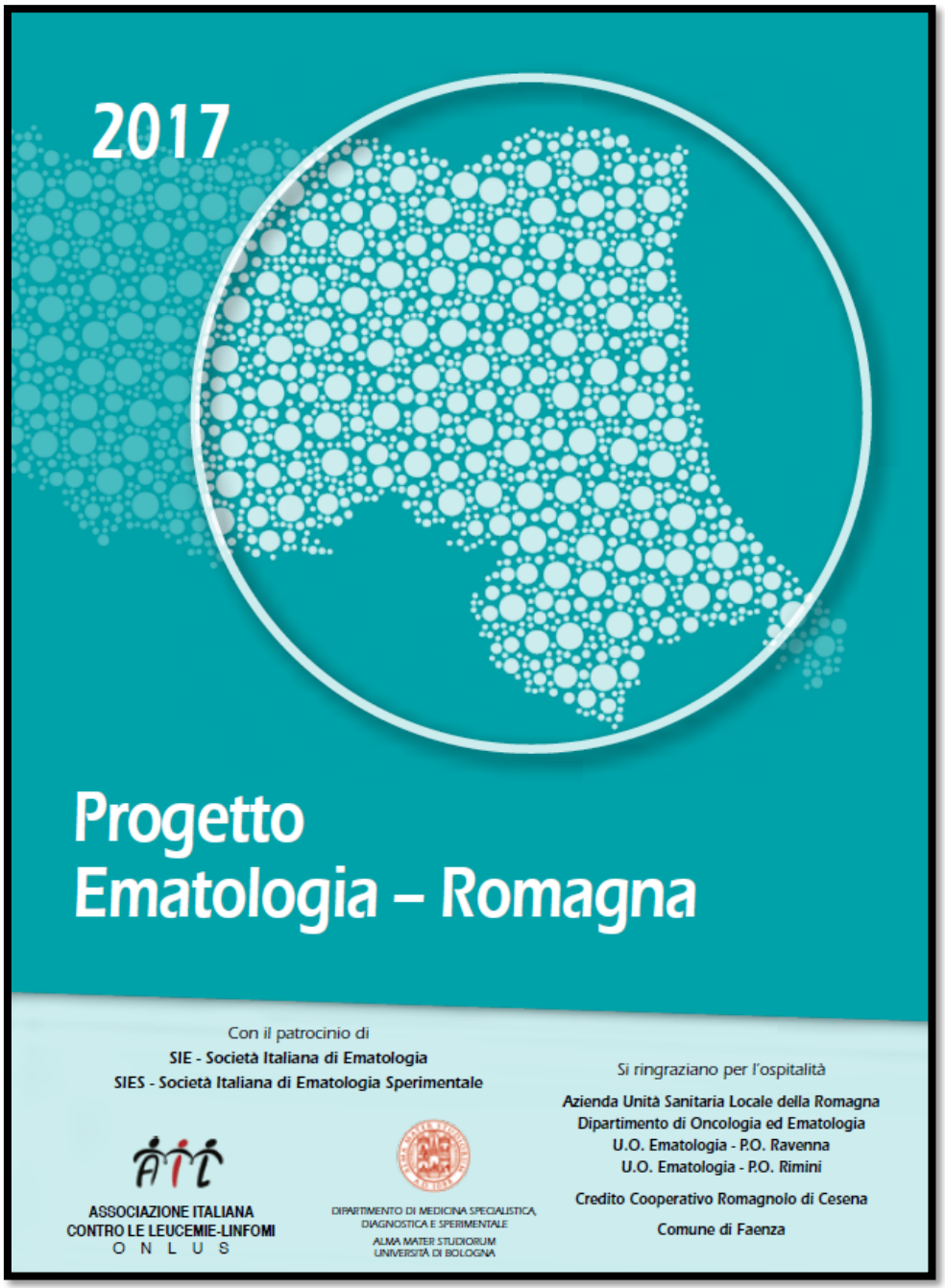


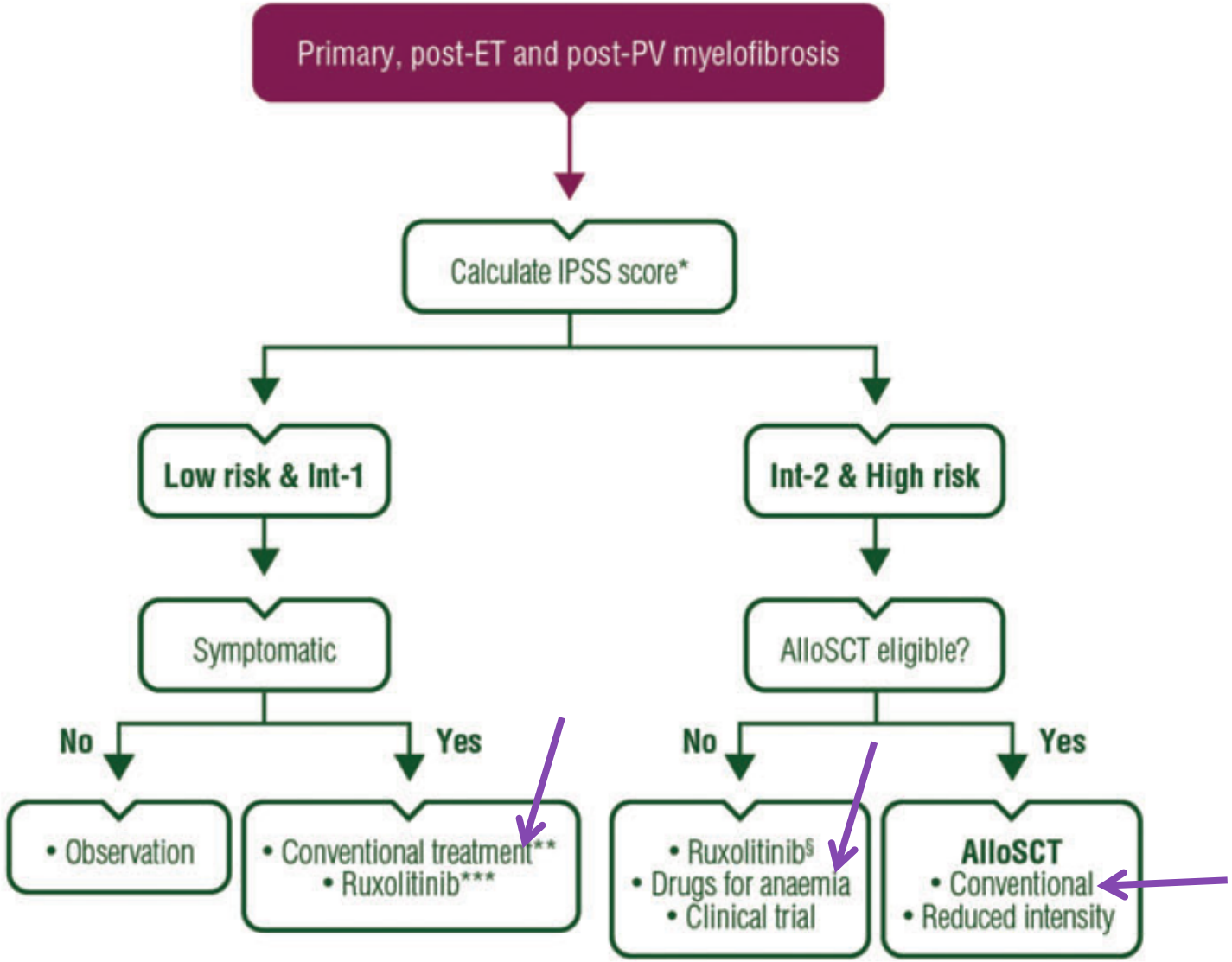
Mielofibrosi: Hanno ancora un ruolo i "vecchi" farmaci?

Nicola Vianelli

Istituto di Ematologia
"L.e A. Seràgnoli"
Ospedale S. Orsola-Malpighi

Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Vannucchi AM et al. Annals of Oncology 2015



Goals of MF treatment

- Suppression of myeloproliferation (spenomegaly, symptoms)
- Improvement of anemia
- Cure of the disease

MF treatment arsenal

- Conventional therapies
- Ruxolitinib
- Clinical trials
- Allogeneic stem cell transplantation (ASCT)

Terapia convenzionale

- **Si intendono farmaci approvati dalla FDA, per i quali esiste una documentazione sufficiente in letteratura scientifica, che ne supporti l'utilità nella cura delle complicanze associate alla malattia**
- **La terapia ha lo scopo di migliorare l'anemia, i sintomi costituzionali, la splenomegalia**
- **Non vi sono dati scientifici che ne dimostrino i vantaggi sulla durata di sopravvivenza**

Idrossiurea (HU)

Steroidi

Androgeni (Fluoxymesterone)

Danazolo

Talidomide

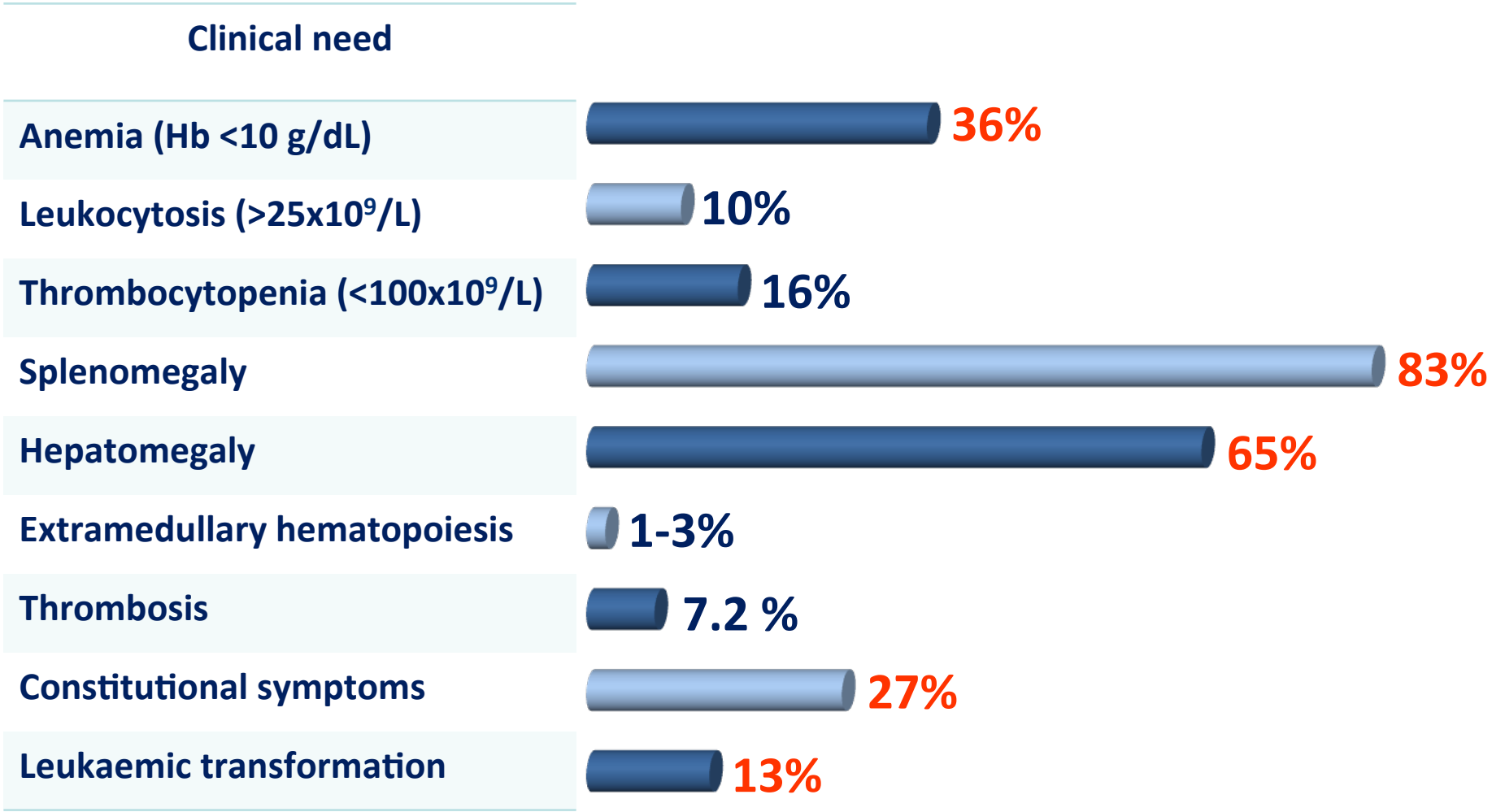
Lenalidomide } **IMiDs**

Pomalidomide

Splenectomia

Tefferi, Blood 2011

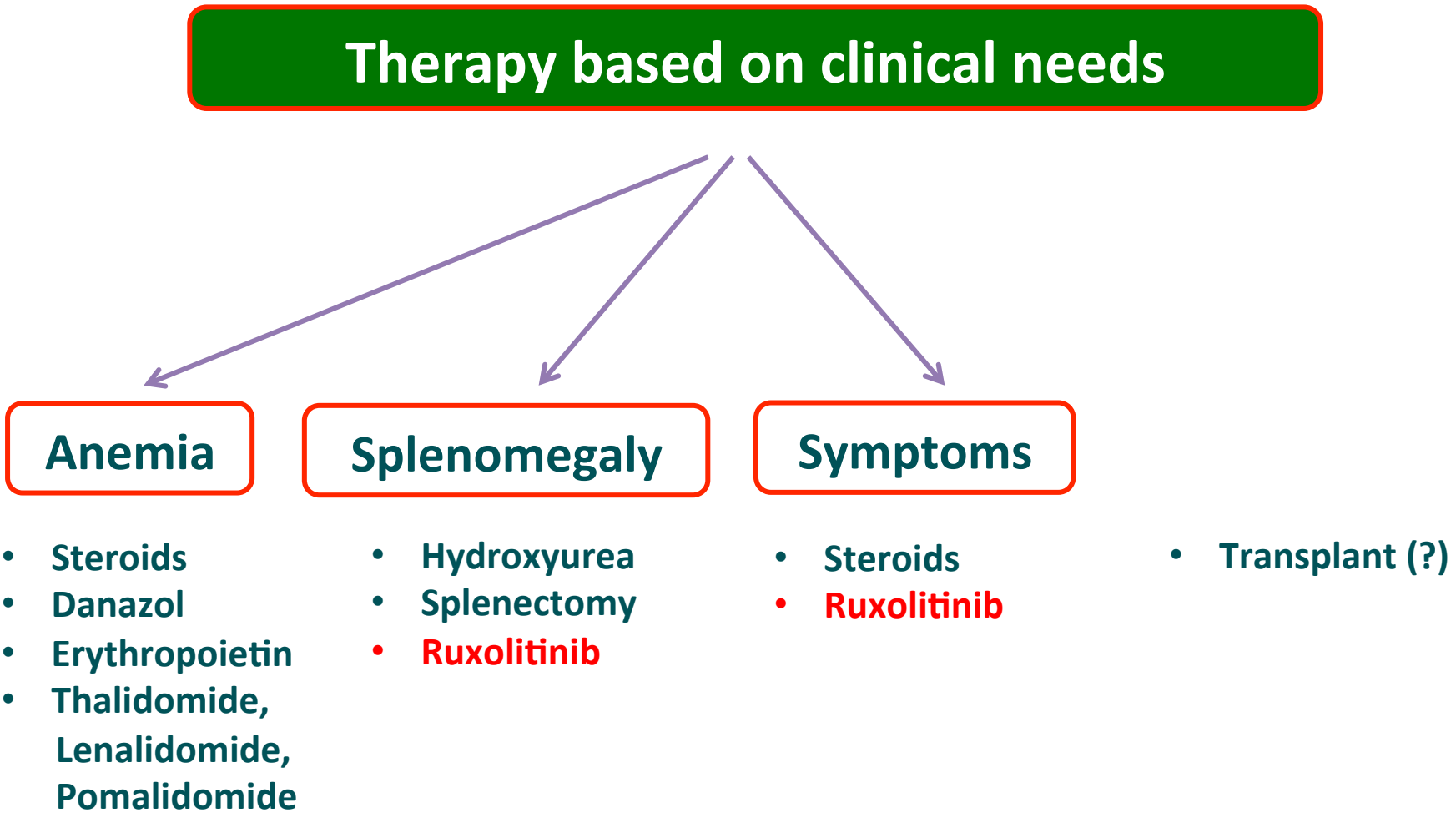
Main Clinical Problems in MF



Passamonti F et al. Blood 2010;115:1703-8;
Barbui T et al. Blood 2010; 115;778-82; Passamonti F et al. Blood 2010; 116:2857-8

Myelofibrosis: Conventional Therapy

Today……



Anemia

Treatment of Anemia in MF

- Corticosteroids
- Danazol
- Erythropoietin

} ≈ 30-40% response, transient

- Thalidomide + PDN
- Lenalidomide
- Pomalidomide*

} ≈ 20-40% response

* no differences vs. placebo in the Phase-3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Compare Efficacy and Safety of Pomalidomide in Subjects With Myelofibrosis and Red Blood Cell Transfusion Dependence

Fontana et al, Hematology 2011; Shimoda et al, Int J Hematol. 2007 May; 85(4):338-43;
Cervantes et al, Br J Haematol. 2005 Jun;129(6):771-5; Hasselbach et al, Am J Hematol. 2002 Jun;70(2):92-9; Damaj et al, Eur J Haematol. 2002 Apr;68(4):233-5; Cervantes et al, Haematologica. 2000 Jun;85(6):595-9; Tsiara et al Acta Haematol. 2007;117(3):156-61; Cervantes et al Br J Haematol. 2006 Jul;134(2):184-6; Mesa et al, Blood. 2010 Nov 25;116(22): 4436-8; Tefferi et al, Blood. 2006 Aug 15;108(4):1158-64; Mesa et al, Blood. 2003 Apr 1;101(7):2534-41; Marchetti et al, J Clin Oncol. 2004 Feb 1;22(3):424-31.

Anemia Sintomatica

No splenomegalia

No trasfusione dipendenza, con Hb< 10g/dl ed EPO < 125U/L

Splenomegalia

Fallimento EPO

Darbapoetina 150-300 µg/ sett

- **risposta ≤ 56% per una durata media di 1aa**

(Huang J et al. Eur J Haematol 2009)

- **Steroide 0.5mg/kg/die**
- **Danazolo 600mg/die**
- **Fluoxymesterone 10mg x 3/die**
- **Talidomide 50mg/die ± S**
- **Lenalidomide 10mg/die ± S**
- **Pomalidomide**

Risposta ≅ 20%

Durata ≅ 1 anno

…Birgegard G, Best Practice & Research Clinical Haematology **2014…**

PMF and anemia: rHuEPO

- **Prospective study involving 20 transfusion dependent PMF pts**

rHuEPO 30.000UI/weekly

60% response rate (40% CR or transfusion independence and 20% PR with increase by 2g/dl or double transfusion interval)
(Tsiara SN et al Acta Haematol 2007)

- **A retrospective study from the Mayo Clinic showed no responders among 16 transfusion dependent and 9 with Hb>10g/dl pts.**
  (Huang j et al. Eur J Haematol 2009)

Eur J Haematol. 2017 Apr;98(4):407-414. doi: 10.1111/ejh.12846. Epub 2017 Jan 19.

Predictive factors for anemia response to erythropoiesis-stimulating agents in myelofibrosis.

Hernández-Boluda JC[1], Correa JG[2], García-Delgado R[3], Martínez-López J[4], Alvarez-Larrán A[5], Fox ML[6], García-Gutiérrez V[7], Pérez-Encinas M[8], Ferrer-Marín F[9], Mata-Vázquez MI[10], Raya JM[11], Estrada N[12], García S[13], Kerguelen A[14], Durán MA[15], Albors M[16], Cervantes F[2].

- **Abstract**
- **OBJECTIVE:**
- Erythropoiesis-stimulating agents (ESAs) are commonly used to treat the anemia of myelofibrosis (MF), but information on the predictors of response is limited.
- **METHODS:**
- Results of ESA therapy were analyzed in **163 MF patients with severe anemia**, most of whom had inadequate erythropoietin (EPO) levels (<125 U/L) at treatment start.
- **rHuEPO 20-40 000 U/week or Darbapoetin alfa 150mcg/week**
- **RESULTS:**
- According to the revised criteria of the International Working Group for Myelofibrosis Treatment and Research, **anemia response was achieved in 86 patients (53%).** Median response duration was 19.3 months. In multivariate analysis, baseline factors associated with a higher response rate were **female sex (P=.007), leukocyte count ≥10×10^9 /L (P=.033), and serum ferritin <200 ng/mL (P=.002)**. Patients with 2 or 3 of the above features had a significantly higher response rate than the remainder (73% vs 28%, respectively; P<.001). Over the 373 patient-years of follow-up on ESA treatment, nine patients developed thrombotic complications (six arterial, three venous), accounting for 2.41 events per 100 patient-years. Survival time from ESA start was longer in anemia responders than in non-responders (P=.011).
- **CONCLUSION:**
- Besides the already established predictive value of EPO levels, these data can help to identify which MF patients are more likely to benefit from ESA treatment.

PMF and anemia: danazole

- **Cervantes 2000 and 2005 (7 and 30 MF pts):**
  danazole 600mg/daily for 6 months → OR 57 and 37% respectively;
  median time to response was 5 months

- **Danazole 200-800mg/daily administered in combination with CHT to 16 MF and 2 ET elderly pts;**
  11/18 (61%) responded (3 pts completely);
  mean duration of response was 45 months (Fontana V et al Hematol Amst Neth 2011)

- **Retrospective study on 39 pts treated with androgen and steroides; 17/39 (44%) responded after a median time of 3 months (Shimoda K et al Int J Hematol 2007)**

NB: Studies are small and with varying drug schedule and response criteria

Ruxolitinib + danazol (14pts)

Schedule:

Ruxolitinib starting dose in order to PLT count

Danazol up to 200 mg die

Although overall well tolerated, the addition of danazol to ruxolitinib therapy has modest incremental efficacy by IWG-MRT criteria. Clinical improvement was observed in 3/14 (21.4%) of treated patients, however responses were limited to spleen reduction. The degree to which danazol may stabilize expected cytopenias is interesting and may require further investigation

Final Analysis of a Multicenter Pilot Phase 2 Study of Ruxolitinib and Danazol in Patients with Myelofibrosis
Krisstina L. Gowin, Heidi E. Kosiorek, Amylou Constance Dueck, John Mascarenhas, Ronald Hoffman, Craig B. Reeder, John Camoriano, Veena Fauble, Raoul Tibes, Katherine Gano, Vineta Ghurye, Patricia Koenig and Ruben A. Mesa
Blood 2015 126:1618

Talidomide/Lenalidomide/Pomalidomide

- In vitro antagonizzano l'angiogenesi, il TNFα e l'IL6; stimolano la produzione di IL2, IFNgamma e la proliferazione e attività di LyT e NK. Inoltre, attività pro-apoptotica
- Non ben conosciuto il meccanismo d'azione, probabile down-regolazione citochinica
- Talidomide o Lenalidomide ± cortisone, efficaci in circa il 20-40% dei casi nel migliorare l'anemia, piastrinopenia o splenomegalia
- in caso di 5q-, possibilità di ottenere la remissione ematologica, citogenetica e molecolare con Lenalidomide
- Talidomide/Lenalidomide tossicità midollare, rischio trombotico, neurotossicità
- Pomalidomide: risultati deludenti (vedi Tefferi et al 2017)

(Mesa RA Blood 2003; Marchetti M JCO 2004; Thomas DA Cancer 2006, Tefferi A Blood 2006; Tefferi A Leukemia 2007; Quintas-Cardama A JCO 2009; Mesa RA Blood 2010)

PMF and anemia: Thalidomide

- **Objective clinical response observed in 13/21 (62%) of pts; 7/10 (70%) transfusion dependent pts improved and 40% became transfusion-independent**
  (Mesa RA et al Blood 2003)

- **Tali 50-100mg/daily + LD predni achieved Hb response rate ranging from 22 to 100% of cases, with acceptable toxicity**
  (Marchetti M et al JCO 2004; Benetatos L et al Eur J Haematol 2005; Weinkove R et al Haematologica 2008)

- **In the study of Weinkove 2008, EUMNET response criteria were considered: 6/15 (40%) of pts achieved an OR within 12 weeks of treatment; median duration of response was 16 weeks**

Long-term results of a phase II trial of lenalidomide plus prednisone therapy for patients with myelofibrosis

Chihara D et al.
Leukemia Research 2016

- **40 pts with previously treated (30) or untreated (10) MF with int/HR disease requiring therapy** according to the Lille scoring system, were enrolled between July 2006 and march 2007 to receive **Lenalidomide** 10mg/day (5mg/day if PLT<100x10^9/L), in 28 days cycles on a 21-day on/7-day off schedule for at least 6 months; **Prednisone** was given orally at 30 mg/day during cycle 1, 15 mg/day during cycle 2, and 15 mg every other day during cycle 3 and then it was discontinued.

- **All responses were assessed according to revised IWG-MRT criteria published in 2013**; however, symptomatic improvement wasn't included in the overall response analysis.

- 23 pts had an enlarged spleen ≥5 cm (by physical examination) and 22 had anemia with Hb<10 g/dl (seven were transfusion dependent). Prior treatment included hydroxyurea in 14 (35%), azacitidine in 6 (15%), steroids in 5 (13%), thalidomide in 4 (10%) and others(27%).

- **Median f-up 109 months; median OS for all pts was 47 months**

- **14/40 (35%) pts responded overall**

- 1 pt achieved CR, 5 pts PR and 8 pts CI (3 for spleen size and hemoglobin, 3 for spleen size and 2 for hemoglobin). **In total, 39% of pts showed a spleen size reduction, and the overall anemia response was 32%**. 3/7 patients that were transfusion dependent became transfusion independent. The median time to first response was 2.9 months. The median duration of response was 34.6 months
- **No significant difference in term of OS between responders and non-responders**

- Most commonly seen grade 3–4 non-hematological toxicities were fatigue in 27% of patients, followed by diarrhea (15%) and infection (15%)

Ruxolitinib + lenalidomide

- 17 patients received 15 mg ruxolitinib orally twice daily in continuous 28-day cycles, plus 5 mg lenalidomide orally once daily on days 1-21.
- The response rate was higher (73%) among patients who did not require early dose interruption than among those who required early interruption (45%).

Ruxolitinib in combination with lenalidomide as therapy for patients with myelofibrosis
Naval Daver, Jorge Cortes, Kate Newberry, Elias Jabbour, Lingsha Zhou, Xuemei Wang, Sherry Pierce, Tapan Kadia, Koji Sasaki, Gautam Borthakur, Farhad Ravandi, Naveen Pemmaraju, Hagop Kantarjian, and Srdan Verstovsek
Haematologica 2015 Aug; 100(8): 1058–1063.

Ruxolitinib + lenalidomide

- All 17 responses included **clinical improvement** in palpable spleen size, including 100% spleen reduction (i.e. non-palpable spleen) in seven patients and ≥50% spleen reduction in ten patients.

- 48% of previously treated
- 70% of untreated patients (P=0.28)
- 61% of JAK inhibitor-naïve patients
- 0 patients previously treated with a JAK inhibitor.

Ruxolitinib in combination with lenalidomide as therapy for patients with myelofibrosis
Naval Daver, Jorge Cortes, Kate Newberry, Elias Jabbour, Lingsha Zhou, Xuemei Wang, Sherry Pierce, Tapan Kadia, Koji Sasaki, Gautam Borthakur, Farhad Ravandi, Naveen Pemmaraju, Hagop Kantarjian, and Srdan Verstovsek
Haematologica 2015 Aug; 100(8): 1058–1063.

A randomized study of pomalidomide vs placebo in persons with myeloproliferative neoplasm-associated myelofibrosis and RBC-transfusion dependence

Tefferi A et al. Leukemia 2017

- **The objective of this study was to determine the rates of RBC-transfusion independence after therapy with pomalidomide vs placebo in persons with MPN-associated myelofibrosis and RBC-transfusion dependence.**

- Two hundred and fifty-two subjects (intent-to-treat (ITT) population) **including 229 subjects** confirmed by central review (modified ITT population) were randomly (blinded) assigned (2:1) to pomalidomide or placebo. One hundred and fifty-two subjects received pomalidomide 0.5 mg/day and 77 placebo.

- **Primary end point** was proportion of subjects achieving RBC-transfusion independence within 6 months.

- **Response rates were 16% (95% confidence interval (CI), 11, 23%) vs 16% (8, 26%; P = 0.87).**

- Pomalidomide was associated with increased rates of oedema and neutropenia, but these adverse effects were manageable.

Ruxolitinib + pomalidomide

6/37 subjects (16%) **responded** with:

spleen reduction (N=3)

or

≥2 mg/dL hemoglobin increase / RBC transfusion independence (N=3).

Mean hemoglobin increased from 8.6 g/dL at baseline to 9.3 g/dL at the end of cycle 12.

Ruxolitinib Plus Pomalidomide in Myelofibrosis: Updated Results from the Mpnsg-0212 Trial (NCT01644110)
Frank Stegelmann, Holger Hebart, Markus Bangerter, Denise Wolleschak, Martin Griesshammer, Steffen Koschmieder, Nikolas von Bubnoff, Robert Möhle, Thomas Kindler, Andreas Hochhaus, Florian H**. H**eidel, Andreas Reiter Christof Scheid, Rebecca Kirschbaum, **R**egina eim, Ulrike Sutter, Katrin Vetter, Hartmut Döhner, Richard F. Schlenk and Konstanze Döhner *Blood 2016 128:1939*

A phase II study of 5-azacitidine for patients with primary and post-essential thrombocythemia/polycythemia vera myelofibrosis

Quintàs-Cardama et al.
Leukemia 2008

- 34 pts (76% previously treated), relapsed, refractory or newly diagnosed with intermediate or HR MF, according to Lille scoring system (Hb<10g/dl, WBC <4x10^9/L or >30x10^9/L)
- 5-azacitidine 75mg/m^2 sc/day for 7 days every 4 weeks; median duration of therapy was 5.5 months (range 2-18)
- 8/34 (24%) pts responded after a median of 5 months (7/8 CI)
- 5-AZA didn't affect JAK2 status nor bone marrow reticulin or collagen fibrosis

"5-azacitidine therapy results in limited clinical activity in this patient population"

Decitabine is an effective treatment of idiopathic myelofibrosis

Danilov AV et al, letter BJH 2009

….case report…. 65 years old male, with PMF and symptomatic anemia and splenomegaly ⇨ CI……following 2 cycle (20mg ev/m^2 /dayx5d/4weeks)

Therapeutic benefit of decitabine, a hypomethylating agent, in patients with high-risk primary myelofibrosis and myeloproliferative neoplasm in accelerated or blastic/acute myeloid leukemia phase

Badar T et al. Leuk Res 2015

- **21 patients with MPN-AML, 13 with MPN-AP and 11 with DIPSS-plus high-risk PMF**
- **Six patients (29%) with MPN-AML responded** to decitabine (3 CR, 2 CRi, and 1 PR); median response duration was 7 months. The median overall survival (OS) was significantly higher in those who responded (10.5 vs 4 months).
- Among patients with **MPN-AP, 8 patients (62%) benefited**; median response duration was 6.5 months. The median OS was 11.8 months in responders vs 4.7 months in non-responders.
- Among patients with **DIPSS-plus high-risk PMF, 9 (82%) benefited**; median response duration was 9 months. The median OS was 32 months in responders vs 16.3 months in non-responders.

Splenomegalia

Idrossiurea nella MF

- **Raccomandazioni ELN 2011:**

  L'Idrossiurea è il farmaco indicato per:

- **la splenomegalia sintomatica**
- il controllo della trombocitosi e/o leucocitosi sintomatica

Studio osservazionale su 40 pazienti

- **Risposta sul dolore osseo (100%), sintomi costituzionali (82%), prurito (50%), splenomegalia (40%) e anemia (12.5%)**
- **Miglioramento clinico (IWG-MRT): 40%**
- **Peggioramento dell'anemia, pancitopenia: 45%**
- **Durata mediana della risposta: 13.2 mesi**

Martinez Trillos et al. Ann Hematol. 2010 Dec; 89 (12):1233-7.
Barbui T. et al. J Clin Oncol. 2011 Feb 20;29(6):761-70

Splenomegalia

- **HU 1g/die; ≅ 35% dei casi riduzione taglia milza ≥ 25%; 17% riduzione 50%**
- **rispondono maggiormente pazienti JAK2+ ed in particolare con carica allelica <50%**

Durata media risposta 1 anno

- **2CDA** (Faoro LN, Eur J Haematol 2005)
- **Talidomide** (Thomas DA, Cancer 2006; Marchetti M, JCO 2004)
- **Lenalidomide** (Tefferi A, Blood 2006)

Risposta 20-50% dei casi

Idrossiurea: effetti collaterali/tossicità

- macrocitosi
- nausea, vomito, stipsi
- dolori addominali o al dorso, stranguria
- tossicità epatica
- polmonite
- febbre
- manifestazioni muco-cutanee

Idrossiurea: eventi avversi dermatologici (10-15%)

- ulcerazioni perimalleolari
- atrofia cutanea
- alopecia
- iperpigmentazione diffusa
- acromelalgia
- cheratosi attinica
- iperpigmentazione o atrofia ungueale
- xerosi/ittiosi
- carcinoma squamocellulare
- eruzioni lichenoidi
- lesioni simil dermatomiositiche

Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN

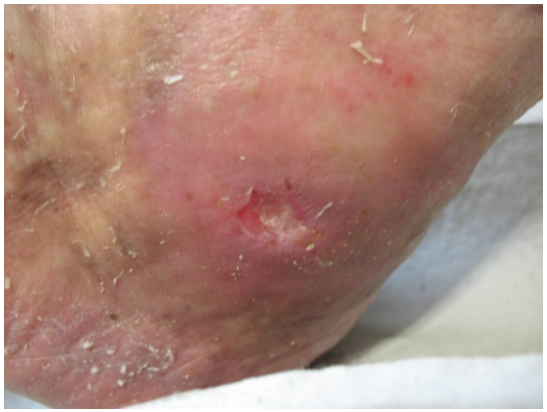
Antonioli E. et al. AJH 2012

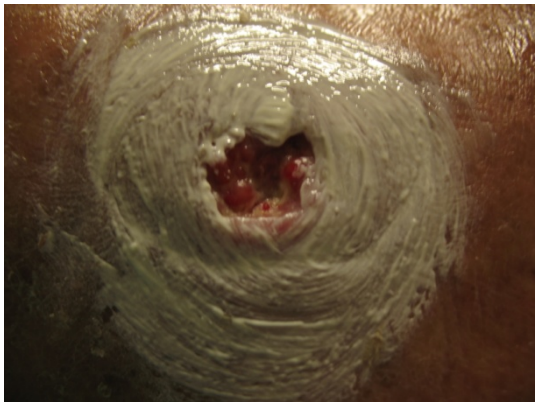
TABLE I. Characteristics of the Patients Who Developed HU-Related Side Effects

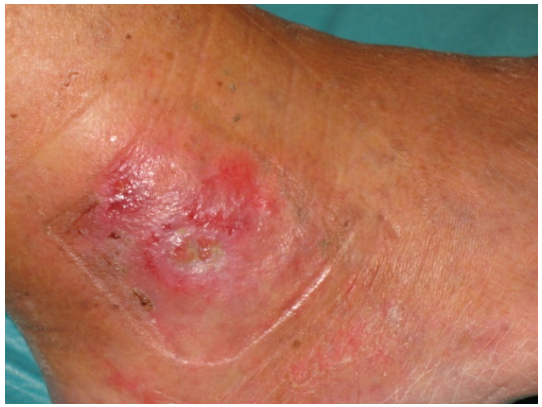
184/3411 (5%)

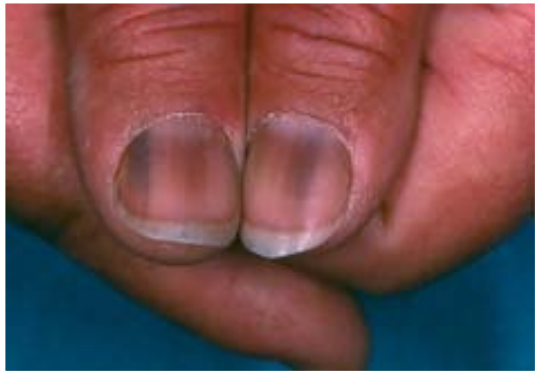
	PV (n = 61)	ET (n = 97)	MF (n = 26)
M/F	26/35	38/59	8/18
Median age, range (years)	65 (40–82)	64 (19–85)	68 (31–81)
*JAK2*V617F mutated, *N* (%)	48/48 (98)	50/82 (62)	15/22 (69)
Other therapies before HU, *N* (%)	7 (11)	7 (7)	4 (16)
Side effects			
Fever, *N* (%)	4 (6)	11 (11)	1 (4)
Pneumonitis, *N*	–	–	1
Ulcers, *N* (%)	57 (94)	86 (88)	24 (96)

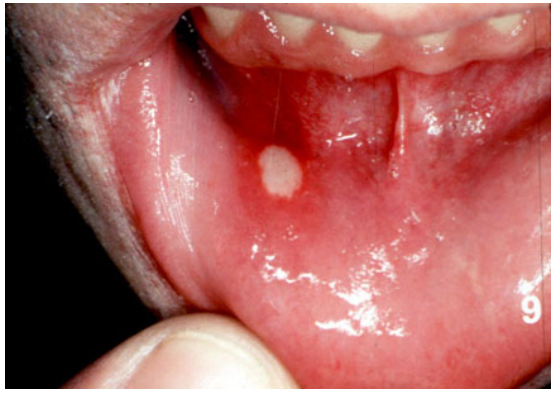
- **Possibile la comparsa di effetti collaterali, anche dopo anni di trattamento**
- **Nel 52% dei casi presente almeno un altro fattore di rischio concomitante**
- **Non sicura relazione con la dose accumulata**

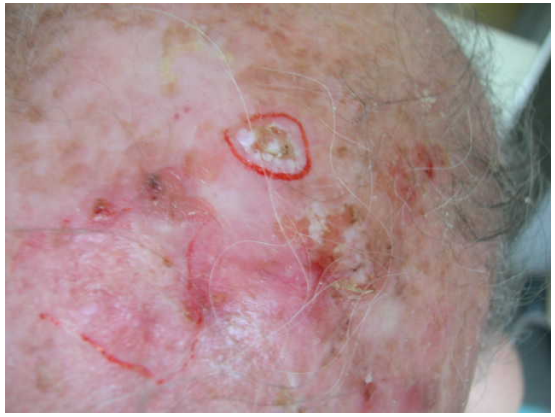












Splenectomia

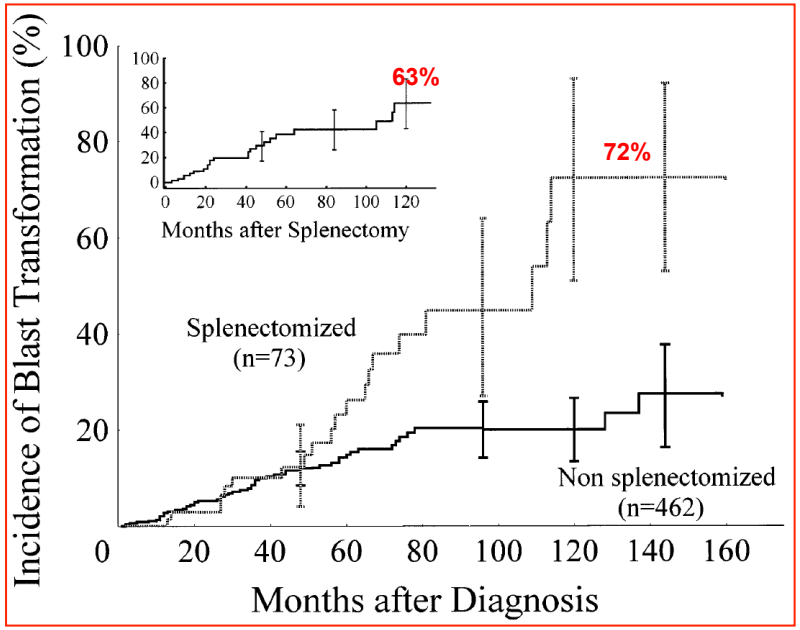
- **Opzione per pazienti refrattari alla terapia medica, con splenomegalia oltre 10 cm dall'emiarcata costale sn, SINTOMATICA (dolore, ingombro, citopenia, ipertensione portale, cachessia)**
- **Risposta nel ≥ 50% dei casi MA…….**
  - **temporanea**
  - **peggioramento epatomegalia ≅ 20% dei casi**
  - **mortalità perioperatoria 5-10%**
  - **morbidità ≅ 25-50%**
  - **impatto sull'evoluzione blastica??? (Barosi G, Blood 1998)**

Tefferi A, Blood 2000; Mesa RA, Cancer 2006

blood 1998 91: 3630-3636

Splenectomy and Risk of Blast Transformation in Myelofibrosis With Myeloid Metaplasia

Giovanni Barosi, Achille Ambrosetti, Antonietta Centra, Antonietta Falcone, Carlo Finelli, Paolo Foa, Alberto Grossi, Roberta Guarnone, Serena Rupoli, Luigiana Luciano, Maria C. Petti, Enrico Pogliani, Domenico Russo, Marco Ruggeri, Silvana Quaglini and the Italian Cooperative Study Group on Myelofibrosis With Myeloid Metaplasia



An unexpectedly high incidence of blast transformation after splenectomy has been reported in patients with myelofibrosis with myeloid metaplasia. However, whether this was associated with spleen removal after adjustment for risk factors was not determined. We conducted a multicenter historical cohort study of patients with myelofibrosis with myeloid metaplasia diagnosed from January 1970 through January 1994. A total of 549 patients (325 men and 224 women from 22 to 92 years of age; median age, 63 years) were included in the final data set. The Cox's proportional-hazards model was used to identify factors associated with blast transformation and death. To further adjust for factors related to spleen removal assignment, a propensity score for splenectomy was estimated using recursive-partitioning analysis. Blast transformation developed in 78 patients (14.2%). Patients who underwent splenectomy developed more blast transformations than those who were not splenectomized (23 of 87 [26.4%] *v* 55 of 462 [11.9%]; $P < .001$). The cumulative incidence of blast transformation 12 years after diagnosis was 27.0% in nonsplenectomized patients and 55.0% in splenectomized ones ($P = .01$). The risk factors independently predictive of blast transformation included prior splenectomy (relative risk = 2.61), platelet count less than 100 × 10^9/L at diagnosis (relative risk = 2.45), and the presence of blasts in peripheral blood at diagnosis (relative risk = 2.31). The relative risk of blast transformation in splenectomized patients increased from 2.2 at 48 months from diagnosis to 14.3 at 12 years. Patients with the same propensity score for splenectomy showed a higher risk for blast transformation on the basis of having undergone splenectomy ($P = .02$). In conclusion, the risk of blast transformation is significantly increased in subjects who underwent splenectomy and appears to be independent of factors related to spleen removal assignment.

Radioterapia

- **Utile (100 cGy, dose unica su tutti i campi polmonari) in caso di ipertensione polmonare sintomatica NON altrimenti spiegabile**
- **In caso di epato-splenomegalia 100 cGy in 5-10 frazioni → durata risposta 3-6 mesi**
- **In caso di mielopoiesi extramidollare non epatosplenica (vertebre, linfonodi, peritoneo, pleura): 100-1000 cGy in 5-10 frazioni**

Eradicazione della malattia

alloHSCT in MF after standard Myelo Ablative conditioning regimen

Authors	N. pts	Med. age	NRM	OS
Ballen, 2010 CIBMTR	134 (sibl.) 23 (other rel.) 72 URD	45 y 40 y 47 y	35% at 5 years 38% at 5 years 50% at 5 years	37% at 5 years 40% at 5 years 30% at 5 years
Guardiola, 1999 EBMT, GITMO, SFGM, FHCRC	55	42 y	27% at 1 year	47% at 5 years
Deeg, 2003 Kerbauy 2007 FHCRC	56 95	43 y 49 y	18 at 3 years 34% at 5 years	58 % at 3 years 61% at 7 years
Patriarca, 2007 GITMO	48	49 y	35% at 1 year	42% at 3 years
Stewart, 2010 BSBMT	27	38 y	41% at 3 years	44% at 3 years
Lissandre, 2011	15	49 y	20% at 3 years	47% at 3 years
Robin, 2010 SFGM-TC	147 (2/3 RIC)	56/47	39 % at 4 years	39 % at 4 years
Scott, 2012	170	51y	34% at 5 years	57% at 5 years

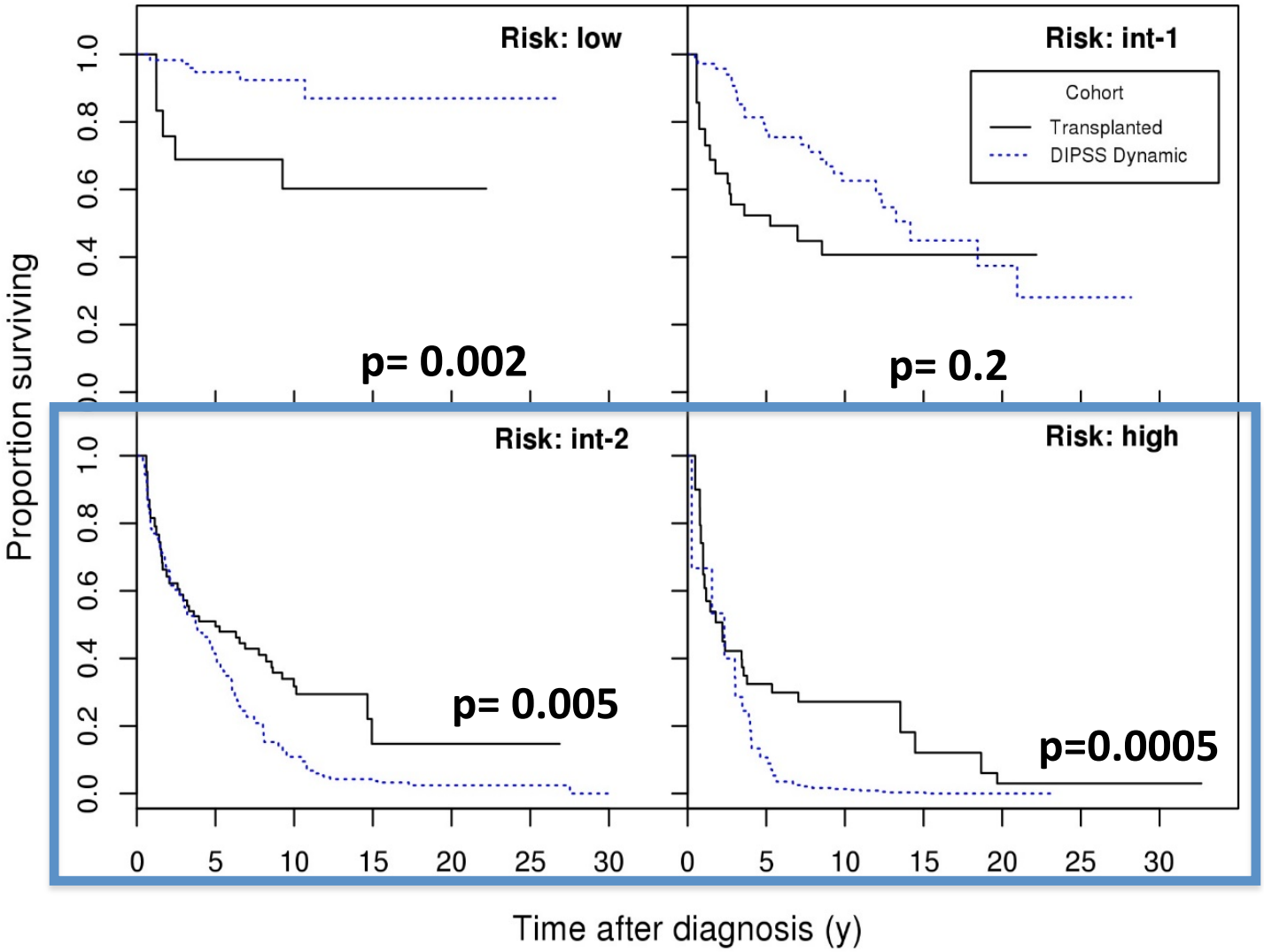
Transplant related mortality ranged from 20% to 50% in the first 5 years

alloSCT in MF after Reduced Intensity Conditioning regimen

Authors	N. pts	Med. age	NRM	OS
Hertenstein, 2002 EU	20	50 y	37% at 1 year	54% at 1 year
Rondelli, 2005 MPN-RC	21	54y	10% at 1 year	85% at 2.5 years
Kroger, 2005 German	21	53 y	16% at 1 year	84% at 3 years
Bacigalupo, 2010 GITMO	46	51 y	24% at 5 years	45% at 5 years
Kroger, 2009 EBMT	103	55 y	16% at 1 year	67% at 5 years
Stewart, 2010	24	54 y	32% at 3 years	31% at 3 years
Lissandre, 2011 SFGM-TC	24	49 y	36% at 3 years	60% at 3 years

Transplant related mortality ranged from 10% to 35% in the first 5 years

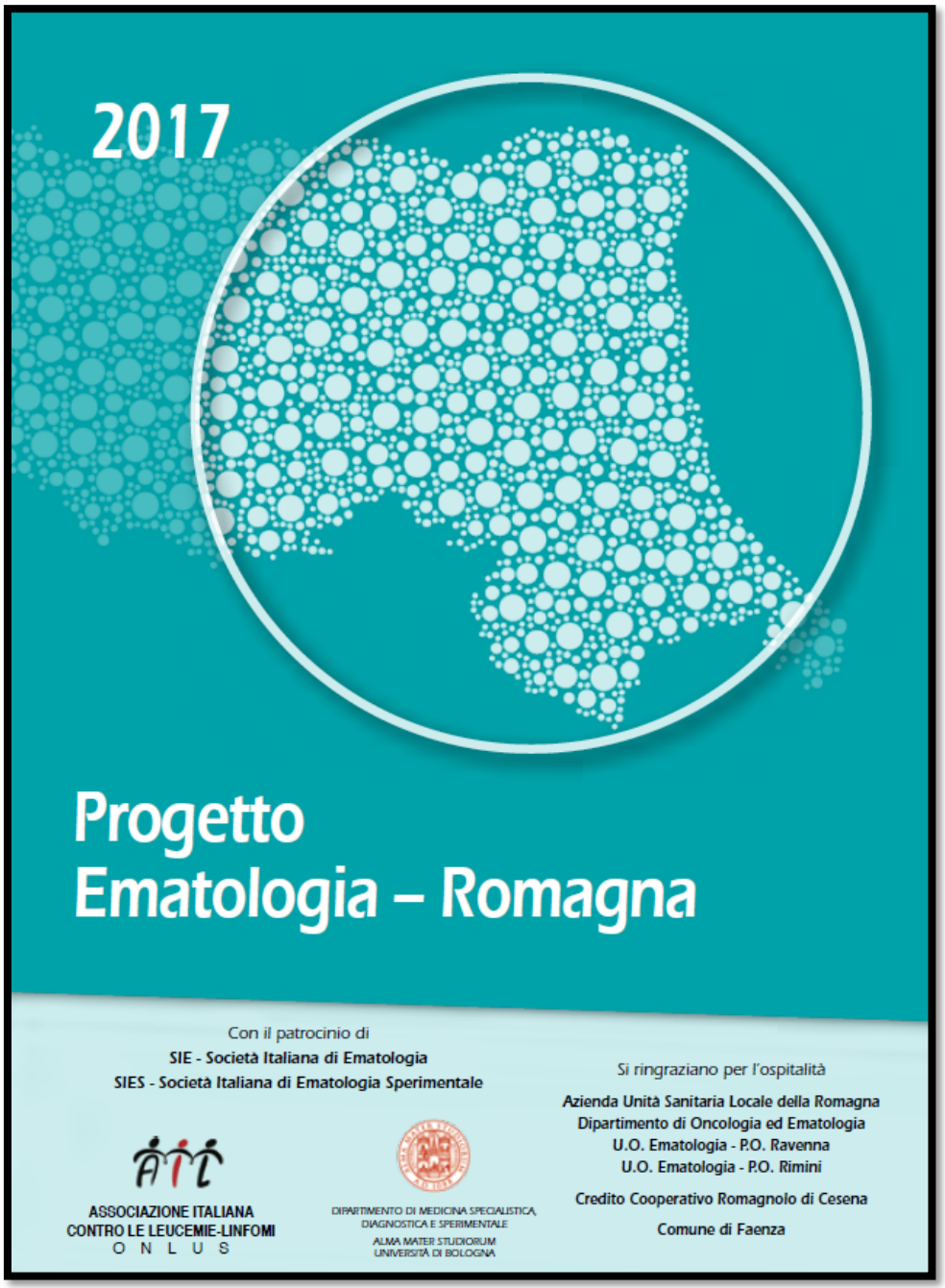
Indication of stem cell transplant for higher risk patients



Kröger N, Giorgino T, Scott BL, Ditschkowski M, Alchalby H, Cervantes F, Vannucchi A, Cazzola M, Morra E, Zabelina T, Maffioli M, Pereira A, Beelen D, Deeg HJ, Passamonti F. Blood. 2015

MF e terapia “convenzionale”: conclusioni

- **Scarsa e transitoria efficacia sugli effetti della mieloproliferazione (splenomegalia e sintomi).**
- **Possibile, seppur transitoria, efficacia in casi selezionati sull’anemia**
- **La tossicità ematologica ed extra-ematologica può essere rilevante**
- **Il trapianto allogenico di cellule staminali emopoietiche è l’unica procedura (ancora ritenuta sperimentale) in grado di eradicare la malattia**
- **I “vecchi” farmaci possono avere un ruolo nella terapia di combinazione con i nuovi, in particolare con il Ruxolitinib (ormai considerabile “convenzionale”)**



Grazie!

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Daver N, Cortes JE, Pemmaraju N, Jabbour EJ, Bose P, Zhou L, et al.
Ruxolitinib in Combination with 5-Azacytidine As Therapy for Patients with Myelofibrosis
ASH; 2016. p. Abstract 1127

- Ruxolitinib was dosed at 15mg or 20mg, Azacitidine was dosed at 25mg/m2 and could be increased to 75mg/m2, which was initiated on days 1-5 starting cycle 4.
- Of the 39 MF patients evaluable for response, 27 patients (69%) achieved an objective IWG response with CI in spleen and TSS in 7 (18%), TSS and hemoglobin in 2 (5%), CI for spleen only in 7 (13%), and CI for TSS only in 9 (21%).
- Two patients had progression to AML and 14 patients had died at time the analysis.
- New onset grade 3/4 anemia and thrombocytopenia occurred in 61% and 27% of patients, respectively. Grade 3/4 non-hematologic toxicity occurred in 3 patients, including fatigue, nausea, and pneumonia.

Ruxolitinib + danazol

Patient	IWG-MRT Response:	Study Cycles (N):	Prior therapy (within 3 mo)	*Hemoglobin Response*: (initial, final g/dL)*	*Platelet Response*: (initial, final 10(9)/L)*
			Ruxolitinib		
1	CI-Spleen	5		D (8.8, 7.6)	S (221,212)
2	SD	4		D (10.3,7.9)	S (54,46)
3	SD	2		S (8.8,8.9)	S (82,101)
4	SD	3		I (8.9,9.8)	S (441,458)
5	SD	3		S (9.6, 9.5)	I (161, 231)
			JAK Inhibitor:		
6	SD	5	Momelotinib	S (9.0, 9.2)	S (132,113)
7	SD	1	NS-018	D (8.3, 7.1)	D (120,43)
8	SD	3	NS-018	D (10.1,9.0)	D (138,111)
9	SD	2	LY2784544	S (8.7,9.1)	S (56,21)
			Other:		
10	CI-Spleen	9	Procrit	I (10.5,11.9)	S (153,198)
11	CI-Spleen	7	None	I (8.9,10.2)	D (338,133)
12	PD	1	Hydroxyurea	S (12.4, 12.2)	D (310, 82)
13	SD	1	Procrit	D (10.1, 8.6)	D (192, 71)
14	SD	1	Hydroxyurea	S (9.1,8.9)	D (346,119

Final Analysis of a Multicenter Pilot Phase 2 Study of Ruxolitinib and Danazol in Patients with Myelofibrosis
Krisstina L. Gowin, Heidi E. Kosiorek, Amylou Constance Dueck, John Mascarenhas, Ronald Hoffman, Craig B. Reeder, John Camoriano, Veena Fauble, Raoul Tibes, Katherine Gano, Vineta Ghurye, Patricia Koenig and Ruben A. Mesa
Blood 2015 126:1618

Ruxolitinib + pomalidomide

POM is given at 0.5 mg/die. RUX is started at 10 mg BID with dose modifications to optimize efficacy and to manage toxicity.

PATIENTS (37 subjects)

Median hemoglobin at study entry was 8.6 g/dL (range, 5.4-11.7 g/dL); 11 subjects (30%) were RBC-transfusion-dependent.

Median spleen size by ultrasound was 18 cm (range, 13-28 cm).

29 subjects (78%) had constitutional symptoms at baseline

Ruxolitinib Plus Pomalidomide in Myelofibrosis: Updated Results from the Mpnsg-0212 Trial (NCT01644110)
Frank Stegelmann, Holger Hebart, Markus Bangerter, Denise Wolleschak, Martin Griesshammer, Steffen Koschmieder, Ni kolas von Bubnoff, Robert Möhle, Thomas Kindler, Andreas Hochhaus, Florian H**. H**eidel, Andreas Reiter Christof Scheid, Rebecca Kirschbaum, **R**egina eim, Ulrike Sutter, Katrin Vetter, Hartmut Döhner, Richard F. Schlenk and Konstanze Döhner *Blood 2016 128:1939*

Ruxolitinib + pomalidomide

12/37 subjects (32%) continued treatment after cycle 12 because of **response or SD plus clinical benefit** (hemoglobin increase <2g/dL or prolongation of RBC-transfusion intervals and/or improvement of symptoms)

Ruxolitinib Plus Pomalidomide in Myelofibrosis: Updated Results from the Mpnsg-0212 Trial (NCT01644110)
Frank Stegelmann, Holger Hebart, Markus Bangerter, Denise Wolleschak, Martin Griesshammer, Steffen Koschmieder, Ni kolas von Bubnoff, Robert Möhle, Thomas Kindler, Andreas Hochhaus, Florian H**. H**eidel, Andreas Reiter Christof Scheid, Rebecca Kirschbaum, **R**egina eim, Ulrike Sutter, Katrin Vetter, Hartmut Döhner, Richard F. Schlenk and Konstanze Döhner *Blood 2016 128:1939*

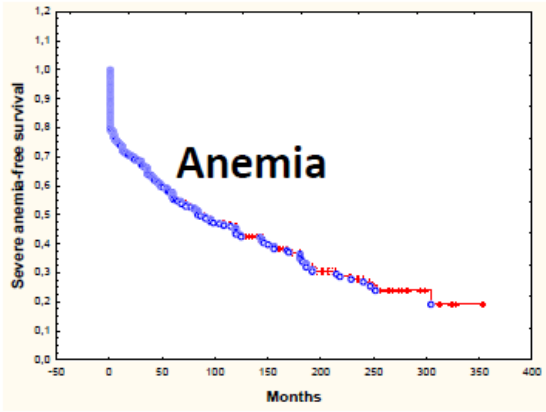
Conclusions

- Ruxolitinib is a new option for clinical practice

- The (near) future:
  - Pacritinib
  - Momelotinib
  - New combo trials:
    - RUX & panobinostat
    - RUX & BKM120
    - RUX & LDE225
  - Imetelstat

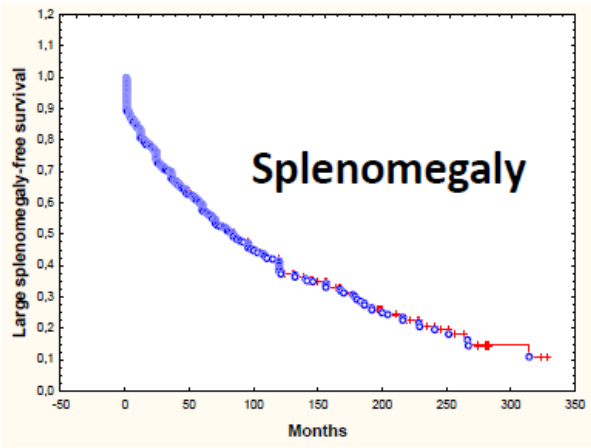
- Issues to investigate:
  - Ruxolitinib earlier in MF
  - Ruxolitinib before / after alloHSCT

Critical Outcomes in MF



20% of the patients have severe anemia (Hb <10 g/dL) at diagnosis.

The cumulative actuarial probability of having severe anemia at 5 years from diagnosis is 46%



10% of the patients have large splenomegaly (> 10 cm form the costal margin) at diagnosis.

The cumulative actuarial probability of having large splenomegaly at 5 years from diagnosis is 50%

Data base of the Center for the Study of Myelofibrosis, Pavia San Matteo Hospital (829 MF cases)

MF and anemia: Lenalidomide

- 68 MF pts ⇨ 26% R (22% complete) (Tefferi A et al. Blood 2006)
- 40 MF pts treated for 6 months in combination with prednisone during the first 3 (monthly) cycles at a dosage of 30, 15 and 10 mg/daily respectively ⇨ anemia response rate was 30%; reduction in fibrosis grade was observed in all responders (Quintas-Cardama A et al. JCO 2009)
- In other studies response rate observed was significantly lower (<15%)
- Anemia could represent a common side effect of the treatment

MF and anemia: Pomalidomide

- **84 MF pts with Hb < 10g/dl**
  Response rate: - Pom 2 mg/day: 23%
  - Pom 2 mg/day + LD predni 16%
  - Pom 0.5 mg/day + LD predni 36%
  - Predni alone 19%
- **15/84 (18%) were relieved of transfusion dependence** (Tefferi A et al. JCO 2009)

- **ASH Mayo Clinic report on a randomized international study in 252 transfusion-dependent MF pts receiving Pom 0.5 mg/day or Placebo, showed similar rate and duration of response (16 vs 16%)**
  (Tefferi A et al. ASH meeting 2013)

Unmet needs of the “convenzional” therapy

- **Little and transitory efficacy on effects of myeloproliferation (splenomegaly, symptoms)**
- **Little and transitory improvement of anemia**
- **Toxicity may be relevant**
- **Cure of the disease only possible with ASCT**

VOLUME 29 · NUMBER 6 · FEBRUARY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Philadelphia-Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations From European LeukemiaNet

Tiziano Barbui, Giovanni Barosi, Gunnar Birgegard, Francisco Cervantes, Guido Finazzi, Martin Griesshammer, Claire Harrison, Hans Carl Hasselbalch, Rudiger Hehlmann, Ronald Hoffman, Jean-Jacques Kiladjian, Nicolaus Kröger, Ruben Mesa, Mary F. McMullin, Animesh Pardanani, Francesco Passamonti, Alessandro M. Vannucchi, Andreas Reiter, Richard T. Silver, Srdan Verstovsek, and Ayalew Tefferi

- The drug of choice for symptomatic **splenomegaly** is hydroxyurea, which is also used for controlling symptomatic **thrombocytosis and/or leukocytosis**.
- Reduction of spleen volume with hydroxyurea reportedly occurs in approximately 40% of patients.

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- Treatment of splanchnic vein thrombosis includes low molecular weight heparin followed by long-life oral anticoagulation with international normalized ratio in the range 2.0 to 3.0.
- Joint management with liver team, follow-up of varices, and warning about pregnancy are recommended in this context.
- **For patients with thrombocytosis, hydroxyurea should be used to restore counts to 400x10^9 /L as soon as possible.**

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- Pulmonary hypertension.

In PH that is inaccessible to surgery, medical therapy including diuretics, anticoagulants, and antihypertensive drugs such as sildenafil should be considered. **In patients with high thrombotic risk, cytoreductive therapy with hydroxyurea is recommended.**

PMF and anemia: rHuEPO

- **Prospective study involving 20 transfusion dependent PMF pts**
- **rHuEPO 30.000UI/weekly**
- **60% response rate (40% CR or transfusion independence and 20% PR with increase by 2g/dl or double transfusion interval)**
  (Tsiara SN et al Acta Haematol 2007)
- **A retrospective study from the Mayo Clinic showed no responders among 16 transfusion dependent and 9 with Hb>10g/dl pts.**
  (Huang j et al. Eur J Haematol 2009)

COMBINATION THERAPY IN MF

- Many available clinical trials are evaluating the combination of ruxolitinib with agents that have shown monotherapy activity in MF, including IMiDs, HDAC inhibitors, hypomethylating agents and anti-fibrotic agents
- Inhibitors of apoptosis, such as the CDK4/6 inhibitor ribociclib (LEE011, Novartis) has demonstrated preclinical synergy with ruxolitinib.
- When pan-PIM inhibitor PIM447 is added to this murine model, further synergy in terms of reduction in leukocyte counts, platelet counts and spleen size are observed [94]. This has prompted initiation of a phase 1 trial of triple therapy in MF.

Rampal RK, Maria P-O, Amritha Varshini HS, Levine RL, Cao A. Synergistic Therapeutic Efficacy of Combined JAK1/2, Pan-PIM, and CDK4/6 Inhibition in Myeloproliferative Neoplasms. Blood. 2016;128(22):634-.

COMBINATION THERAPY IN MF

Agent/Combination	Phase	Clinical Trial	Additional Agent Target
Ruxolitinib + Thalidomide	2	NCT03069326	IMiD
Ruxolitinib + Pomalidomide	1/2	NCT01644110	IMiD
Ruxolitinib + INCB050465	2	NCT02718300	PI3K-delta
Ruxolitinib + TGR-1202	1	NCT02493530	PI3K-delta
Ruxolitinib + PIM447 + Ribociclib	1	NCT02370706	Pan-PIM kinase, CDK4/6
Ruxolitinib + Azacytidine	2	NCT01787487	DNMT
Ruxolitinib + Pracinostat	2	NCT02267278	HDAC
Ruxolitinib + Peg-interferon Alpha-2a	1/2	NCT02742324	Biologic*
Ruxolitinib + Danazol	2	NCT01732445	Fc receptor

DNMT = DNA Methyltransferase; HDAC = histone deacetylase; IMiD = immunomodulatory
*interferon alpha is a recombinant biologic with pleiotropic effects that appear to influence hematopoietic stem and progenitor cell compartments through yet poorly defined mechanisms

Conventional treatment

- **FDA-approved drugs for which there is sufficient documentation in the scientific literature that supports the utility in the treatment of complications associated with the disease**
- **The therapy aims to improve anemia, constitutional symptoms, splenomegaly**
- **There are no scientific data that demonstrate the benefits on the duration of survival**

Hydroxyurea (HU)
Steroids
Androgens (fluoxymesterone)
Danazol
Thalidomide
Lenalidomide
Pomalidomide
Splenectomy

Tefferi, Blood 2011

IWG-MRT and ELN response criteria (2013)

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
CR	Bone marrow: * Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF† and Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥ 1 × 10^9/L and <UNL; Platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or Bone marrow: * Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF†, and peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥50, but <100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
CI	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
Anemia resp	Transfusion-independent patients: a ≥20 g/L increase in hemoglobin level‖ Transfusion-dependent patients: becoming transfusion-independent¶
Spleen resp Simptoms resp	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable** or A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%** A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction A ≥50% reduction in the MPN-SAF TSS††
PD	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥20% or A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10(9)/L that lasts for at least 2 weeks
SD	Belonging to none of the above listed response categories
relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or Loss of anemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month

Tefferi et al. **Blood** 2013; 122: 1395-1398

Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Vannucchi AM et al. Annals of Oncology 2015

Table 5. Risk stratification in primary myelofibrosis (MF)

Variable	IPSS [18]		DIPSS [19]		DIPSS-plus [20]	
Age >65 years	✓		✓		✓	
Constitutional symptoms	✓		✓		✓	
Haemoglobin (Hb) <10 g/dl	✓		✓		✓	
Leukocyte count >25 × 10^9/l	✓		✓		✓	
Circulating blasts >1%	✓		✓		✓	
Platelet count <100 × 10^9/l					✓	
RBC transfusion need					✓	
Unfavourable karyotype[a]					✓	
	1 point each		1 point each but Hb = 2		Calculated by the DIPSS score (Int 1 = 1, Int 2 = 2, High = 3) plus one additional point for each of the three additional variables	
Risk group	Points	Median survival (years)	Points	Median survival (years)	Points	Median survival (years)
Low	0	11.3	0	n.r.	0	15.4
Intermediate-1	1	7.9	1–2	14.2	1	6.5
Intermediate-2	2	4.0	3–4	4	2–3	2.9
High	≥3	2.3	5–6	1.5	≥4	1.3

[a]Unfavourable karyotype includes +8, –7/7q–, i(17q), inv(3), –5/5q–, 12p–, 11q23 rearrangements.

IPSS, International Prognostic Scoring System; DIPSS, dynamic International Prognostic Scoring System; RBC, red blood cell; Int, intermediate; n.r., not reached.

TABLE 4 Multivariate analysis of baseline factors associated with a higher probability of anemia response with ESA treatment in 163 patients with myelofibrosis[a]

Favorable factor	OR (95% CI)	*P*
Female sex	3.64 (1.43-9.25)	**.007**
Leukocyte count ≥10×10^9/L	2.99 (1.10-8.16)	**.033**
Ferritin level <200 ng/mL	4.35 (1.73-10.9)	**.002**
Post-PV/ET MF		.98
Spleen size <5 cm		.07
Serum EPO <125 U/L		.20
Bone marrow fibrosis grade 1-2		.15
Prior transfusion support		
Yes, without dependency		.59
No		

Numbers in bold are those with a significant value on the statistical analysis ($P < 0.05$).

[a]The model was adjusted with data from the 97 patients in whom complete information of the eight variables selected in the univariate analysis was available.

blood 1998 91: 3630-3636

Splenectomy and Risk of Blast Transformation in Myelofibrosis With Myeloid Metaplasia

Giovanni Barosi, Achille Ambrosetti, Antonietta Centra, Antonietta Falcone, Carlo Finelli, Paolo Foa, Alberto Grossi, Roberta Guarnone, Serena Rupoli, Luigiana Luciano, Maria C. Petti, Enrico Pogliani, Domenico Russo, Marco Ruggeri, Silvana Quaglini and the Italian Cooperative Study Group on Myelofibrosis With Myeloid Metaplasia

- **Risk factors for blastic evolution (multivariate analysis):**

  1) Splenectomy (RR 2.61)

  2) thrombocytopenia <100x10^9/L at diagnosis (RR 2.45)

  3) blasts in the blood smear at diagnosis (RR 2.31)

- **36.5%, cumulative incidence to 12aa of blast evolution of the entire cohort (549pz)**

- **Splenectomy as an independent risk factor for the blastic evolution (26.4% vs. 11.9%; cumulative incidence 55% vs. 27% from diagnosis to 12aa)**

- **Splenectomy retains its negative impact on outcome, even when using the "propensity score" (obtained from a combination of factors that have contributed to the indication for splenectomy)**

….Come «rivitalizzare» il «vecchio»….?

.....Combinazione con Ruxolitinib…..!!!!

……Dr.ssa Palandri…..

Complicanze a breve-medio termine

- **Complicanze infettive post-intervento nel 9.9% (31/314) dei casi (polmonite), associate a piastrinopenia pre-intervento.**
- **Aumento mediano dei leucociti di 8 x10^9/L al momento della dimissione**
- **21/314 (6.7%) pz <u>deceduti</u> entro 45 giorni dall'intervento per cause correlate:**
  - **8 infezioni**
  - **7 emorragie**
  - **2 trombosi**
  - **5 per altre complicanze**

Mesa RA et al. Cancer 2006

OUTCOME POST-SPLENECTOMIA A LUNGO TERMINE

- **La piastrinopenia pre-operatoria (<50 o 100 x10^9/L) gioca un ruolo sfavorevole nella sopravvivenza post-splenectomia, indipendentemente dall'occorrere di complicanze perioperatorie**
- **La splenectomia dà un beneficio palliativo per almeno un anno, a fronte di una mortalità e morbidità a breve e lungo termine non trascurabili**

Mesa RA et al. Cancer 2006

Tefferi A, Passamonti F, Barbui T, Barosi G, Begna K, Cazzola M, et al.
Phase 3 Study Of Pomalidomide In Myeloproliferative Neoplasm (MPN)-Associated Myelofibrosis With RBCTransfusion-Dependence.
Blood. 2013;122(21):394-.

- 252 patients with MF were randomized 2:1 to pomalidomide 0.5 mg daily or placebo.
- Anemia response rates were similar between the two groups, as was duration of transfusion independence. However, platelet response was 22% in pomalidomide versus 0% in the placebo arm.
- Given these disappointing results, pomalidomide is now being explored in combination therapy.

- Taken together, pomalidomide and other IMiDs may be appropriate for select patients with anemia as the main goal of therapeutic intervention, however their single agent efficacy appears limited in the absence of prednisone.