Stem Cell Transplantation for Myelofibrosis in the era of JAK inhibitors

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Disclosures

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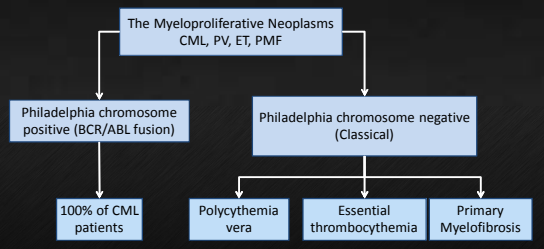
Scientific Advisory Board	Incyte, Novartis

Objectives

- Molecular Genetics of Myeloproliferative Neoplasms
- Therapeutic Options for Myelofibrosis
  - JAK inhibitor therapy
  - Hematopoietic cell transplantation
- Future Directions

Classification of Myeloproliferative Neoplasms



Molecular Genetics of MPN in 2015
Where are we 10 years after discovery of JAK2V617F?

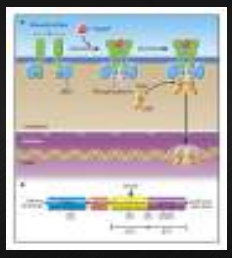
Molecular Genetics of MPN

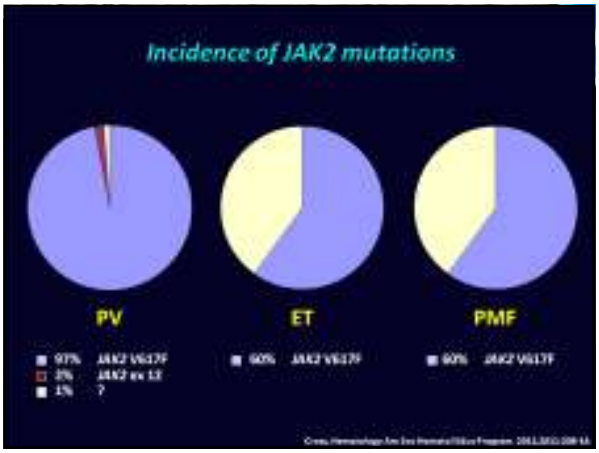
- Q1. Which of the following is **true** about classical philadelphia negative MPN?
  1. JAK2 mutation is seen in majority of patients with MPN
  2. Calreticulin (CALR) mutation is commonly seen in PV
  3. JAK2 and CALR mutations co-occur in about 20% of patients with Myelofibrosis and ET
  4. All of the above are true
  5. I am not sure

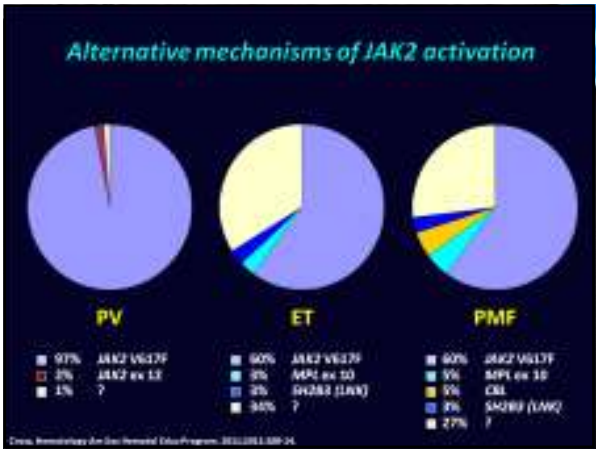
Results

Major discovery in the pathogenesis of MPNs (2004)

- In a short time frame….
  - Green (UK)
    - Lancet 2005 365 : 1054-61
  - Gilliland (USA)
    - Cancer Cell 2005 7 : 387-97
  - Vainchenker (France)
    - Nature 2005 434 : 1144-8
  - Skoda (Switzerland)
    - NEJM 2005 352;17 : 1779-90



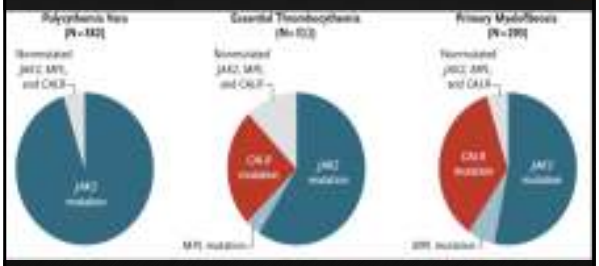




Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms

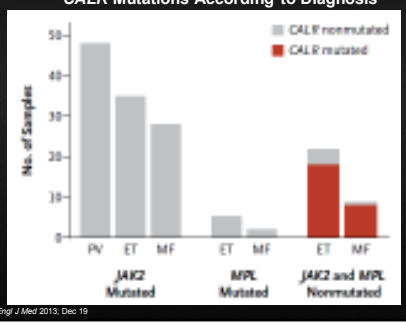
Somatic *CALR* Mutations in Myeloproliferative Neoplasms with Nonmutated *JAK2*

CALR Mutations – Another Piece of MPN Puzzle



Klampfl et al. NEJM; Dec 19, 2013

CALR and *JAK2/MPL* Mutations are Mutually Exclusive



Nangalia J, et al. *N Engl J Med* 2013; Dec 19

Epidemiology of MPN

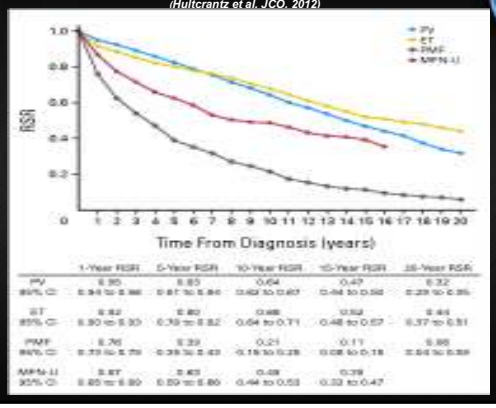
Q2. Which of the following is **false** about PV and ET patients?

1. Approximately 25% of patients have a h/o of thrombosis at the time of diagnosis
2. Approximately 25% will develop thrombosis during the natural course of the disease
3. The life expectancy of PV/ET patients is similar to age and gender matched normative population.
4. None of the above
5. I am not sure

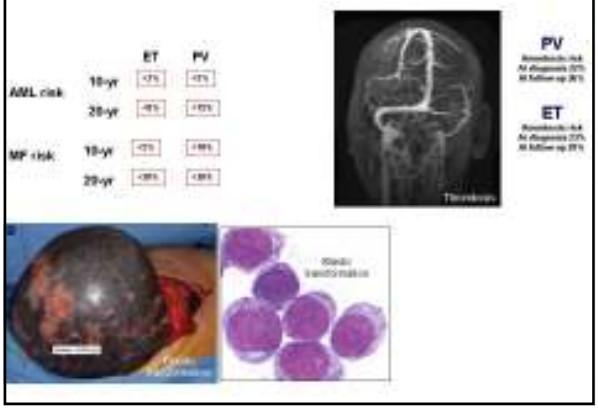
Results

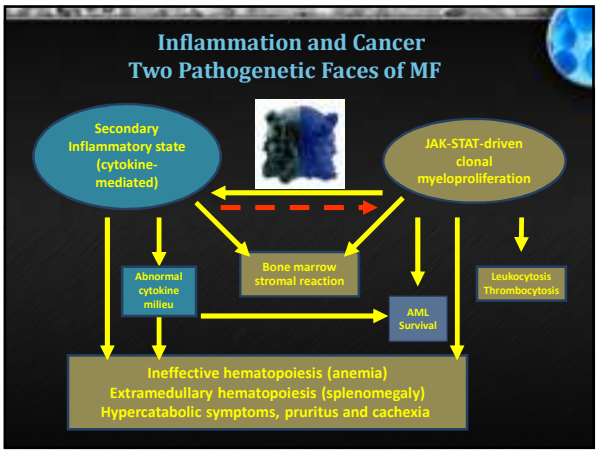
Cumulative relative survival among patients with MPNs in Sweden

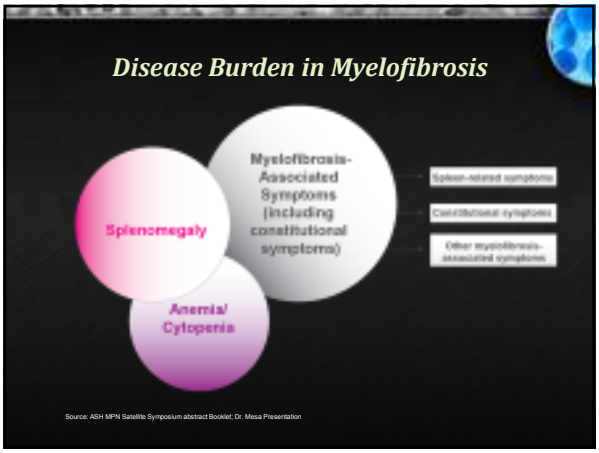
(Hultcrantz et al. JCO. 2012)



Life-threatening Complications in PV and ET







Case Study

- 58 yrs, F, Oct. 2006
  - Aquagenic pruritis, headache and numbness in fingers and toes
  - Hb 184 g/L, HCT 60%, WBC 29.6 x 10^9/L, ANC 26.1 x 10^9/L, platelets 287 x 10^9/L
  - Diagnosed with JAK2V617F positive PV
  - Treated with intermittent phlebotomies / aspirin and Hydroxyurea

ANC, absolute neutrophil count

Case Study

- May 2013 – noted to have palpable spleen
- August 2013
  - Rapidly enlarging spleen, bony aches/pains
  - Constitutional symptoms +++
  - Hb 98 g/L, WBC 21 x 10^9/L, plts 116 x 10^9/L, PB: 3% blasts
  - BM – C/W Post Polycythemic MF (PPV-MF)
  - Cytogenetics – normal karyotype
  - Referred to MPN clinic at Princess Margaret
  - Donor search – 9/10 A antigen mismatched URD

PB, peripheral blood; URD, unrelated donor

What would be your treatment preference in this patient?

1. Upfront JAK inhibitor therapy
2. Hydroxyurea (HU), and JAK inhibitor therapy on failure of HU
3. Upfront unrelated donor transplantation (9/10 donor)
4. Not sure

Results

What are the treatment options for Myelofibrosis in 2015?

Therapeutic Options available to Patients with Myelofibrosis

- **Transplant options**
  - Myeloablative
  - Reduced-intensity

Experimental drug therapy

1. Novel JAK inhibitors
2. Others
   a. Hypomethylating agents
   b. HIDAC inhibitors
   c. mTOR inhibitors
   d. IMids

- **Non-transplant options**
  - **Conventional**
  - **Treatment for anemia**
    - **Transfusion support**
    - **Erythropoietin**
    - **Corticosteriods**
    - **Androgen + prednisone**
    - **IMiDs**
  - **Treatment for splenomegaly**
    - **Hydroxyurea**
    - **Splenectomy**
    - **Low-dose irradiation**
  - **Novel Option**
    - **Ruxolitinib**

Abbreviations: HIDAC, histone deacetylase; IMiD, immunomodulatory drug; JAK, Janus kinase; mTOR, mammalian target of rapamycin.

Ever Growing Prognostic scores for MF - What should I use?

- Lille score
- International Prognostic Scoring system (IPSS)
- Dynamic IPSS (DIPSS)
- DIPSS plus
- MIPSS, perhaps N_{GS}IPSS in near future

Clinical scores for risk stratification in PMF

Variable	IPSS	DIPSS	DIPSS-plus
Age >65 y	√	√	**If DIPSS:**
Constitutional symptoms	√	√	
Hemoglobin <10 g/dL	√	√	**Low= 0**
Leukocyte count >25x10^9/L	√	√	**Int-1= 1**
Circulating blasts ≥ 1%	√	√	**Int-2=2**
			High= 3
Platelet count <100x10^9/L			√
RBC transfusion need			√
Unfavorable karyotype +8,-7/7q-,i(17q),inv(3), -5/5q-,12p-, 11q23 rearr.			√

Cervantes et al, Blood 2009;113:2895-901
Passamonti et al, Blood 2010; 115:1703-8
Gangat N et al, J Clin Oncol 2011; 29:392-7

Survival according to clinical scores stratification in PMF

Risk	Median survival (mo)		
	IPSS	DIPSS	DIPPS-plus
Low	135	*Not reach.*	210
Int-1	95	170	92
Int-2	48	48	42
High	27	18	20

Lower risk categories

Higher risk categories

Cervantes et al, Blood 2009;113:2895-901
Passamonti et al, Blood 2010; 115:1703-8
Gangat N et al, J Clin Oncol 2011; 29:392-7

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2. Novel JAK inhibitors
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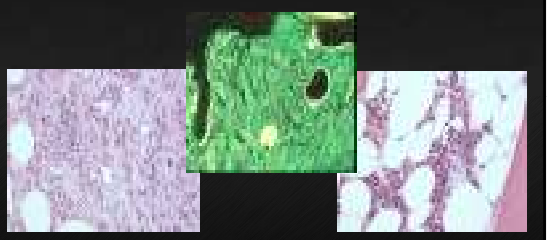
    - **Splenectomy**
    - **Low-dose irradiation**
  - **Novel emerging option**
    - **Ruxolitinib**

Abbreviations: HIDAC, histone deacetylase; IMiD, immunomodulatory drug; JAK, Janus kinase; mTOR, mammalian target of rapamycin.

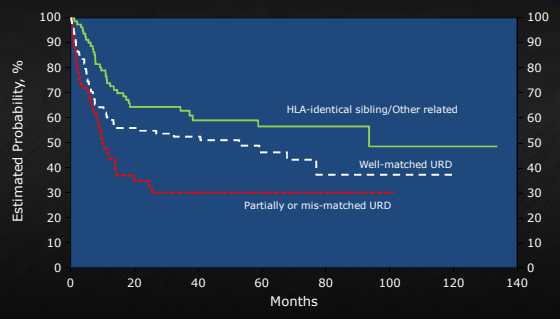
Potential Impact of BMT on Resolution of Myelofibrosis



Allogeneic Transplant in Myelofibrosis (n≥20)

Study	N	Med. Age	MF Subtype	Regimen	I/H Risk %	TRM at 1 y %	OS
Guardiola 1999	55	42	PMF=47	Ablative	76	27	14% at 5 y (age > 45 y) 62% (age < 45y)
Daly 2003	25	48	PMF=19	Ablative	84	48	41% at 2 y
Deeg 2003	56	43	PMF=33 Blastic=3	Ablative	54	32	58% at 3 y
Ditschokowsky 2004	20	37	PMF=12 Blastic=3	Ablative	65	20	39% at 5 y I/H risk 16% Low risk 67%
Kerbauy 2007	104	49	PMF=62 Blastic=7	Ablative	58	34	61% I/H risk 46% Low risk 80%
Ballen 2005	320	44		Ablative	n/a	30	33% at 5 y
Hertenstein 2002	20	50		RIC	75	37	54% at 1 y
Rondelli 2005	21	54		RIC	100	10	85% at 2.5 y
Kroger 2005	21	53	PMF=15	RIC	80	16	84% at 3 y
Gupta 2009	46	51	PMF=32	RIC/Ablative	85	32	49% at 3 y
Kroger 2009	103	55	PMF=63	RIC	86	16	67% at 5 y

Outcome of RIC in MF according to Donor Type (CIBMTR data, BBMT 2014)



Utilization of HCT in MF

- Important modality, however not applicable to large proportion of patients
  - A significant proportion of patients are not candidates for transplant due to age/co-morbidities
  - Suitable optimal donors (MSD or well matched URD) are found in about 2/3 of patients.
  - High procedure related complications
  - Overall utilization 5-10% of all patients diagnosed with MF
    - PMH approximate 8%

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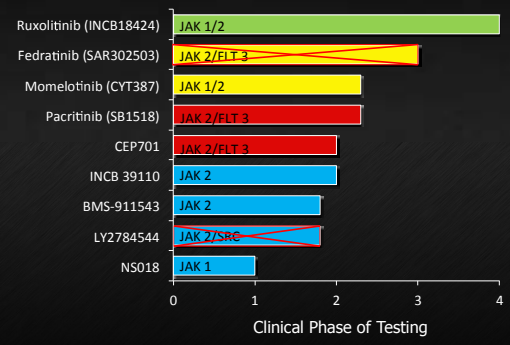
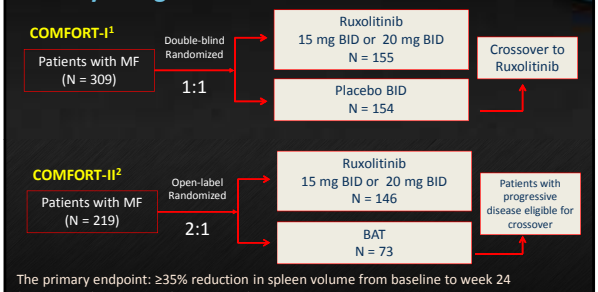
    - Splenectomy
    - Low-dose irradiation
  - **Novel emerging option**
    - Ruxolitinib

Abbreviations: HIDAC, histone deacetylase; IMiD, immunomodulatory drug; JAK, Janus kinase; mTOR, mammalian target of rapamycin.

JAK Inhibitors in Development in MF



Phase III Trials With Ruxolitinib: Study Designs



The primary endpoint: ≥35% reduction in spleen volume from baseline to week 24 (COMFORT-I) or week 48 (COMFORT-II), as measured by MRI or CT

Abbreviations: BAT, best available therapy; BID, twice daily; COMFORT, Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment; CT, computed tomography; MF, myelofibrosis; MRI, magnetic resonance imaging.
1. Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807; 2. Harrison CN, et al. *N Engl J Med*. 2012;366:787-798.

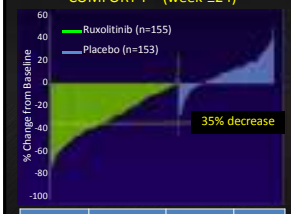
Patient Treatments on BAT Arm

Class	BAT (n = 73) n (%)
Antineoplastic agents	37 (51)
Hydroxyurea	34 (47)
Glucocorticoids	12 (16)
Epoetin alfa	5 (7)
Immunomodulators	5 (7)
Purine analogs	4 (6)
Androgens	3 (4)
Interferons	3 (4)
Nitrogen mustard analogs	2 (3)
Pyrimidine analogs	2 (3)

- 49 (67%) patients received one or more BAT medications
- 24 (33%) patients received no medication

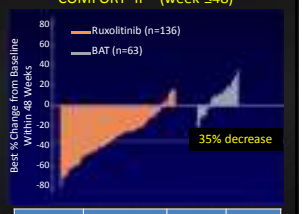
COMFORT-I and –II: Effect on Spleen Volume Reduction

COMFORT-I[1] (week ≤24)



	Ruxolitinib (n = 155)	Placebo (n = 153)	P value
Response[a]	41.9%	0.7%	<.001

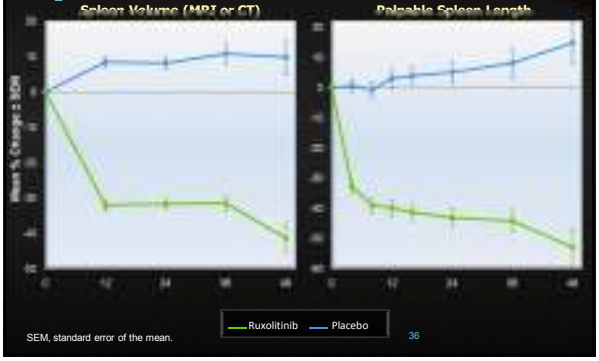
COMFORT–II[2] (week ≤48)



	Ruxolitinib (n = 144)	BAT (n = 72)	P Value
Response[a]	28.5%	0%	<.001

Abbreviation: BAT, best available therapy; COMFORT, Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment.
[a]Reduction in spleen volume of ≥ 35%.
1. Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807; 2. Harrison CN, et al. *N Engl J Med*. 2012;366:787-798.

Mean % Change From Baseline in Spleen Size Over Time



SEM, standard error of the mean.

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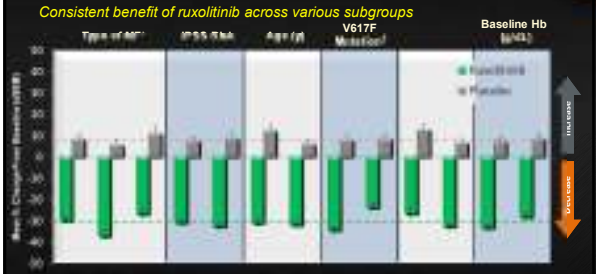
Percent of Patients With ≥50% Decrease in Total Symptom Score at Week 24 (ITT)

- Total Symptom Score = the sum of scores for night sweats, itching, abdominal discomfort, pain under the ribs on the left, early satiety, muscle or bone pain, and inactivity
- Patients who discontinued prior to week 24 or crossed over prior to week 24 were counted as failures

Abbreviation: ITT, intention to treat.
Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807.

Reduction in Spleen Volume—Subgroup Analysis

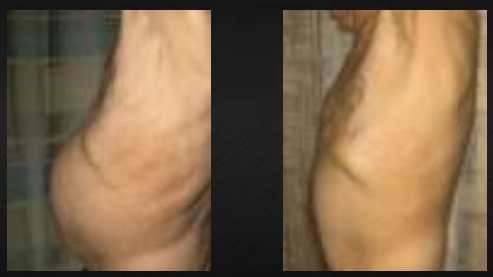
Consistent benefit of ruxolitinib across various subgroups



*P-value for interaction of MF subtype by treatment = 0.52; †P-value for interaction of mutation status by treatment = 0.07; Dashed lines, represent the mean percent change from baseline for overall treatment group.

em;
MF, myelofibrosis; PET, post essential thrombocythemia; PMF, primary myelofibrosis; PPV, post polycythemia vera; SEM, standard error of mean.
Verstovsek S, et al. Presented at: 53rd Annual Meeting of the American Society of Hematology; December 2011; San Diego, CA..

Spleen Size Reduction in Patient Treated with Ruxolitinib

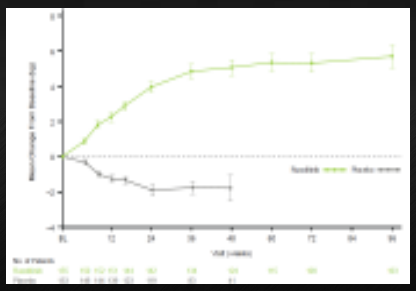


Myelofibrosis Patient Pre-Therapy | Patient After 2 Months of Therapy

Photos Courtesy of Serge Verstovsek, M. D. Anderson Cancer Center.

Change in weight in COMFORT-I trial on Ruxolitinib vs. Placebo

(Mesa et al, Lymphoma, Myeloma and Leukemia 2015)



Non-Hematologic Adverse Events Observed in at Least 10% of Ruxolitinib-Treated Patients

Adverse Event	Ruxolitinib, n = 155 % With Adverse Event		Placebo, n = 151 % With Adverse Event	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Fatigue	25	5	14	2
Dizziness	23	1	11	1
Peripheral edema	18	0	11	1
Diarrhea	18	0	9	0
Dyspepsia	17	1	11	0
Nasopharyngitis	16	1	7	0
Nausea	16	0	10	1
Headache	16	0	5	0
Constipation	13	0	12	0
Vomiting	12	1	6	1
Pain in extremity	12	1	6	0
Dyspnea	12	0	6	0
Arthralgia	11	1	8	1
Pyrexia	11	1	3	1
Abdominal pain	10	1	10	1

Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807.

Hematology Laboratory Values (Worst Grade on Study)*

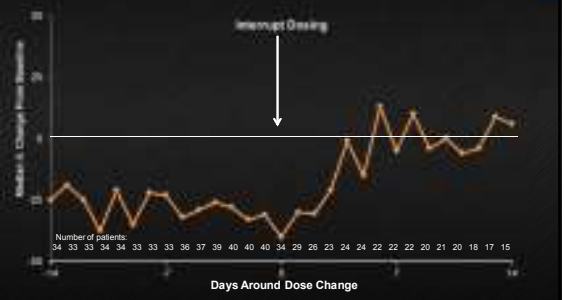
	Ruxolitinib (n = 155)		Placebo (n = 151)	
	Grade 3 %	Grade 4 %	Grade 3 %	Grade 4 %
Hemoglobin	34.2	11.0	11.9	3.3
Platelets	9.0	1.9	1.3	0
Neutrophils	5.2	1.9	0.7	1.3

- Grade 3 and grade 4 anemia and thrombocytopenia were more common in those with higher baseline grade
- Discontinuation of treatment because of anemia and thrombocytopenia was rare (1 patient in each treatment group for each event)

*Patients are included at their worst on-study grade regardless of whether this represents a change from their baseline.

Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807.

Total Symptom Score Before and During Interruption



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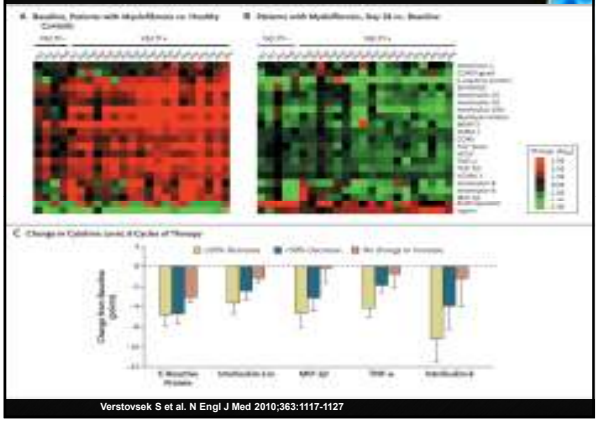
Verstovsek et al. Oral presentation at ASH Annual Meeting; December 10-13, 2011. Abstract 278.

Mechanisms of action of Ruxolitinib

- Mechanism of action not well understood
- Rapid response on splenomegaly; but no significant decrease in JAK2 allele burden
  - More than 20% reduction in allele burden seen only in approximately 20% patients.
  - Pronounced reduction in inflammatory cytokines

Effect of Ruxolitinib on Cytokines/Biomarkers



Verstovsek S et al. N Engl J Med 2010;363:1117-1127

Limitations of Ruxolitinib

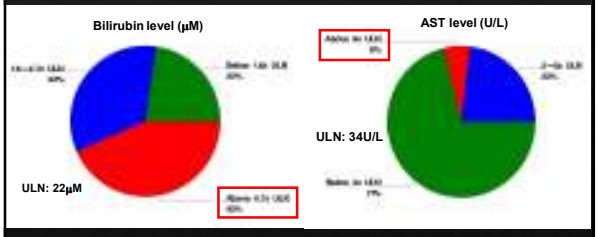
- Disease persistence
- Limited anti-clonal activity
- Lack of improvement or worsening of cytopenias
- No convincing data on resolution of fibrosis yet
- Atypical infections
  - Mycobacterial, Hepatitis reactivation etc
- Does not decrease the risk of LT
- Rates of discontinuation

  @1 year, 21%; @2 year, 35%; @3 year, 51%

Barriers to successful outcomes of HCT in Myelofibrosis

- Regimen-related toxicities
- Graft failure
- Graft-versus-host disease

Hepatic toxicity in Myelofibrosis patients undergoing HCT



ULN, upper limit of normal; AST, aspartate aminotransferase

Wong KM et al. BBMT 2012;18:1589-99.

Graft failure in prospective studies in Myelofibrosis

	EBMT N=103 *(Kroger et al, Blood, 2009)*	MPD-RC N=66 *(Rondelli et al, Blood, 2014)*
Low-risk pts	17%	5%
% URD tx	70/103 (68%)	34/66 (52%)
Survival	68% @5-yrs	78% at 2-yrs (MRD) 44% at 1-yr (MUD)
LFS	40% @5-yrs	NR
Primary graft failure	2%*, 11% needed stem cell boost	24% URD Tx

EBMT, European group for blood and marrow transplantation; MPD-RC, myeloproliferative disorders research consortium; URD, unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; LFS, leukemia-free survival

Kroger N et al. Blood 2009;114:5264-70.; Rondelli D et al. Blood 2014;124:1183-91.

High-risk of Graft Failure in MF Bad soil or more than that?

- Potential causes
  - Marrow fibrosis
  - Significant Splenomegaly
  - Transfusion dependency
  - ??Cytokines - TNF-alpha is a negative regular of expansion and renewal of normal HSC, and facilitates expansion of JAK2+ cells

    (Bryder et al, J Exp Med, 2001)
  - ??Interaction between Stem cells and Niche

GVHD in Myelofibrosis

- GVHD in RIC in MF
  - Grade II-IV aGVHD 37% (95% CI 30-43)
  - Grade III-IV aGVHD 19% (95% CI 15-25)
  - RR of NRM 2.4 in those with acute GVHD
  - cGVHD @ 5-yrs 51%

    (Gupta et al, BBMT, 2014)

Could acute GVHD be higher in MF due to underlying chronic inflammatory state?

Facing the difficulties associated with HCT for Myelofibrosis

- Graft failure?
  - Bone marrow fibrosis – poor environment for the stem cell
  - Significant Splenomegaly
  - Cytokines?
- GVHD?
  - Decreased cytokine levels may reduce the risk of severe GVHD
- TRM?
  - Better performance status prior to HCT may yield improved outcomes

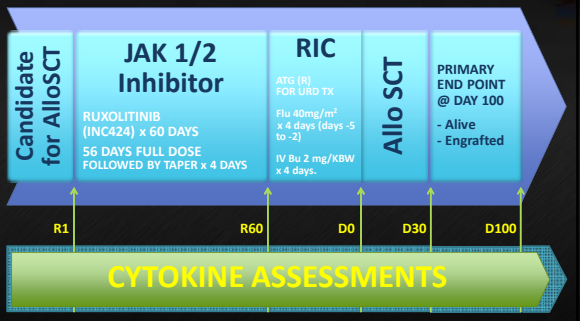
JAK-1/2 #

1. ↓ Spleen Size
2. ↑ QoL scores
3. ↓ Cytokine levels (anti-JAK1 mediated)

→ Improve constitutional symptoms

GVHD, graft versus host disease; TRM, transplant-related mortality

MPD-RC Study 114



Conclusions

- Recent Discovery of CALR mutations is an important advance in the diagnosis of MPN, and a potential therapeutic target.
- Long-term safety and efficacy of Ruxolitinib justify the inclusion of Ruxolitinib in routine clinical care in appropriate patients.
- The trials of including JAK inhibitor therapy in the transplant protocol are in progress at present, and should guide the best way to include JAK# in BMT protocols.

THANK YOU!!

Any Questions?