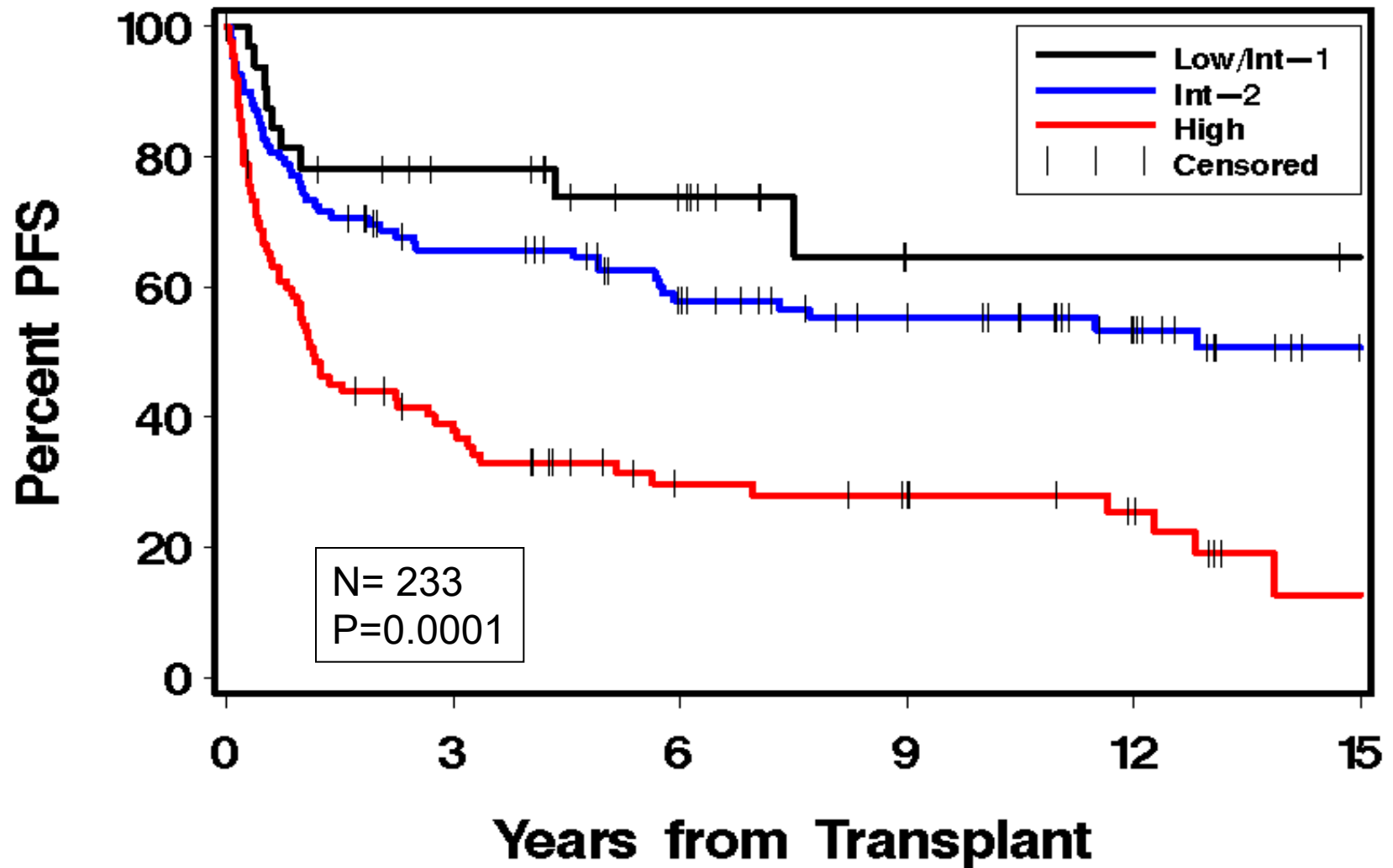
# Patient and Disease Characteristics

| Characteristic                         | N (%)           |
|----------------------------------------|-----------------|
| Donor type, no. (%)                    |                 |
| Syngeneic                              | 3 (1)           |
| Allogeneic                             | 230 (99)        |
| <b>Related donor</b>                   | <b>102 (46)</b> |
| HLA-matched                            | 101 (99)        |
| HLA-mismatched                         | 1 (1)           |
| <b>Unrelated donor</b>                 | <b>127 (57)</b> |
| 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)         |
| <b>Peripheral blood</b>                | <b>185 (79)</b> |
| Cord blood                             | 1               |

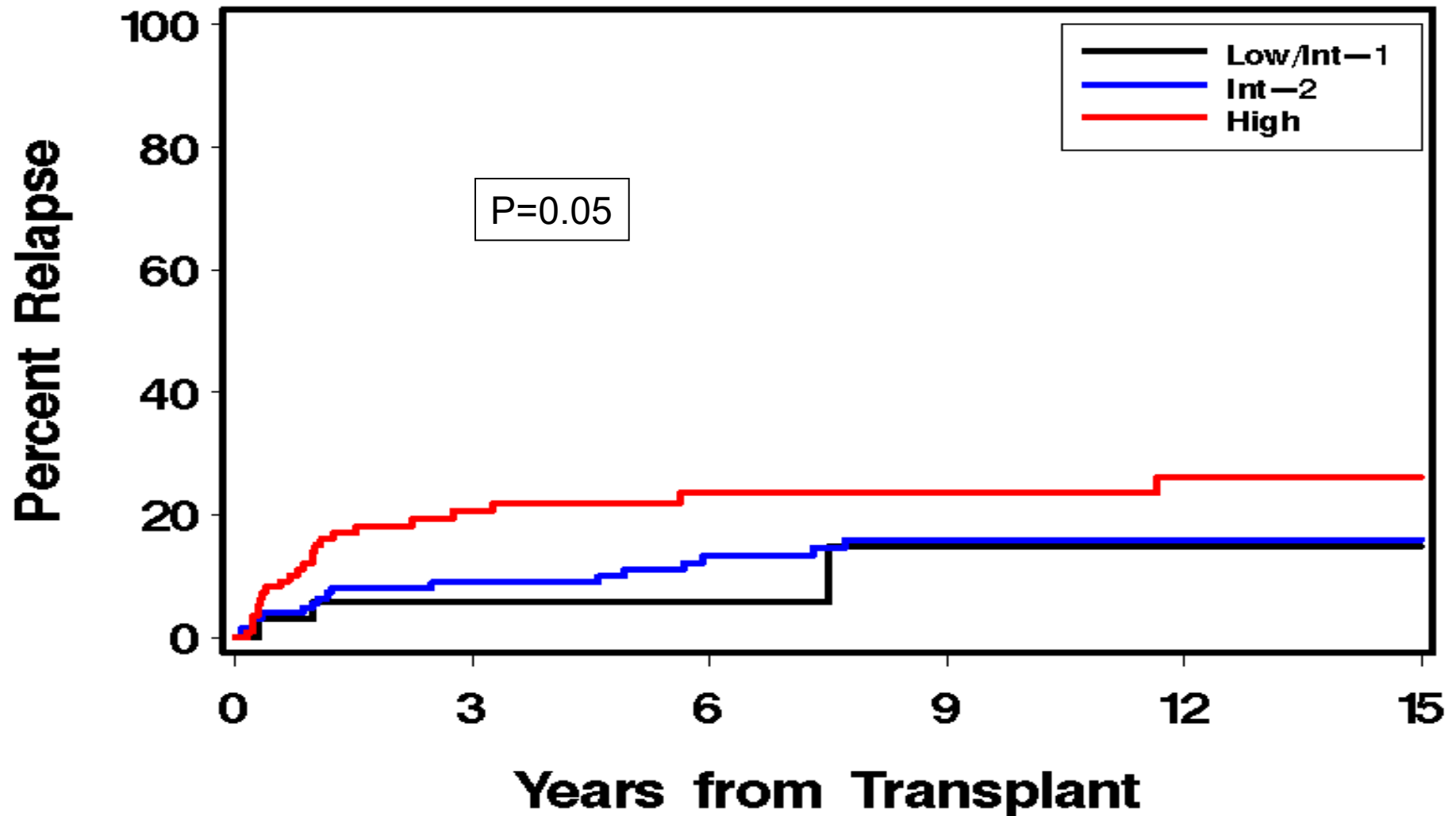
# Transplant Characteristics

Samuelson, Salit et al

# Progression-free survival by DIPSS *plus*

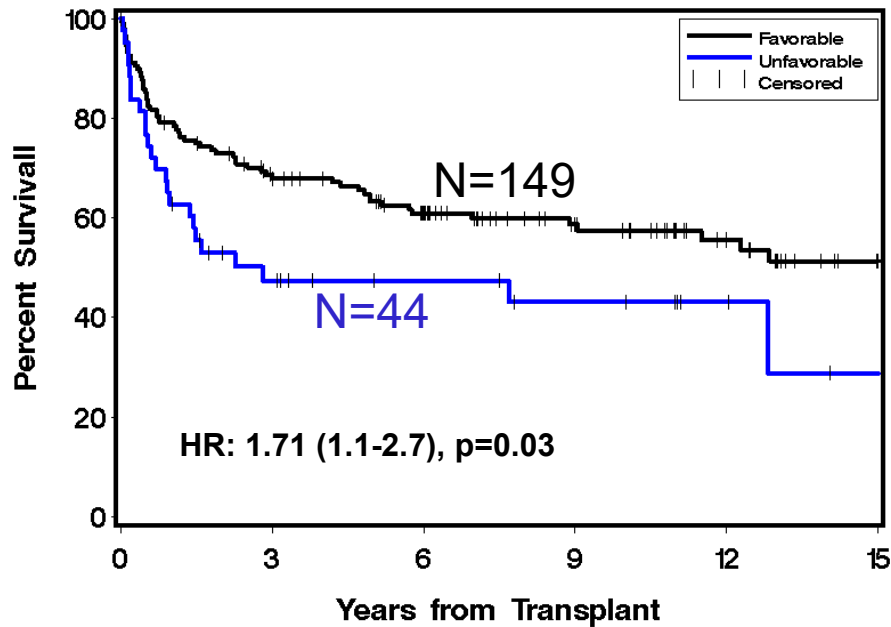


# Relapse by DIPSS plus (adjusted)

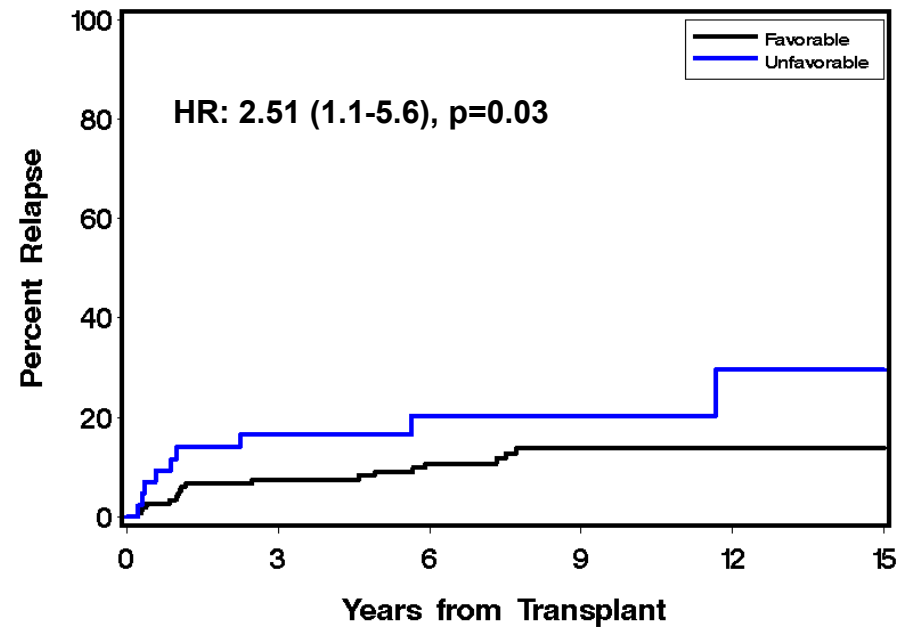


# Cytogenetics and Outcome

## Survival

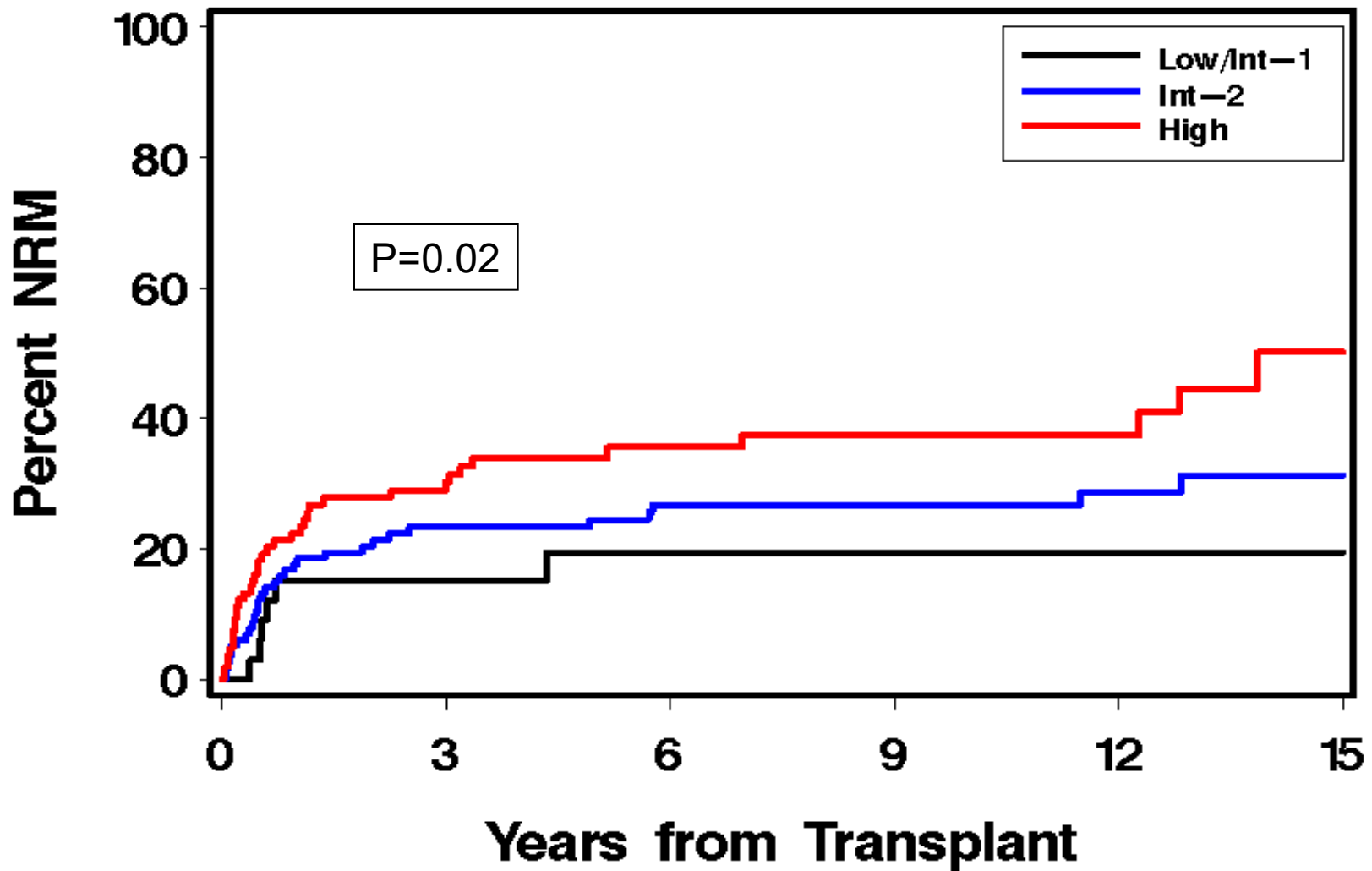


## Relapse

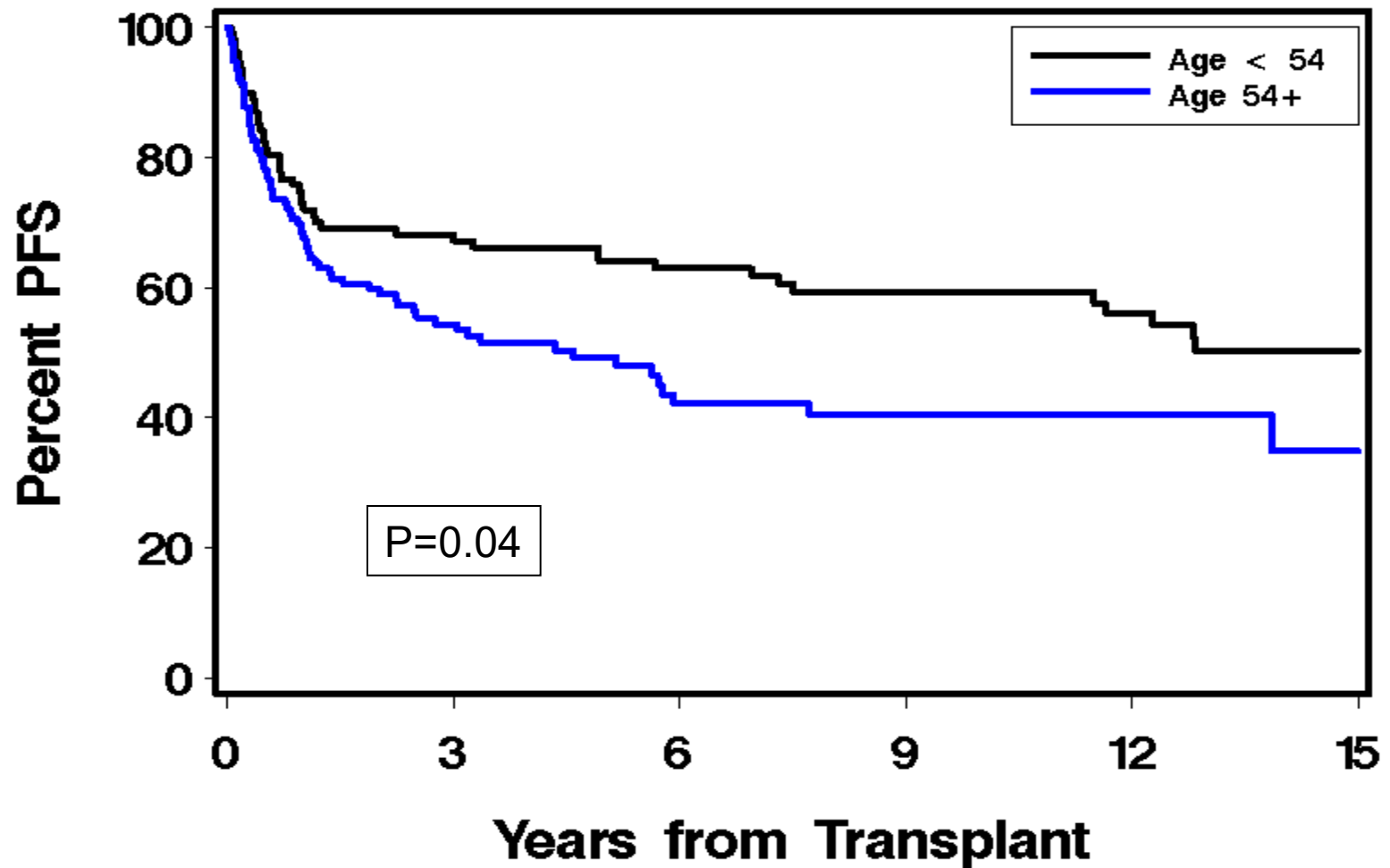


Unfavorable: +8, -7/7q-, i17q, inv3, -5/5q-, 12p-, 11q23, or  $\geq 3$  abnml

# Non-Relapse Mortality (adjusted)



# Age and Survival

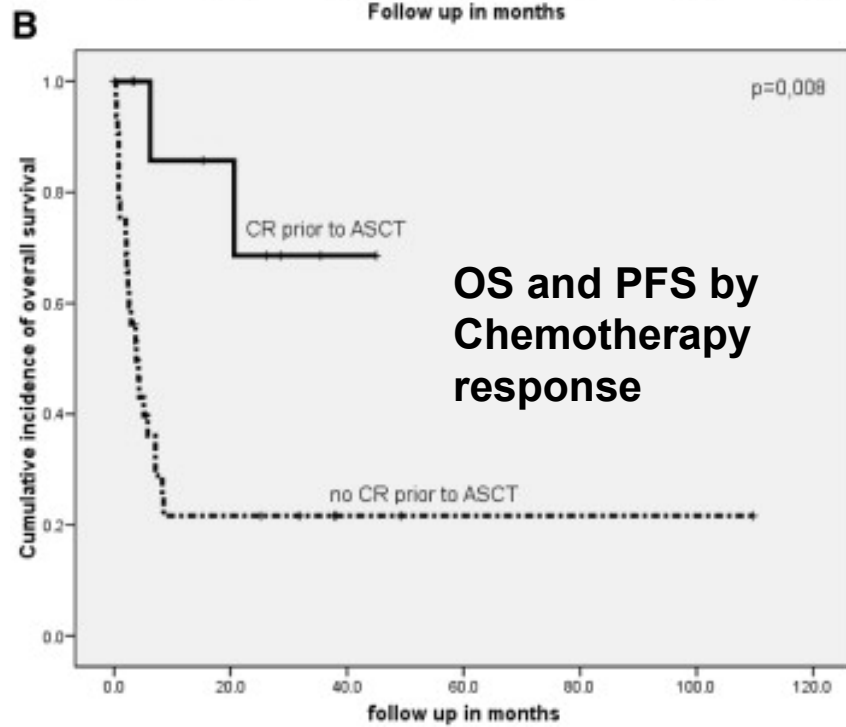
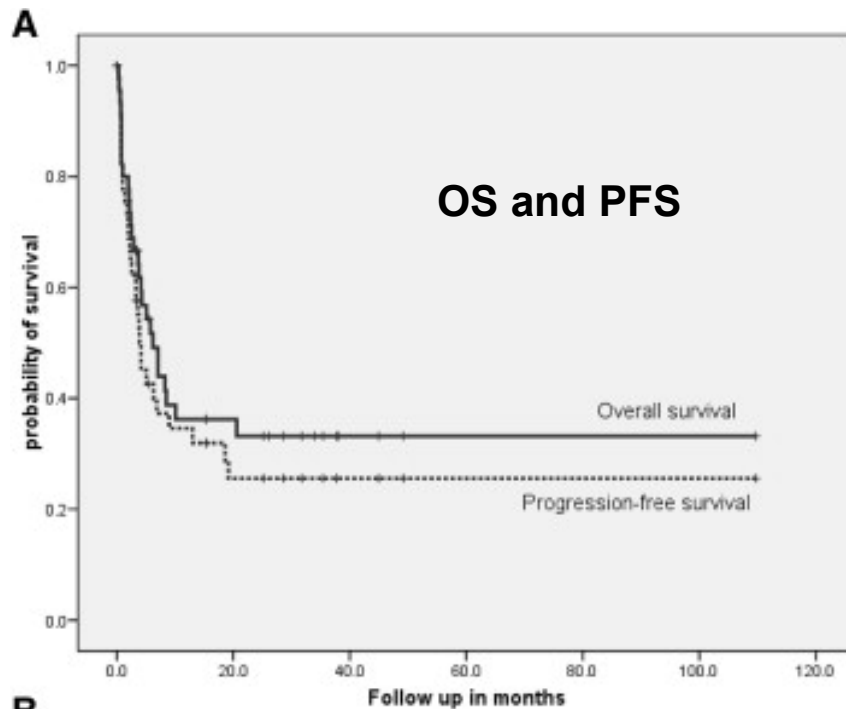


# **Progression to Leukemia**

# Risk Factors for Leukemic Transformation

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

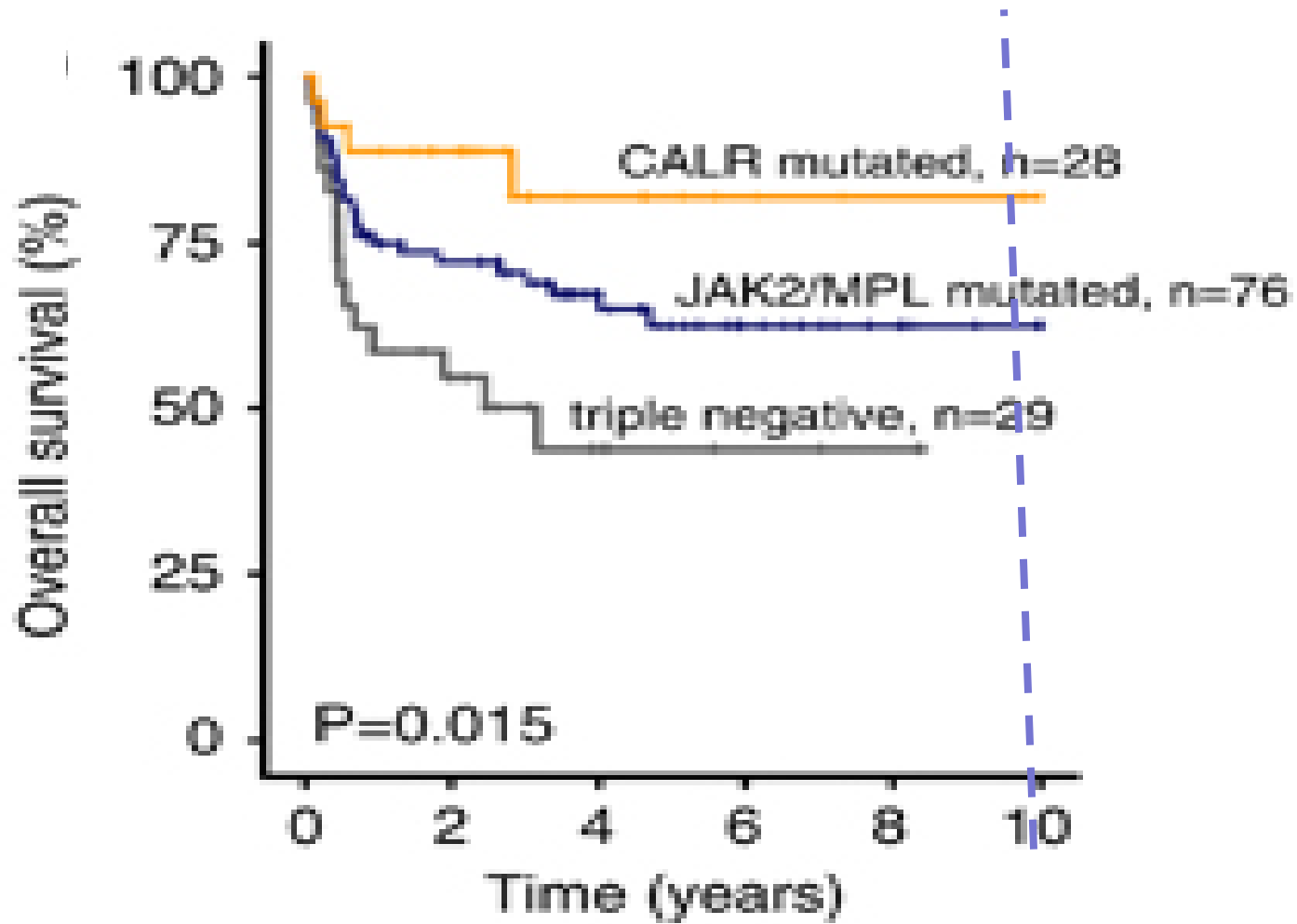
# Transplantation for Myelofibrosis with Leukemic Transformation



**And Mutations?**

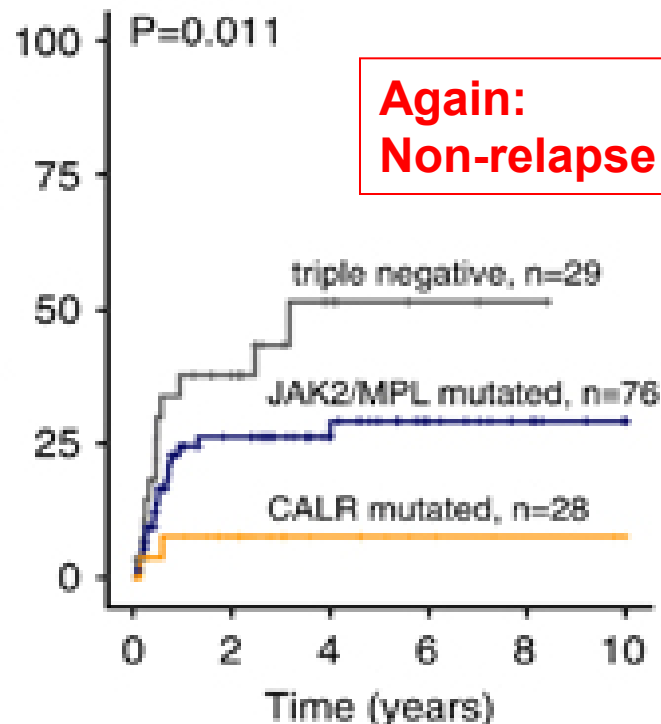
# Mutations and transplant outcome

-Survival-

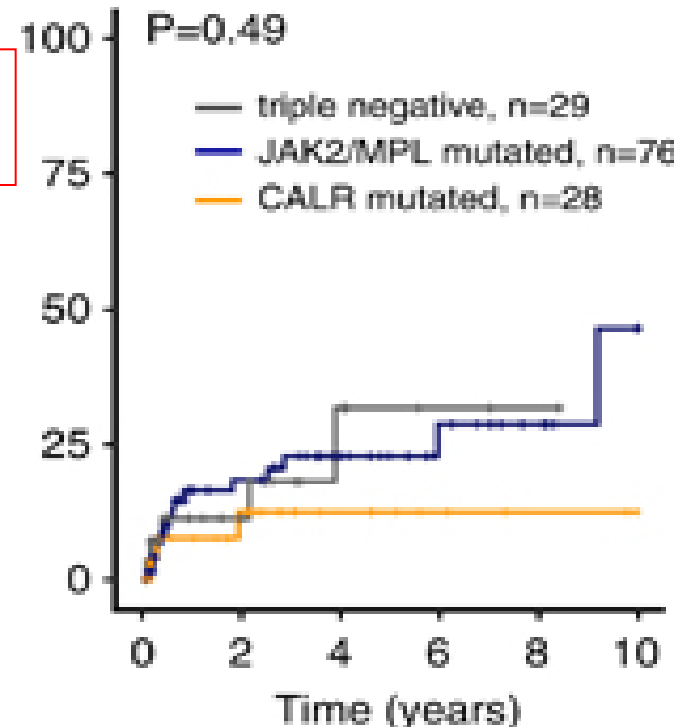


# Mutations and transplant outcome

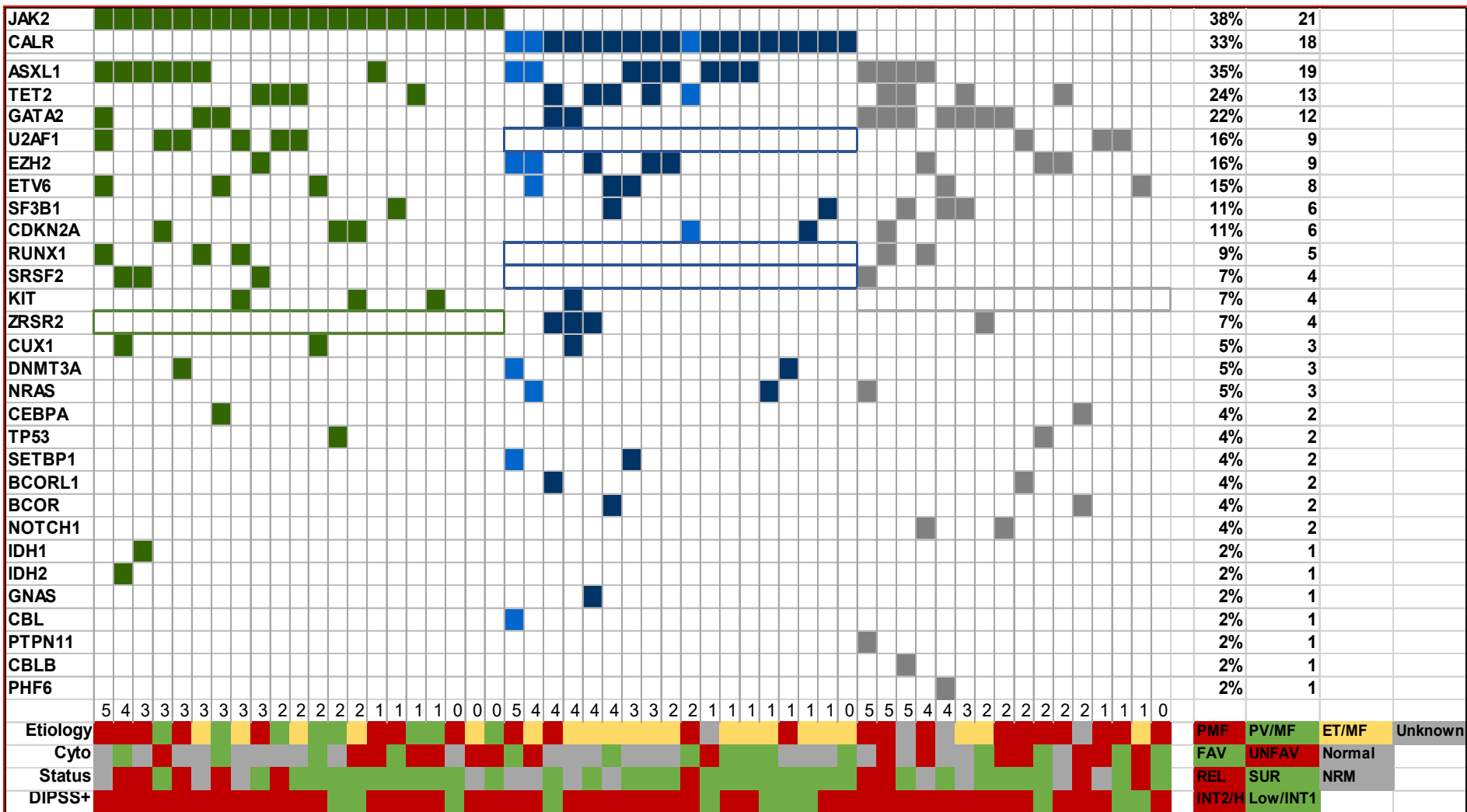
Non-Relapse Mortality



Relapse

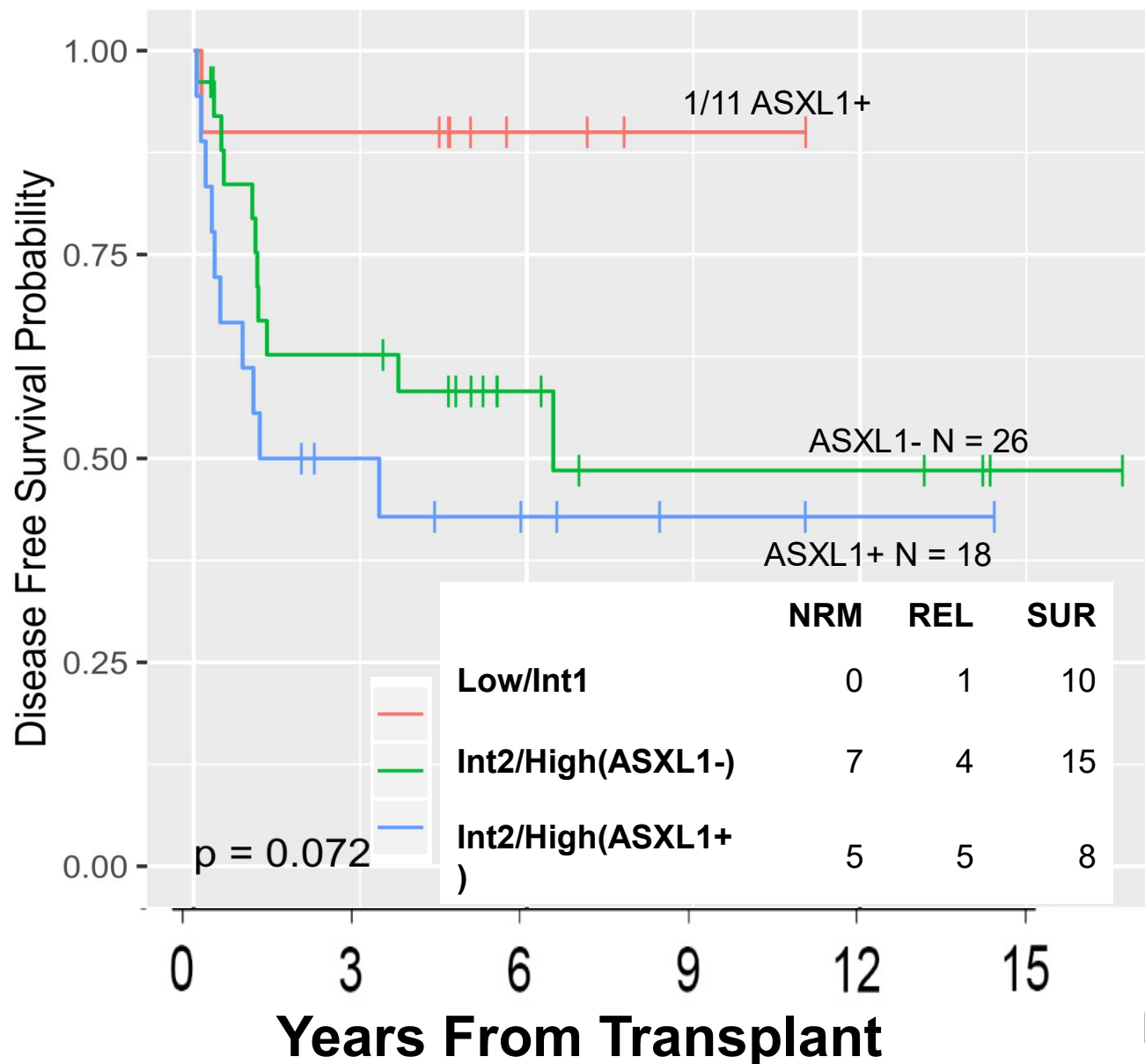


# Mutation Patterns and Outcome



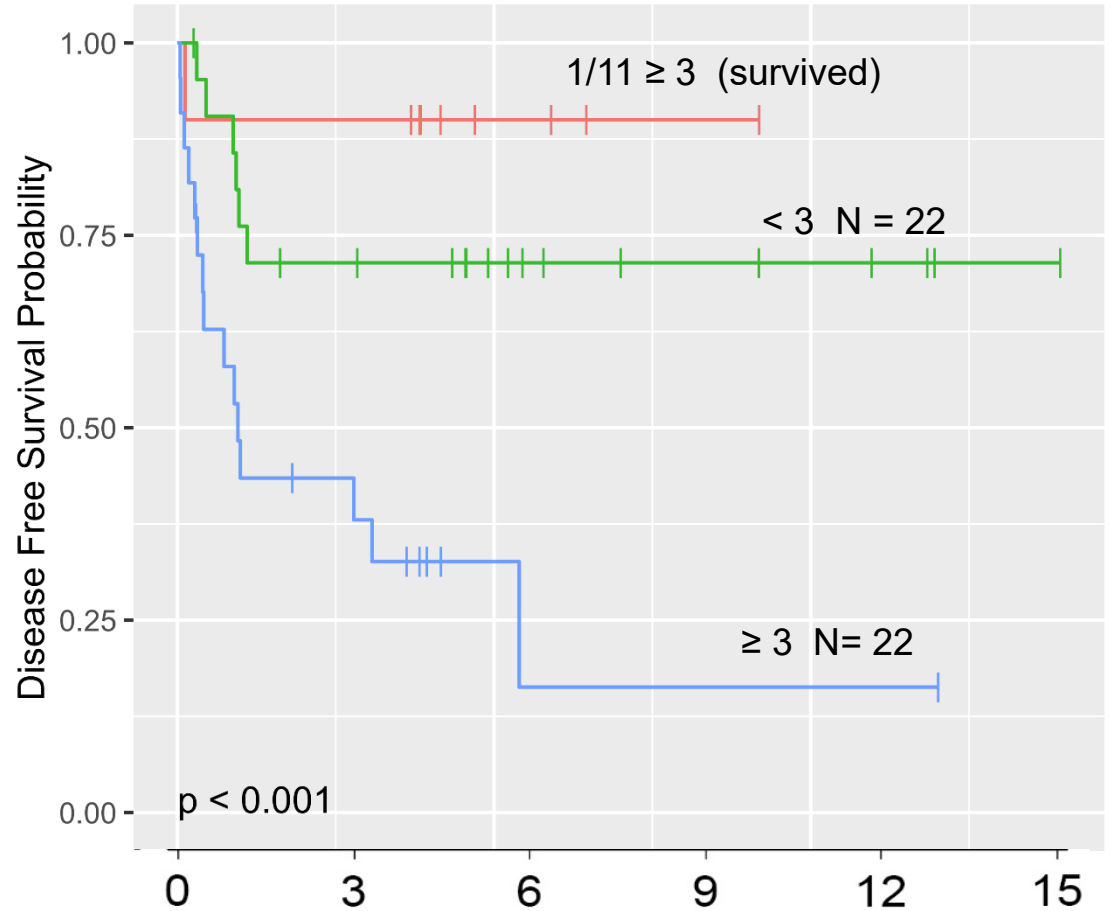
98%  $\geq 1$  mutation (ave 2.3/pt)  
PV/MF JAK2+  
CALR+ rare Unfav Cyto

# Disease-Free Survival by ASXL1

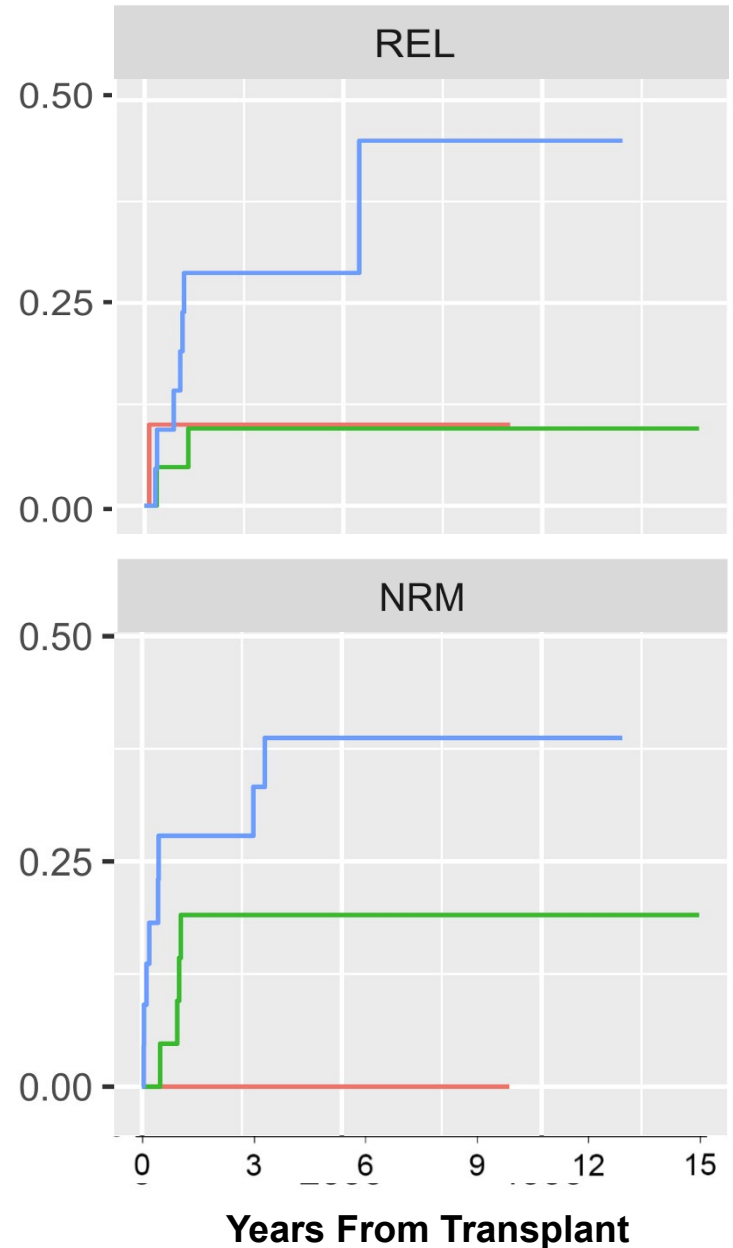


E.Stevens, unpublished

# Relapse-Free Survival by Mutation #



|                       | NRM | REL | SUR |
|-----------------------|-----|-----|-----|
| Low/Int1              | 0   | 1   | 10  |
| Int2/High(<3)         | 4   | 2   | 16  |
| Int2/High( $\geq 3$ ) | 8   | 7   | 7   |



# Association of Mutations with Other Variables

|                              | Total<br>(n = 55) | ASXL1 <sup>-</sup><br>(n = 36) | ASXL1 <sup>+</sup><br>(n = 19) | <i>p</i>         | Adjusted<br><i>p</i> |
|------------------------------|-------------------|--------------------------------|--------------------------------|------------------|----------------------|
| <b>DIPSS+ Var</b>            |                   |                                |                                | <b>&lt;0.001</b> | <b>0.0068</b>        |
| 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)                       |                  |                      |
| <b>Peripheral<br/>Blasts</b> |                   |                                |                                | <b>&lt;0.001</b> | <b>0.0062</b>        |
| No                           | 55% (30)          | 72% (26)                       | 21% (4)                        |                  |                      |
| Yes                          | 44% (24)          | 28% (10)                       | 74% (14)                       |                  |                      |

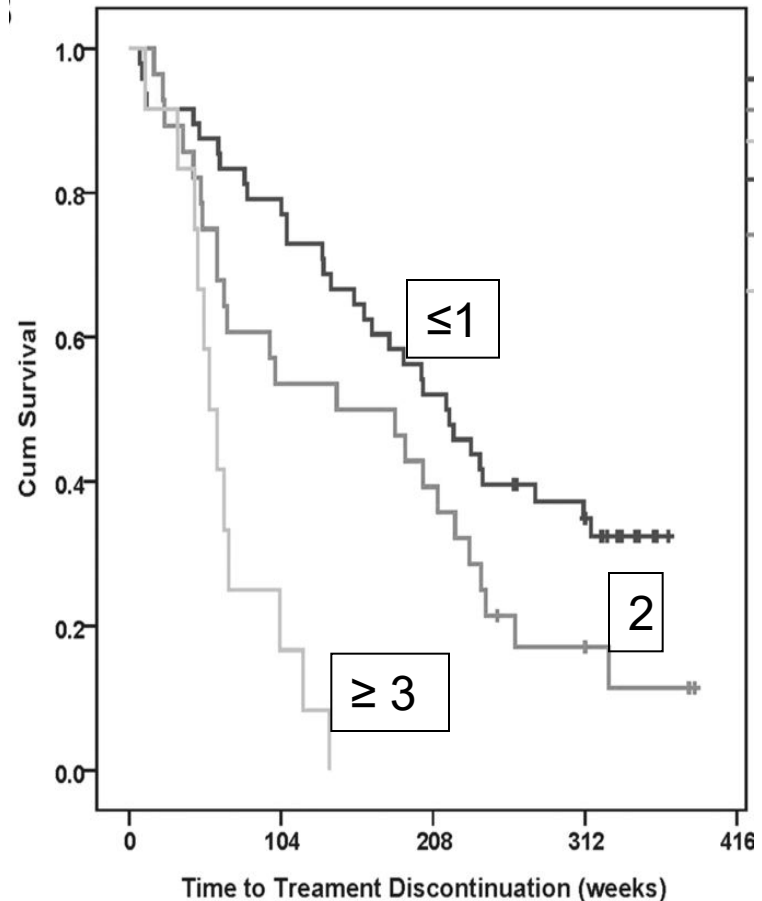
# **“Additional” Mutations and Transplant Outcome**

**(48 patients)**

|                                                      | <b>≤2<br/>mutations</b> | <b>≥3<br/>mutations</b> |
|------------------------------------------------------|-------------------------|-------------------------|
| <b>Survived &gt;1 year after<br/>Transplantation</b> | <b>79%</b>              | <b>41%</b>              |
| <b>Death from Non-Relapse<br/>Causes</b>             | <b>13%</b>              | <b>35%</b>              |
| <b>Relapse</b>                                       | <b>8%</b>               | <b>24%</b>              |

# Mutations and response to Ruxolitinib

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



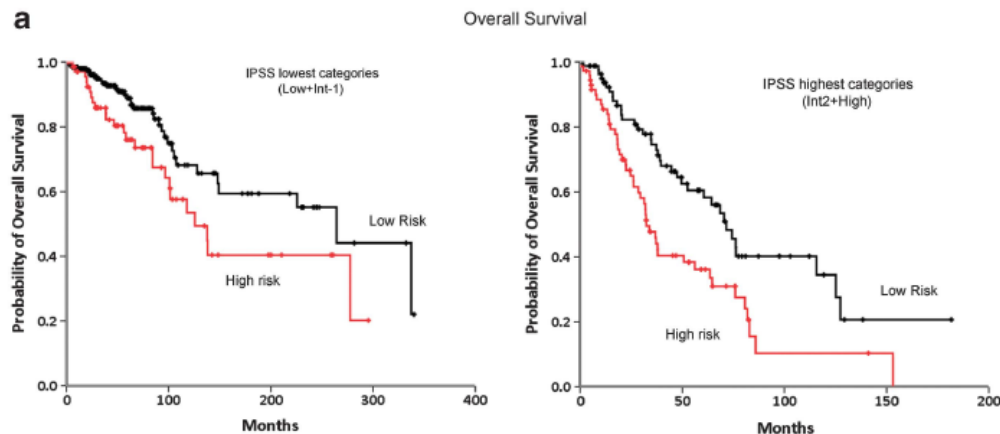
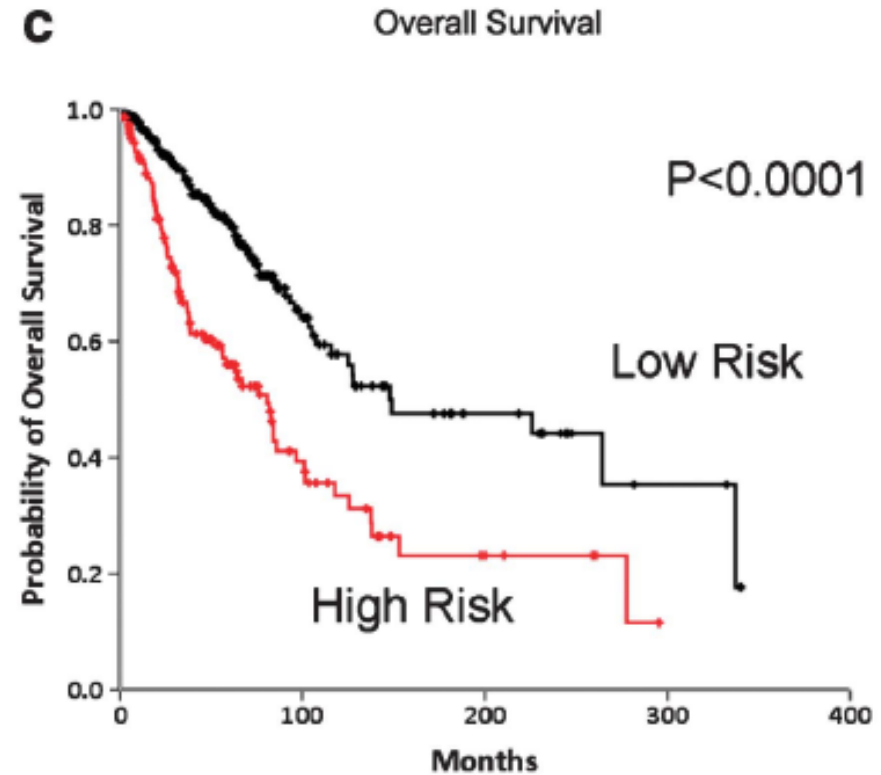
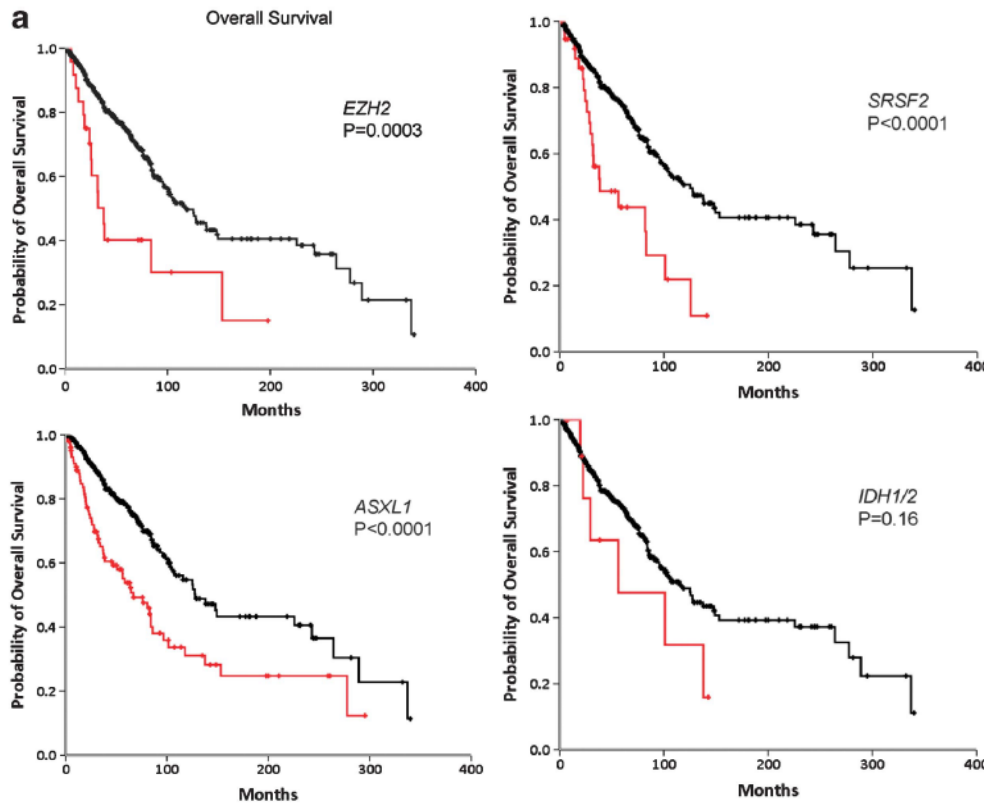
# Summary and Conclusions

- 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

# Molecular IPSS

- Growing evidence that mutations affect prognosis, some independent of the clinical risk category.
- In a European cohort of MF patients mutations in *ASXL1*, *EZH2*, *SRSF2* and *IDH1/2* were associated with poor outcomes (Vannucchi *et al.* ).
- In a cohort from Mayo Clinic, mutations in *ASXL1*, *SRSF2*, and *EZH2* were associated with worse OS, and mutations in *IDH1* and *SRSF2* with leukemic transformation.
- In a multivariate analysis, mutations in *ASXL1*, had negative prognostic significance, independent of the IPSS and DIPSS-plus category in *primary* MF.

# Overall Survival by ASXL1



**\*ASXL1, EZH2, SRSF2 and IDH1/2**

# Modified Prognostic Models

|                                      | Hazard Ratio<br>(95%CI)    | <i>p</i>      |
|--------------------------------------|----------------------------|---------------|
| CALR vs Triple-Negative              | 0.41 (0.13, 1.27)          | 0.1219        |
| JAK2 vs Triple-Negative              | 0.71 (0.27, 1.84)          | 0.4772        |
| ASXL1 + vs -                         | 1.90 (0.82, 4.41)          | 0.1339        |
| <b>≥3 vs &lt;3 Mutations</b>         | <b>3.88 (1.57, 9.55)</b>   | <b>0.0032</b> |
| Int2/High vs Low/Int1                | 6.08 (0.82, 45.28)         | 0.0781        |
| Int2/High(<3) vs Low/Int1            | 2.93 (0.35, 24.40)         | 0.3193        |
| <b>Int2/High(≥3) vs<br/>Low/Int1</b> | <b>10.91 (1.43, 82.97)</b> | <b>0.0210</b> |



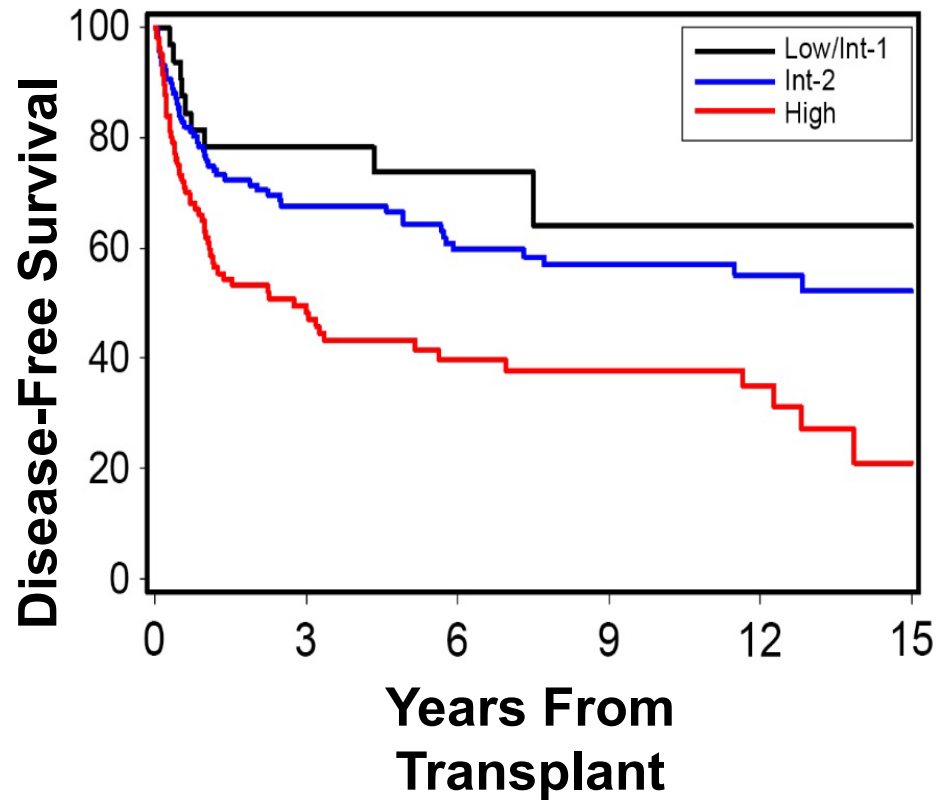
# Associated Variables

|                     | Total<br>(n = 55) | <3 mutations<br>(n = 31) | ≥3 mutations<br>(n = 24) | <i>p</i>      | Adjusted<br><i>p</i> |
|---------------------|-------------------|--------------------------|--------------------------|---------------|----------------------|
| <b>Cytogenetics</b> |                   |                          |                          | <b>0.0058</b> | 0.087                |
| <b>Normal</b>       | 42% (23)          | 26% (8)                  | 62% (15)                 |               |                      |
| <b>Abnormal</b>     | 58% (32)          | 74% (23)                 | 38% (9)                  |               |                      |
| <b>Cytogenetics</b> |                   |                          |                          | <b>0.0386</b> | 0.502                |
| <b>Unfavorable</b>  | 29% (16)          | 39% (12)                 | 17% (4)                  |               |                      |
| <b>Normal</b>       | 44% (24)          | 29% (9)                  | 62% (15)                 |               |                      |
| <b>Favorable</b>    | 27% (15)          | 32% (10)                 | 21% (5)                  |               |                      |

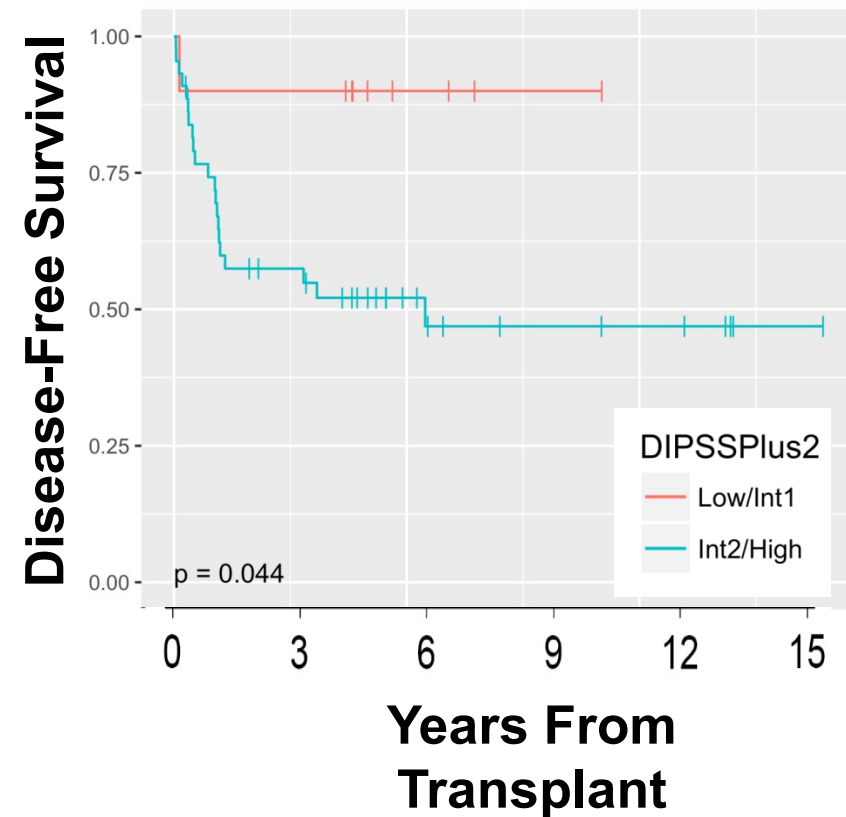
|                              | Total<br>(n = 55) | ASXL1 <sup>-</sup><br>(n = 36) | ASXL1 <sup>+</sup><br>(n = 19) | <i>p</i>         | Adjusted<br><i>p</i> |
|------------------------------|-------------------|--------------------------------|--------------------------------|------------------|----------------------|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

# Disease-Free Survival by DIPSS-Plus

**DIPPS + cohort (n= 233)**



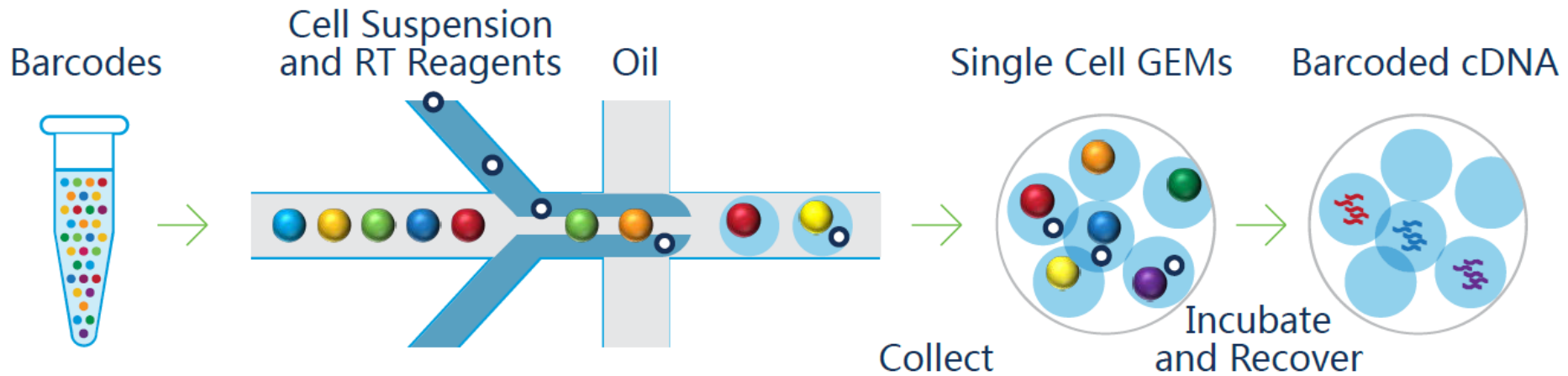
**Molecular cohort (n= 55)**



# Additional Mutations (48 Patients)

|         | CALR+ (38%) |  |  |  |  |         |  |  |  |  | JAK2+ (29%) |  |  |  |  |  |  |  |  |  | Triple Negative (33%) |  |  |  |  |  |  |  |  |  | % patients |  |
|---------|-------------|--|--|--|--|---------|--|--|--|--|-------------|--|--|--|--|--|--|--|--|--|-----------------------|--|--|--|--|--|--|--|--|--|------------|--|
|         | Type I      |  |  |  |  | Type II |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  |            |  |
|         |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  |            |  |
| ASXL1   |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 31%        |  |
| ETV6    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 23%        |  |
| U2AF1   |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 17%        |  |
| SF3B1   |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 17%        |  |
| EZH2    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 13%        |  |
| RUNX1   |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 10%        |  |
| TET2    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 10%        |  |
| CDKN2A  |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 8%         |  |
| DNMT3A  |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 8%         |  |
| GATA2   |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 8%         |  |
| ZRSR2   |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 8%         |  |
| NRAS    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 6%         |  |
| BCOR    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 4%         |  |
| BCORL1  |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 4%         |  |
| CEBPA   |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 4%         |  |
| NOTCH1  |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 4%         |  |
| SETBP1A |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 4%         |  |
| CBL     |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 2%         |  |
| CBLB    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 2%         |  |
| CUX1    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 2%         |  |
| GNAS    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 2%         |  |
| PHF6    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 2%         |  |
| PTPN11  |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 2%         |  |
| SRSF2   |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 2%         |  |
| TP53    |             |  |  |  |  |         |  |  |  |  |             |  |  |  |  |  |  |  |  |  |                       |  |  |  |  |  |  |  |  |  | 2%         |  |

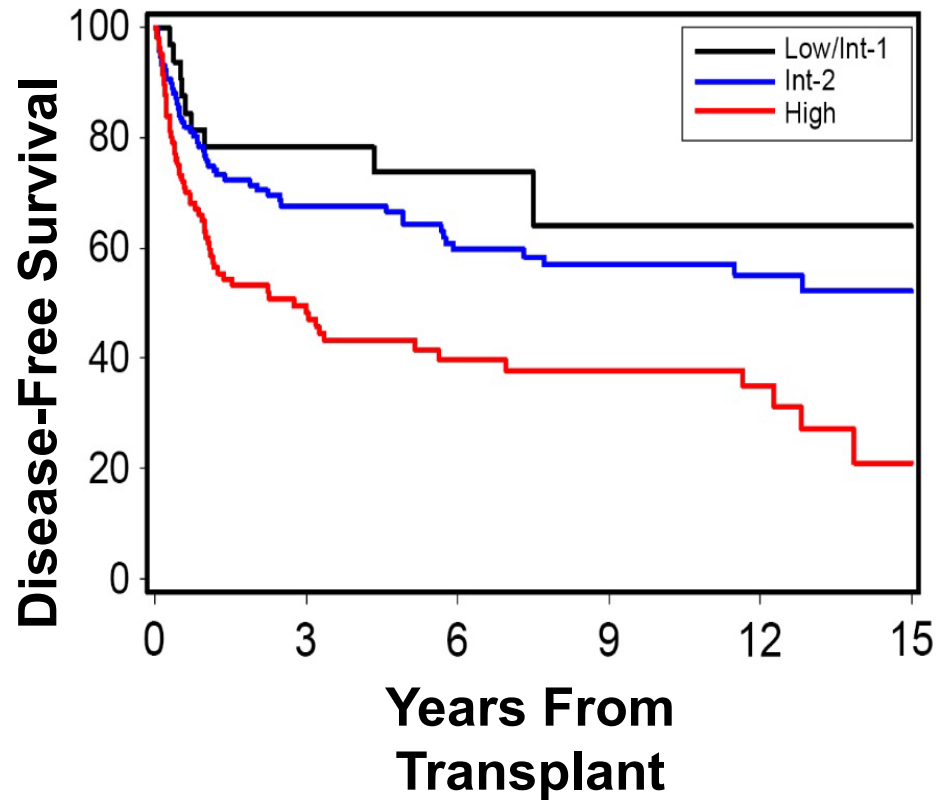
# 10x Genomics 3' Single Cell RNAseq



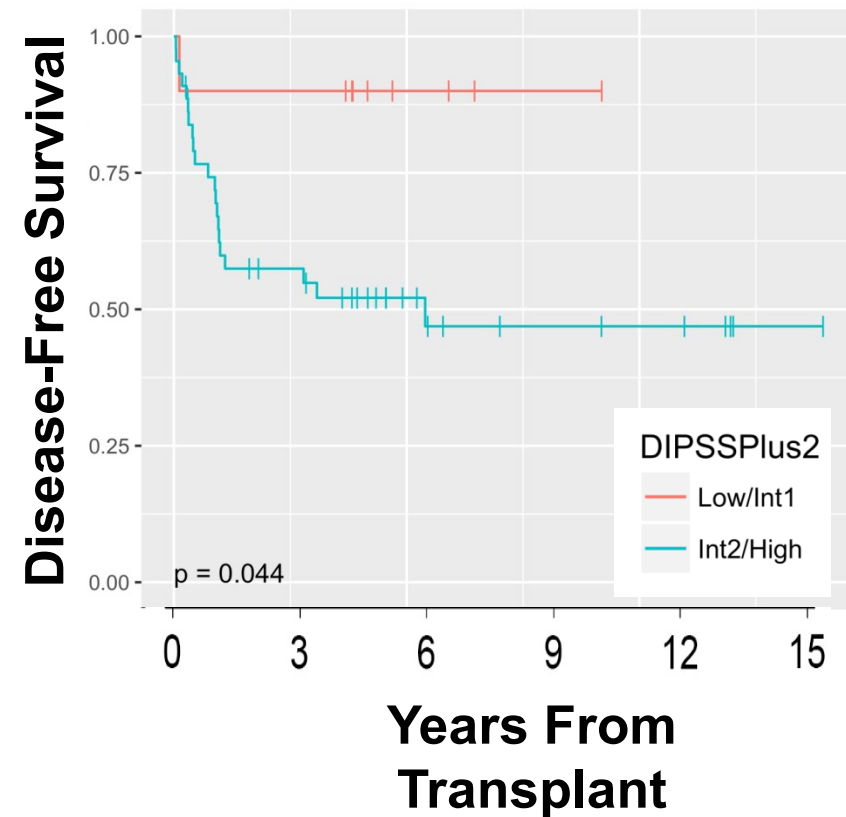
- Use RNAseq expression profile to identify cell subtype
- 3'SNVs to characterize donor/host origin

# Disease-Free Survival by DIPSS-Plus

**DIPPS + cohort (n= 233)**



**Molecular cohort (n= 55)**



# Thank you

H.J.Deeg, MD  
[jdeeg@fhcrc.org](mailto:jdeeg@fhcrc.org)



# Transplantation

# **Factors not considered in classification *but important for transplantation***

- **Fibrosis in liver, lung, other organs**
- **Duration of the disease**
- **Big spleen/Portal hypertension**
- (Mutations
  - JAK2, MPL1, CALR
  - ASXL1, TP53 etc))

# **Transplant Results**

# Patient and Disease Characteristics

|                                                              |                         |
|--------------------------------------------------------------|-------------------------|
| <b>No. of patients</b>                                       | <b>170</b>              |
| <b>Age (ys) range (median)</b>                               | <b>12.1–78.9 (51.5)</b> |
| <b>Months from diagnosis to HCT<br/>(ms), range (median)</b> | <b>2-314 (15)</b>       |
| <b>Type of myelofibrosis,#</b>                               |                         |
| <b>Primary /post-ET/-post-PV</b>                             | <b>102 / 46/22</b>      |
| <b>JAK2 mutation, #</b>                                      |                         |
| <b>yes/no</b>                                                | <b>43/51</b>            |
| <b>Unknown</b>                                               | <b>76</b>               |

# Disease Characteristics (No./%)

- **Splenectomy<sup>1</sup>**

|           |                 |
|-----------|-----------------|
| <b>No</b> | <b>136 (80)</b> |
|-----------|-----------------|

|            |                |
|------------|----------------|
| <b>Yes</b> | <b>31 (18)</b> |
|------------|----------------|

- **DIPSS Score**

|              |                |
|--------------|----------------|
| • <b>Low</b> | <b>21 (12)</b> |
|--------------|----------------|

|                         |                |
|-------------------------|----------------|
| • <b>Intermediate-1</b> | <b>48 (28)</b> |
|-------------------------|----------------|

|                         |                |
|-------------------------|----------------|
| • <b>Intermediate-2</b> | <b>50 (30)</b> |
|-------------------------|----------------|

|               |                |
|---------------|----------------|
| • <b>High</b> | <b>51 (30)</b> |
|---------------|----------------|

1 = Data missing in 3

# Transplant Characteristics

- **Related Donor** **N= 83 (50%)**
- **Unrelated Donor** **N= 84 (50%)**
- **Source of Stem Cells**
  - **Bone Marrow** **N= 45 (26%)**
  - **Peripheral Blood** **N=125 (74%)**

# Targeted Sequencing

- 48 patients with MF (36% PMF)
- Pre-HCT BM (3w-5m pre-HCT)
- 2000-2015
- 55% female
- 50% splenomegaly
- Average age 55 (23-72)
- 55% abnormal cytogenetics
- DIPSS+ low/Int1—12.5%, Int-2/high—87.5%
- 77% High-dose Conditioning
- 25% sibling donor
- 15% relapsed, 23% NRM
- Ave 2.4 variants per patient
- Most common variants: ASXL1 and IKZF1

|                                                            | Chronic myeloid neoplasms                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                      |
|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
|                                                            | Myelodysplastic syndromes                                                                                                  | Myelodysplastic syndromes/<br>myeloproliferative neoplasms<br>overlap                                                                                                                                                                                                                                                                                                                                 | Myeloproliferative neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                            | Myeloid and lymphoid<br>neoplasms with eosinophilia<br>and <i>PDGFR/FGFR1</i> mutation                               |
| Peripheral blood or bone<br>marrow morphology              | Absence of cytosis                                                                                                         | Dyserythropoiesis<br>Dysgranulopoiesis                                                                                                                                                                                                                                                                                                                                                                | Monocytosis<br>Granulocytosis<br>Thrombocytosis                                                                                                                                                                                                                                                                                                                                                                                                                         | Erythrocytosis<br>Mastocytosis<br>Eosinophilia                                                                       |
| Disease<br>Associated mutation(s)<br>(estimated frequency) | Myelodysplastic syndrome<br><i>TET2</i> (20%)<br><br>Refractory anemia with ring<br>sideroblasts<br><i>SF3B1</i> (80%-90%) | Chronic myelomonocytic<br>leukemia<br><i>TET2</i> (40%-60%)<br><i>SRSF2</i> (30%-50%)<br><i>ASXL1</i> (40%)<br><br>Refractory anemia with ring<br>sideroblasts associated with<br>marked thrombocytosis<br><i>SF3B1</i> (80%-90%)<br><i>JAK2V617F</i> (50%)<br><br>Atypical chronic myeloid<br>leukemia<br><i>SETBP1</i> (30%)<br><br>Myelodysplastic/myeloprolif-<br>erative neoplasm—unclassifiable | Chronic myeloid leukemia<br><i>BCR-ABL1</i> (100%)<br><br>Polycythemia vera<br><i>JAK2</i> (99%)<br><br>Essential thrombocythemia<br><i>JAK2/CALR/MPL</i> (85%)<br><br>Primary myelofibrosis<br><i>JAK2/CALR/MPL</i> (90%)<br><br>Chronic neutrophilic leukemia<br><i>CSF3R</i> (80%-100%)<br><i>SETBP1</i> (30%)<br><br>Systemic mastocytosis<br><i>KITD816V</i> (80%-100%)<br><br>Chronic eosinophilic leukemia<br><br>Myeloproliferative neoplasm—<br>unclassifiable | Myeloid and lymphoid neoplasms<br>with eosinophilia and <i>PDGFRA</i> ,<br><i>PDGFRB</i> , or <i>FGFR1</i> mutations |

## From: Myeloproliferative Neoplasms: A Contemporary Review

JAMA Oncol. 2015;1(1):97-105. doi:10.1001/jamaoncol.2015.89

Table. Mutations in Myeloproliferative Neoplasms (MPNs)

|                                                       |                     | Approximate Mutational Frequency, % |                           |                       |                 |
|-------------------------------------------------------|---------------------|-------------------------------------|---------------------------|-----------------------|-----------------|
| Mutation                                              | Chromosome Location | Polycythemia Vera                   | Essential Thrombocythemia | Primary Myelofibrosis | Blast-Phase MPN |
| Specific to MPN                                       |                     |                                     |                           |                       |                 |
| JAK2                                                  |                     |                                     |                           |                       |                 |
| Exon 14 mutation; ie, JAK2V617F                       | 9p24                | 95                                  | 55                        | 60                    | 40              |
| Exon 12 mutations                                     | 9p24                | 3                                   | Infrequent                | Infrequent            | Infrequent      |
| CALR Exon 9 deletions and insertions                  | 19p13.2             | Infrequent                          | 25                        | 25                    | 25              |
| MPL Exon 10 mutations                                 | 1p34                | Infrequent                          | 3                         | 7                     | 8               |
| LNK (as in Links; aka SH2B3) exon 2 mutations         | 12q24.12            | Infrequent                          | Infrequent                | Infrequent            | 10              |
| Nonspecific to MPN                                    |                     |                                     |                           |                       |                 |
| TET2 Mutations involve several exons                  | 4q24                | 16                                  | 5                         | 17                    | 17              |
| ASXL1 Exon 12 mutations                               | 20q11.1             | 7                                   | 4                         | 20                    | 18              |
| IDH1/IDH2 Exon 4 mutations                            | 2q33.3/15q26.1      | 2                                   | 1                         | 4                     | 22              |
| EZH2 Mutations involve several exons                  | 7q36.1              | Infrequent                          | Infrequent                | 5                     | Infrequent      |
| DNMT3A Most frequent mutations affect amino acid R882 | 2p23                | 7                                   | 3                         | 7                     | 17              |
| CBL Exon 8/9 mutations                                | 11q23.3             | Infrequent                          | Infrequent                | 4                     | Infrequent      |
| IKZF1 Mostly deletions including intragenic           | 7p12                | Infrequent                          | Infrequent                | Infrequent            | 21              |
| TP53 Exons 4 through 9                                | 17p13.1             | Infrequent                          | Infrequent                | 4                     | 11              |
| SF3B1 Exons 14 and 15, mostly                         | 2q33.1              | Infrequent                          | Infrequent                | 7                     | 4               |
| SRSF2 Exon 2                                          | 17q25.1             | Infrequent                          | Infrequent                | 17                    | 19              |
| U2AF1                                                 | 21q22.3             | Infrequent                          | Infrequent                | 16                    | 6               |
| SETBP1 Exon 4                                         | 18q21.1             | Infrequent                          | Infrequent                | 2.5                   | 7               |

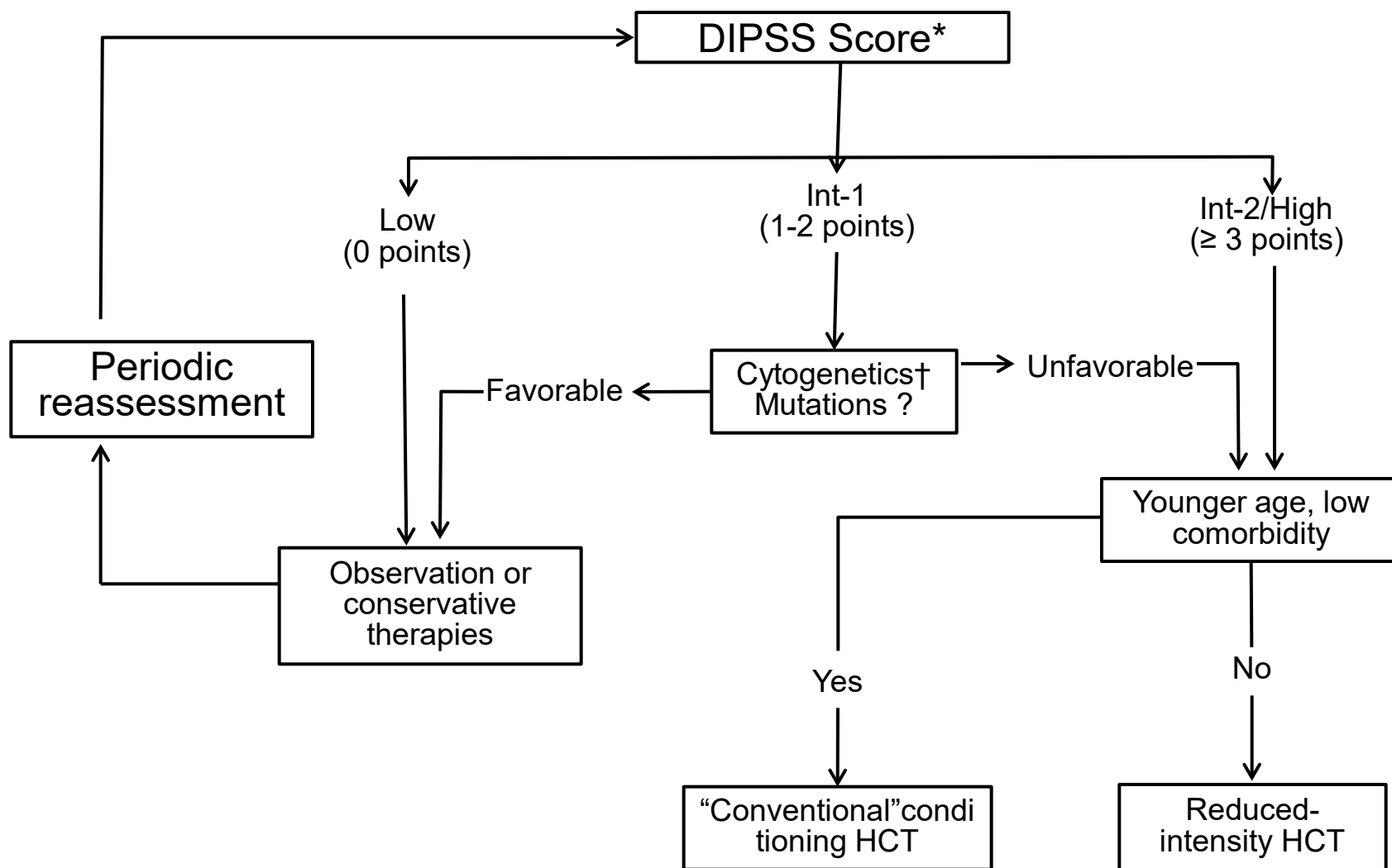
Abbreviations: *ASXL1*, additional sex combs-like 1; *CALR*, calreticulin; *CBL*, casitas B-lineage lymphoma proto-oncogene; *DNMT3A*, DNA cytosine methyltransferase; *EZH2*, enhancer of zeste homologue 2; *IDH1/IDH2*, isocitrate dehydrogenase; *IKZF1*, IKAROS family zinc finger 1; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukemia virus oncogene; *SETBP1*, SET binding protein 1; *SF3B1*, splicing factor 3B subunit 1; *SRSF2*, serine/arginine-rich splicing factor; *TET2*, TET oncogene family member; *TP53*, tumor protein p53.

Table Title:

Mutations in Myeloproliferative Neoplasms (MPNs)

# More Questions:

- New drugs and transplantation
  - What effects?
- Do those therapies *reduce or increase* co-morbidities?
- Role of calreticulin receptor?
- .....and more

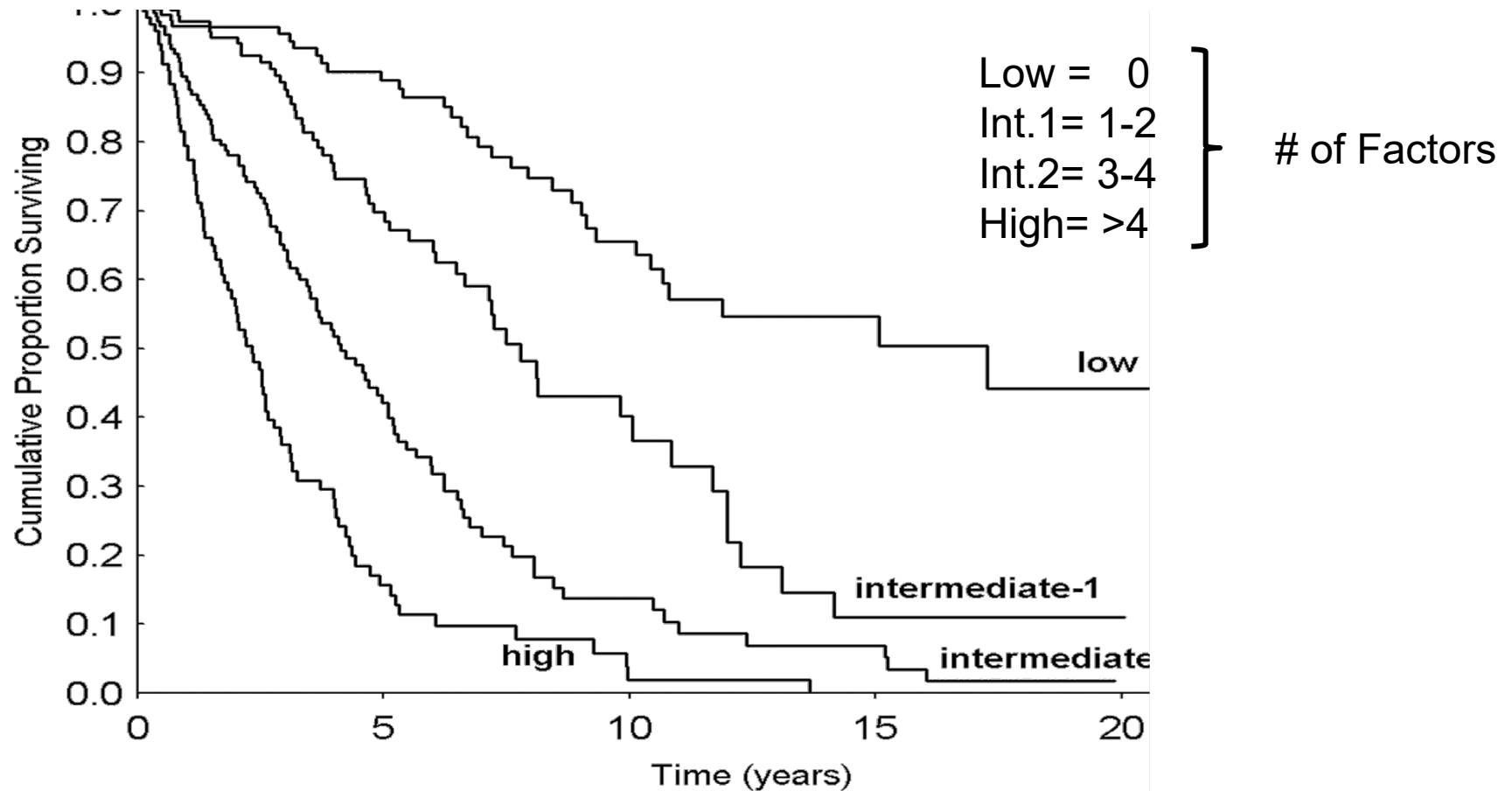


\*Dynamic International Prognostic Scoring System: age > 65 years (1 point), leukocyte count > 25,000/ $\mu$ L (1 point), hemoglobin < 10 g/dL (2 points), circulating blast cells  $\geq$  1% (1 point), presence of constitutional symptoms [weight loss > 10%, night sweats, or fever] (1 point).

†Unfavorable cytogenetics: +8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), 11q23 rearrangements, or complex.

# DIPSS and Survival

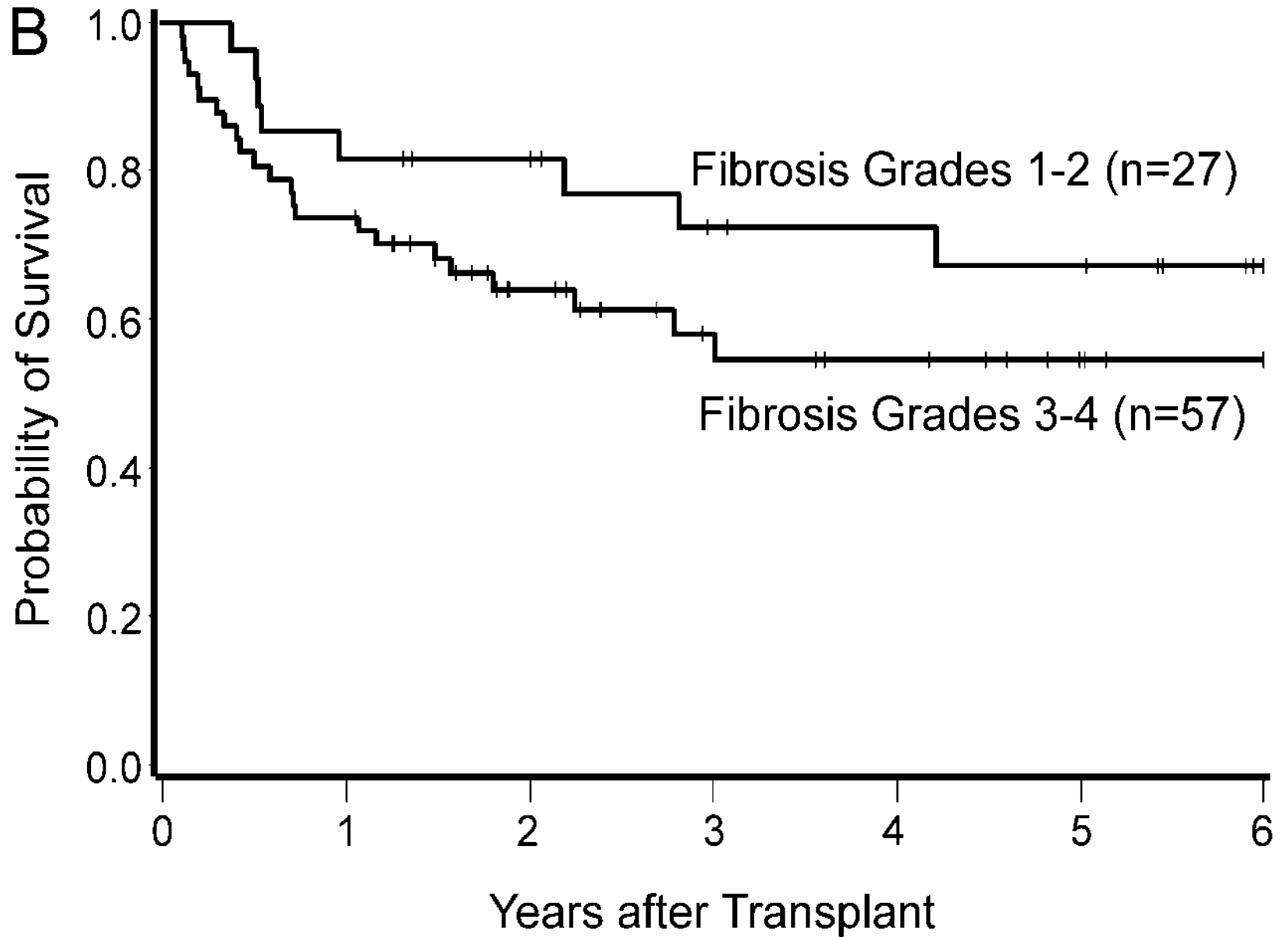
(no transplant – *without* JAK2 inhibitors)



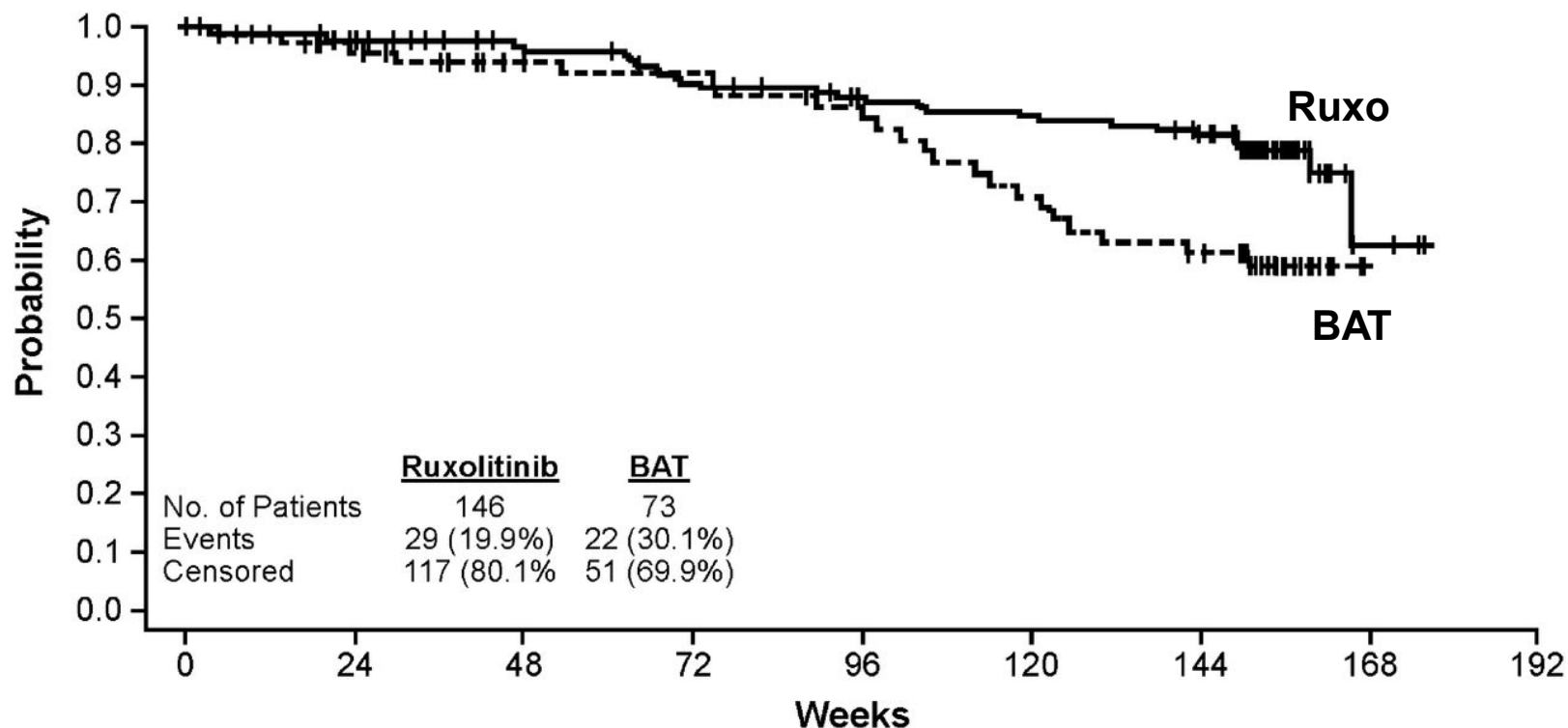
# More Questions:

- Donor selection
  - Related vs unrelated, cord blood and HLA-haploidentical relatives
- GVHD prevention
- Is it appropriate to offer HCT to patients of any age?

# Marrow Fibrosis



# Overall survival (COMFORT-II Trial)



— Ruxolitinib, n=

146      138      127      117      109      105      98      4      0

--- BAT, n=

73      61      51      49      45      37      31      0      0

Hazard ratio, 0.48; 95% CI, 0.28-0.85; log-rank  $P = .009$ ; unadjusted for multiple comparisons.

Cervantes F et al. Blood 2013;122:4047-4053

# A few questions:

- Is *any* treatment indicated ?
- Which factors help us make a decision?
- Relevance of parameters *not currently scored*
- What is special about transplantation?
- What makes a good transplant candidate?
- What should it be?

# DIPSS and Survival

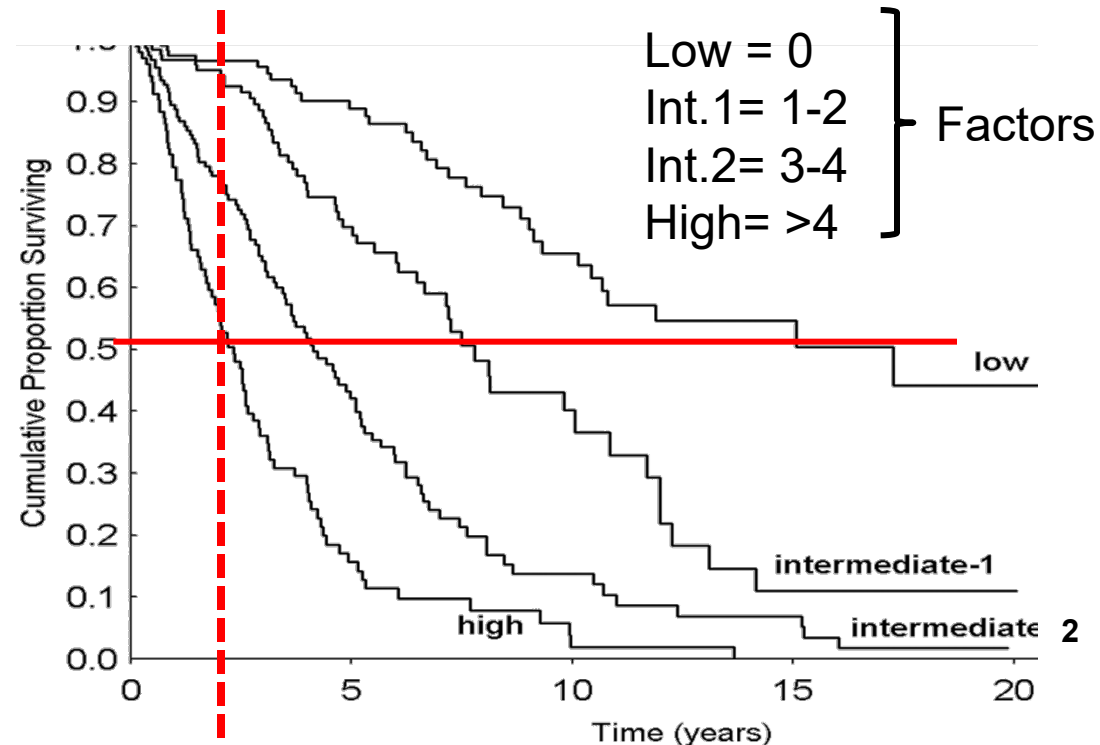
(no transplant –  
*without* JAK2 inhibitors)

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

**DIPSS**

**DIPSS plus**

- Abnormal chromosomes
- Low platelet count
- Requiring transfusions



# Will (currently available) Jak1/2 inhibitors be useful?

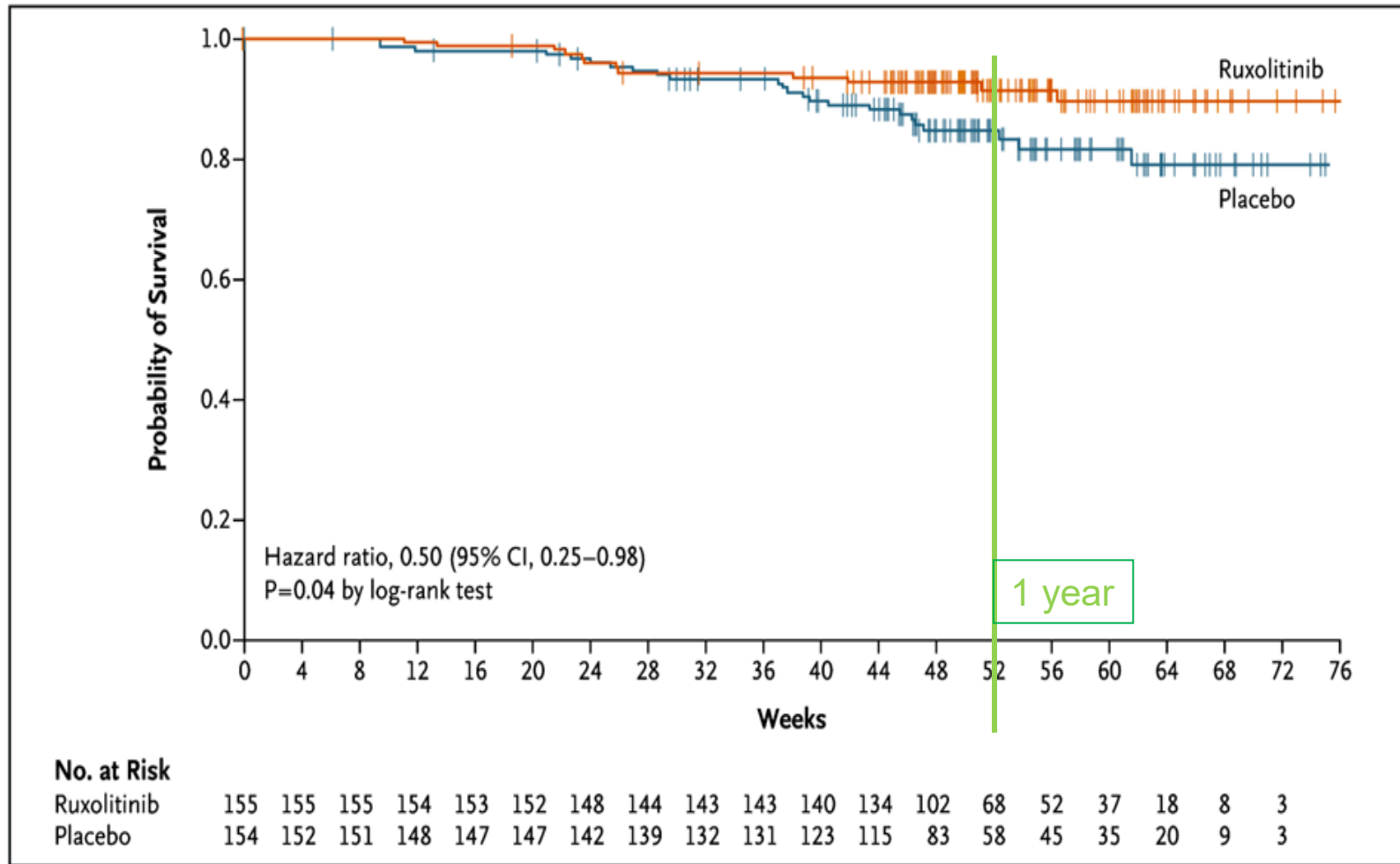
- PMF
  - Systemic symptoms
  - Painful splenomegaly
- P.vera
  - Elevated hematocrit
- E.T.
  - Elevated platelets

} Yes, but not in all patients

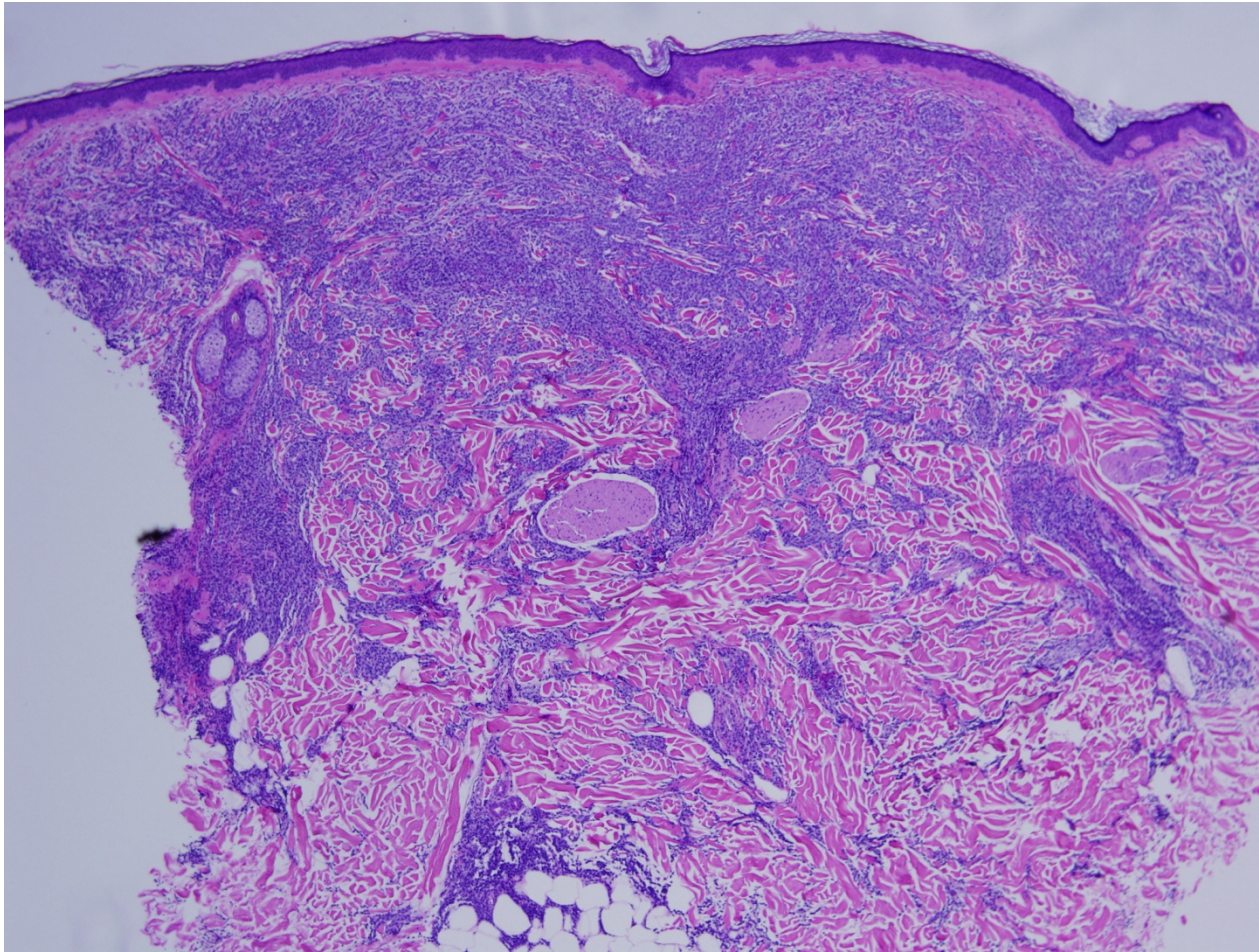
?

?

# MF, phase III - survival

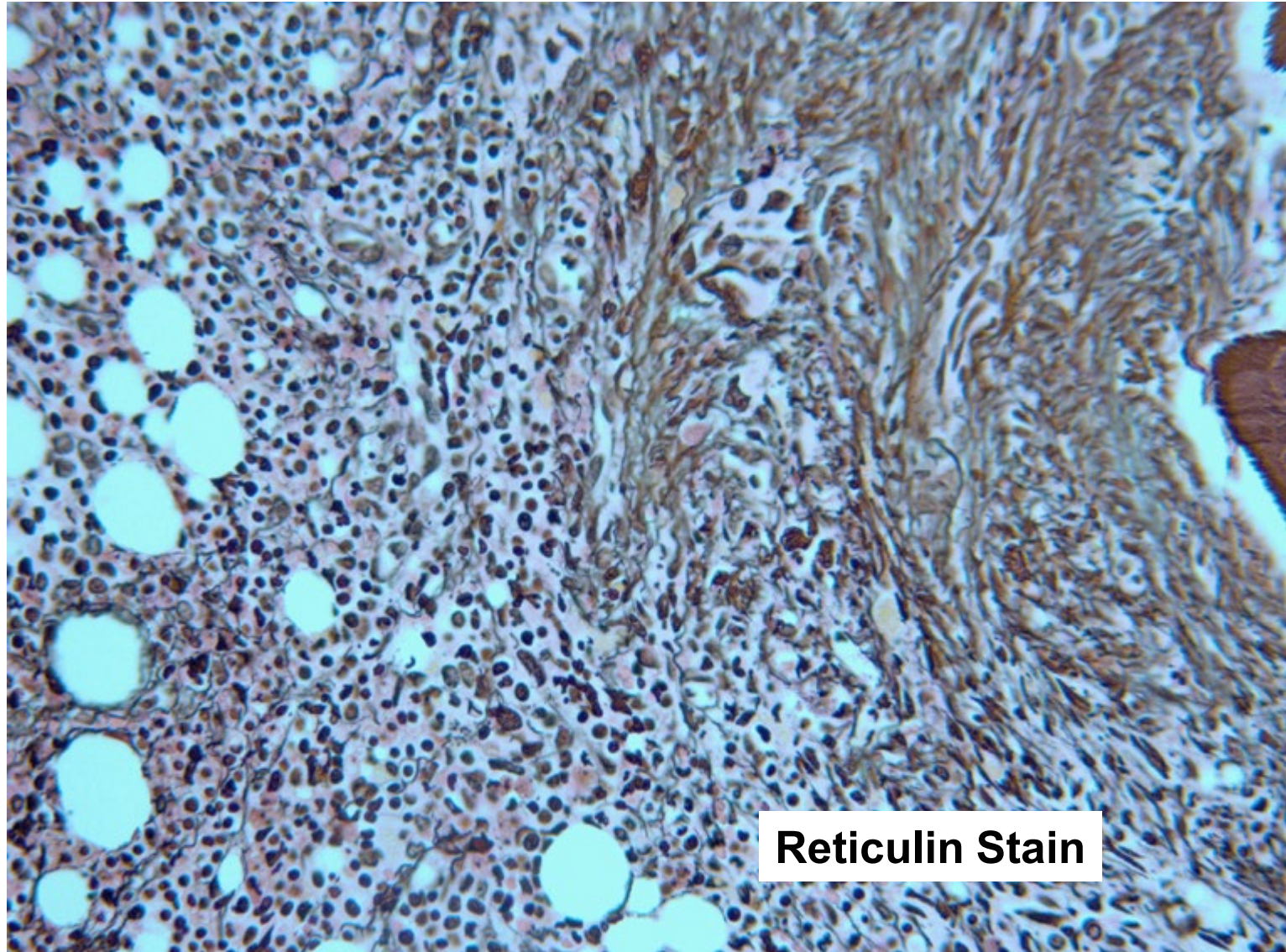


# Leukemia cutis



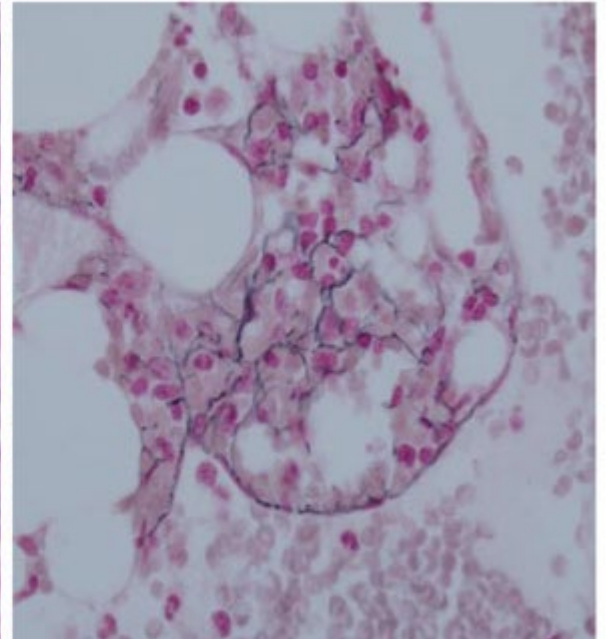
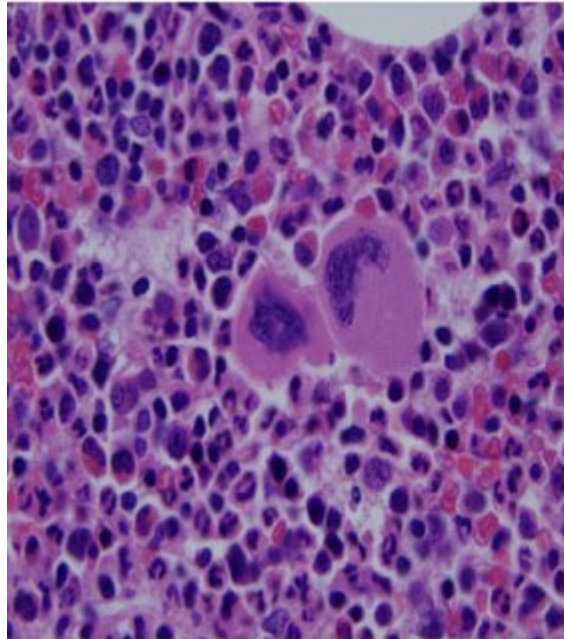
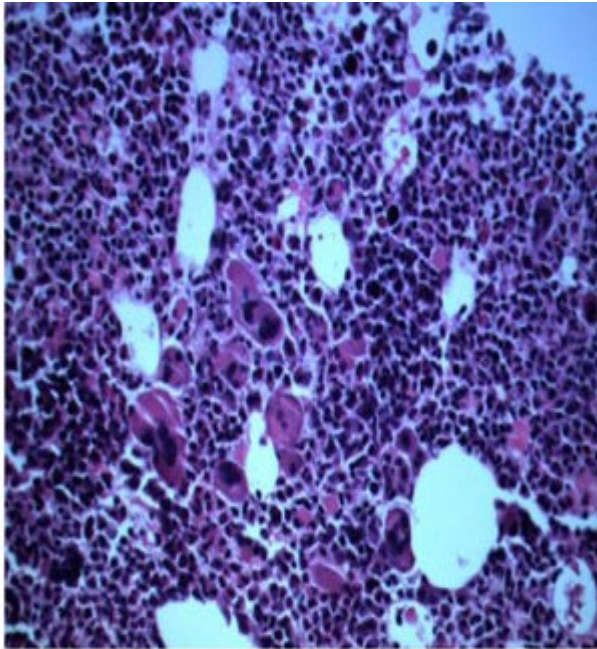
M. Kremyanskaya et al, unpublished

# PMF *Pre* -Transplant



Reticulin Stain

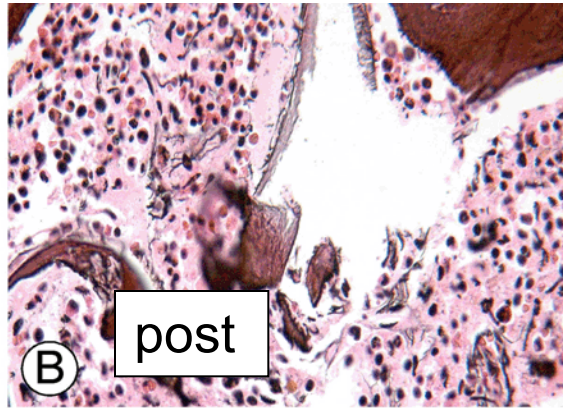
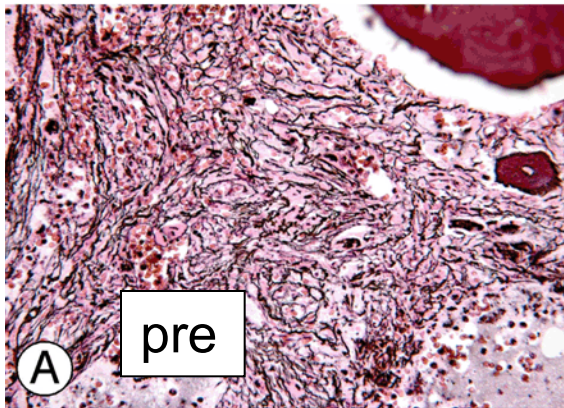
# Lung: Extramedullary Hematopoiesis and Fibrosis



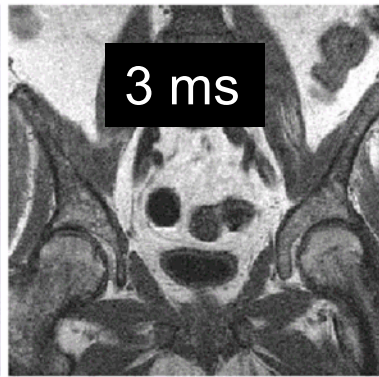
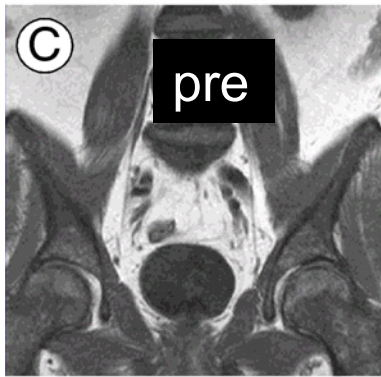
# Survival without and **with** Transplantation (by DIPSS)

| DIPPS Risk     | Survival (median; years)        |                                        |
|----------------|---------------------------------|----------------------------------------|
|                | No Transplant<br>(at reporting) | <b>Transplant<br/>(med F/U 5.9 ys)</b> |
| Low            | Not reached                     | <b>Not reached</b>                     |
| Intermediate 1 | 14.2                            | <b>Not reached</b>                     |
| Intermediate 2 | 4                               | <b>7</b>                               |
| High           | 1.5                             | <b>2.5</b>                             |

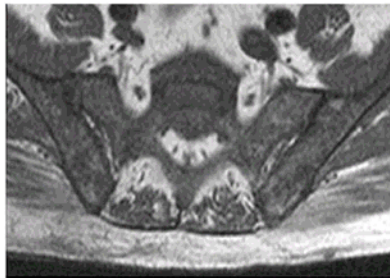
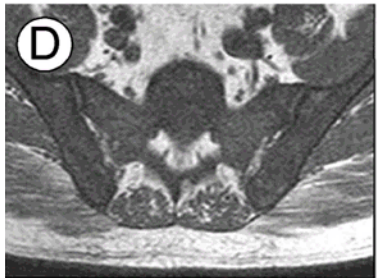
# Disease Resolution



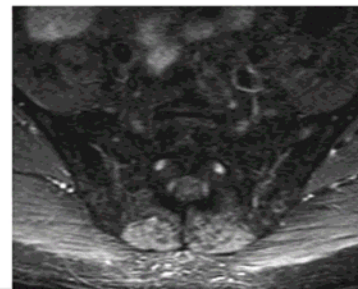
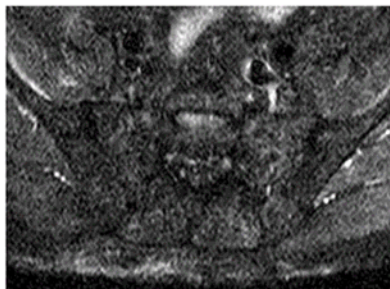
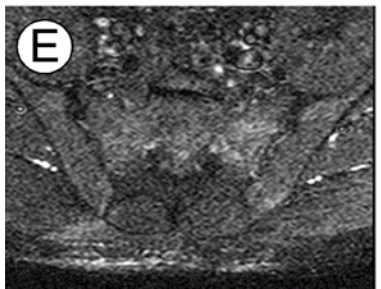
Reticulin (x300)



T1 Spin Echo  
(coronal)



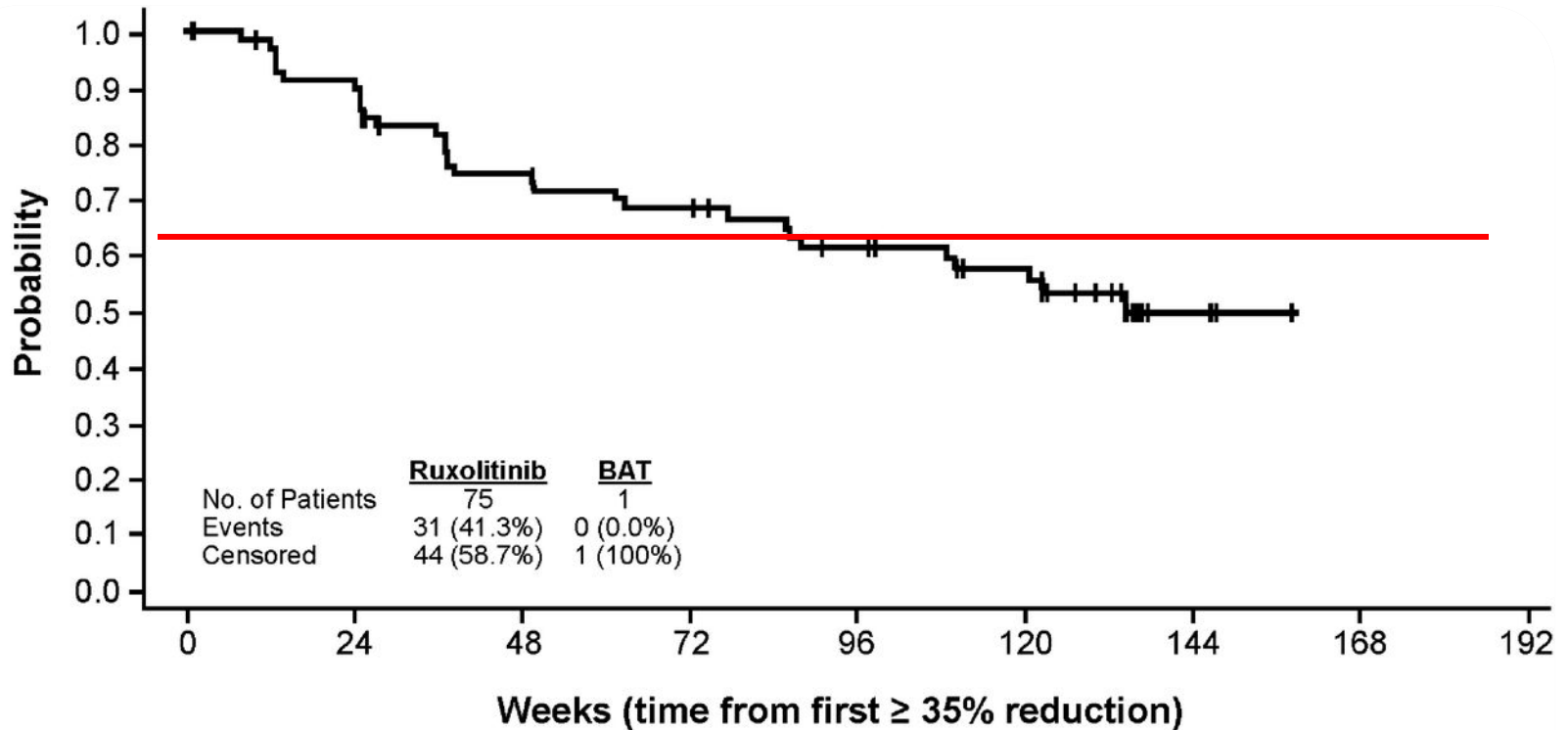
T1 Spin Echo  
(transverse)



STIR Image

# MF, duration of spleen response

## (Comfort II study)

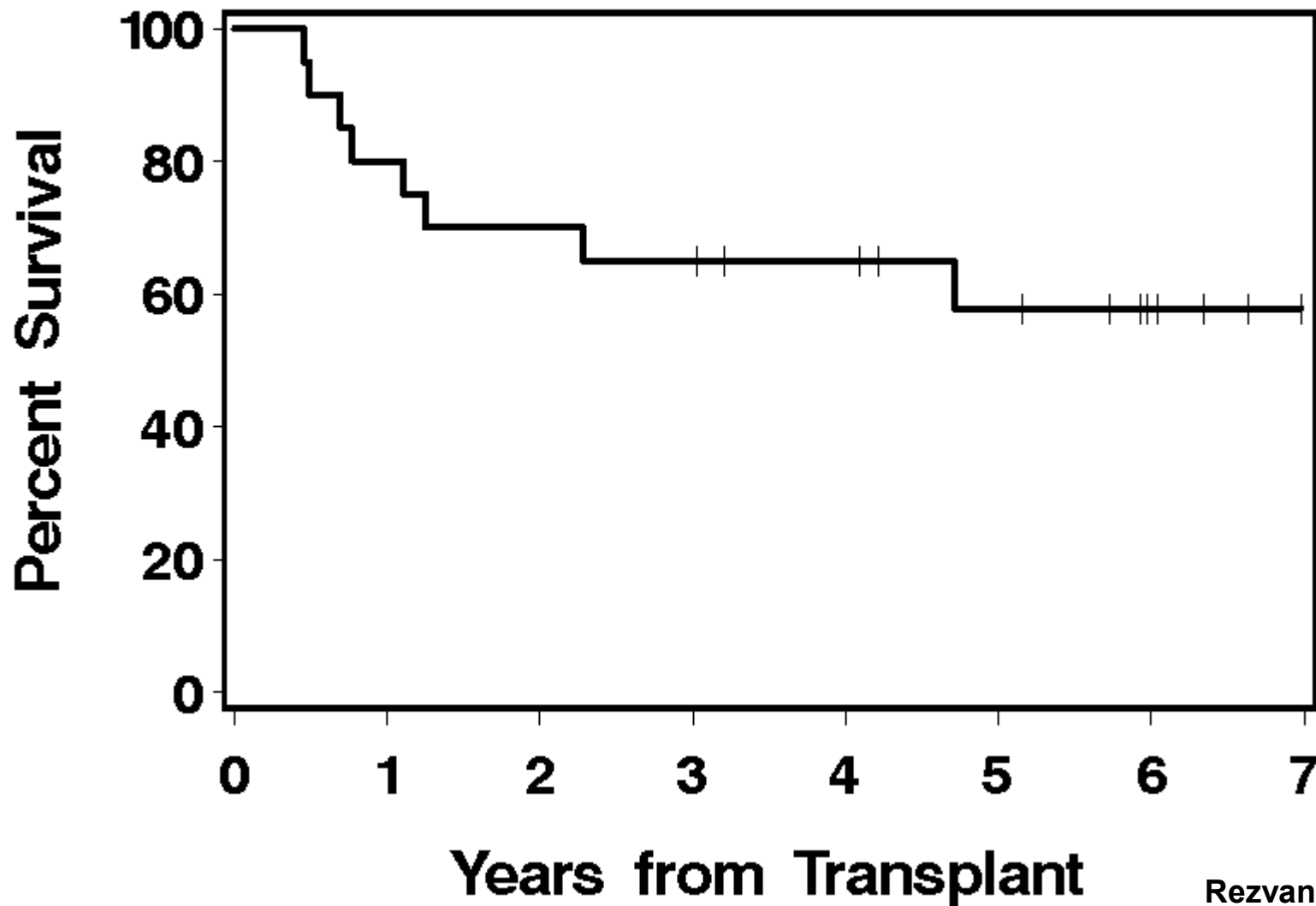


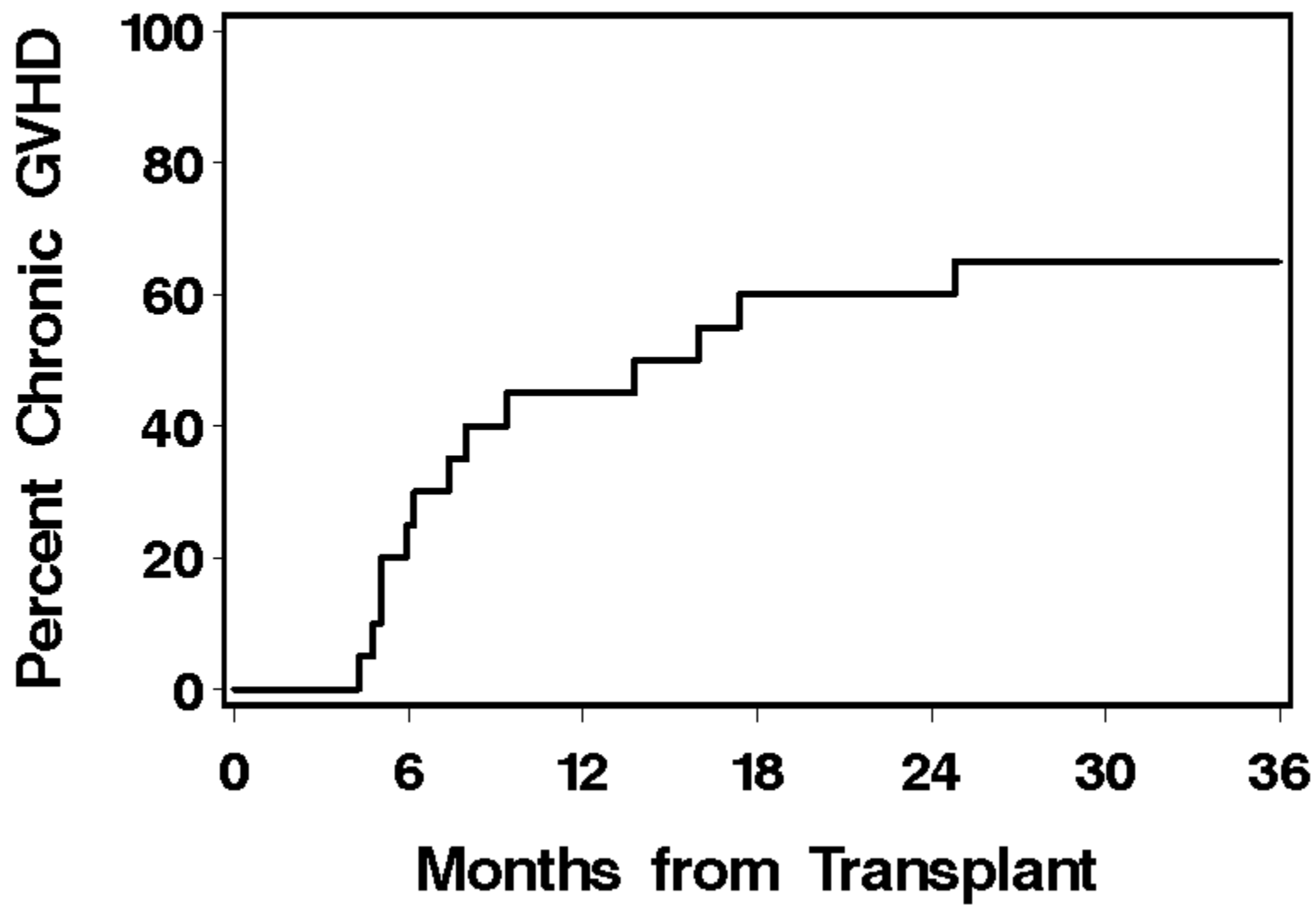
# Clonal evolution of PMF to AML while on Ruxolitinib



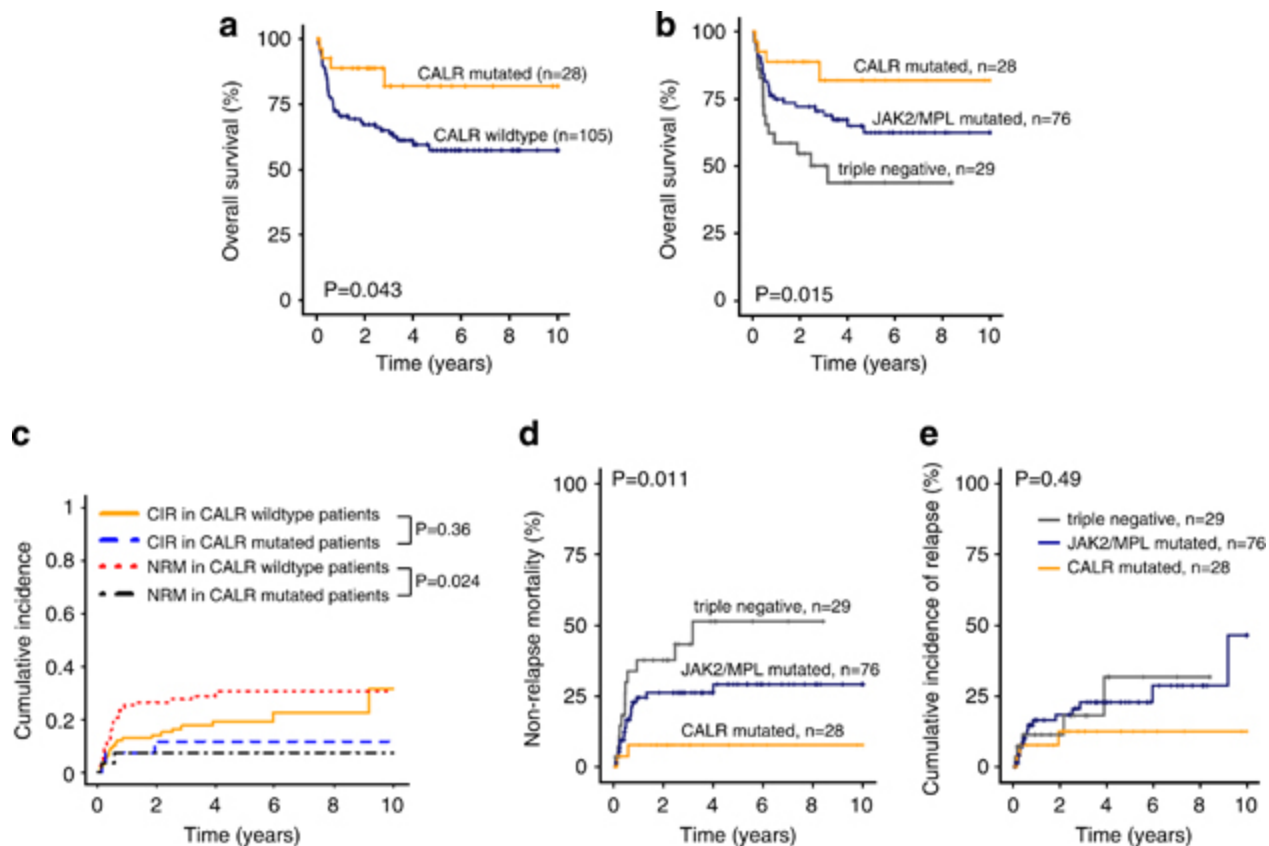
M. Kremyanskaya et al, unpublished

# MF: CY $\rightarrow$ BU Conditioning

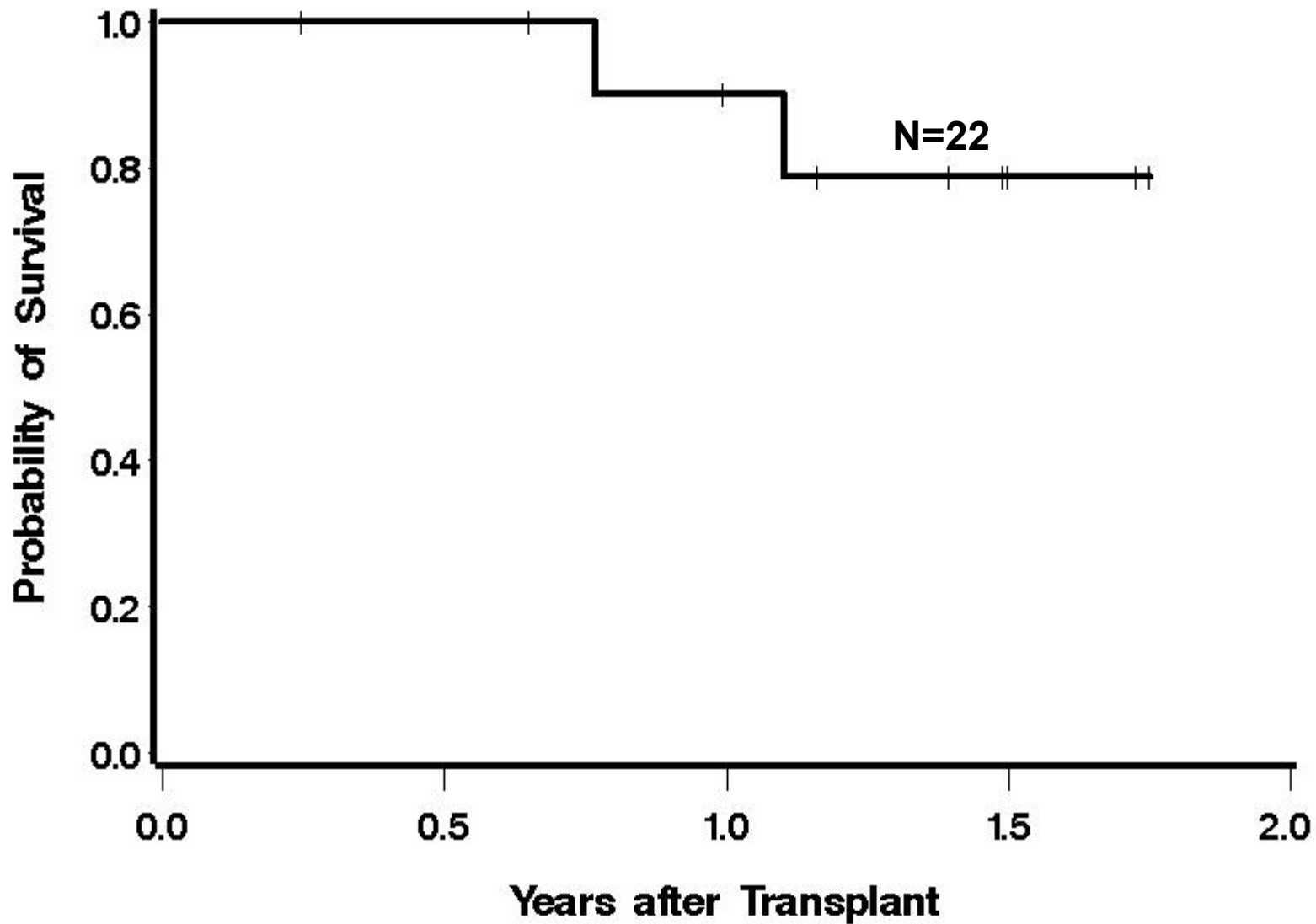




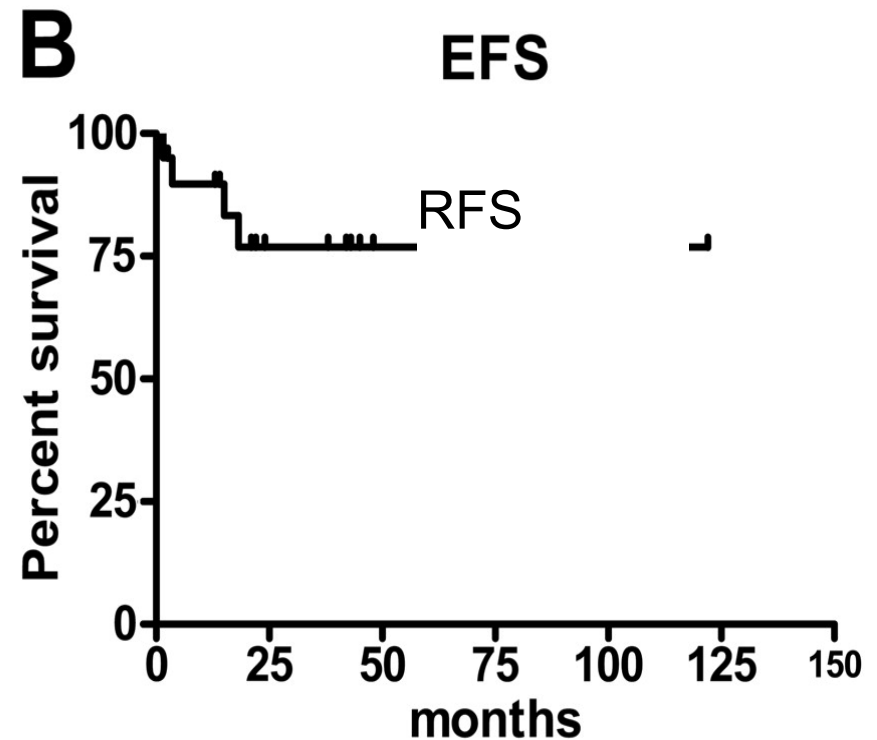
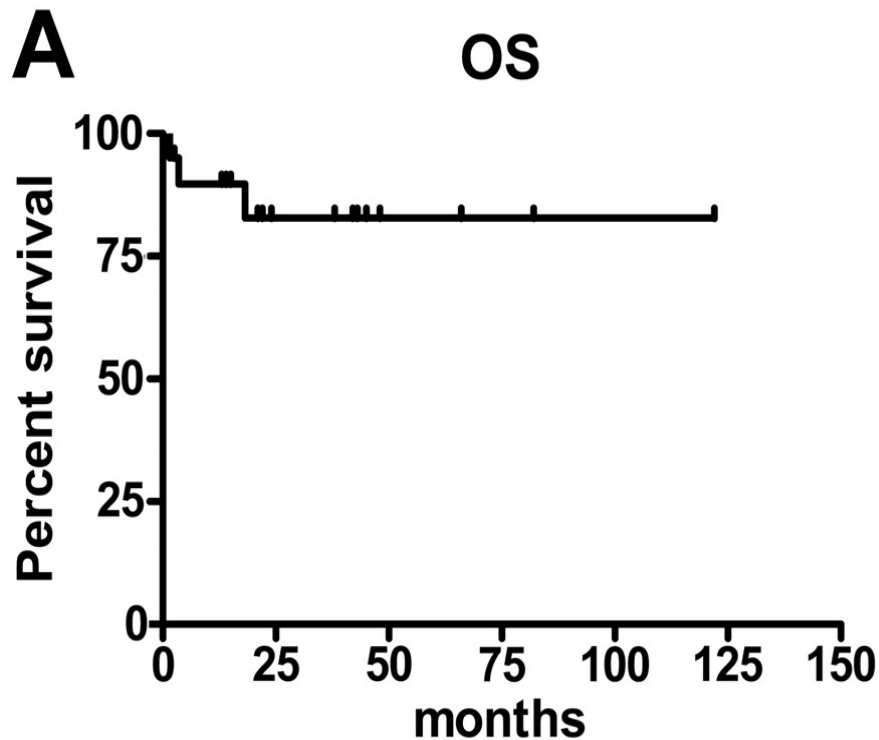
# Mutations and Transplanation



# CY → BU Conditioning

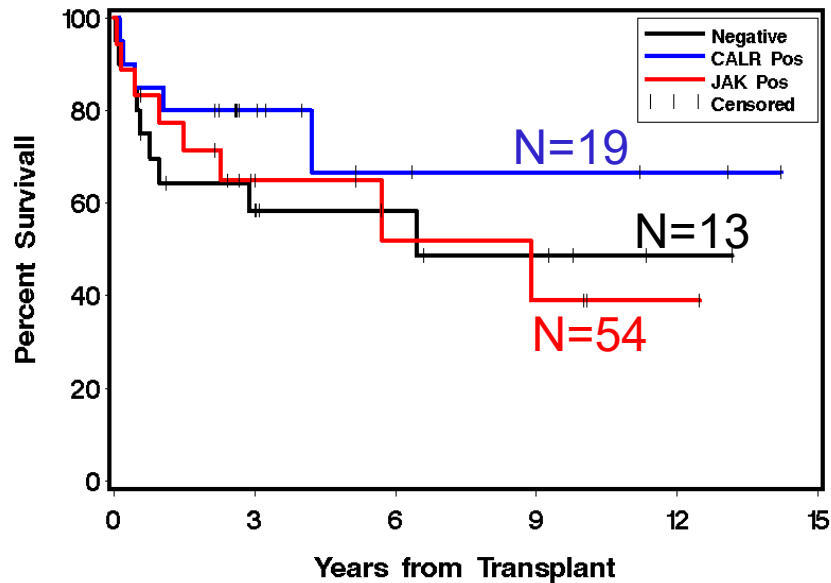


# Reduced Intensity Conditioning for PMF (various regimens)

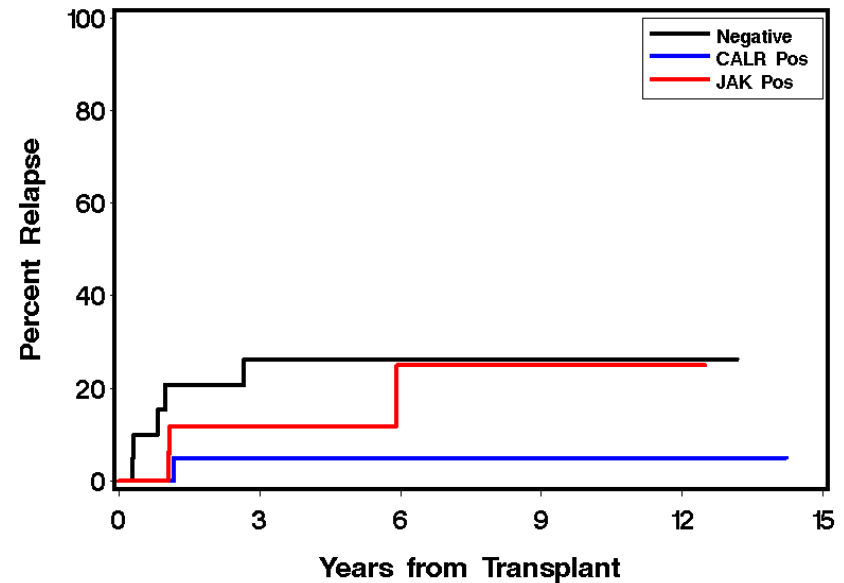


# HCT Outcomes by Mol. Driver

OS



Relapse

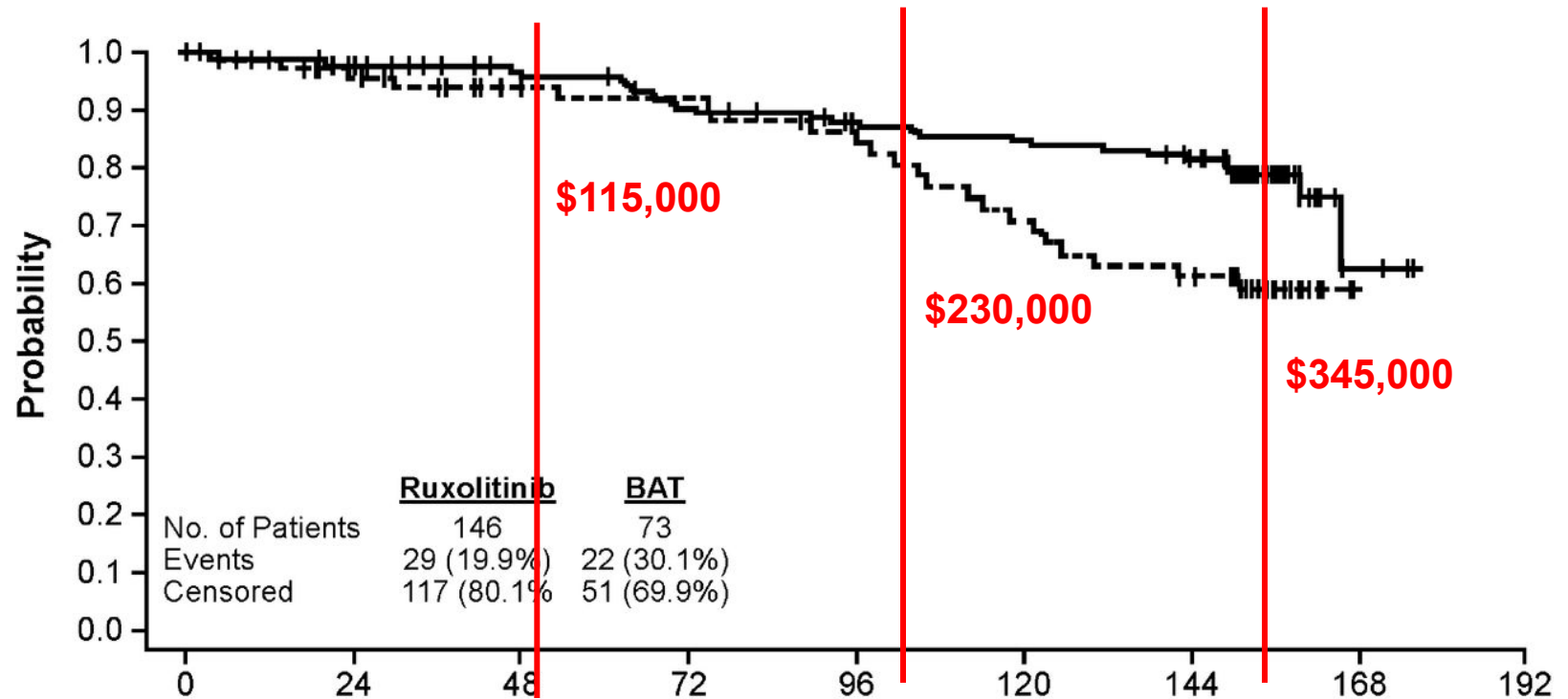


**The goal:  
The best treatment for the  
patient !**

# ***Any Treatment?***

- You are well, no symptoms, good appetite, stable weight, no problems with a large spleen, stable blood counts - You probably do **NOT** need treatment!

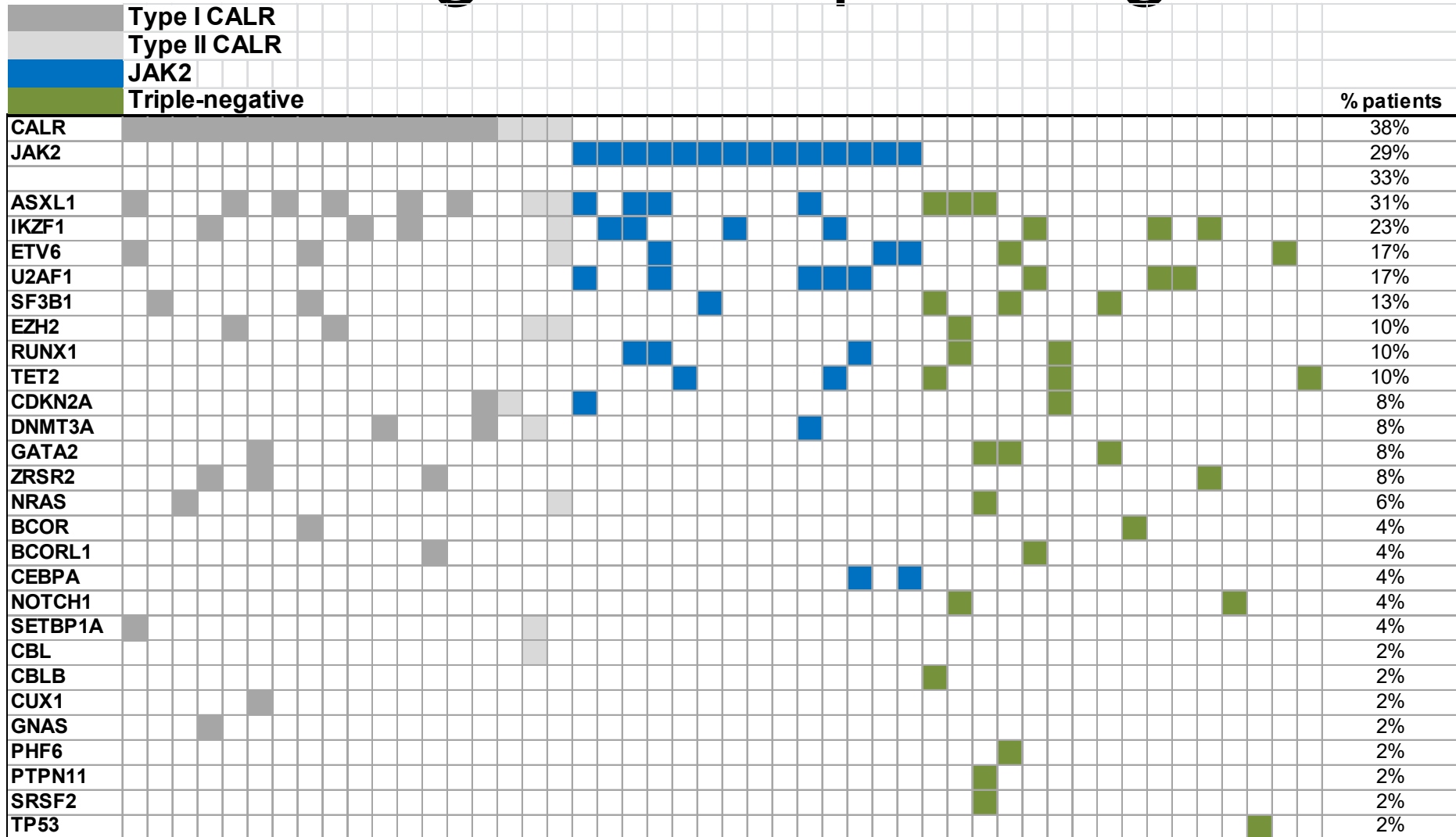
# .....some Financial Toxicity?



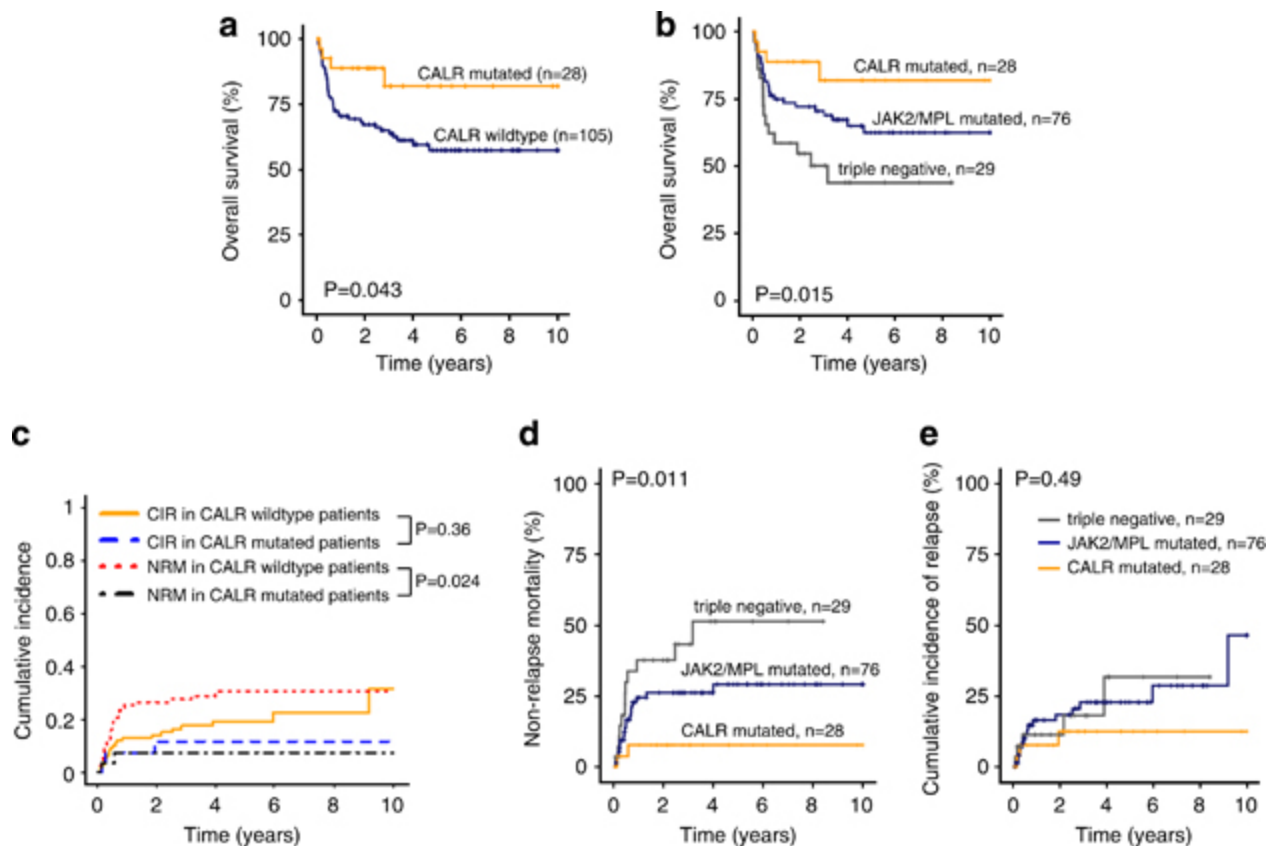
# Targeted Sequencing

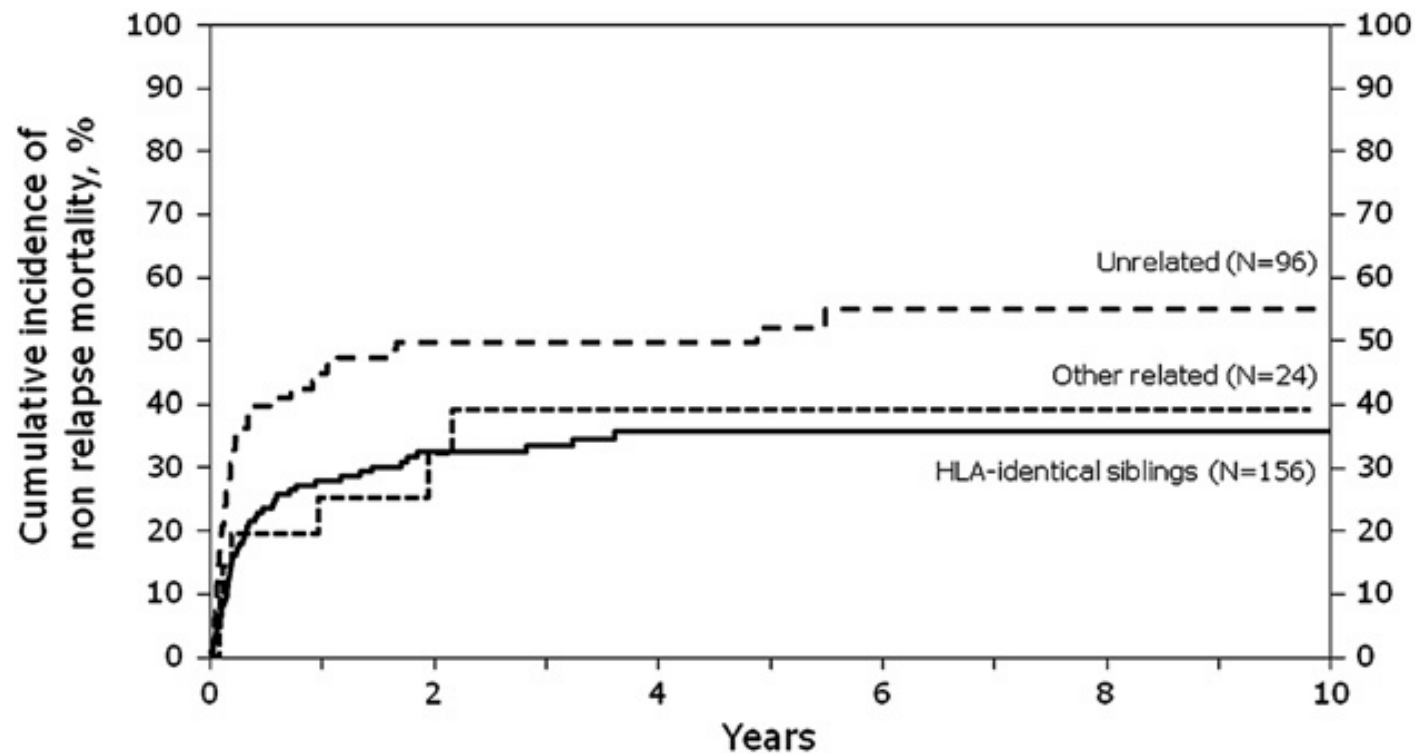
- 48 patients with MF (36% PMF)
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- 2000-2015
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- Ave 2.4 variants per patient
- Most common variants: ASXL1 and IKZF1

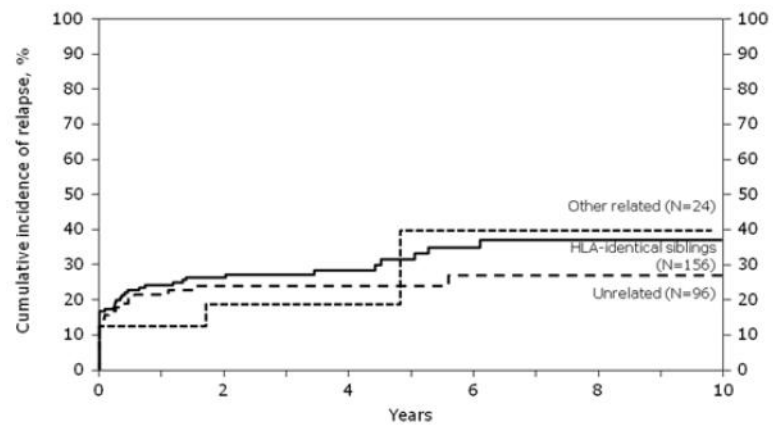
# Targeted Sequencing

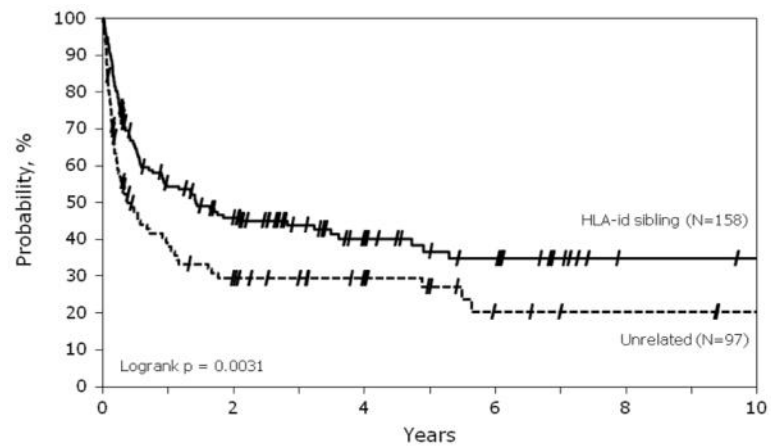


# Mutations and Transplananation







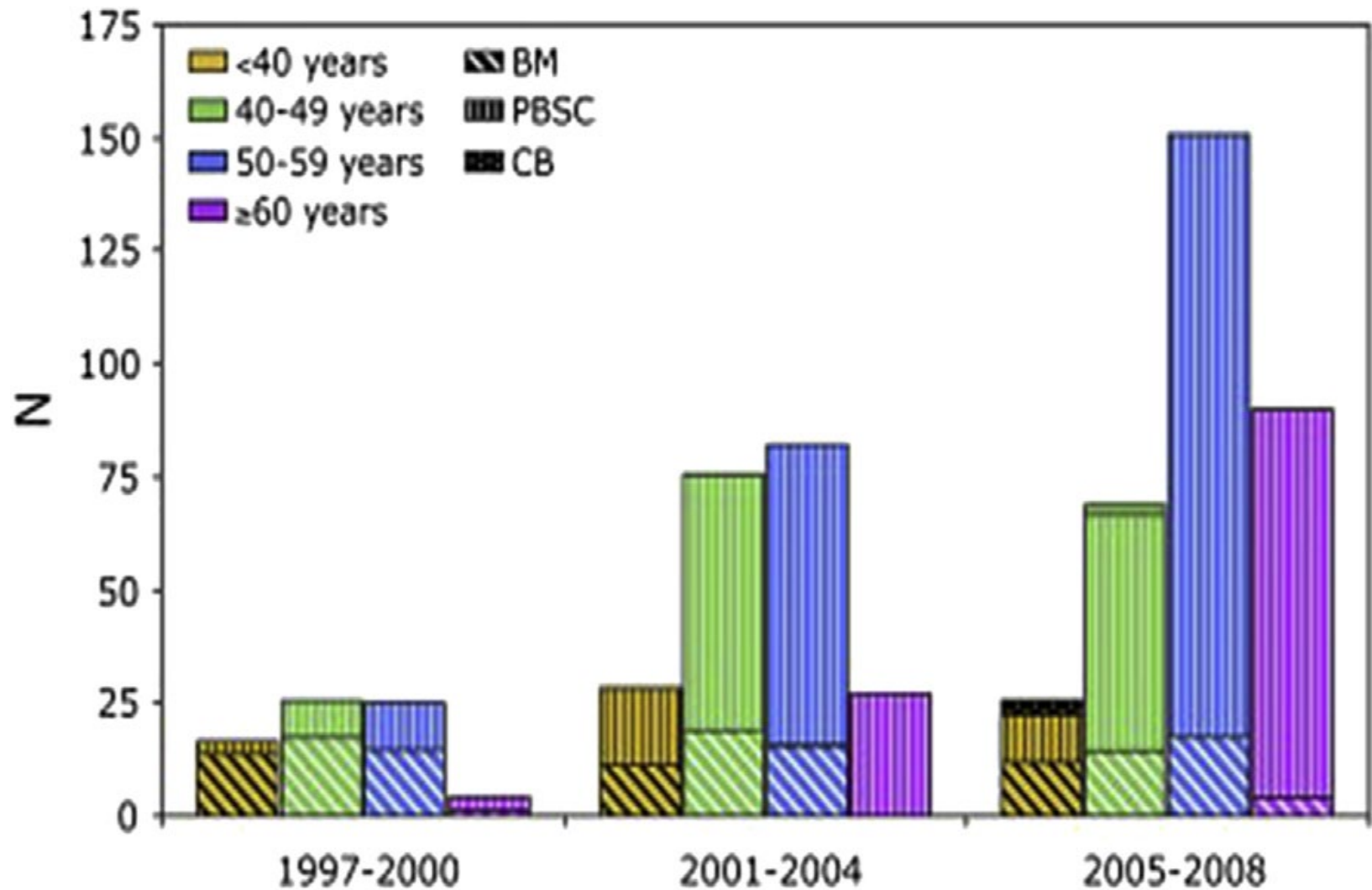


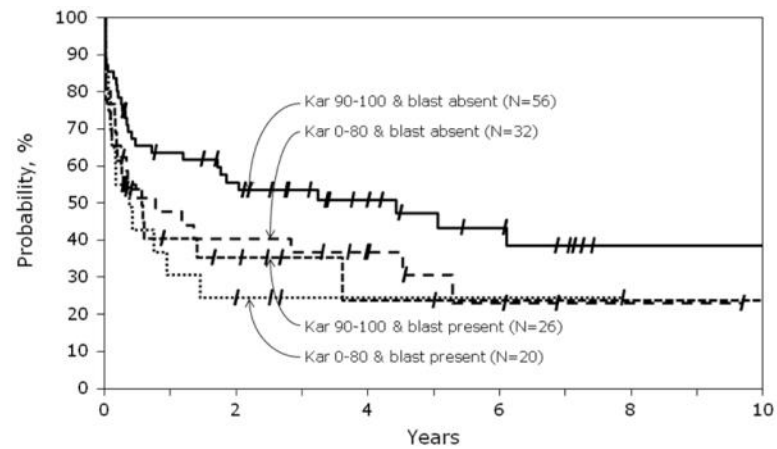
Survival

# Mutations

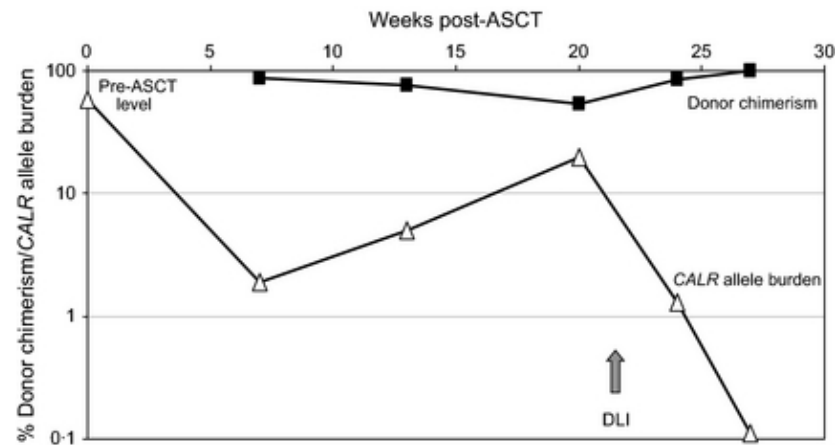
- **JAK2, MPL1, CALR** (type1 and type 2)
- ASXL1, TET2,
- SRSF2, U2AF1
- IDH1, IDH2, TP53, DNMT3a, IKZF1, LNK
- Other

# Age and Source of Stem Cells



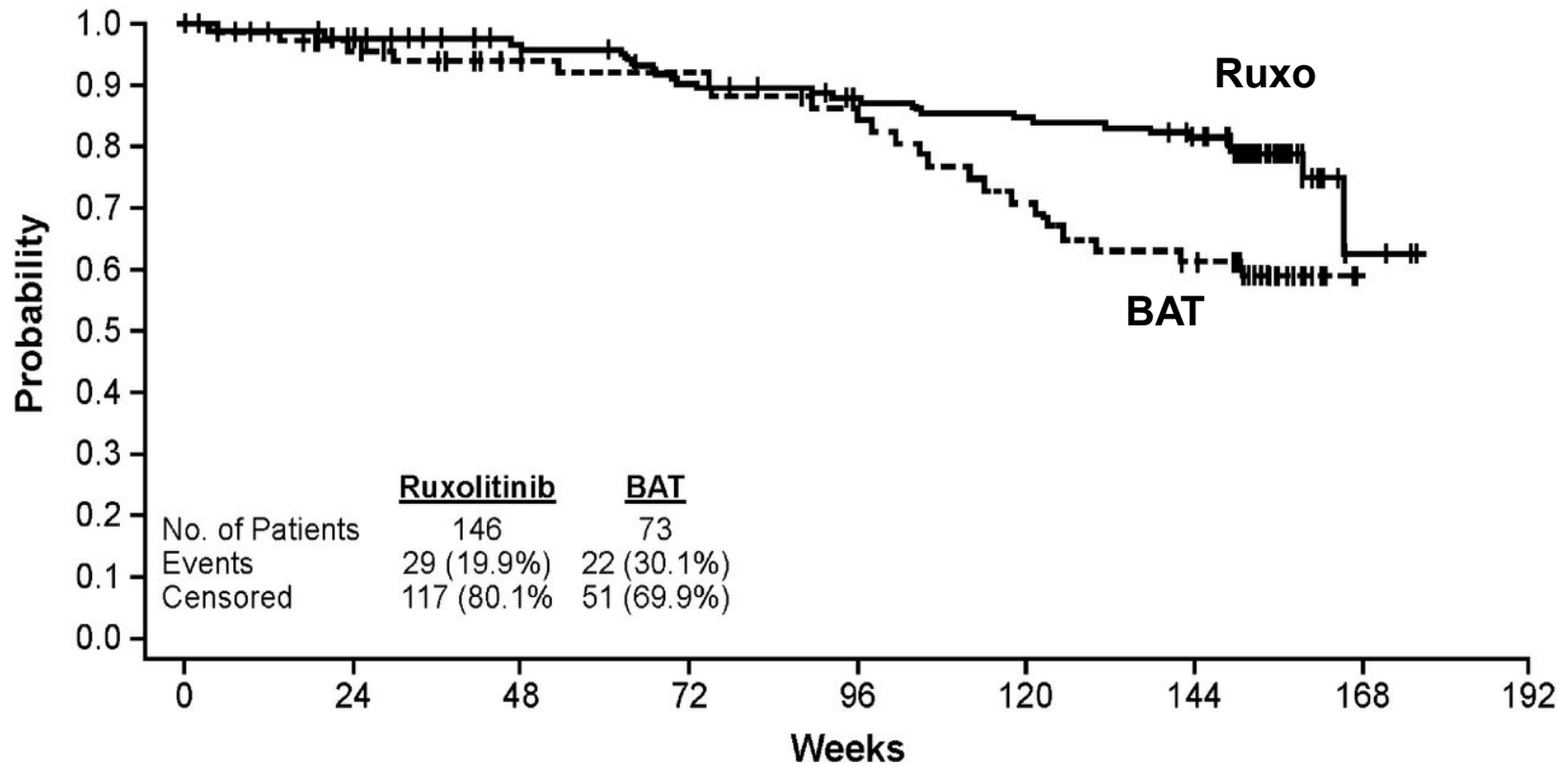


Relapse-free survival.

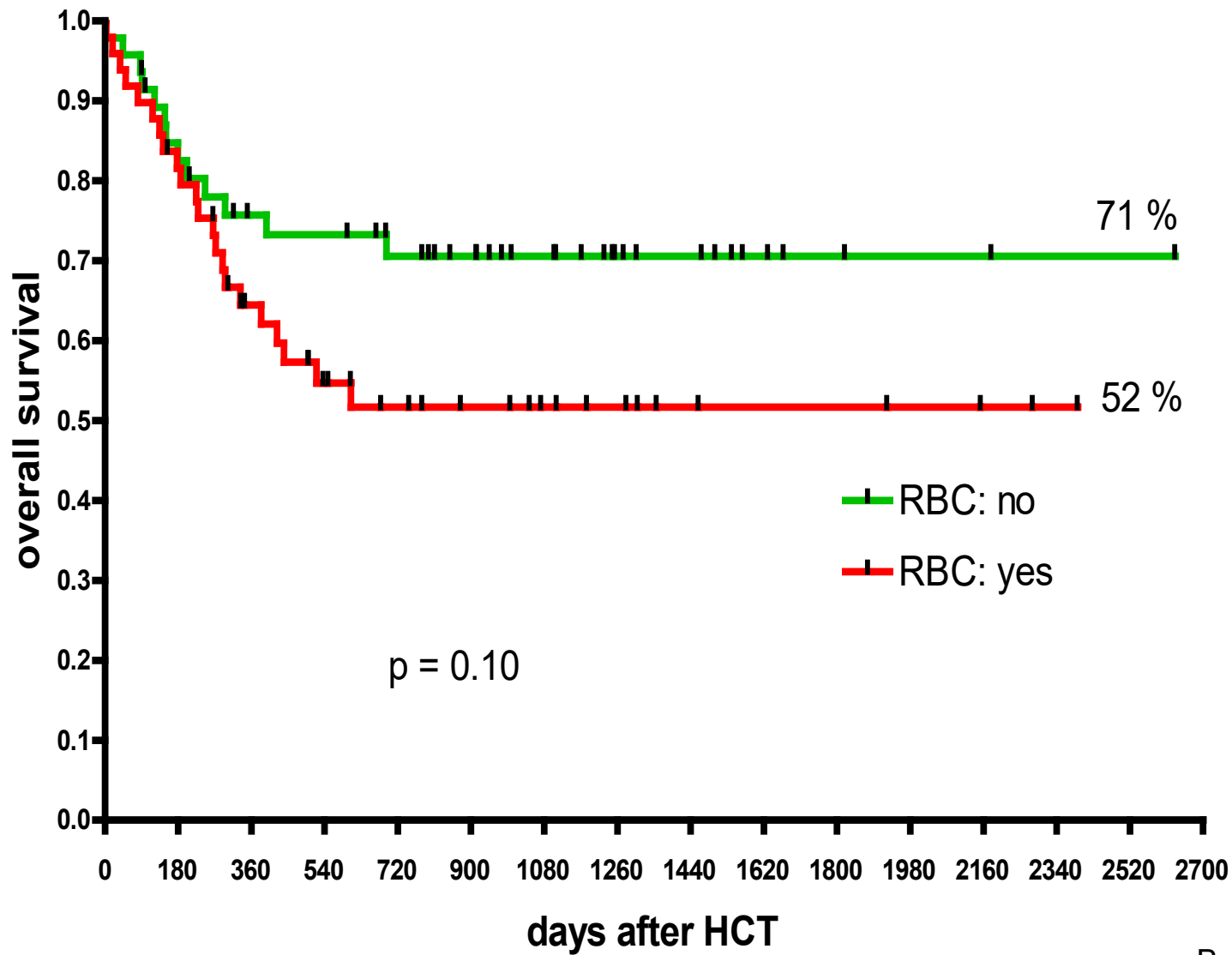


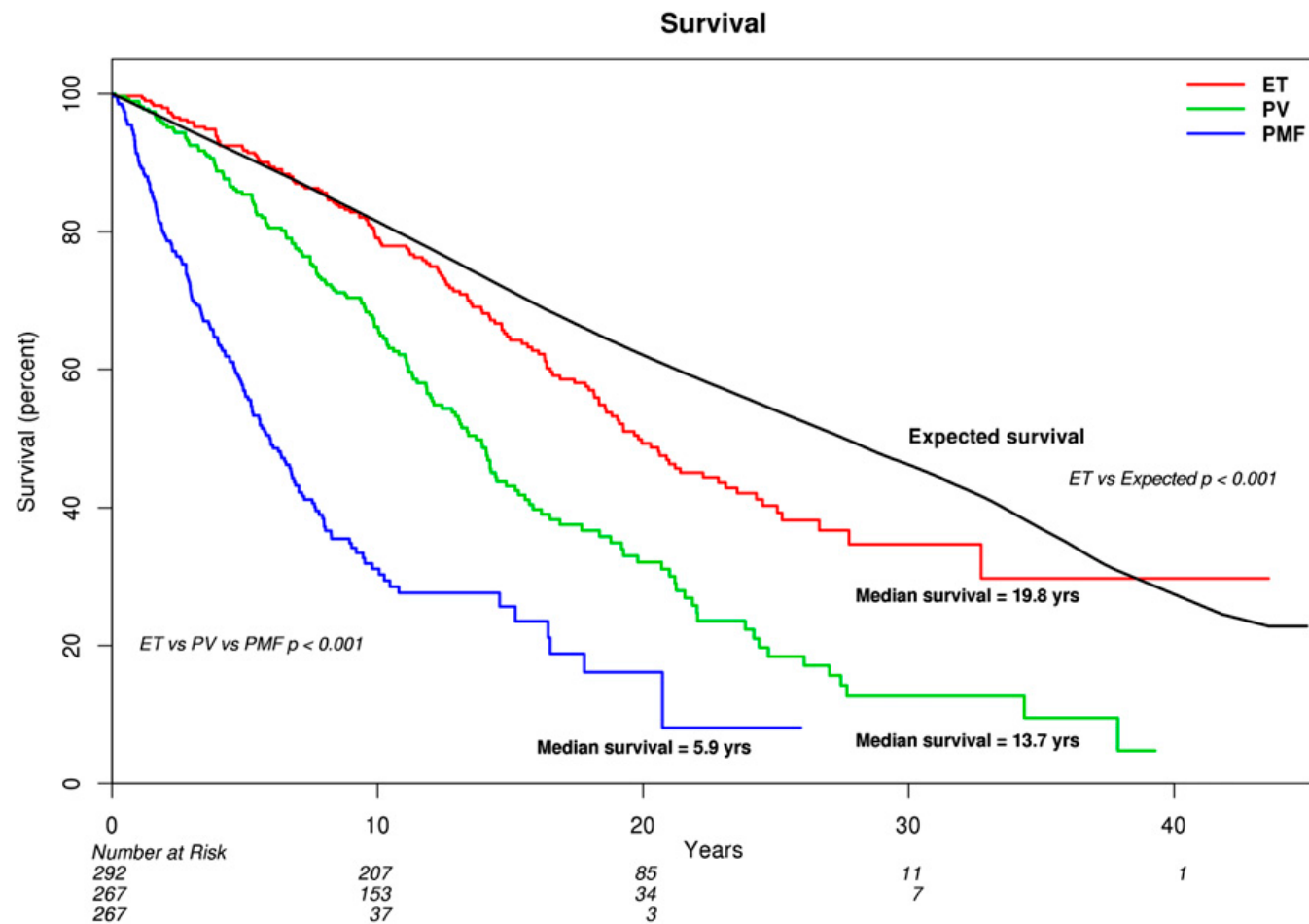
Correlation of *CALR* mutation allele burden with donor chimerism status in Patient 4. ASCT, allogeneic stem cell transplant; DLI, donor lymphocyte infusion.

# Overall survival (COMFORT-II Trial)



## survival according to transfusion dependance

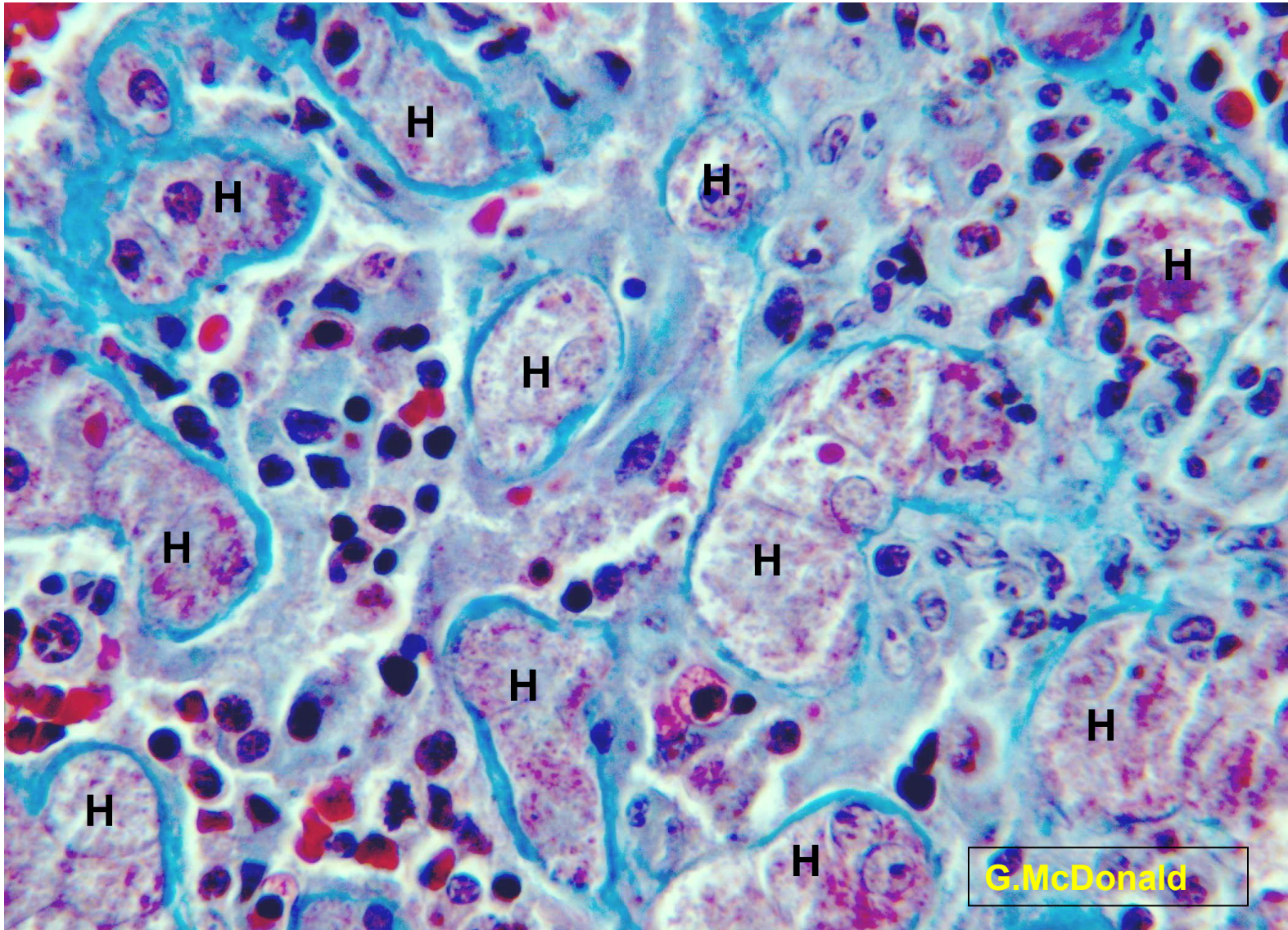




# ***Risks of JAK2 inhibitor for Transplantation ?***

- Obscuring comorbid conditions?
- Rebound of cytokines when stopped before transplantation

# Liver: Sinusoidal fibrosis associated with extramedullary hematopoiesis

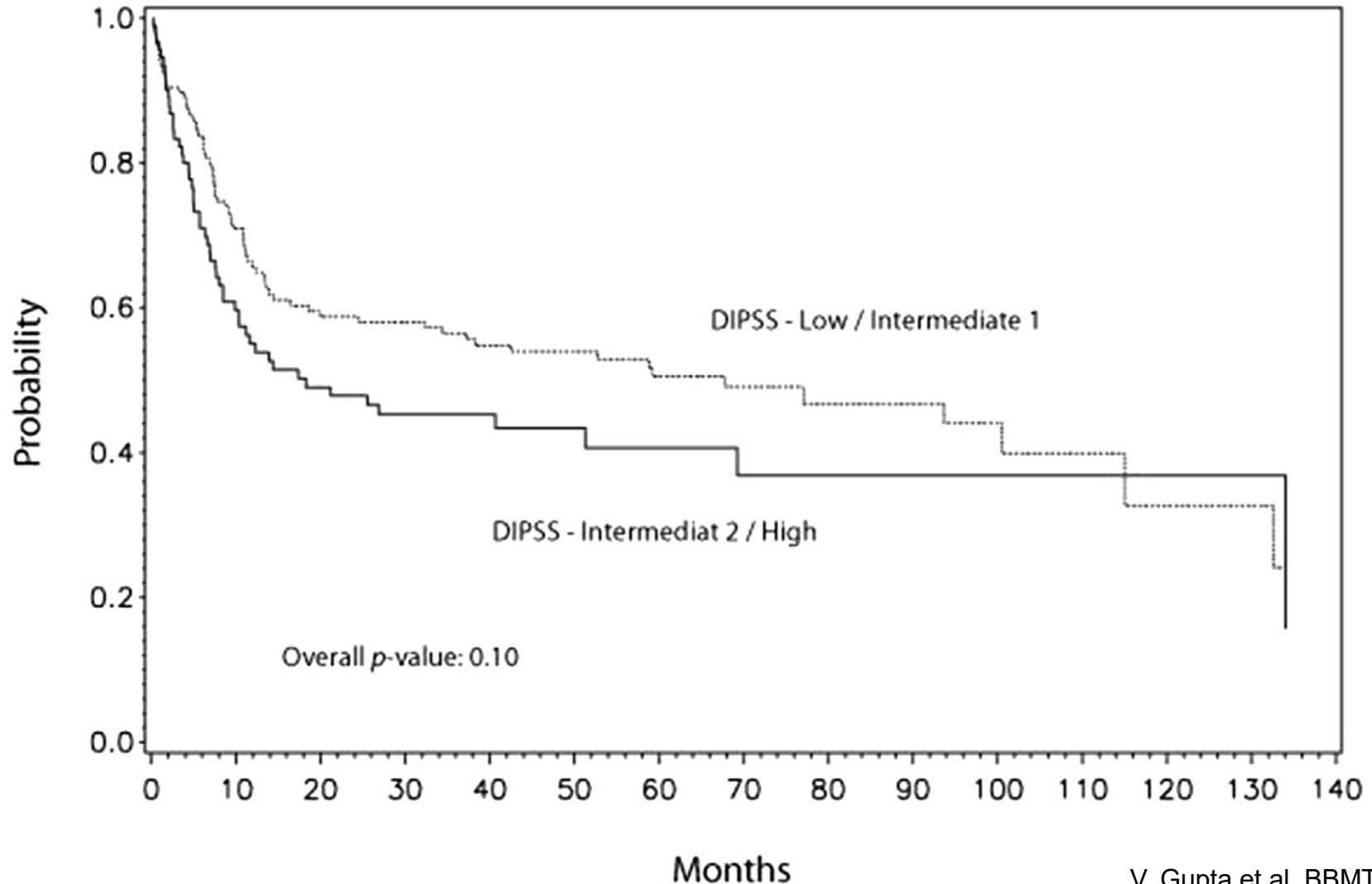


G.McDonald

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

# ***Reduced Intensity Conditioning and HCT***

**Adjusted OS according to DIPSS**



# **JAK2 Inhibitors**

## **Benefits**

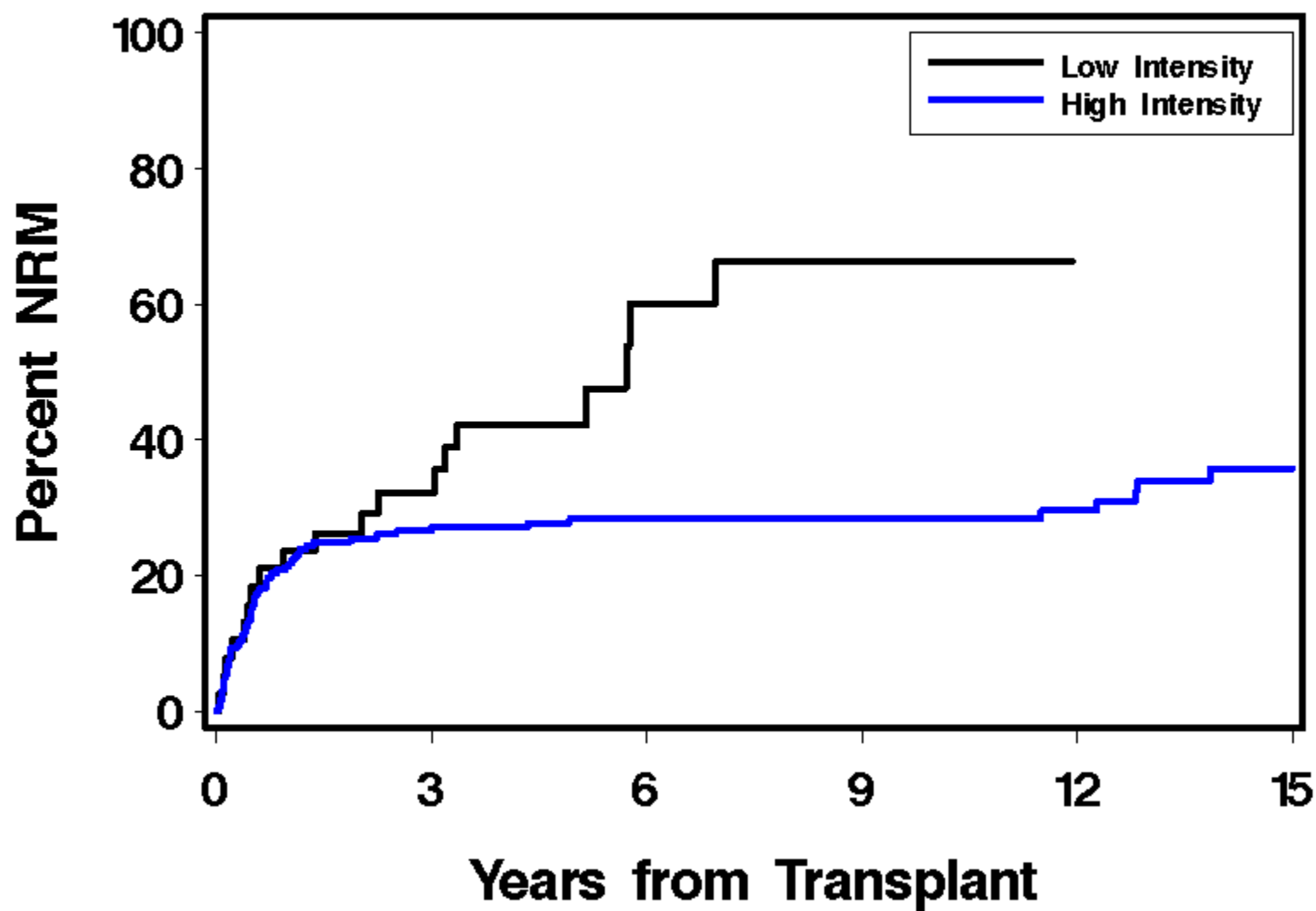
**Patient feels better,  
Spleen shrinks,  
May live longer**

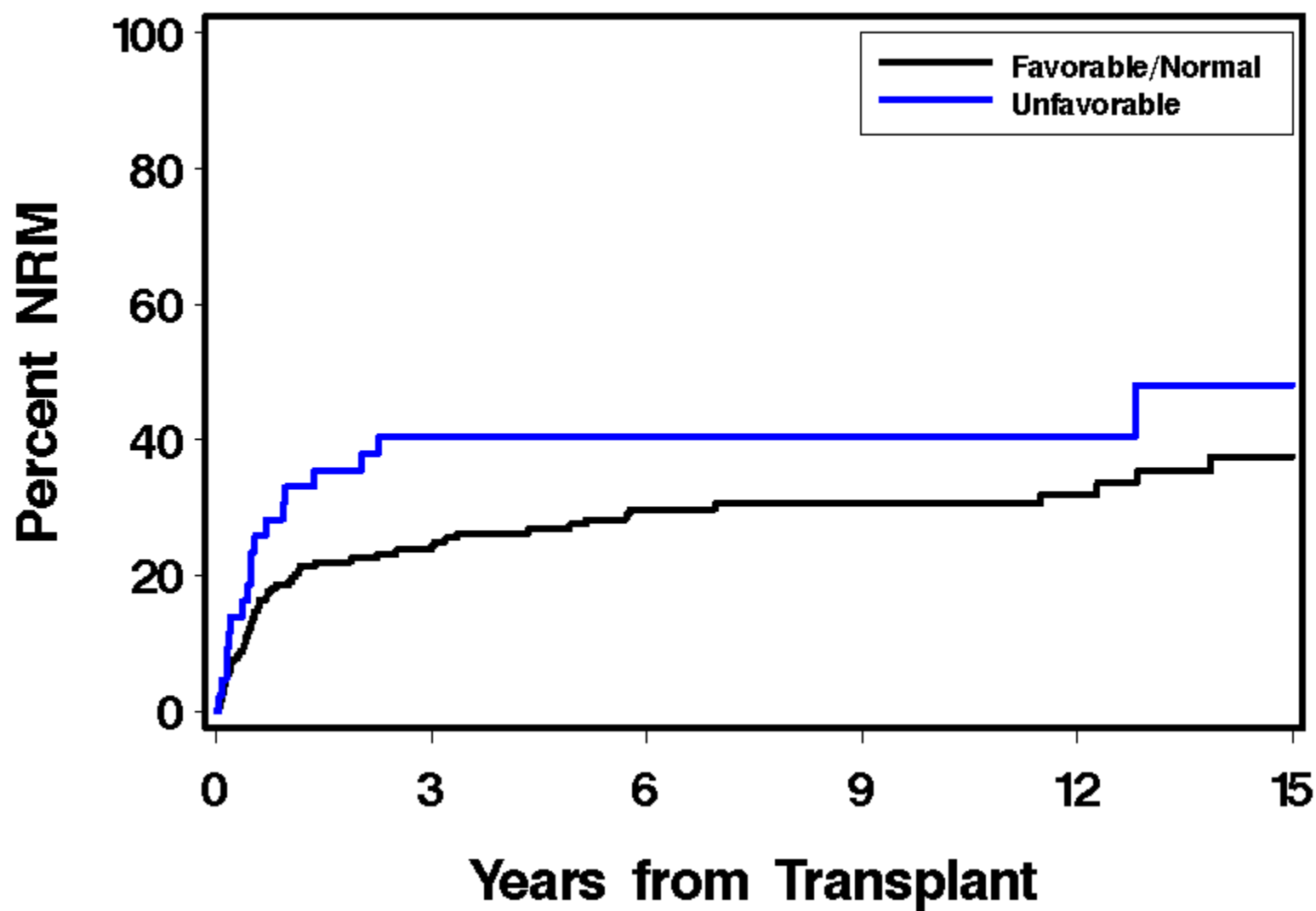
**JAK2 inhibitors**

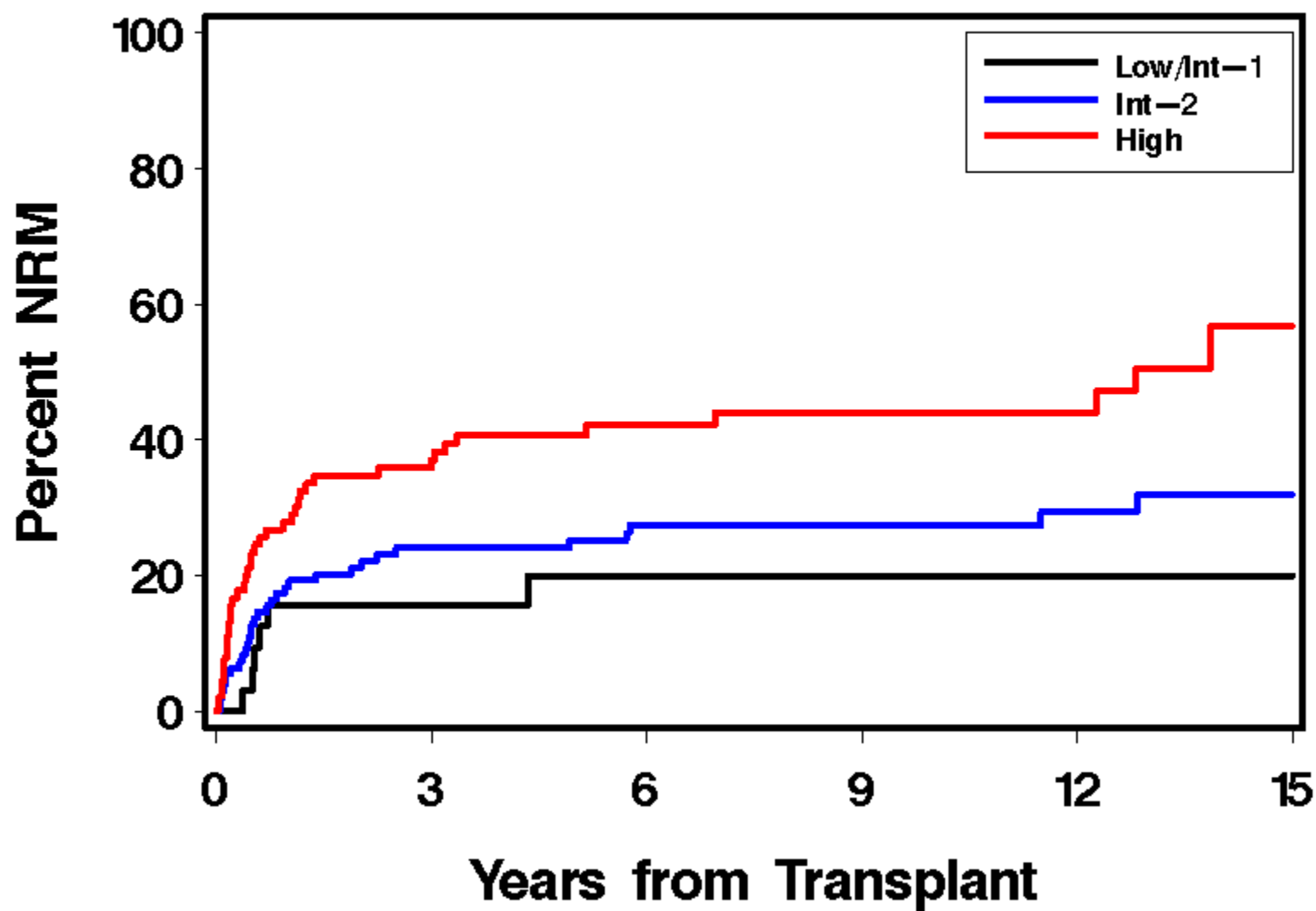
**Potential *Risks***

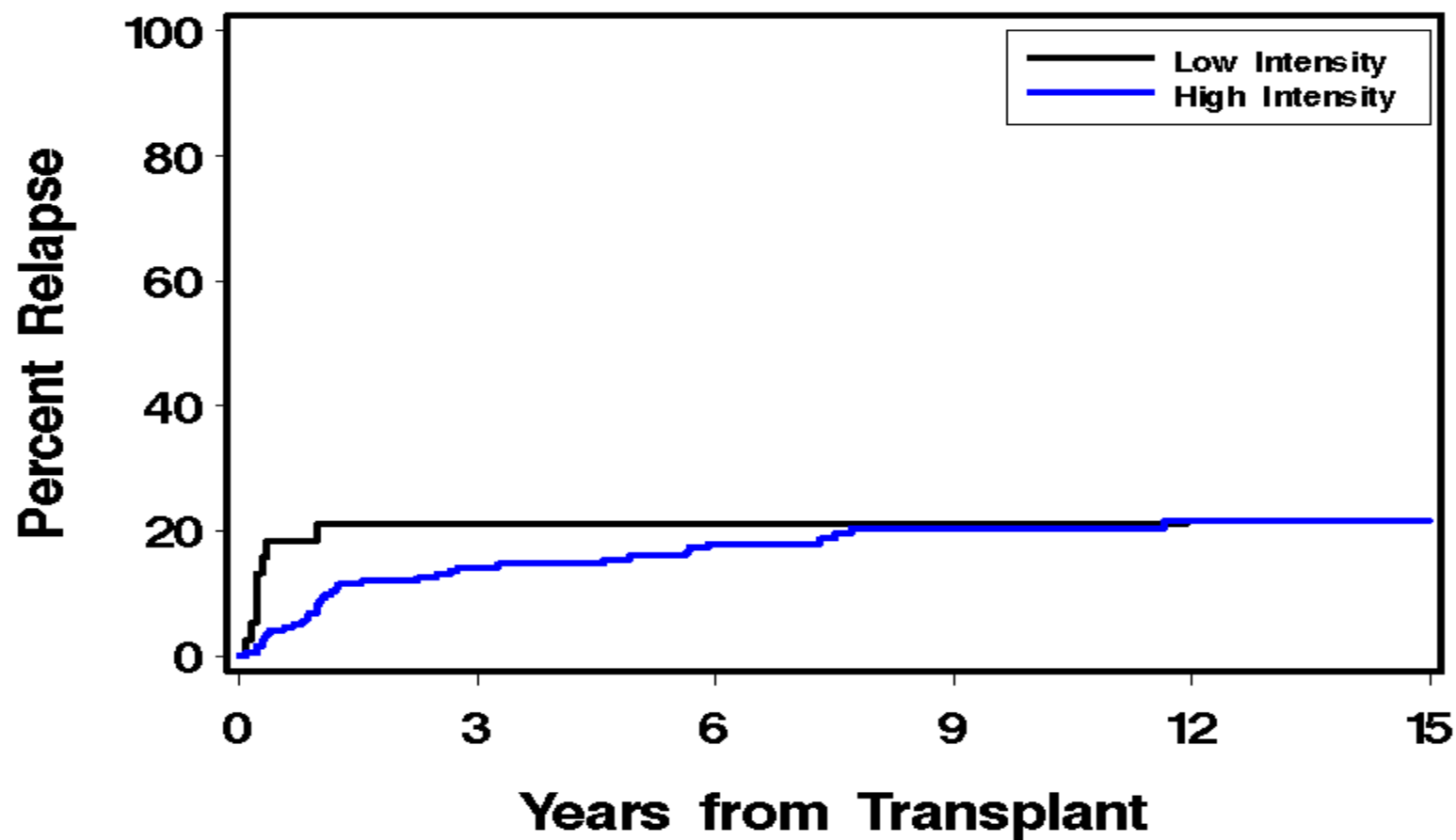
# “Bone marrow” in the Lung



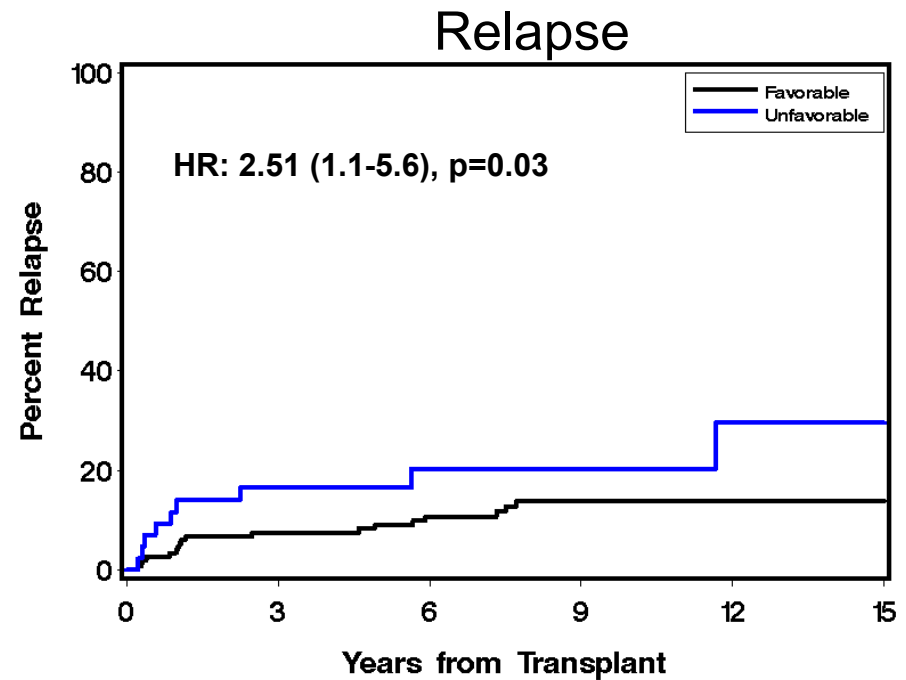
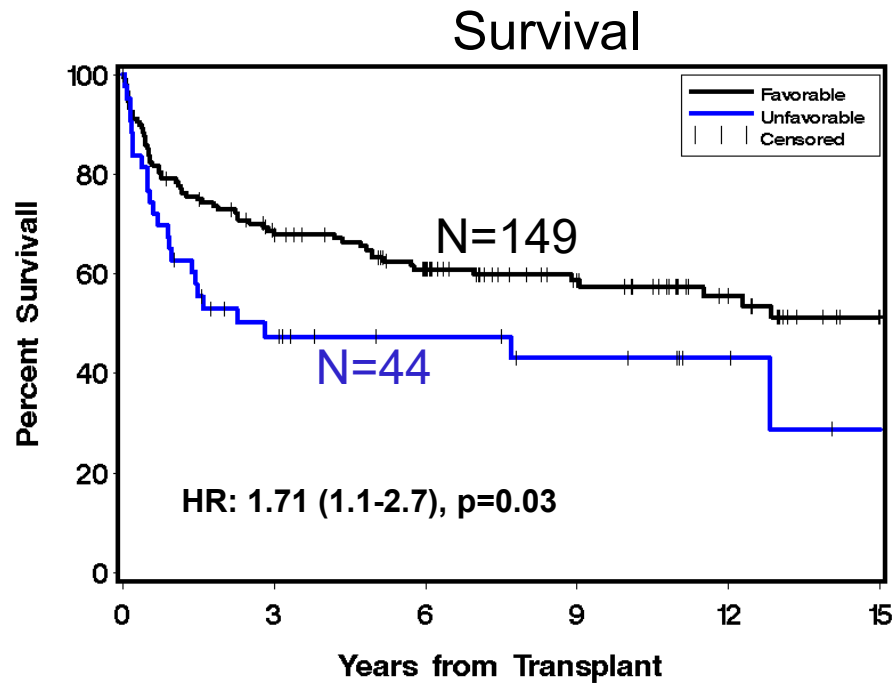








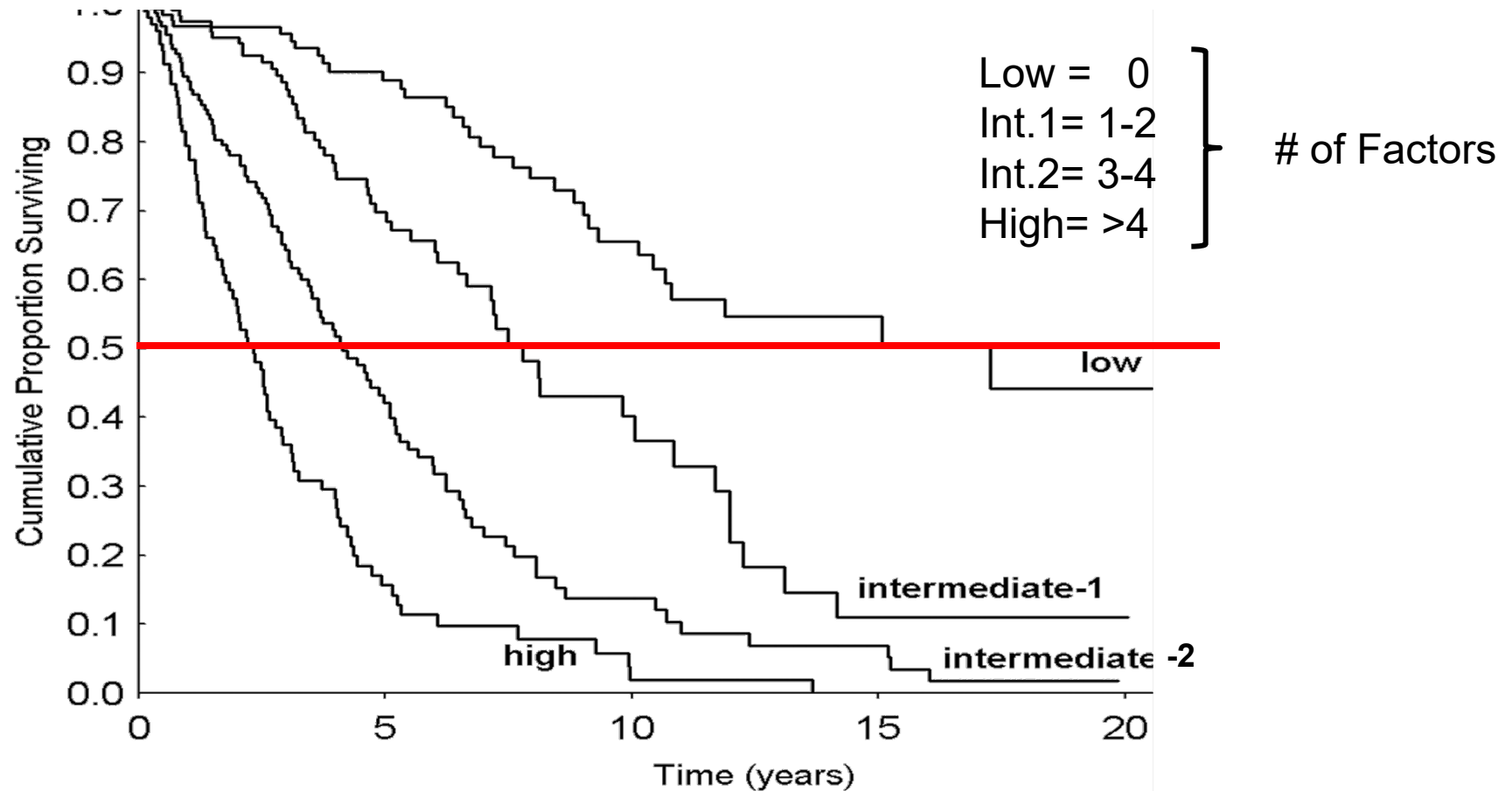
# Cytogenetics and Transplant Results



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

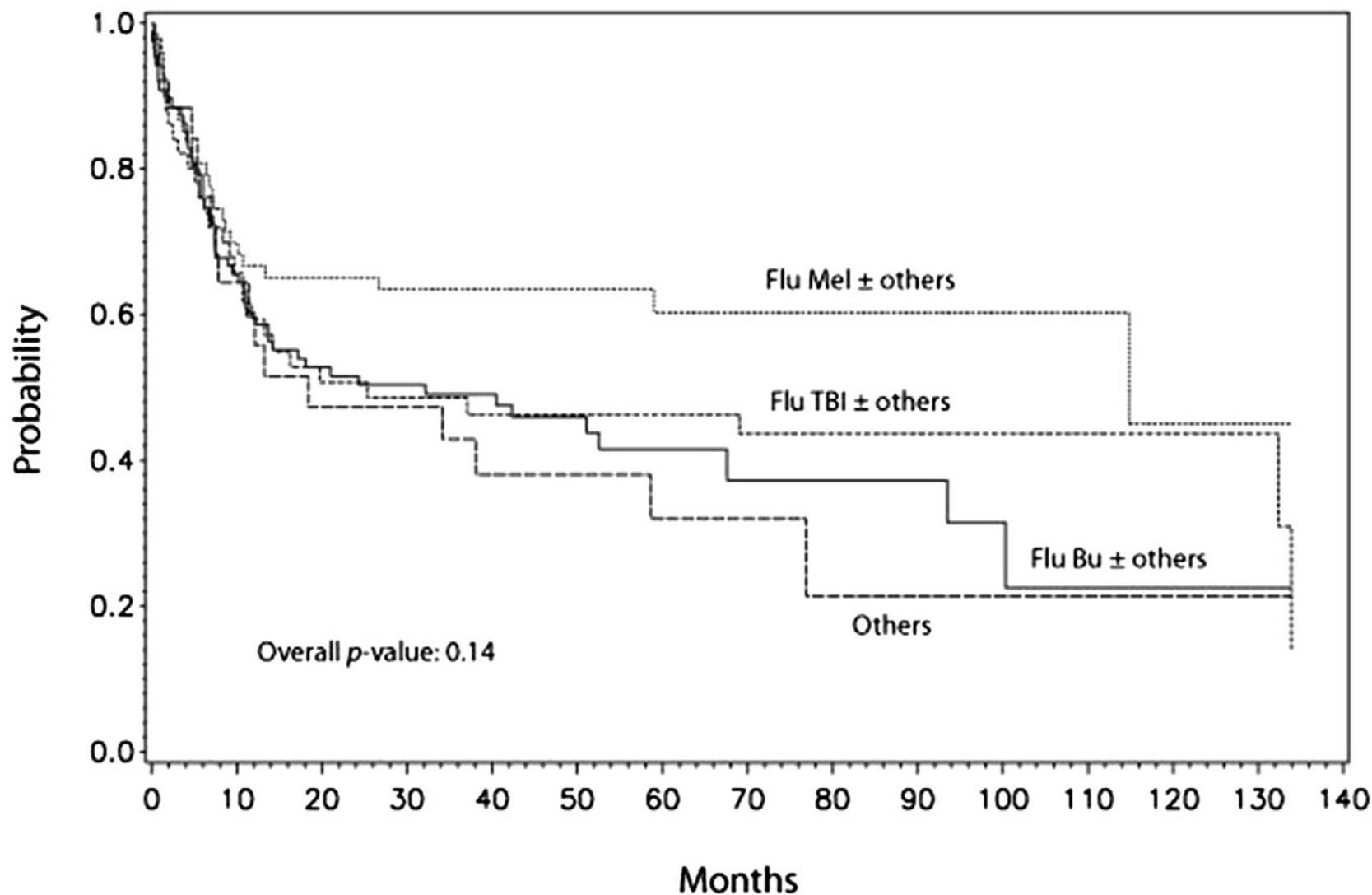
# DIPSS and Survival

(no transplant – no treatment with *JAK2* inhibitors)



# ***RIC – Adjusted OS by Regimen***

***-Is there a best regimen? -***



# **What about JAK Inhibitors?**

- **Impact of JAK inhibitor(s) pre-transplant ?**
- **Splenectomy yes or no?**
- **Disease duration – more comorbidities?**
- **Mutations – indication for transplantation?**
- **Progressive fibrosis – transplant?**

# Potential Benefits

- JAK inhibition with ruxolitinib has reduced plasma inflammatory cytokines and resulted in prompt resolution of constitutional symptoms.
- Many patients experienced a reduction in spleen size (including non-mutated patients).

# Timing of Transplantation

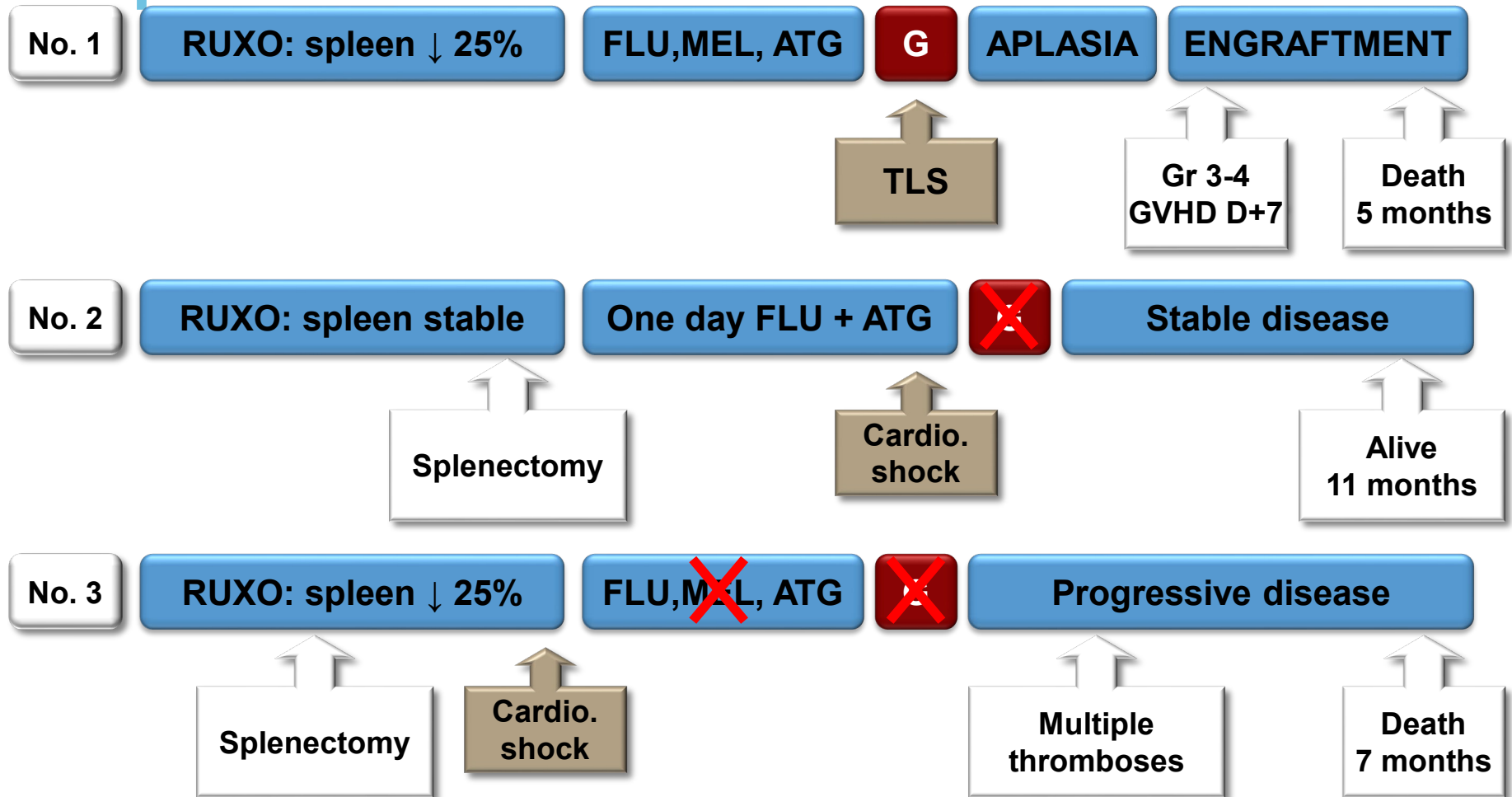
- No prospective studies have evaluated the optimal timing of HSCT in MF
- No decision analyses have rigorously compared outcomes of HSCT to non-transplant therapies
- Optimal timing of transplant is becoming a major challenge in patients responding well to JAK-inhibitor therapy.

# Clinical Vignette

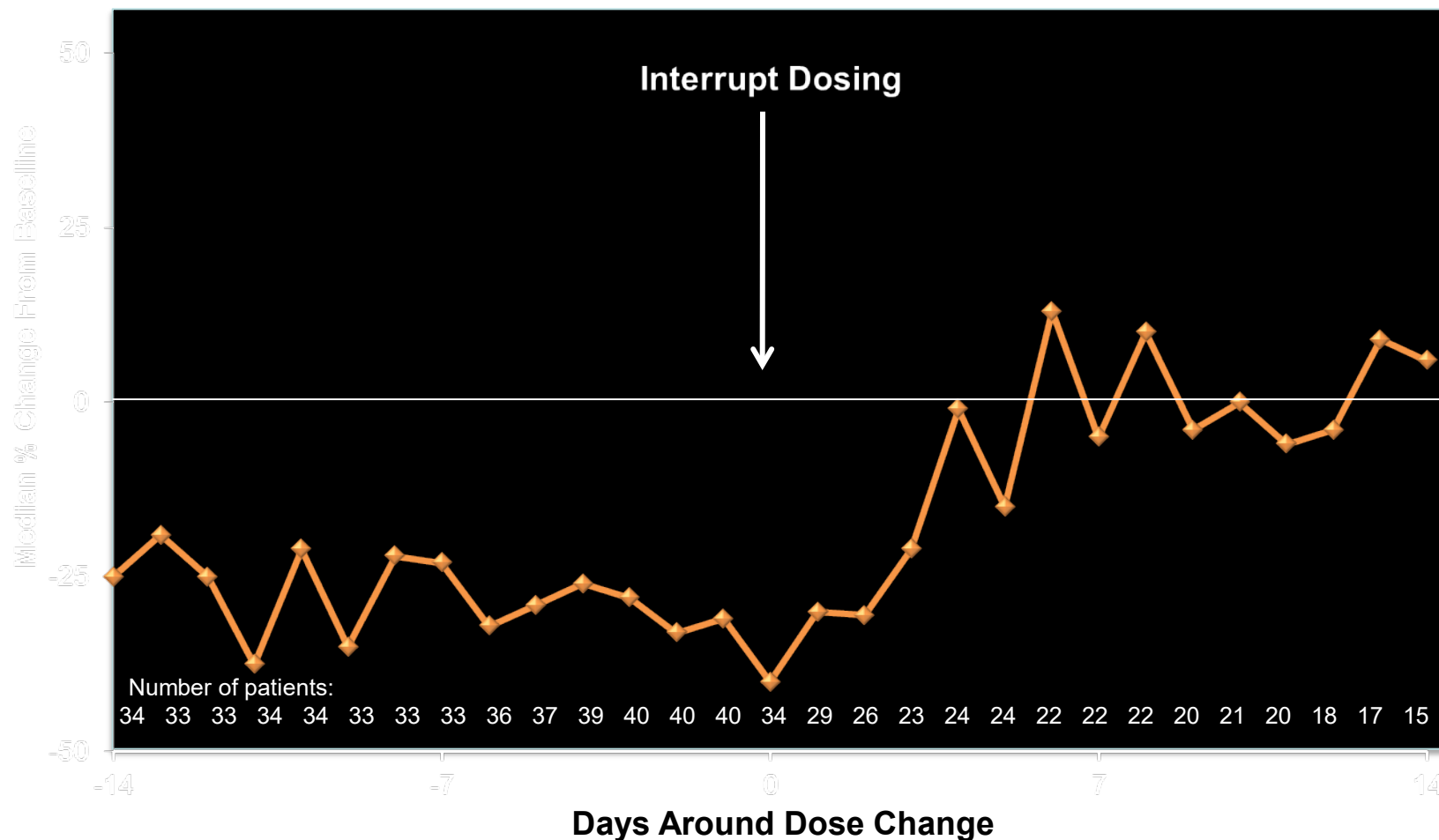
- 61 yo male diagnosed with JAK2 positive MF. He presented with Hb = 9.0, WBC 30,000 and platelets of 258,000. Peripheral blood showed 2% blasts. Cytogenetics were normal. Spleen 22cm. He has had a 10% weight loss in 3 mos.
- Diagnosis: High Risk MF by DIPSS
- Started on Ruxolitinib 20mg BID.
- Within 3 months his spleen measures 10cm and symptoms had significantly improved. Blood counts stabilized.
- A 10/10 matched URD is found.
- *How do we advise the patient?*

Do JAK inhibitors have a role  
in the peri-transplant period?

# JAK ALLO: Recruitment stopped after 22 patients enrolled due to unexpected SAEs in 3 patients



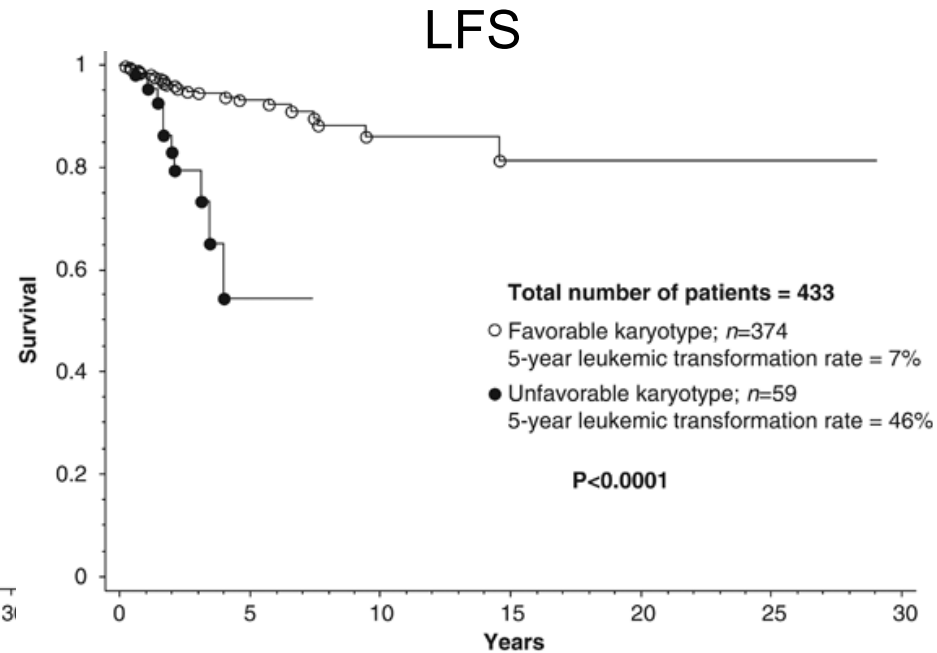
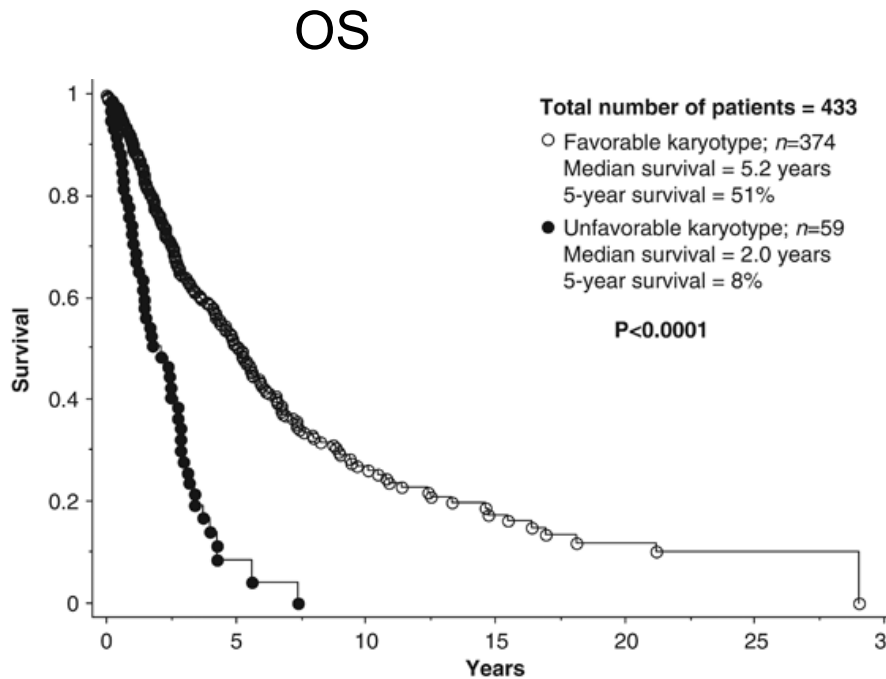
# COMFORT-I: Total symptom score before and during interruption



# ***Benefits of pre-transplant JAK2 inhibitor ?***

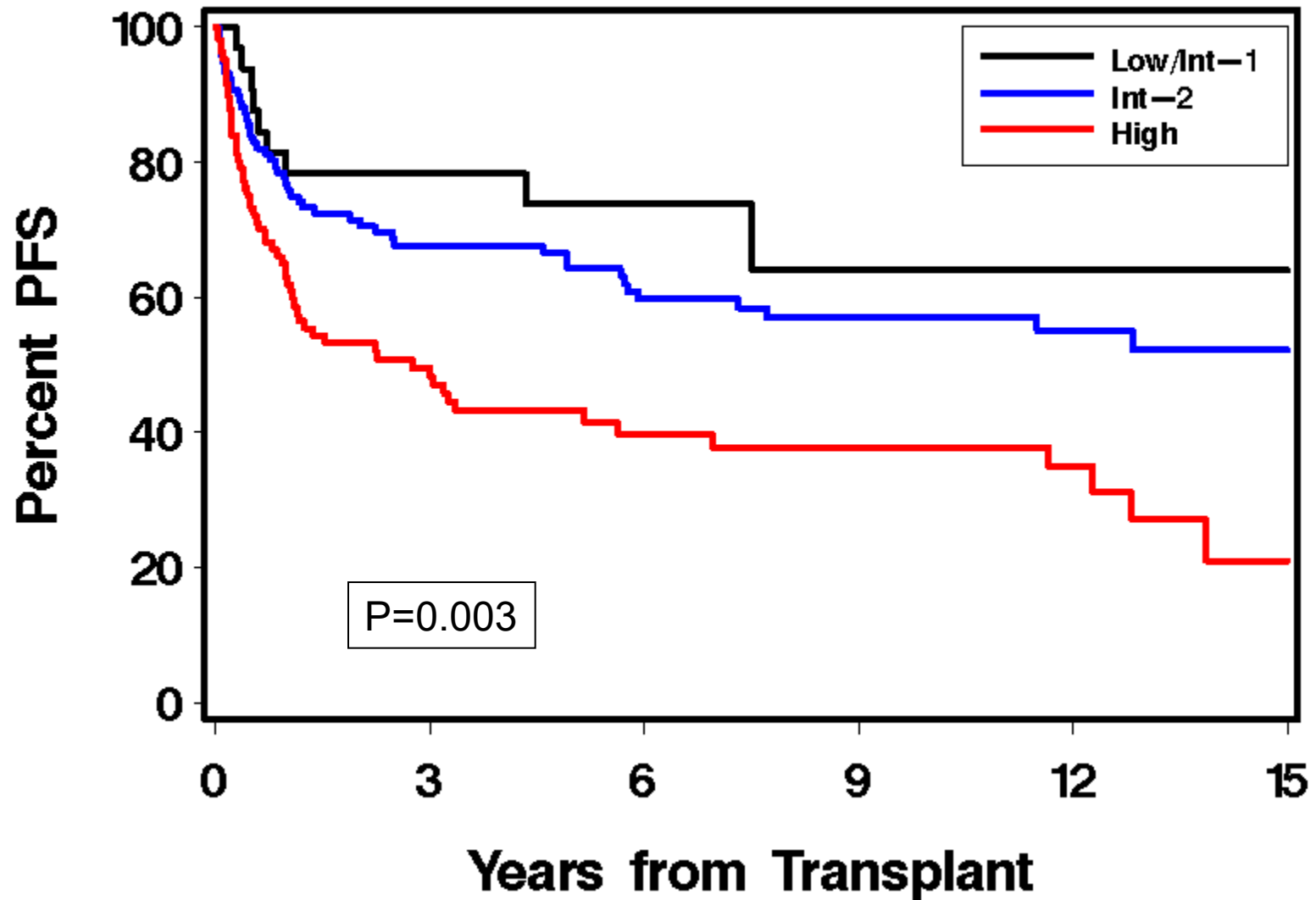
- Reduced spleen size: Faster engraftment
- Suppressed “inflammation”: Less GVHD?
- Weight gain: Better performance status?

# Cytogenetics and Survival in MF



Unfavorable: +8, -7/7q-, i17q, inv3, -5/5q-, 12p-, 11q232, or  $\geq 3$  abnml

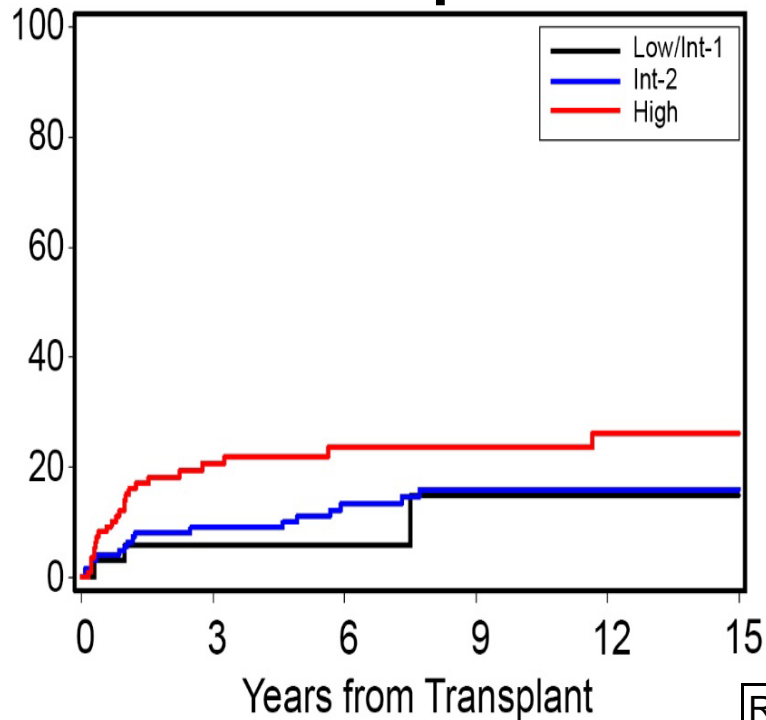
# PFS by DIPSS plus (adjusted)



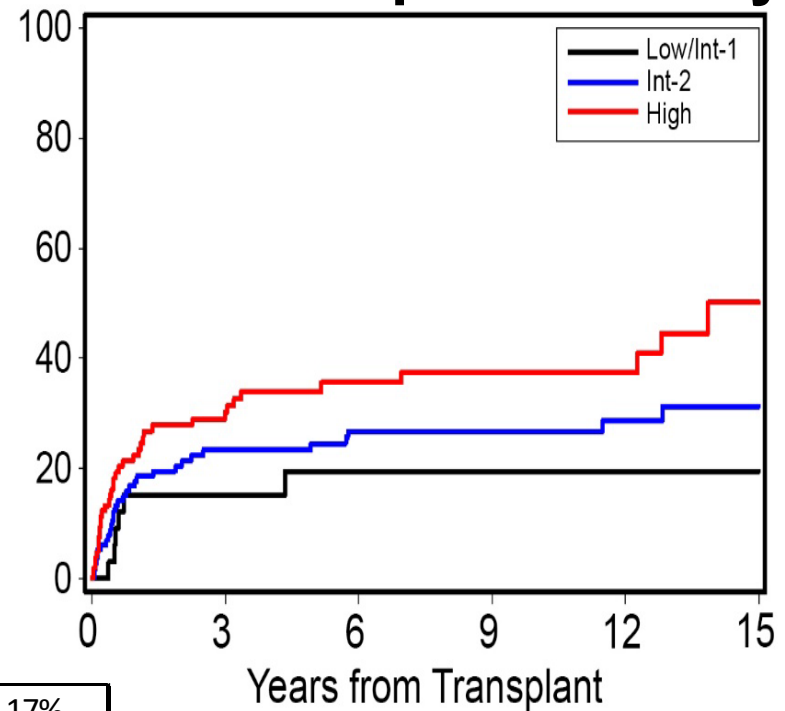
# PostHCT Outcomes by DIPSS-Plus

**NRM is twice as likely as relapse.**

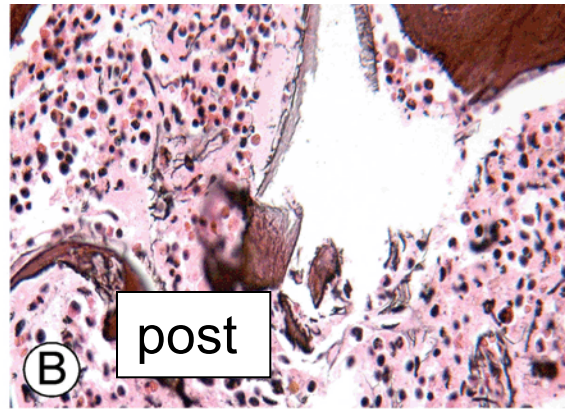
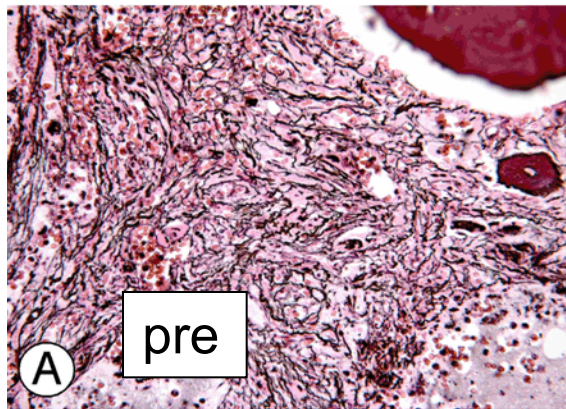
## Relapse



## Non-Relapse Mortality

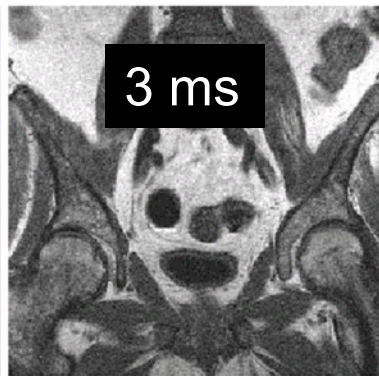
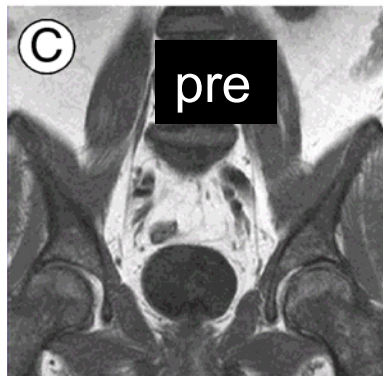


|                  |      |
|------------------|------|
| REL/PD           | 17%  |
| GvHD ± infection | 10%  |
| Infections       | 8%   |
| Organ failure    | 8%   |
| Graft failure    | 2-5% |
| Miscellaneous    | 1%   |

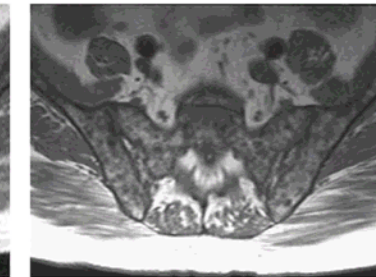
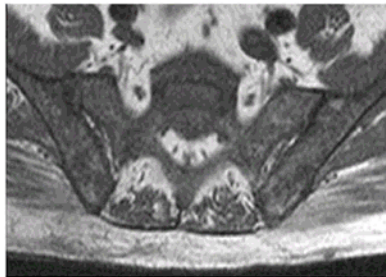
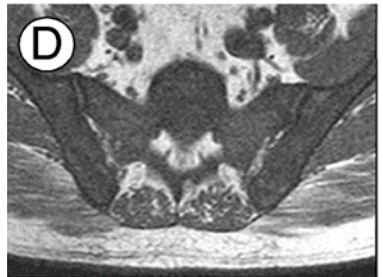


# Disease Resolution After Transplantation

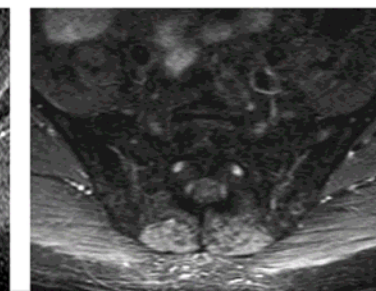
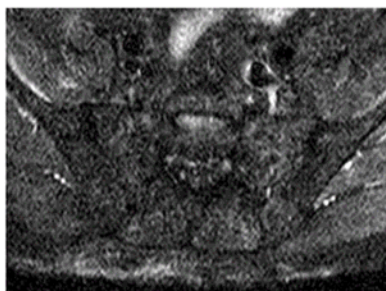
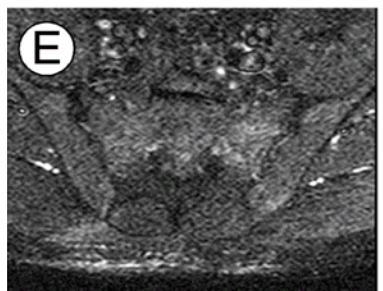
Reticulin (x300)



T1 Spin Echo  
(coronal)

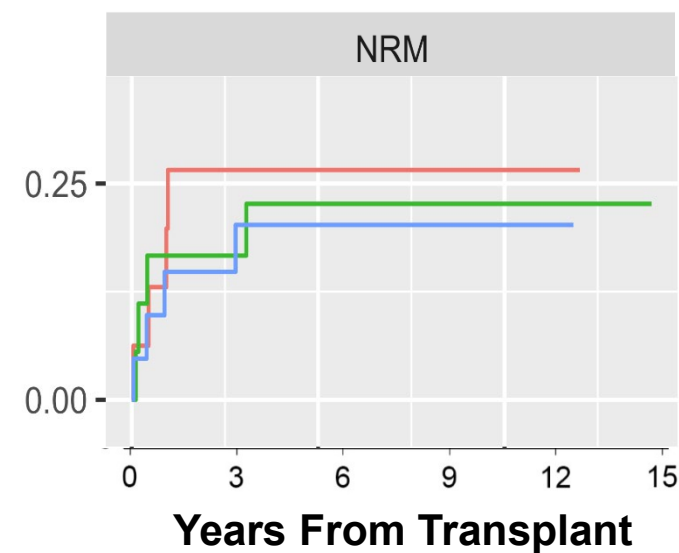
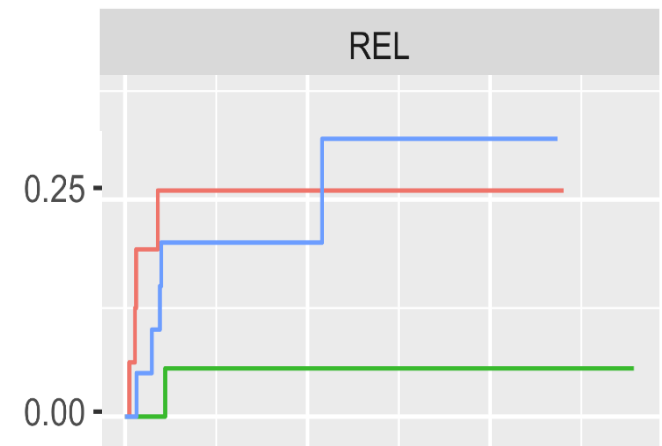
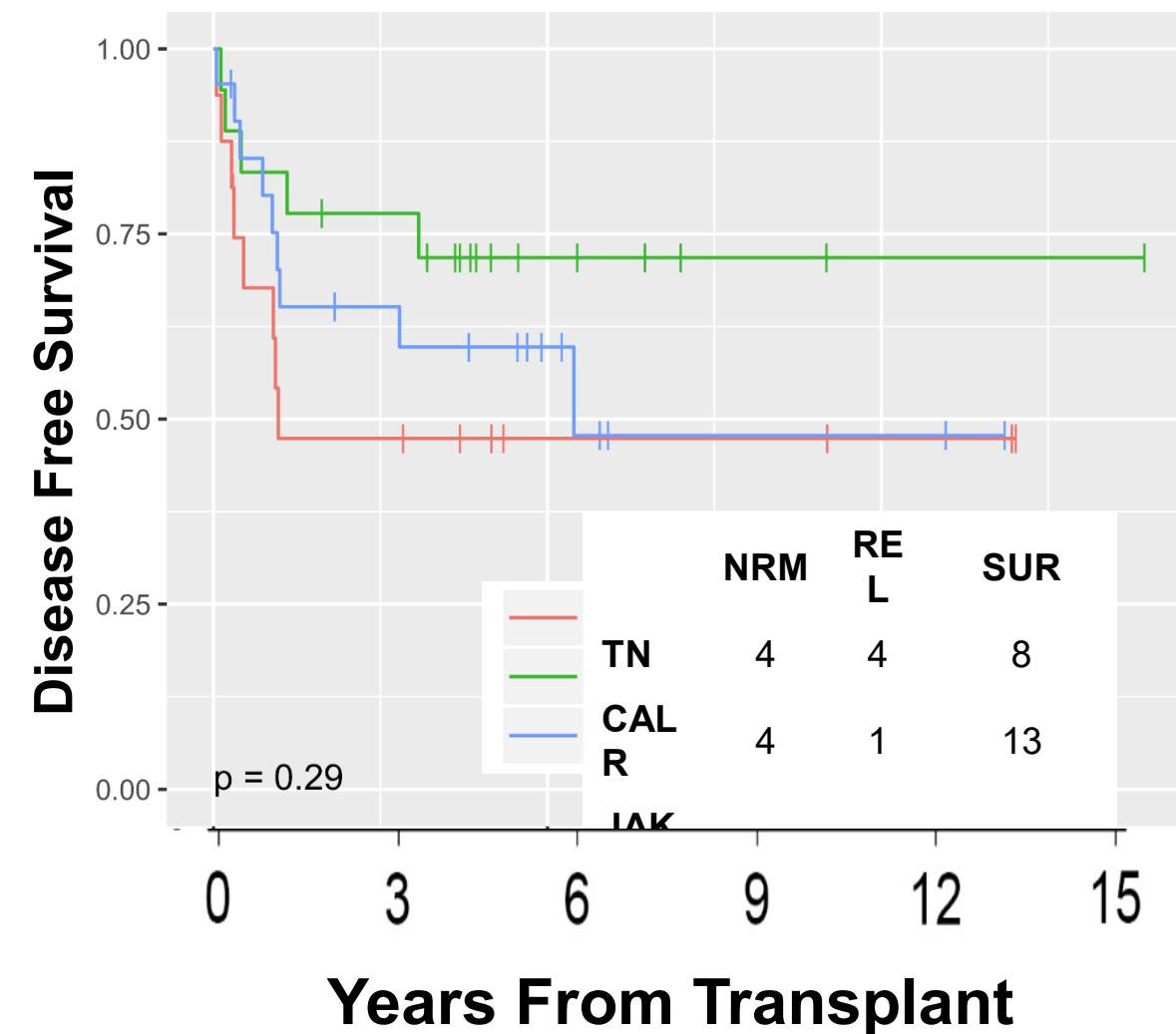


T1 Spin Echo  
(transverse)



STIR Image

# Disease-Free Survival by Driver Mutation



# Digging deeper

**So, we have been moving from**

***Cells* (myeloblasts, cytopenias) to**

***Chromosomes* (breakage, loss, gain) to**

***Genes* (DNA mutations)**

Should we delay transplant in  
patients responding to JAK  
inhibitors?