Transplantation for MPN
(PMF, PV, ET)

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11th J. Niblack Conference on MPN, Scottsdale, AZ, March 2019
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)
- Adverse karyotype
- Low platelet count
- Needing RBC transfusions
- Absence of CALR
- High risk mutations
- Marrow fibrosis
DIPSS and Survival
(no transplant – without JAK2 inhibitors)

Low = 0
Int.1 = 1-2
Int.2 = 3-4
High = >4

Cumulative Proportion Surviving

Time (years)

Overall Survival by Mutation

Vannucchi et al. 2013. Leukemia. 27: 1861
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

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

Survival Estimates
With Number of Subjects at Risk

Survival Probability

Months Since Transplant

Group
1: Likely by 1 Test
2: Unlikely by 1 Test
3: Unlikely by 2 Tests

R. Salit et al, unpublished
Transplantation

before Leukemic Transformation
Relapse-free Survival  (DIPSS plus)

N= 233
P=0.0001
Non-Relapse Mortality (adjusted)

Percent NRM

Years from Transplant

Low/Int—1
Int—2
High

P=0.02

Samuelson B, Salit R et al BBMT 2018
Ruxolitinib before Transplant

R. Salit et al, under review

Jakafi → Transplantation
Related or unrelated donors, cord blood
Median age: 58 years

N=27
Mutations

• **Driver mutations**
  – JAK2, MPL1, **CALR** (type 1 and type 2)

• **Other mutations**
  – **ASXL1, SRSF2, EZH1, IDH1/2, p53**
  – **other**
Mutations and transplant outcome
-Survival-

V. Panagiota et al, Leukemia 28:1552, 2014
Mutations and transplant outcome

Again: Non-relapse mortality!
ASXL1 mutations: Relapse and PFS

N. Kroeger et al, BBMT 23: 1095, 2017
98% ≥1 mutation (ave 2.3/pt)
PV/MF JAK2+
CALR+ rare Unfav Cyto
The *Number* of mutations matters

E. Stevens, J. Radich et al, under review
## DIPSS plus, Mutations and PFS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>HR (95% CI)</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driver</td>
<td>CALR vs TN</td>
<td>0.40 (0.14, 1.10)</td>
<td>0.076</td>
</tr>
<tr>
<td></td>
<td>JAK2 vs TN</td>
<td>0.55 (0.22, 139)</td>
<td>0.205</td>
</tr>
<tr>
<td></td>
<td>JAK2 vs CALR</td>
<td>1.38 (0.52, 3.62)</td>
<td>0.517</td>
</tr>
<tr>
<td>Nr. of mutations</td>
<td>≥3 vs &lt;3</td>
<td>4.03 (1.77, 9.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASXL1</td>
<td>Yes vs No</td>
<td>1.48 (0.67, 3.30)</td>
<td>0.335</td>
</tr>
<tr>
<td>DIPSS plus</td>
<td>Int2/High vs Low/Int1</td>
<td>3.58 (0.84, 15.23)</td>
<td>0.084</td>
</tr>
<tr>
<td></td>
<td>Int2/High&lt;3 vs Low/Int1&lt;3</td>
<td>2.52 (0.57, 11.19)</td>
<td>0.224</td>
</tr>
<tr>
<td></td>
<td>Int2/High≥3 vs Low/Int1&lt;3</td>
<td>8.45 (1.83, 39.12)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Int2/High ASXL1- vs Low/Int1ASXL1-</td>
<td>5.38 (0.71, 40.94)</td>
<td>0.104</td>
</tr>
<tr>
<td></td>
<td>Int2/High ASXL1+ vs Low/Int1ASXL1-</td>
<td>6.42 (0.81, 50.74)</td>
<td>0.078</td>
</tr>
</tbody>
</table>
Transplantation and Mutation Kinetics

[Graph showing VAF (Variant Allele Frequency) over time for different events post-transplant (Pre HCT 50d, Pre HCT 21d, Post HCT 28d, Post HCT 60d, Post HCT 85d, Post HCT 1y).]

- DFL1388
- JP1462
- MAG1147
- MMT1391

Event markers and VAF peaks for ASXL1, CDKN2A, GNAS, TET2, ZRSR2, CALR, CUX1, JAK2, and TP53.

E. Stevens, J. Radich et al, under review
10x Genomics 3’ Single Cell RNAseq

Gu et al. 2017. Nature Communications
Impact of Ruxolitinib
Mutations and decisions before and during ruxolitinib therapy

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

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

Overall Survival after Ruxolitinib Discontinuation

- Transplant: not reached
- Salvage Therapy: 15.0 months
- No Treatment/Observation: 4.9 months

Percent patients surviving (%)

Overall Survival (months)

Number at risk:
- Transplant: 16
- Salvage Therapy: 25
- No Treatment/Observation: 22

A. Kuykendall et al, Annals of Hematology, 97: 435, 2018
Transplantation after progression/leukemic transformation
Transplantation after Leukemic Transformation

**TP53**

Survival

Effect of Chemotherapy before Transplantation

H. Alchalby et al, BBMT 2014
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 Cytoxan; 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

H.J.Deeg, MD
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Age and Transplantation

CIBMTR data 2015
"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**
Mutations and survival

A. Tefferi et al, Blood 124: 2507, 2014
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>Hazard Ratio (95%CI)</th>
<th>p</th>
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<td>Driver</td>
<td>CALR vs TN</td>
<td>0.40 (0.14, 1.10)</td>
<td>0.0759</td>
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<tr>
<td>Driver</td>
<td>JAK2 vs TN</td>
<td>0.55 (0.22, 1.39)</td>
<td>0.2048</td>
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<tr>
<td>Driver</td>
<td>JAK2 vs CALR</td>
<td>1.38 (0.52, 3.62)</td>
<td>0.5168</td>
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<tr>
<td>Mutation-3</td>
<td>≥3 mutations vs &lt;3 mutations</td>
<td>4.03 (1.77, 9.16)</td>
<td>&lt;0.001</td>
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<tr>
<td>ASXL1</td>
<td>Yes vs No</td>
<td>1.48 (0.67, 3.30)</td>
<td>0.3351</td>
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<td>DIPSSPlus</td>
<td>Int2/High vs Low/Int1</td>
<td>3.58 (0.84, 15.23)</td>
<td>0.0840</td>
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<td>Int2/High(&lt;3) vs Low/Int1(&lt;3)</td>
<td>2.52 (0.57, 11.19)</td>
<td>0.2243</td>
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<tr>
<td>DIPSSPlus-3</td>
<td>Int2/High(3+) vs Low/Int1(&lt;3)</td>
<td>8.45 (1.83, 39.12)</td>
<td>0.0063</td>
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<td>DIPSSPlus-A</td>
<td>Int2/High(ASXL1-) vs Low/Int1(ASXL1-)</td>
<td>5.38 (0.71, 40.94)</td>
<td>0.1043</td>
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<tr>
<td>DIPSSPlus-A</td>
<td>Int2/High(ASXL1+) vs Low/Int1(ASXL1-)</td>
<td>6.42 (0.81, 50.74)</td>
<td>0.0780</td>
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</tbody>
</table>
Figure 1: Progression-free survival, Relapse, and NRM by DIPSS plus classification (low/intermediate-1 vs. Intermediate-2/high).
triple negative (no mutations in JAK 2, CALR or MPL1). Vertical columns indicate individual patients. Horizontal lines indicate individual genes. % figures indicate frequency within the cohort.
**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
- Abnormal chromosomes
- Low platelet count
- Requiring transfusions
- Mutations
  - JAK2, MPL1, CALR
  - ASXL1, p53, etc
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 ≥ 3 abnml
Mutations

- JAK2, MPL1, CALR (type 1 and type 2)
- ASXL1, TET2,
- SRSF2, U2AF1
- IDH1, IDH2, TP53, DNMT3a, IKZF1, LNK
- Other
JAK2 Inhibitors

Benefits
Overall survival (COMFORT-II Trial)

![Graph showing overall survival comparison between Ruxo and BAT groups.](Image)

- **Ruxo**
- **BAT**

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>146</td>
<td>73</td>
</tr>
<tr>
<td>Events</td>
<td>29 (19.9%)</td>
<td>22  (30.1%)</td>
</tr>
<tr>
<td>Censored</td>
<td>117 (80.1%)</td>
<td>51  (69.9%)</td>
</tr>
</tbody>
</table>
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)
“Bone marrow” in the Lung

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

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

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

Treatment Schema FHCRC 9033

- JAK-2 Inhibitor x 8 weeks or best response
  - Meets transplant criteria
  - Fails to meet transplant criteria
    - Spleen >22 cm *consider* splenectomy
    - Off Study

- HLA matched sib, or URD donor
  - Meets transplant criteria
    - UCBT donor
      - RIC: Fludarabine eMelphalan
      - HIC: Cytoxan Busulfan + (Fludarabine for UCBT)
      - RIC: Fludarabine Melphalan (TBI 400 for UCBT)
Other Factors
DIPSS \textit{plus}

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Points</th>
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<tbody>
<tr>
<td>DIPSS-Low</td>
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</tr>
<tr>
<td>DIPSS-Int-1</td>
<td>1</td>
</tr>
<tr>
<td>DIPSS-Int-2</td>
<td>2</td>
</tr>
<tr>
<td>DIPSS-High</td>
<td>3</td>
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<tr>
<td>PLUS</td>
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<tr>
<td>Unfavorable Karyotype(^2)</td>
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<tr>
<td>Transfusion Dependence</td>
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<td>Platelet &lt;100,000/ul</td>
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<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>Points</th>
<th>Median Survival (mo)</th>
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<tbody>
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<td>Low</td>
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<td>Intermediate-1</td>
<td>1</td>
<td>78</td>
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<tr>
<td>Intermediate-2</td>
<td>2-3</td>
<td>35</td>
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<tr>
<td>High</td>
<td>4-6</td>
<td>16</td>
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<tr>
<td>Characteristic</td>
<td>Value</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>----------------------------</td>
<td></td>
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<tr>
<td>No. of patients</td>
<td>233</td>
<td></td>
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<tr>
<td>Age range, y (median)</td>
<td>12.9 – 78.9 (54.1)</td>
<td></td>
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<td>Sex, male/female, no (%) of patients</td>
<td>133 (57)/100 (43)</td>
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<td>Months from diagnosis to HSCT, range (median)</td>
<td>0.7-313.7 (15.5)</td>
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<tr>
<td>Type of myelofibrosis, no. (%)</td>
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<tr>
<td>Primary</td>
<td>139 (60)</td>
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<tr>
<td>Secondary</td>
<td>94 (40)</td>
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<td>Essential thrombocytemia</td>
<td>56 (24)</td>
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<td>Polycythemia vera</td>
<td>28 (12)</td>
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<tr>
<td>Other/uncertain</td>
<td>10 (4)</td>
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<td>Cytogenetic classification, no. (%)</td>
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<tr>
<td>Favorable</td>
<td>183 (79)</td>
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<tr>
<td>Unfavorable</td>
<td>44 (19)</td>
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<td>Undetermined</td>
<td>6 (3)</td>
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<td>Mutational status, no. (%)</td>
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<tr>
<td>JAK2-V617F mutant</td>
<td>64 (27)</td>
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<tr>
<td>CALR mutant</td>
<td>18 (4)</td>
<td></td>
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<tr>
<td>MPL</td>
<td>1 (0.4)</td>
<td></td>
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<tr>
<td>Triple negative</td>
<td>13 (5)</td>
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<tr>
<td>N/D</td>
<td>137 (59)</td>
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<td>DIPPSPlus score, no. (%)</td>
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<tr>
<td>Low</td>
<td>10 (4)</td>
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<tr>
<td>Intermediate-1</td>
<td>25 (11)</td>
<td></td>
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<tr>
<td>Intermediate-2</td>
<td>107 (46)</td>
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<td>High</td>
<td>91 (39)</td>
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</table>

Samuelson, Salit et al
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
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<tr>
<td><strong>Donor type, no. (%)</strong></td>
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<tr>
<td>Syngeneic</td>
<td>3 (1)</td>
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<td>Allogeneic</td>
<td>230 (99)</td>
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<td>102 (46)</td>
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<td>HLA-matched</td>
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<td>HLA-mismatched</td>
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<tr>
<td>Unrelated donor</td>
<td>127 (57)</td>
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<tr>
<td>HLA-matched</td>
<td>106 (83)</td>
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<td>HLA-mismatched</td>
<td>21 (17)</td>
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<tr>
<td><strong>Conditioning</strong></td>
<td></td>
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<tr>
<td>Bu 16 mg/kg oral + Cy 120mg/kg</td>
<td>128 (55)</td>
</tr>
<tr>
<td>Bu 16mg/kg oral + Cy 120mg/kg + ATG</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Cy 120mg/kg + Bu 16mg/kg IV</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Flu 120mg/m2 + Bu 16 mg/kg oral</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Flu 250 mg/m2+ Bu 16mg/kg IV + ATG</td>
<td>3 (1)</td>
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<tr>
<td>Flu 120 mg/m2 + Bu 12.8 mg/kg IV + ATG</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Bu 7mg/kg oral + TBI 12Gy</td>
<td>10 (4)</td>
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<tr>
<td>Cy 120 mg/kg + TBI 12-14 Gy</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Flu 150mg/m2 + Melphalan 140mg/kg</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Flu 90mg/m2 + TBI 2Gy</td>
<td>36 (15)</td>
</tr>
<tr>
<td><strong>Source of stem cells</strong></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>47 (21)</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>185 (79)</td>
</tr>
<tr>
<td>Cord blood</td>
<td>1</td>
</tr>
</tbody>
</table>
Progression-free survival by DIPSS plus

N= 233
P=0.0001
Relapse by DIPSS plus (adjusted)

P=0.05

Samuelson B, Salit R et al…BBMT 2018
Cytogenetics and Outcome

Survival

- HR: 2.51 (1.1-5.6), p=0.03
- N=149

Relapse

- HR: 1.71 (1.1-2.7), p=0.03
- N=44

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

Samuelson B et al…BBMT 2018
Non-Relapse Mortality (adjusted)

P=0.02

Years from Transplant

Percent NRM

Low/Int-1
Int-2
High
Age and Survival

P = 0.04

Samuelson B et al…BBMT 2018
Progression to Leukemia
Risk Factors for Leukemic Transformation

- Severe thrombocytopenia (Plt <41)
- Higher blasts in peripheral blood (>2%)
- High risk cytogenetics (monosomomal 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

OS and PFS by Chemotherapy response

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!
### Mutation Patterns and Outcome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Count</th>
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<tbody>
<tr>
<td>JAK2</td>
<td>38%</td>
<td>21</td>
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<tr>
<td>CALR</td>
<td>33%</td>
<td>18</td>
</tr>
<tr>
<td>ASXL1</td>
<td>35%</td>
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<tr>
<td>TET2</td>
<td>24%</td>
<td>13</td>
</tr>
<tr>
<td>GATA2</td>
<td>22%</td>
<td>12</td>
</tr>
<tr>
<td>U2AF1</td>
<td>16%</td>
<td>9</td>
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<tr>
<td>EZH2</td>
<td>16%</td>
<td>9</td>
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<tr>
<td>ET6</td>
<td>33%</td>
<td>18</td>
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<td>SF3B1</td>
<td>15%</td>
<td>8</td>
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<tr>
<td>CDKN2A</td>
<td>11%</td>
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<td>RUNX1</td>
<td>11%</td>
<td>6</td>
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<tr>
<td>SRSF2</td>
<td>9%</td>
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<tr>
<td>KIT</td>
<td>7%</td>
<td>4</td>
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<td>ZRSR2</td>
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<tr>
<td>CUX1</td>
<td>5%</td>
<td>3</td>
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<tr>
<td>DNMT3A</td>
<td>5%</td>
<td>3</td>
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<tr>
<td>CEBPA</td>
<td>4%</td>
<td>2</td>
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<td>TP53</td>
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<td>SETBP1</td>
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<td>2</td>
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<tr>
<td>BCR1</td>
<td>4%</td>
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<tr>
<td>BCR1</td>
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<td>NOTCH1</td>
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<td>2</td>
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<tr>
<td>ID1</td>
<td>4%</td>
<td>2</td>
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<td>IDH2</td>
<td>2%</td>
<td>1</td>
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<td>GNAS</td>
<td>2%</td>
<td>1</td>
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<tr>
<td>CBL</td>
<td>2%</td>
<td>1</td>
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<tr>
<td>PTPN11</td>
<td>2%</td>
<td>1</td>
</tr>
<tr>
<td>CBLB</td>
<td>2%</td>
<td>1</td>
</tr>
<tr>
<td>PHF6</td>
<td>2%</td>
<td>1</td>
</tr>
</tbody>
</table>

**Etiology**
- **PMF**
- **PV/MF**
- **ET/MF**
- **Unknown**

**Cyto**
- **FAV**
- **UNFAV**
- **Normal**
- **Unknown**

**Status**
- **REL**
- **SUR**
- **NRM**

**DIPSS+**
- **INT2/Hi**
- **Low/INT1**

98% ≥1 mutation (ave 2.3/pt)

PV/MF JAK2+
CALR+ rare Unfav Cyto
Disease-Free Survival by ASXL1

E. Stevens, unpublished

Years From Transplant

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

1/11 ASXL1+
ASXL1- N = 26
ASXL1+ N = 18

p = 0.072
Relapse-Free Survival by Mutation #

- 1/11 ≥ 3 (survived)
- < 3 N = 22
- ≥ 3 N = 22

Years From Transplant

<table>
<thead>
<tr>
<th>Mutation Level</th>
<th>NRM</th>
<th>REL</th>
<th>SUR</th>
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</thead>
<tbody>
<tr>
<td>Low/Int1</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Int2/High(&lt;3)</td>
<td>4</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Int2/High(≥3)</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

p < 0.001

Graphs showing disease-free survival probability over years from transplant, with distinct Kaplan-Meier curves for different mutation levels.
## Association of Mutations with Other Variables

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

E. Stevens, unpublished
“Additional” Mutations and Transplant Outcome (48 patients)

<table>
<thead>
<tr>
<th></th>
<th>≤2 mutations</th>
<th>≥3 mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived &gt;1 year after Transplantation</td>
<td>79%</td>
<td>41%</td>
</tr>
<tr>
<td>Death from Non-Relapse Causes</td>
<td>13%</td>
<td>35%</td>
</tr>
<tr>
<td>Relapse</td>
<td>8%</td>
<td>24%</td>
</tr>
</tbody>
</table>

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
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

Vannucchi et al. 2013. Leukemia. 27: 1861
## Modified Prognostic Models

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

E.Stevens, unpublished
## Associated Variables

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Total (n = 55)</th>
<th>&lt;3 mutations (n = 31)</th>
<th>≥3 mutations (n = 24)</th>
<th>p</th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>42% (23)</td>
<td>26% (8)</td>
<td>62% (15)</td>
<td>0.0058</td>
<td>0.087</td>
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<tr>
<td>Abnormal</td>
<td>58% (32)</td>
<td>74% (23)</td>
<td>38% (9)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Total (n = 55)</th>
<th>&lt;3 mutations (n = 31)</th>
<th>≥3 mutations (n = 24)</th>
<th>p</th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>44% (24)</td>
<td>29% (9)</td>
<td>62% (15)</td>
<td>0.0386</td>
<td>0.502</td>
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<tr>
<td>Unfavorable</td>
<td>29% (16)</td>
<td>39% (12)</td>
<td>17% (4)</td>
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<td></td>
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<tr>
<td>Favorable</td>
<td>27% (15)</td>
<td>32% (10)</td>
<td>21% (5)</td>
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</table>

<table>
<thead>
<tr>
<th>DIPSS+ Var</th>
<th>Total (n = 55)</th>
<th>ASXL1⁻ (n = 36)</th>
<th>ASXL1⁺ (n = 19)</th>
<th>p</th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/Int1</td>
<td>20% (11)</td>
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<td>5% (1)</td>
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</table>

<table>
<thead>
<tr>
<th>Peripheral Blasts</th>
<th>Total (n = 55)</th>
<th>ASXL1⁻ (n = 36)</th>
<th>ASXL1⁺ (n = 19)</th>
<th>p</th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>55% (30)</td>
<td>72% (26)</td>
<td>21% (4)</td>
<td>&lt;0.001</td>
<td>0.0062</td>
</tr>
<tr>
<td>Yes</td>
<td>44% (24)</td>
<td>28% (10)</td>
<td>74% (14)</td>
<td></td>
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</tbody>
</table>

E.Stevens, unpublished
Disease-Free Survival by DIPSS-Plus

DIPPS + cohort (n= 233)

Molecular cohort (n= 55)

Years From Transplant

Disease-Free Survival

Years From Transplant

Disease-Free Survival

p = 0.044
Additional Mutations
(48 Patients)

<table>
<thead>
<tr>
<th></th>
<th>CALR+ (38%)</th>
<th>JAK2+ (29%)</th>
<th>Triple Negative (33%)</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type I</td>
<td>Type II</td>
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<tr>
<td>ASXL1</td>
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<td>31%</td>
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<tr>
<td>IKZF1</td>
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<td>23%</td>
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<td>ETV6</td>
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<td>U2AF1</td>
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<td>17%</td>
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<td>EZH2</td>
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<td>6%</td>
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<td></td>
<td>4%</td>
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<td></td>
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<tr>
<td>SETBP1A</td>
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<td>4%</td>
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<td>SRSF2</td>
<td></td>
<td></td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td></td>
<td></td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

E. Stevens et al
• Use RNAseq expression profile to identify cell subtype
• 3'SNVs to characterize donor/host origin

Gu et al. 2017. Nature Communications
Disease-Free Survival by DIPSS-Plus

DIPPS + cohort (n= 233)

Molecular cohort (n= 55)

Years From Transplant

Disease-Free Survival

Years From Transplant

Disease-Free Survival

p = 0.044
Thank you

H.J. Deeg, MD
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

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

Scott et al., Blood 119:2657-2664, 2012
Disease Characteristics (No./%)

• Splenectomy\(^1\)
  - No: 136 (80)
  - Yes: 31 (18)

• DIPSS Score
  - Low: 21 (12)
  - Intermediate-1: 48 (28)
  - Intermediate-2: 50 (30)
  - High: 51 (30)

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%)

Scott et al., Blood 119:2657-2664, 2012
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
# Myeloproliferative Neoplasms

<table>
<thead>
<tr>
<th>Chronic myeloid neoplasms</th>
<th>Myelodysplastic syndromes</th>
<th>Myelodysplastic syndromes/myeloproliferative neoplasms overlap</th>
<th>Myeloproliferative neoplasms</th>
<th>Myeloid and lymphoid neoplasms with eosinophilia and PDGFR/FGFR1 mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral blood or bone marrow morphology</td>
<td>Absence of cytosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyserythropoiesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysgranulopoiesis</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Monocytosis</td>
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<td></td>
<td></td>
<td></td>
<td>Granulocytosis Thrombocytosis</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Myelodysplastic syndrome</td>
<td>Chronic myelomonocytic leukemia</td>
<td>Chronic myeloid leukemia</td>
<td>Myeloid and lymphoid neoplasms with eosinophilia and PDGFR, PDGFRB, or FGFR1 mutations</td>
</tr>
<tr>
<td>Associated mutation(s) (estimated frequency)</td>
<td>TET2 (20%)</td>
<td>TET2 (40%-60%)</td>
<td>BCR-ABL1 (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Refractory anemia with ring sideroblasts</td>
<td>SRSF2 (30%-50%)</td>
<td>Polycythemia vera</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SF3B1 (80%-90%)</td>
<td>Asxl1 (40%)</td>
<td>JAK2 (99%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Essential thrombocythemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>JAK2/CalR/MPL (85%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary myelofibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>JAK2/CalR/MPL (90%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic neutrophilic leukemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CSF3R (80%-100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SETBP1 (30%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systemic mastocytosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KITD816V (80%-100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic eosinophilic leukemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Myeloproliferative neoplasm—unclassifiable</td>
<td></td>
</tr>
</tbody>
</table>

The 2008 World Health Organization (WHO) Classification of Chronic Myeloid Neoplasms

### Table: Mutations in Myeloproliferative Neoplasms (MPNs)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Chromosome Location</th>
<th>Approximate Mutational Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Polycythemia Vera</td>
</tr>
<tr>
<td><strong>Specific to MPN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAK2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 14 mutation; ie, JAK2/V617F</td>
<td>9p24</td>
<td>95</td>
</tr>
<tr>
<td>Exon 12 mutations</td>
<td>9p24</td>
<td>3</td>
</tr>
<tr>
<td>CALR Exon 9 deletions and insertions</td>
<td>19p13.2</td>
<td>Infrequent</td>
</tr>
<tr>
<td>MPL Exon 10 mutations</td>
<td>1p34</td>
<td>Infrequent</td>
</tr>
<tr>
<td>LNK (as in Links; aka SH2B3) exon 2 mutations</td>
<td>12q24.12</td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Nonspecific to MPN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TET2 Mutations involve several exons</td>
<td>4q24</td>
<td>16</td>
</tr>
<tr>
<td>ASXL1 Exon 12 mutations</td>
<td>20q11.1</td>
<td>7</td>
</tr>
<tr>
<td>IDH1/IDH2 Exon 4 mutations</td>
<td>2q33.3/15q26.1</td>
<td>2</td>
</tr>
<tr>
<td>EZH2 Mutations involve several exons</td>
<td>7q36.1</td>
<td>Infrequent</td>
</tr>
<tr>
<td>DNM3A Most frequent mutations affect amino acid R882</td>
<td>2p23</td>
<td>7</td>
</tr>
<tr>
<td>CBL Exon 8/9 mutations</td>
<td>11q23.3</td>
<td>Infrequent</td>
</tr>
<tr>
<td>IKZF1 Mostly deletions including intragenic</td>
<td>7p12</td>
<td>Infrequent</td>
</tr>
<tr>
<td>TP53 Exons 4 through 9</td>
<td>17p13.1</td>
<td>Infrequent</td>
</tr>
<tr>
<td>SF3B1 Exons 14 and 15, mostly</td>
<td>2q33.1</td>
<td>Infrequent</td>
</tr>
<tr>
<td>SRSF2 Exon 2</td>
<td>17q25.1</td>
<td>Infrequent</td>
</tr>
<tr>
<td>U2AF1</td>
<td>21q22.3</td>
<td>Infrequent</td>
</tr>
<tr>
<td>SETBP1 Exon 4</td>
<td>18q12.1</td>
<td>Infrequent</td>
</tr>
</tbody>
</table>

**Abbreviations:** ASXL1, additional sex combs-like 1; CALR, calreticulin; CBL, casitas B-lineage lymphoma proto-oncogene; DNM3A, DNA cytosine methyltransferase; EZH2, enhancer of zest 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.
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 (DIPSS)**

- **Periodic reassessment**
- **Low (0 points)**
  - **Observation or conservative therapies**
  - **Favorable**
- **Int-1 (1-2 points)**
  - **Cytogenetics†**
    - **Mutations ?**
      - **Favorable**
      - **Unfavorable**
    - **Younger age, low comorbidity**
      - **Yes**
        - **“Conventional” conditioning HCT**
      - **No**
        - **Reduced-intensity HCT**

---

*Dynamic International Prognostic Scoring System: age > 65 years (1 point), leukocyte count > 25,000/μL (1 point), hemoglobin < 10 g/dL (2 points), circulating blast cells ≥ 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)

Low = 0
Int.1= 1-2
Int.2= 3-4
High= >4

Cumulative Proportion Surviving

Time (years)

# of Factors

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

B

Fibrosis Grades 1-2 (n=27)

Fibrosis Grades 3-4 (n=57)

Years after Transplant

D.Kerbauy et al, BBMT, 2007
Overall survival (COMFORT-II Trial)

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

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
- Abnormal chromosomes
- Low platelet count
- Requiring transfusions

Factors
- Low = 0
- Int.1 = 1-2
- Int.2 = 3-4
- High = >4

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

- PMF
  - Systemic symptoms
  - Painful splenomegaly Yes, but not in all patients

- P. vera
  - Elevated hematocrit ?

- E.T.
  - Elevated platelets ?
MF, phase III - survival

Hazard ratio, 0.50 (95% CI, 0.25–0.98)
P = 0.04 by log-rank test

No. at Risk
Ruxolitinib: 155, 155, 154, 153, 152, 148, 144, 143, 143, 140, 134, 102, 68, 52, 37, 18, 8, 3
Placebo: 154, 152, 151, 148, 147, 147, 142, 139, 132, 131, 123, 115, 83, 58, 45, 35, 20, 9, 3

Leukemia cutis

M. Kremyanskaya et al, unpublished
PMF Pre-Transplant

Reticulin Stain

G. Sale
Lung: Extramedullary Hematopoiesis and Fibrosis

Survival without and with Transplantation (by DIPSSS)

<table>
<thead>
<tr>
<th>DIPPS Risk</th>
<th>Survival (median; years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Transplant (at reporting)</td>
</tr>
<tr>
<td></td>
<td>Transplant (med F/U 5.9 ys)</td>
</tr>
<tr>
<td>Low</td>
<td>Not reached</td>
</tr>
<tr>
<td>Intermediate 1</td>
<td>14.2</td>
</tr>
<tr>
<td>Intermediate 2</td>
<td>4</td>
</tr>
<tr>
<td>High</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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. Kremyansskaya et al, unpublished
MF: CY → BU Conditioning

Rezvani, et al, BBMT 2013
Mutations and Transplanation

V. Panagiota et al, Leukemia 28:1552, 2014
Reduced Intensity Conditioning for PMF (various regimens)

HCT Outcomes by Mol. Driver

OS

N=13

N=19

N=54

Relapse

B.Scott, HJ Deeg et al
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!
Based on Cervantes F et al. Blood 2013;122:4047-4053
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
### Targeted Sequencing

<table>
<thead>
<tr>
<th>Type I CALR</th>
<th>Type II CALR</th>
<th>JAK2</th>
<th>Triple-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALR</td>
<td></td>
<td></td>
<td>38%</td>
</tr>
<tr>
<td>JAK2</td>
<td></td>
<td></td>
<td>29%</td>
</tr>
<tr>
<td>ASXL1</td>
<td></td>
<td></td>
<td>33%</td>
</tr>
<tr>
<td>IKZF1</td>
<td></td>
<td></td>
<td>31%</td>
</tr>
<tr>
<td>ETV6</td>
<td></td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>U2AF1</td>
<td></td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>SF3B1</td>
<td></td>
<td></td>
<td>13%</td>
</tr>
<tr>
<td>EZH2</td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>RUNX1</td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>TET2</td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td></td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>DNMT3A</td>
<td></td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>GATA2</td>
<td></td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>ZRSR2</td>
<td></td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>NRAS</td>
<td></td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>BCR</td>
<td></td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>BCORL1</td>
<td></td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>CEBPA</td>
<td></td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>NOTCH1</td>
<td></td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>SETBP1A</td>
<td></td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>CBL</td>
<td></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>CBLB</td>
<td></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>CUX1</td>
<td></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>GNAS</td>
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<td>2%</td>
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<td>PHF6</td>
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<tr>
<td>PTPN11</td>
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<td></td>
<td>2%</td>
</tr>
<tr>
<td>SRSF2</td>
<td></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>TP53</td>
<td></td>
<td></td>
<td>2%</td>
</tr>
</tbody>
</table>

*% patients*
Mutations and Transplantation

V. Panagiota et al, Leukemia 28:1552, 2014
Cumulative incidence of non-relapse mortality, %

- Unrelated (N=96)
- Other related (N=24)
- HLA-identical siblings (N=156)

Years

K. Ballen et al 2010
Survival
Mutations

- JAK2, MPL1, CALR (type 1 and type 2)
- ASXL1, TET2,
- SRSF2, U2AF1
- IDH1, IDH2, TP53, DNMT3a, IKZF1, LNK
- Other
Age and Source of Stem Cells

CIBMTR data 2015
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)

- Ruxo
- BAT

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>146</td>
<td>73</td>
</tr>
<tr>
<td>Events</td>
<td>29 (19.9%)</td>
<td>22 (30.1%)</td>
</tr>
<tr>
<td>Censored</td>
<td>117 (80.1%)</td>
<td>51 (69.9%)</td>
</tr>
</tbody>
</table>

Probability vs. Weeks
survival according to transfusion dependence

- Green line: RBC: no
- Red line: RBC: yes

Overall survival:
- 71% for RBC: no
- 52% for RBC: yes

p = 0.10

Bauermann et al
Risks of JAK2 inhibitor for Transplantation?

• Obscuring comorbid conditions?
• Rebound of cytokines when stopped before transplantation
Liver: Sinusoidal fibrosis associated with extramedullary hematopoiesis

H = hepatocytes. Extensive EMH and collagen deposition (blue) in sinusoids.
Reduced Intensity Conditioning and HCT

Adjusted OS according to DIPSS

Probability

DIPSS - Low / Intermediate 1

DIPSS - Intermediate 2 / High

Overall p-value: 0.10

Months

V. Gupta et al, BBMT 2014
JAK2 Inhibitors

Benefits
Patient feels better,
Spleen shrinks,
May live longer
JAK2 inhibitors

Potential *Risks*
“Bone marrow” in the Lung

The graph shows the percentage of NRM (non-relapse mortality) over years from transplant. The black line represents Favorable/Normal cases, and the blue line represents Unfavorable cases. The x-axis represents years from transplant, ranging from 0 to 15, and the y-axis represents the percentage of NRM, ranging from 0 to 100.

FHCRC, Unpublished
Cytogenetics and Transplant Results

Survival

HR: 2.51 (1.1-5.6), p=0.03
N=149

Relapse

HR: 2.51 (1.1-5.6), p=0.03

Unfavorable: +8, -7/7q-, i17q, inv3, -5/5q-, 12p-, 11q23, or ≥ 3 abnml
DIPSS and Survival
(no transplant – no treatment with JAK2 inhibitors)

Low = 0
Int.1 = 1-2
Int.2 = 3-4
High = >4

# of Factors

RIC – Adjusted OS by Regimen
-Is there a best regimen? -

V. Gupta et al, BBMT 2014
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?

Viswabandya et al 2016
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

No. 1
RUXO: spleen ↓ 25%
FLU, MEL, ATG
G
APLASIA
ENGRAFTMENT

TLS
Gr 3-4 GVHD D+7
Death 5 months

No. 2
RUXO: spleen stable
One day FLU + ATG
Stable disease

Splenectomy
Cardio. shock
Alive 11 months

No. 3
RUXO: spleen ↓ 25%
FLU, MEL, ATG
Progressive disease

Splenectomy
Cardio. shock
Multiple thromboses
Death 7 months

Splenectomy
Cardio. shock
COMFORT-I: Total symptom score before and during interruption

Interrupt Dosing

Days Around Dose Change

Number of patients:
34 33 33 34 34 33 33 33 36 37 39 40 40 40 34 29 26 23 24 24 22 22 22 20 21 20 18 17 15

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-, 11q23.2, or ≥ 3 abnml
PFS by DIPSS plus (adjusted)

P = 0.003
NRM is twice as likely as relapse.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>REL/PD</td>
<td>17%</td>
</tr>
<tr>
<td>GvHD ± infection</td>
<td>10%</td>
</tr>
<tr>
<td>Infections</td>
<td>8%</td>
</tr>
<tr>
<td>Organ failure</td>
<td>8%</td>
</tr>
<tr>
<td>Graft failure</td>
<td>2-5%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1%</td>
</tr>
</tbody>
</table>
Disease Resolution After Transplantation

Reticulin (x300)

T1 Spin Echo (coronal)

T1 Spin Echo (transverse)

STIR Image

G. Sale et al BBMT
Disease-Free Survival by Driver Mutation

Years From Transplant

NRM  REL  SUR
TN  4  4  8
CALR  4  1  13
JAK

p = 0.29
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?