PROGRAM

Treatment of higher-risk myelodysplastic syndromes

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Session 2: ***Advances in the diagnosis and treatment of myelodysplastic syndromes***

September 24, 2017

Chairmen: **F. Lo Coco, M.A. Sanz**
Honorary President: **F. Mandelli**

Conflicts of Interest disclosure*

- **Honoraria:** Celgene, Novartis
- **Membership on advisory committees:** AbbVie, Amgen, Celgene, Janssen – Cilag
- **Research grants:** Celgene

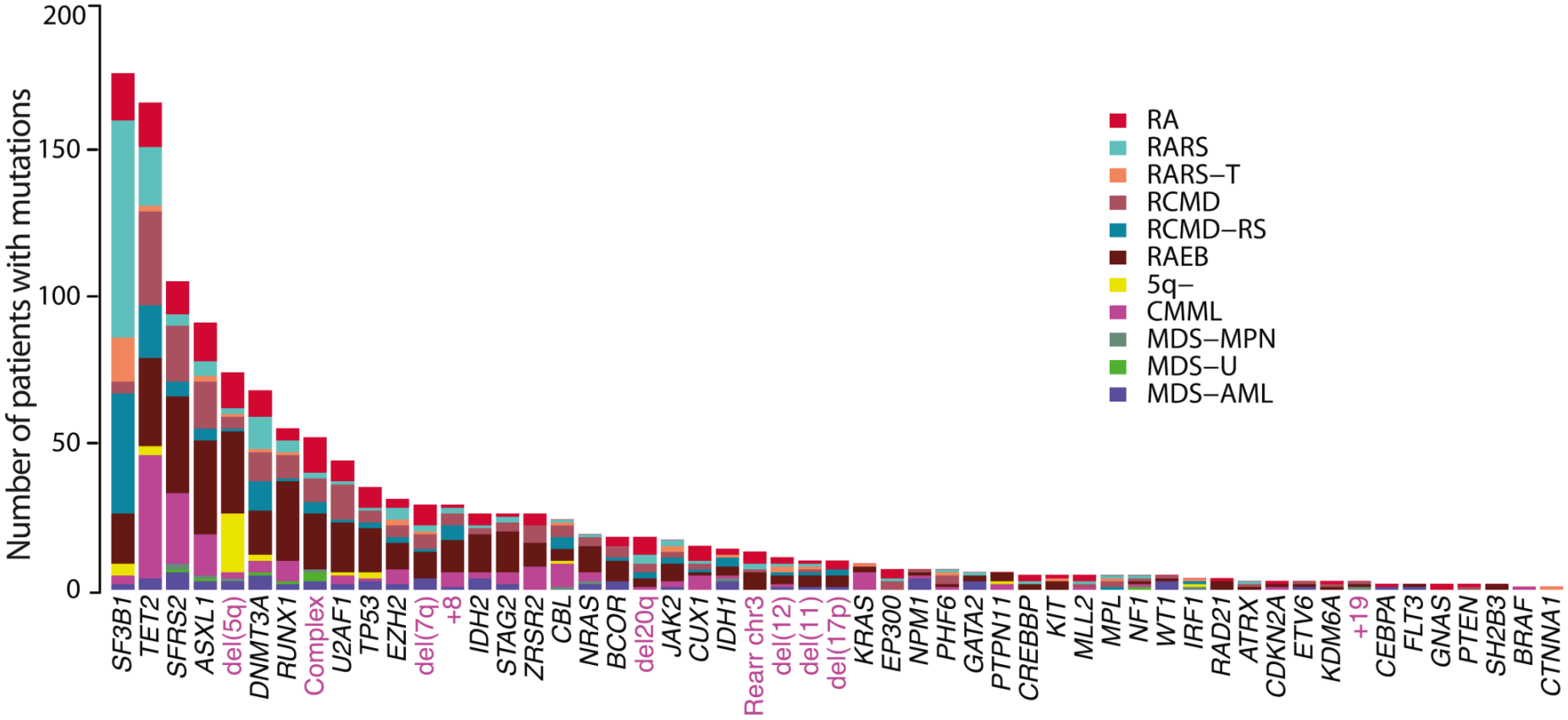
* As of September 2017 (2 previous years).

Treatment of higher-risk MDS

Contents of the talk

- Definition of higher-risk MDS
- Current approaches
- Challenges
- Upcoming treatment modalities

The genomic landscape of MDS



- Somatic mutations present in more than 90% of the patients.
- None of them is pathognomonic of MDS
- **Should mutations guide risk assessment & treatment selection?**

Papaemmanuil E, et. al. *Blood* 2013:122:3616-3627.

Should molecular genetics guide the decision for treatment in MDS?

- **LIKELY NO** because**:**
  - **Lack of standardization** of molecular techniques
    - Consensus assessment & interpretation of results is mandatory before entering clinical practice.
  - **Data** still **scarce** (clear only for *TP53* & *SF3B1*)
  - **Clinical benefit** for patients derived from its use is still **unproven**.
  - **Very limited treatment** alternatives
    - Allogeneic HCT remains the only curative approach.
    - Clinical benefit of azacitidine disputed.

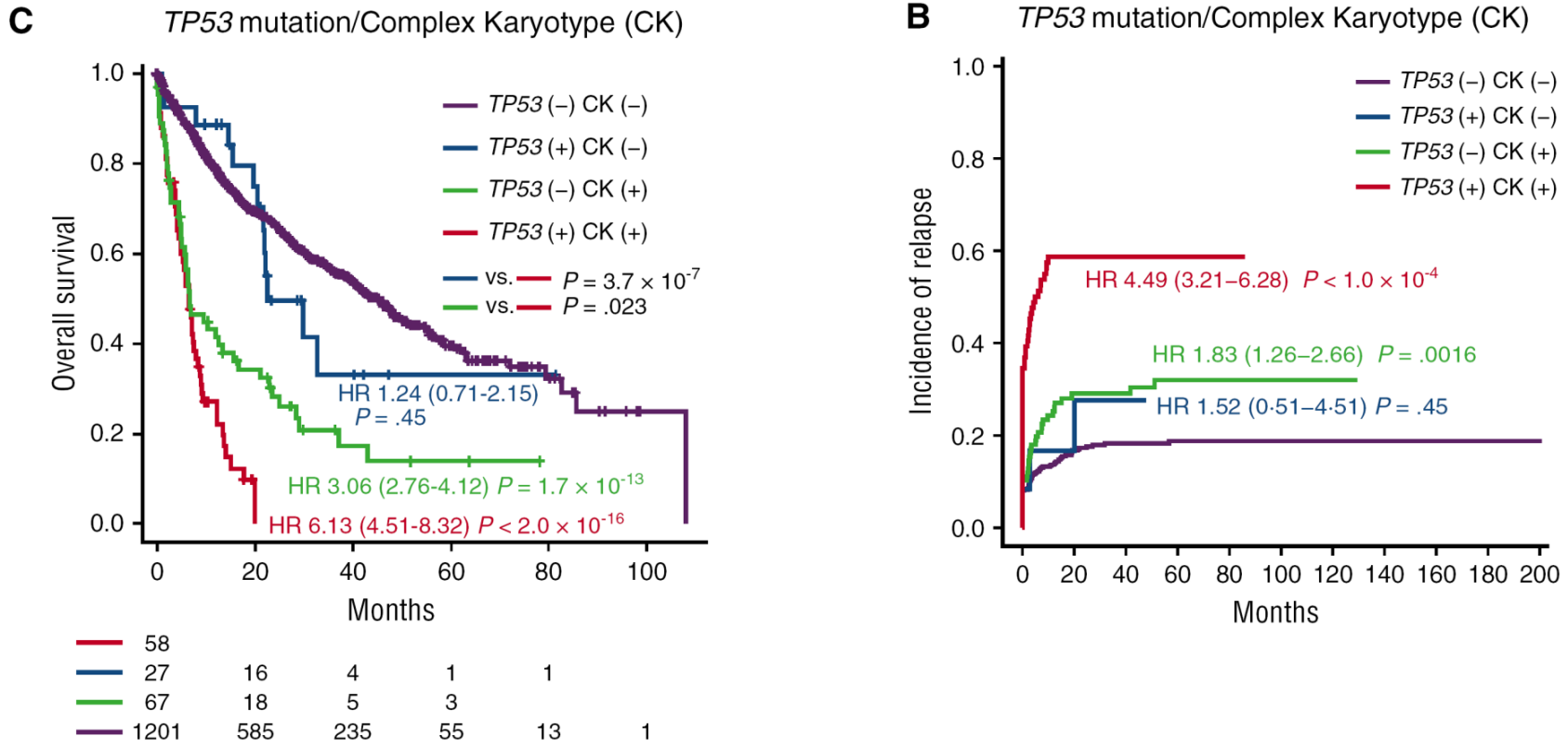
mds foundation
the myelodysplastic syndromes foundation, inc.
THE 14TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES
2017 MAY 3 - 6 Valencia, Spain
ADVANCING RESEARCH & PATIENT CARE
MDS2017

Spanish guidelines for the use of targeted deep sequencing in myelodysplastic syndromes and chronic myelomonocytic leukemia

Laura Palomo, Mariam Ibáñez, María Abáigar, Iria Vázquez, Sara Álvarez, Marta Cabezón, Bárbara Tazón-Vega, Pamela Acha, Rocío Benito, José Cervera, Juan C Cigudosa, Francisco Fuster-Tormo, Jesús María Hernández Sánchez, María José Larrayoz, David Valcárcel, Lurdes Zamora, Rosa Ayala, Maria Teresa Cedena, María Dïez-Campelo, Inmaculada Rapado, Guillermo Sanz, María José Calasanz, Francesc Solé, Esperanza Such, on behalf of the Spanish Group of MDS (GESMD)

GESMD GRUPO ESPAÑOL DE SÍNDROMES MIELODISPLÁSICOS

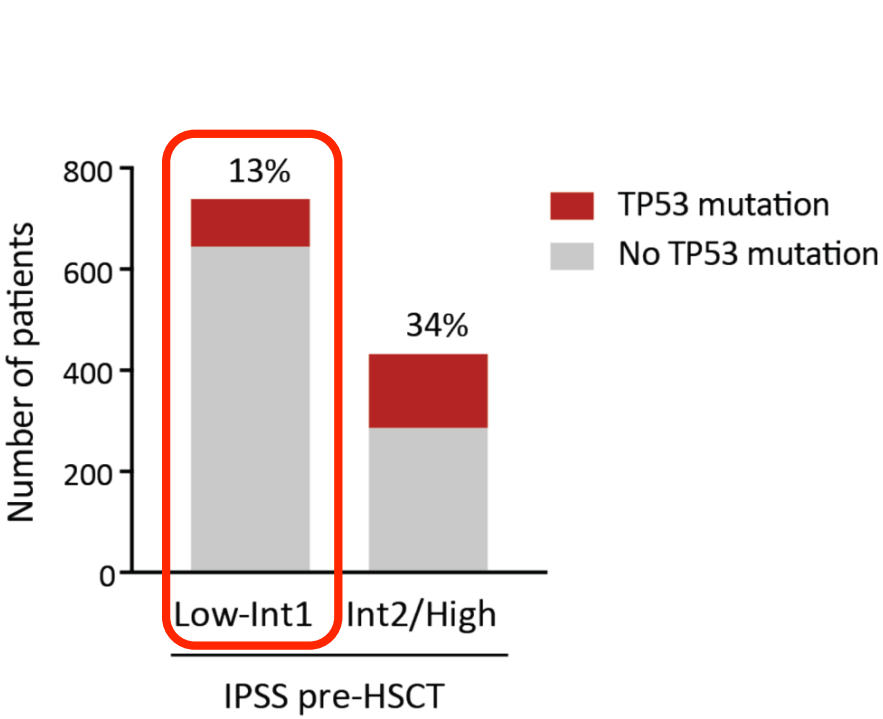
Overall survival after allogeneic HCT according to *TP53* mutations and complex karyotype

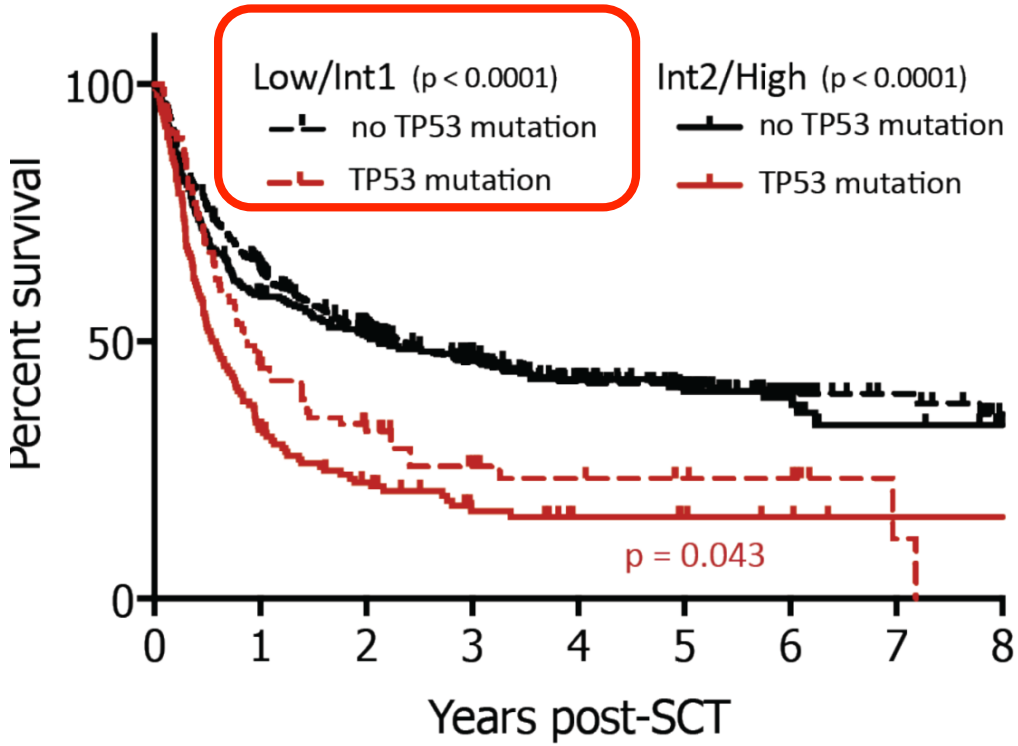


- *TP53* mutations in 13% of the patients.
- 82% of *TP53* mutated cases had a complex karyotype.
- ***TP53* mutations without complex karyotype (5% of all patients) had better OS than with complex karyotype.**

Yoshizato T, et al. *Blood* 2017; 129(17):2347-58.

Treatment choice by considering molecular data would not change too much





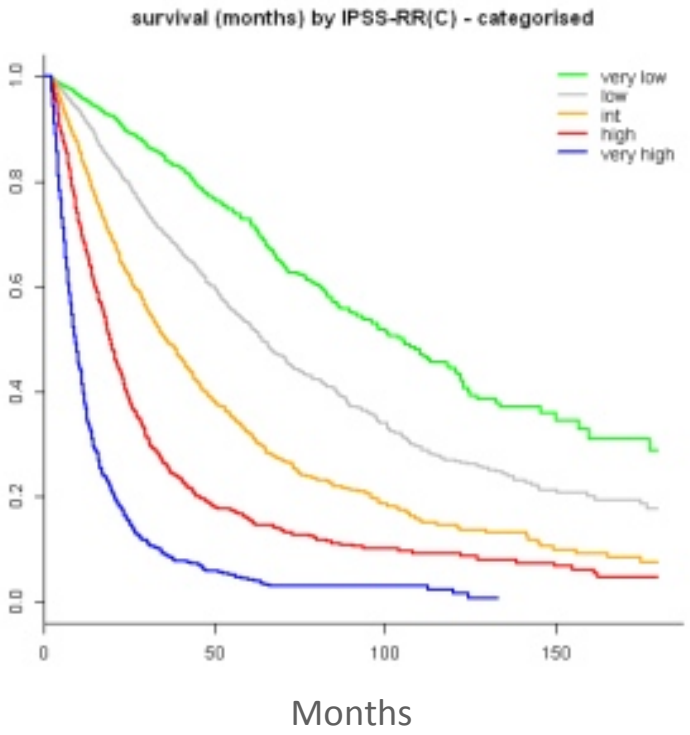
- **Only 13% of patients with low/Int-1 IPSS have TP53 mutations.**

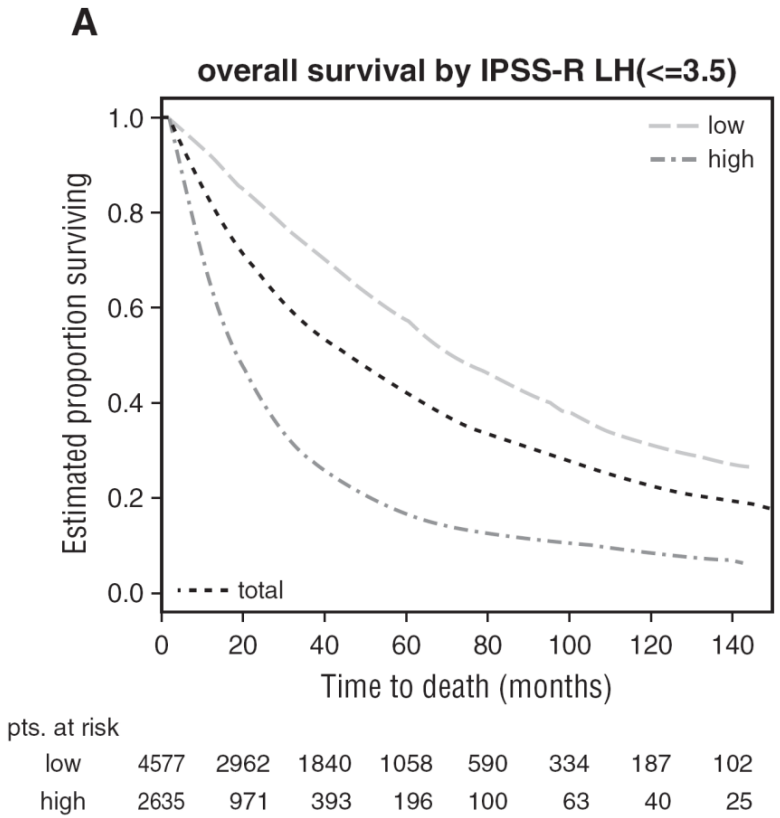
Lindsley RC, et al. *NEJM* 2017; 376:536-47.

Risk-adapted treatment of MDS

IPSS-R should be used for defining higher-risk MDS

Overall survival

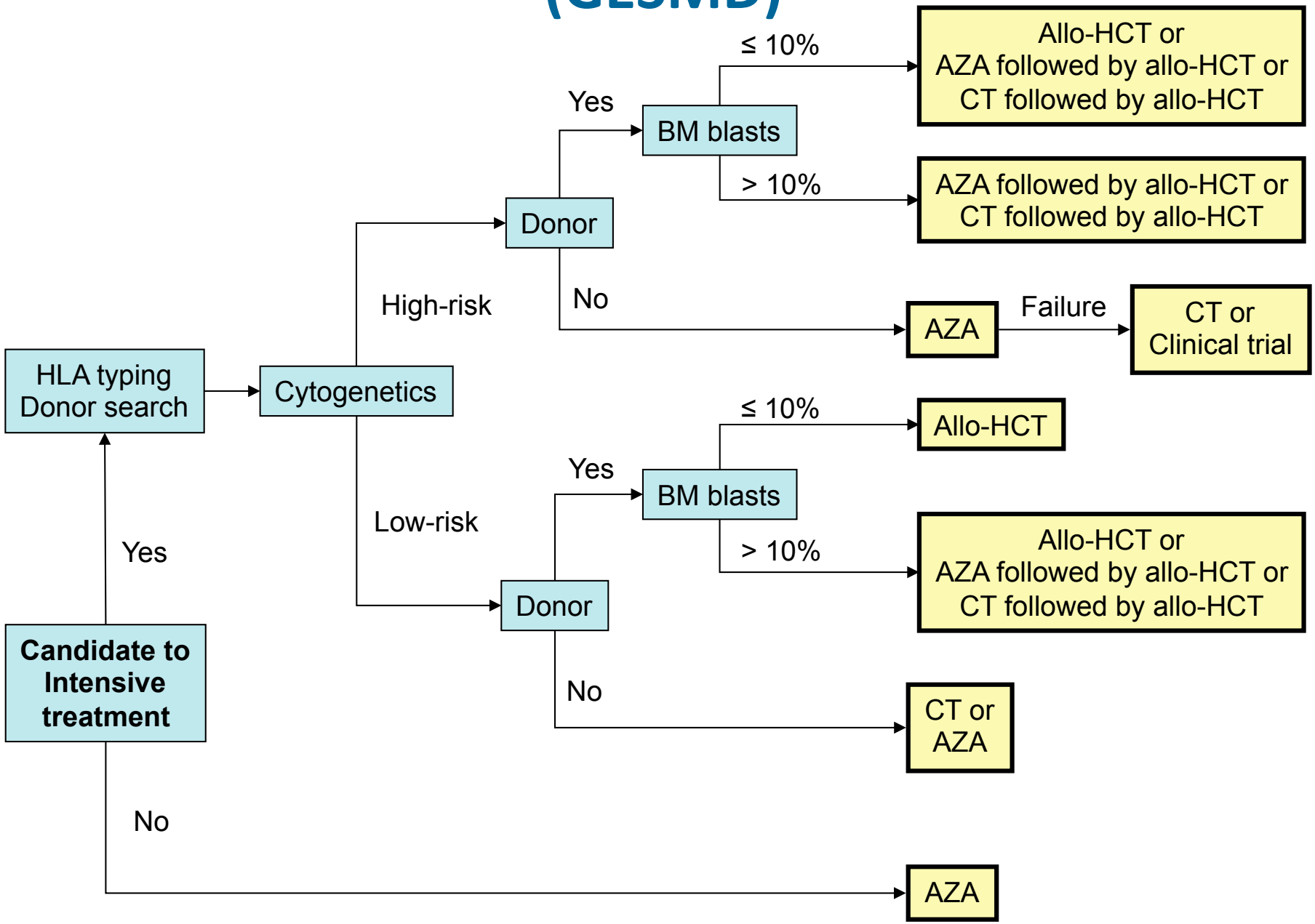




- Improved predictive power, & validated
- **Higher-risk MDS: > 3.5 points**

Greenberg PL, et al. *Blood* 2012; 120: 2454-2465.
Pfeilstöcker M, et al. Blood 2016; 128; 902-910.

Treatment algorithm for higher-risk MDS patients (GESMD)



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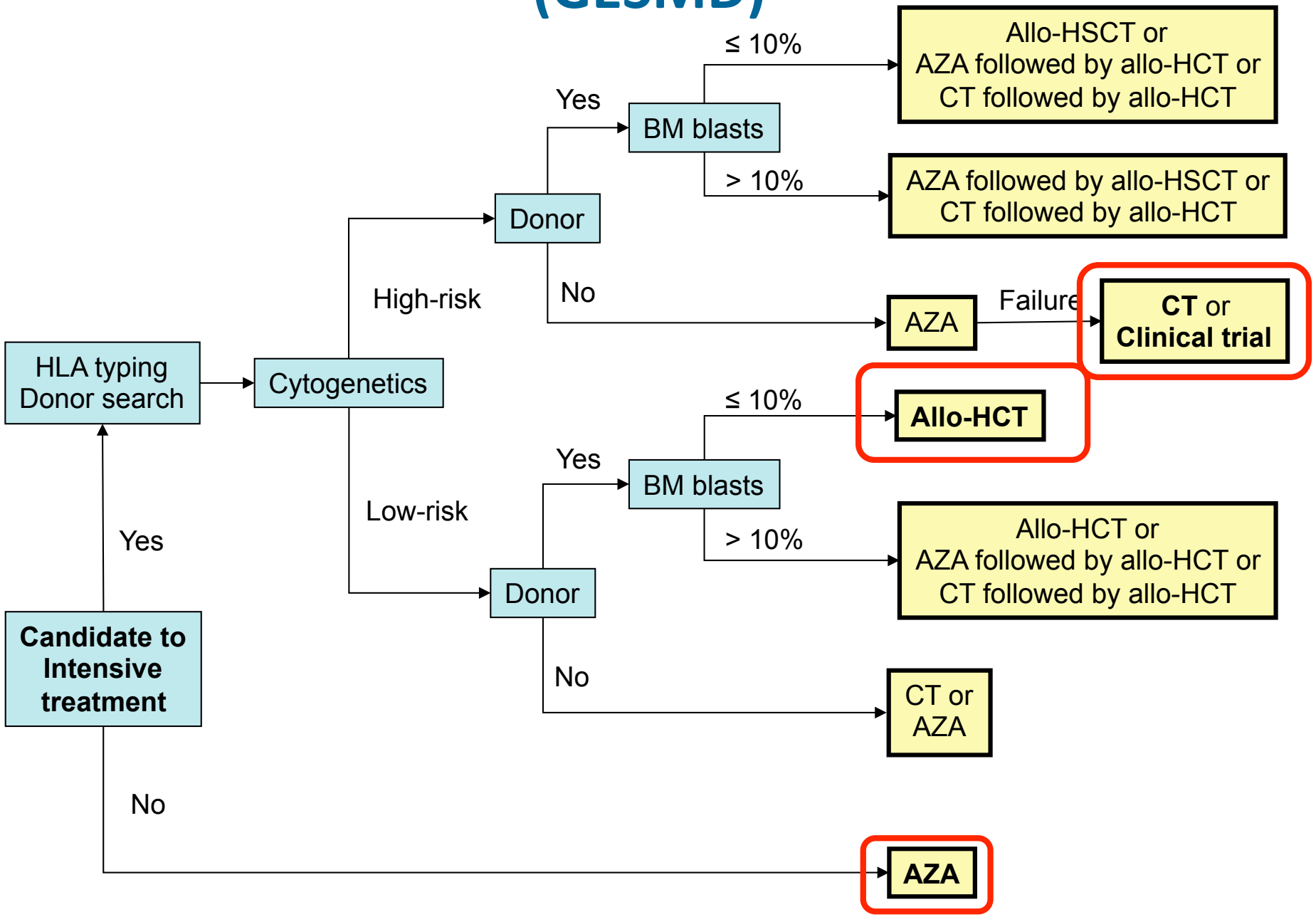
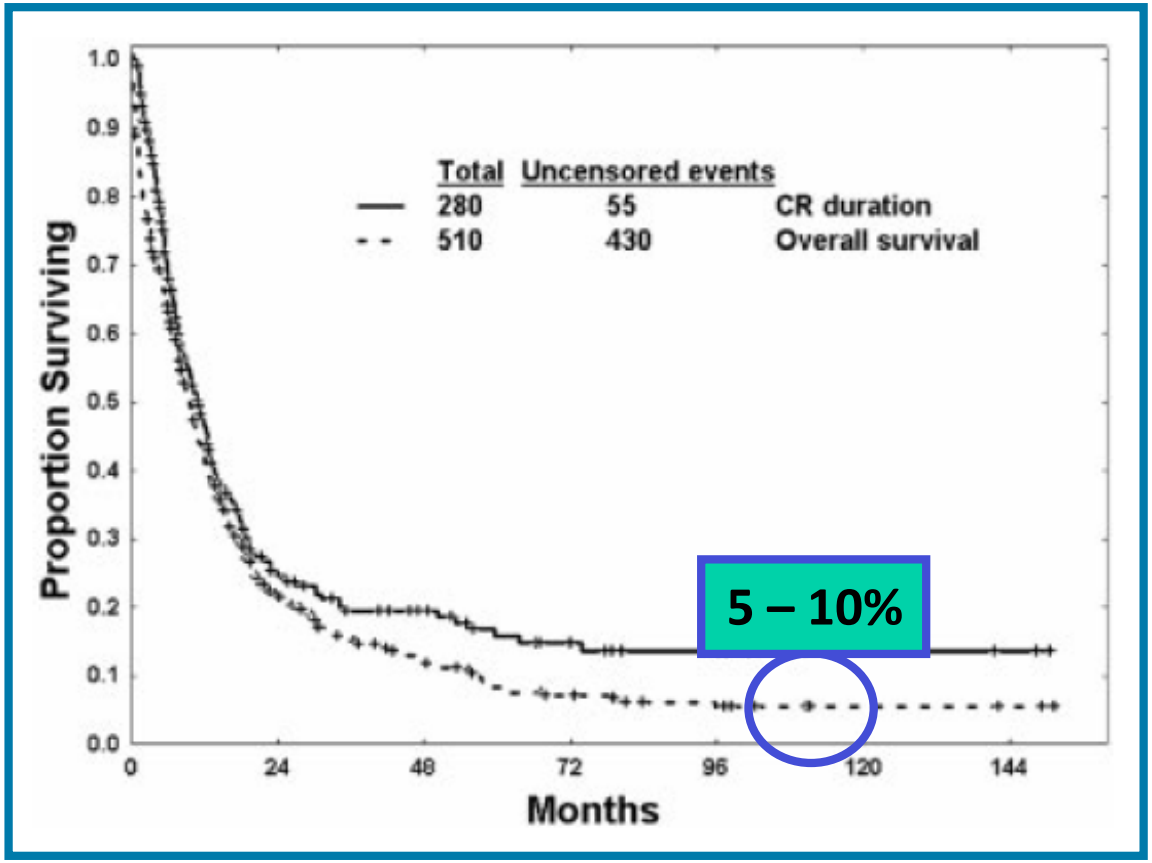


Role of allogeneic HCT in higher-risk MDS still limited

- Only proven curative modality for MDS.
- Must be considered as first-line treatment in higher-risk MDS who are candidates for intensive therapy.
- Results have improved despite greater use of transplants from alternative donors (URD, UCB & haplo) and older patient age (increase of RIC).
- **Access to transplant has increased but still limited to a minority of patients (~ 10%).**
- Key questions unclear.

The role of AML-type chemotherapy in higher-risk MDS is very limited

Long term results

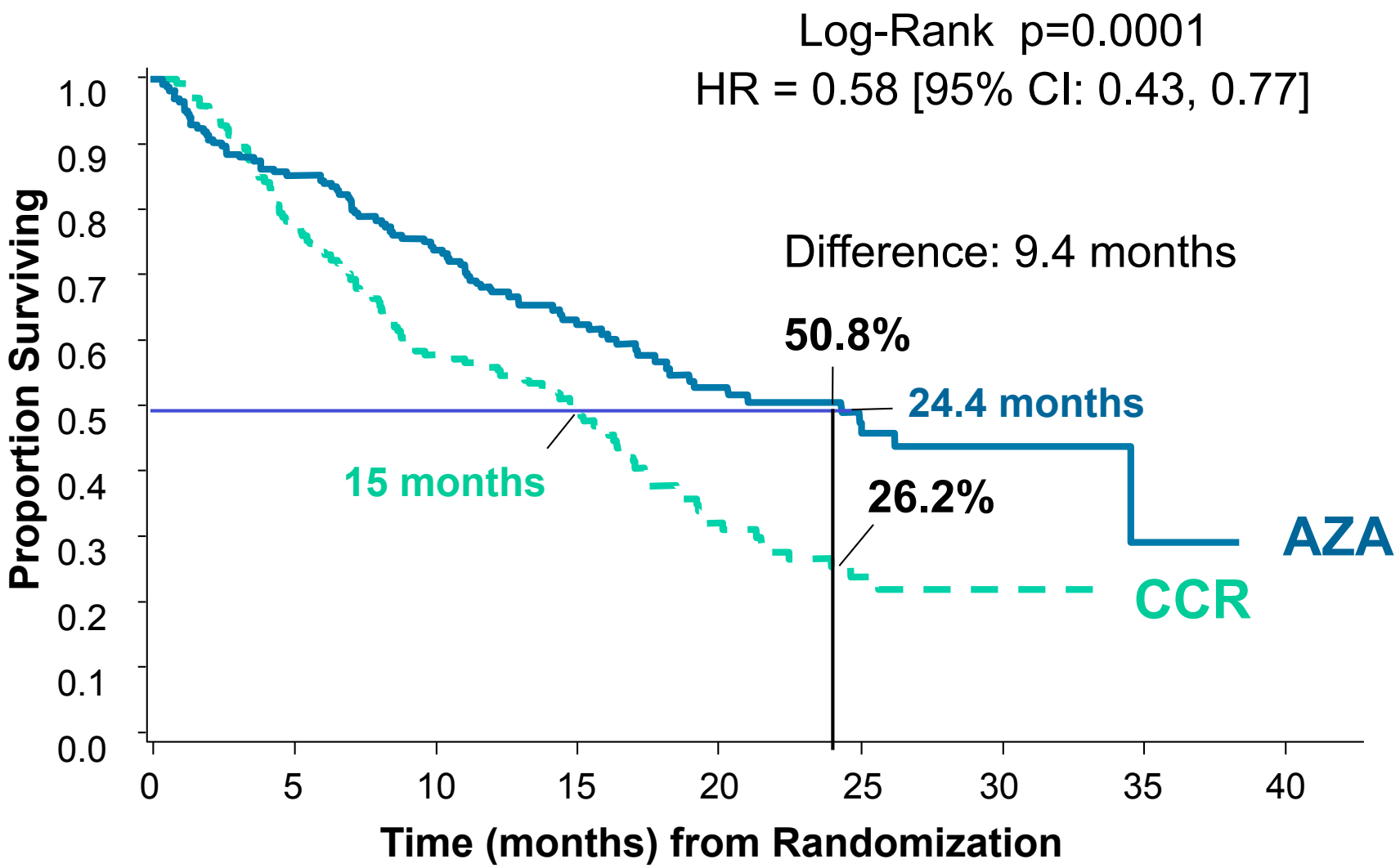


Candidates

- **Only those with high probability of long-term DFS (~30%):**
  - Age < 60 yr
  - No comorbidity
  - Favorable cytogenetics

Kantarjian H, et al. *Cancer* 2006; 106:1099-1109.

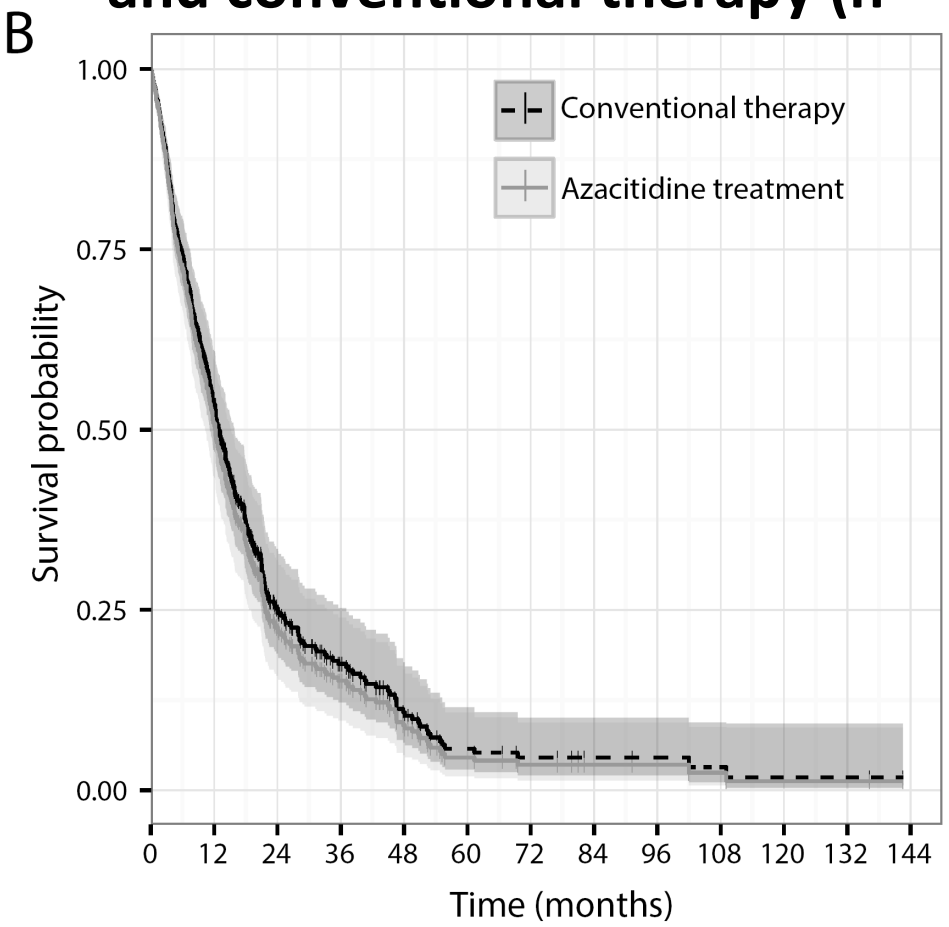
Azacitidine has showed to prolong overall survival in higher-risk MDS but clinical benefit not substantial



Fenaux P, et al. *Lancet Oncol* 2009;10:223-232

Effectiveness of azacitidine in unselected higher-risk MDS: Results from the Spanish Registry

Adjusted OS (multivariable analysis) comparing azacitidine (n = 251) and conventional therapy (n = 570)



- **No benefit for azacitidine-treated patients** (median OS: AZA, 13.5 mo; CT, 12 mo; HR, 1.08; 95% CI, 0.86-1.35; P=0.49).

Bernal T, et al. *Leukemia* 2015; 9(9):1875-81.

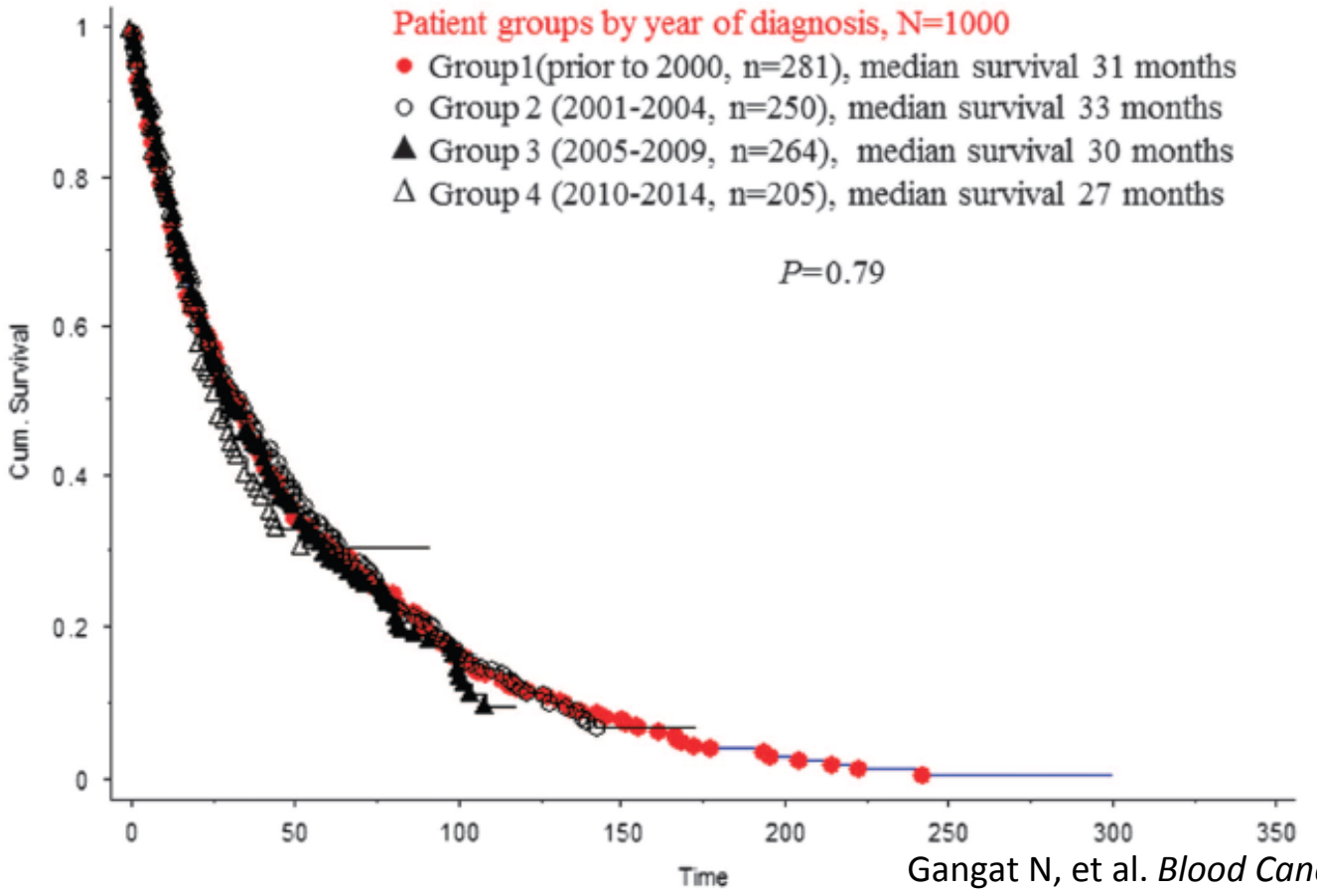
Reasons for poorer outcomes of higher-risk MDS patients in real life populations unclear

- Inclusion of **patients** with older age, poor performance status and more comorbidities
- Short **experience** and relevant issues still unsolved
  - Antibiotic and antifungal prophylaxis?
  - G-CSF prophylaxis for neutropenia?
  - Dose reduction and delay between cycles for relevant hematological toxicity?
- Inappropriate **management**
  - Less stringent follow-up than required
  - Early termination (low number of cycles for assessing response)
  - Non-stopping on time
- Others?

Survival of higher-risk MDS patients in real life populations remains unchanged

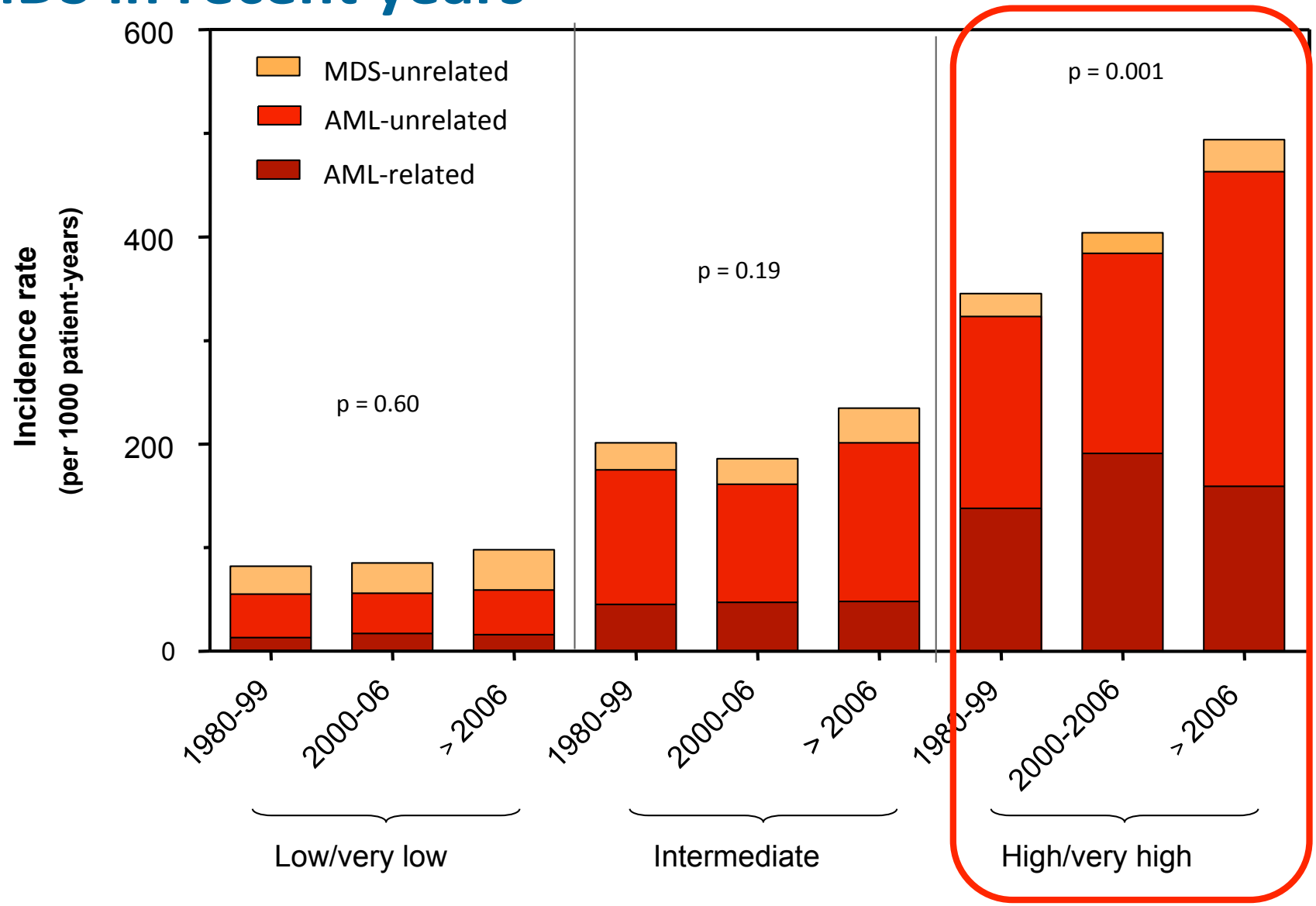
LETTER TO THE EDITOR

Survival trends in primary myelodysplastic syndromes: a comparative analysis of 1000 patients by year of diagnosis and treatment



Gangat N, et al. *Blood Cancer J* 2016 Apr 8;6:e414.

Increased rate of excess mortality* for higher-risk MDS in recent years



* Compared to the Spanish matched control population

Pereira A, et al. *Am J Hematol* 2017; 92:149-154.

Outcomes after azacitidine are dismal

- Data available on 435 pts
  - *from AZA001, J9950, J0443, French compassionate program*
- **Overall median survival after azacitidine failure: 5.6 months**

Subsequent therapy	Number of patients (%)	Median survival
Allogeneic transplant	37 (9%)	19.5 months
Investigational therapy (e.g. IMiD, HDACi, other)	44 (10%)	13.2 months
Intensive cytotoxic therapy (e.g., 3&7)	35 (8%)	8.9 months
Low-dose chemotherapy (e.g. LDAC, 6-MP)	32 (7%)	7.3 months
Palliative / supportive care	122 (28%)	4.1 months
Subsequent therapy unknown	165 (38%)	3.6 months

Prébet T et al. *J Clin Oncol* 2011; 29:3322-7; Jabbour E et al. *Cancer* 2010;116(16):3830-4

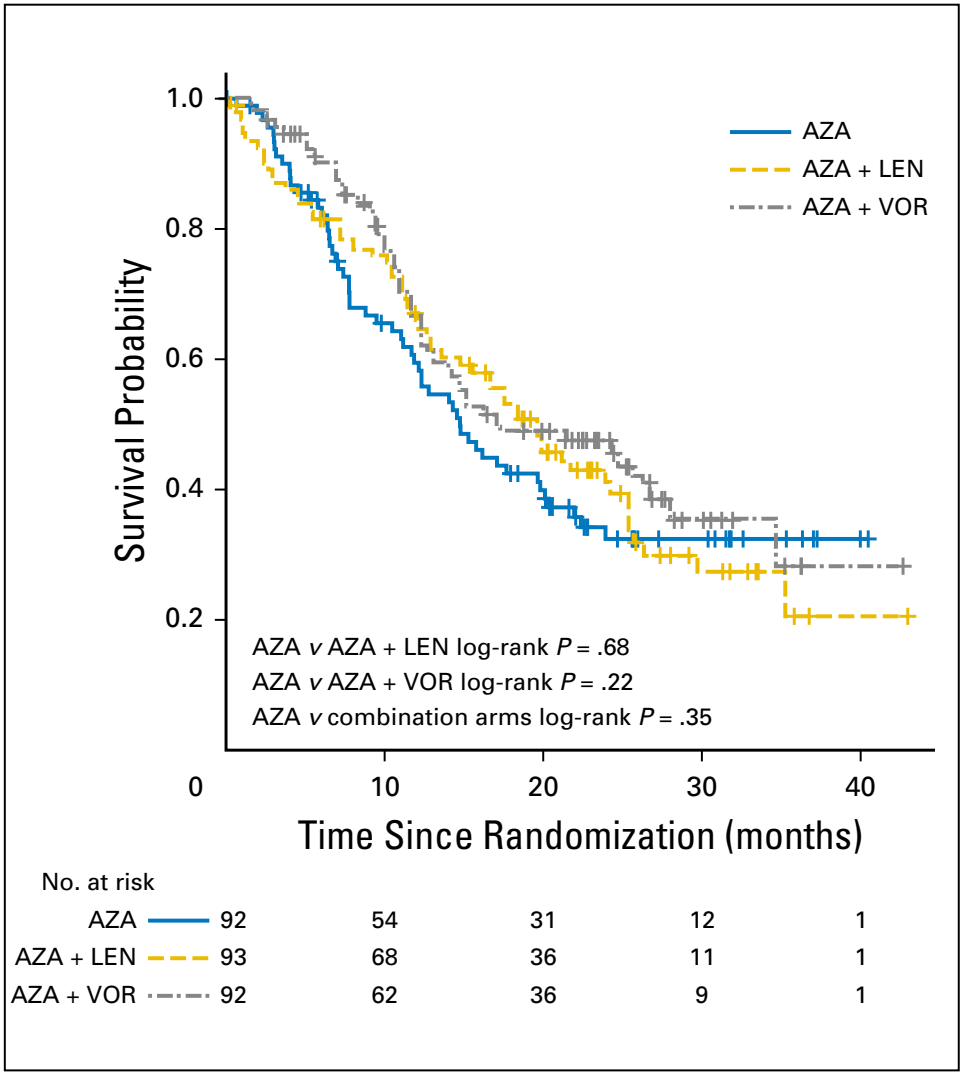
Current challenges for higher-risk MDS:
The unmet needs

- New first line approaches
  - New schedules of old drugs & HMAs
    - 10 days decitabine / azacitidine: TP53 mutations?
    - Guadecitabine
    - Oral azacitidine
  - New drugs
  - Combinations
    - Azacitidine plus other drug?
    - Combination of two other drugs?
- Alternatives for first-line failures (desperately needed)

The results of new drugs for higher-risk MDS are still scarce and preliminary (any effect on OS?)

- Involving relevant cellular pathways
  - *BCL-2* inhibitirors (venetoclax)
  - Neddylation inhibitors (pevonidostat)
  - Polo-kinase inhibitors (rigosertib, volasertib)
- Targeted drugs: small role (for the moment)
  - *FLT-3* (midostaurin) & *IDH1-2* inhibitors (enasidenib)
  - Spliceosome inhibitors?
- Monoclonal antibodies
  - Anti CD33 (vadastuximab talirine) & CD123 (talacotuzumab)
- Immune checkpoint inhibitors
  - Durbalumab, nivolumab, atezolizumab, & others

The results of combinations of azacitidine and another drug in higher-risk MDS have failed to improve survival



- **Including** among others
  - AZA + lenalidomide
  - AZA + vorinostat
  - AZA + volasertib
  - AZA + eltrombopag
  - AZA + romiplostim

- **Is azacitidine related-toxicity to be blamed for this fact?**
  - Would combination of 2 other drugs make sense?

Sekeres MA, et al. *J Clin Oncol* 2017; 5(24):2745-2753.

Rigosertib may have some role for some patients after azacitidine failure but still unproven

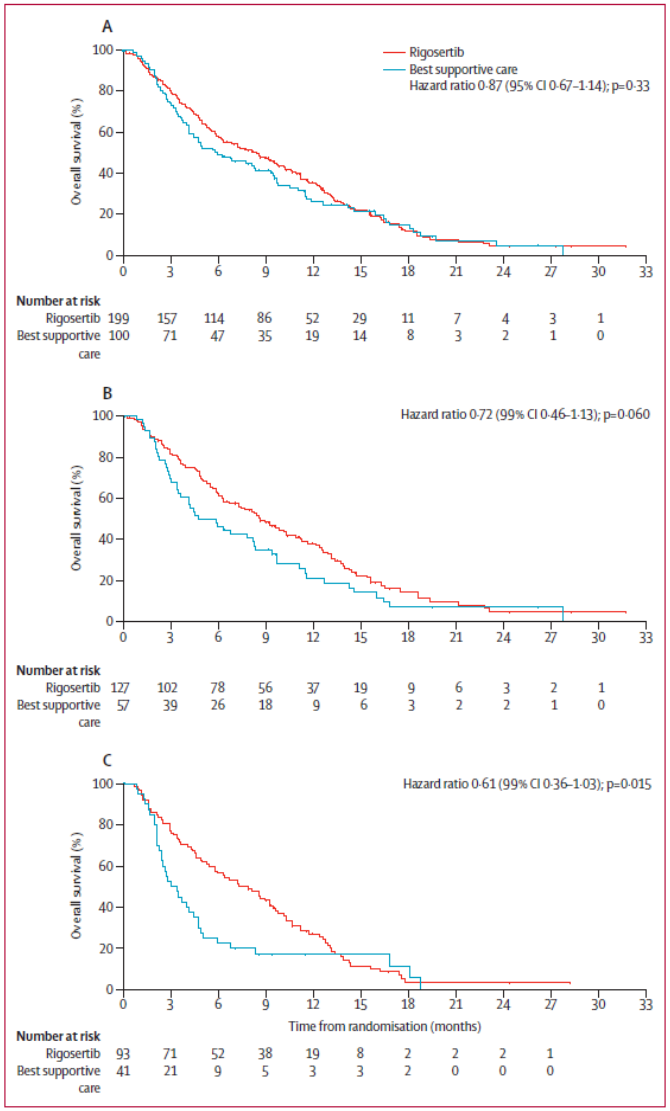


Figure 2: **Overall survival curves for the rigosertib group and best supportive care group**
(A) For the intention-to-treat population, (B) patients with primary hypomethylating drug failure, and (C) patients with IPSS-R very high risk. IPSS-R=Revised International Prognostic Scoring System.

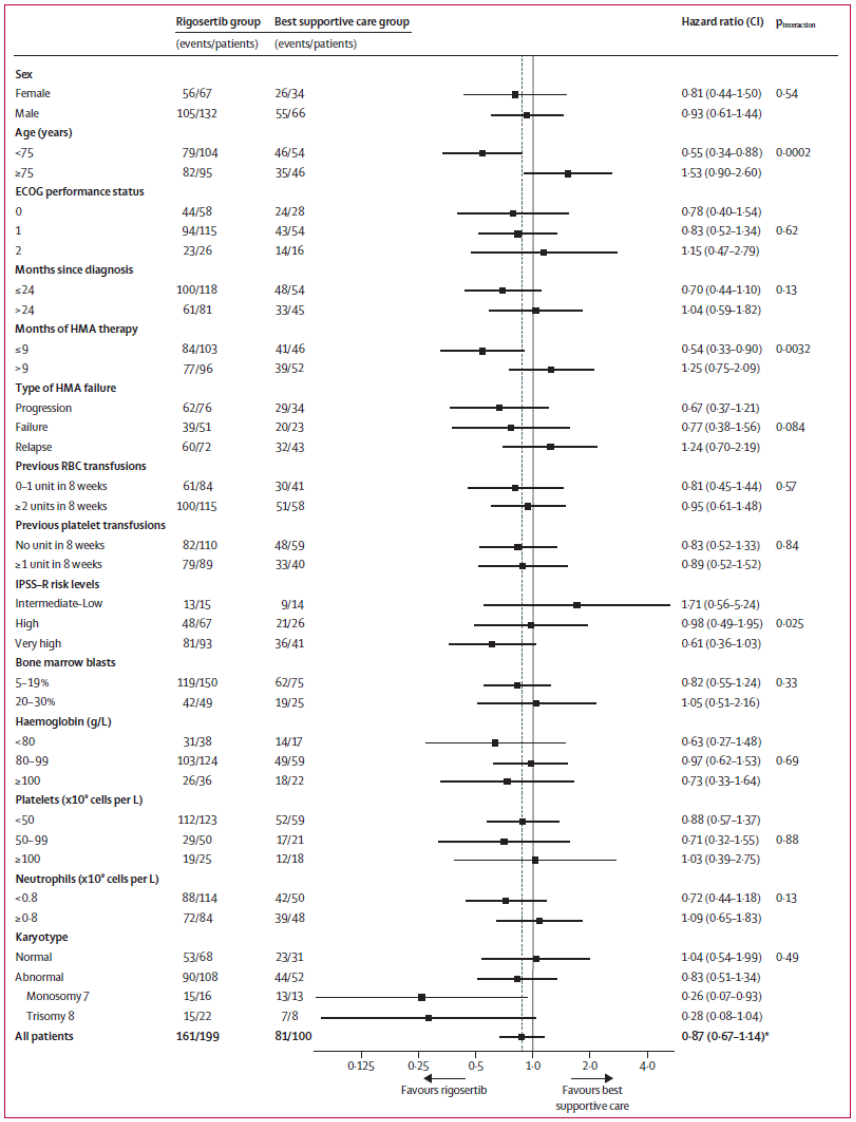


Figure 3: **Subgroup analyses of overall survival in the intention-to-treat population**
Confidence intervals are 99% CIs unless stated otherwise. *95% CI. IPSS-R=Revised International Prognostic Scoring System. HMA=hypomethylating drug. ECOG=Eastern Cooperative Oncology Group.

García-Manero G et al. *Lancet Oncol* 2016; 17(4):496-508.

Treatment of higher-risk MDS

Summary

- Despite recent advances treatment remains unsatisfactory for most patients.
- Outcomes after new drugs & combinations very preliminary.
- Treatment must always be considered as investigational.

Include patients in clinical trials and prospective registries whenever possible!!!