Allogeneic Hematopoietic Stem Cell transplantation in MDS

Theo de Witte, on behalf of the
International expert panel which developed recommendations of HSCT for patients with MDS, MDS subgroup of EBMT CMWP

Age and Vitality!

Introduction

- Allogeneic hematopoietic stem cell transplantation (HSCT) is an increasingly used, curative treatment option for patients with MDS
- **Lower intensity conditioning regimens** have extended the indication for HSCT to patients with increased comorbidities and reduced fitness/vitality
- Nontransplant treatment modalities for patients with MDS, including lenalidomide, hypomethylating agents (HMA) and investigational drugs, may influence the indication, timing, and preparation for HSCT

De Witte T, et al. Blood 2017; 129: 1753-62

Introduction (2)

We will focus on the following issues:

- selection of appropriate patients
- timing of transplantation of patients treated with nontransplant interventions
- Post-transplant strategies
- presentation of our new interactive website EUMDS/MDS-RIGHT

This published review with the recommendations for MDS and CMML is the backbone of the current interactive recommendations

De Witte T, et al. Blood 2017; 129: 1753-62

Introduction (3)

The recommendations for HSCT in MDS will distinguish:

- HSCT as standard practice
- HSCT as non-standard (investigational) practice in patients who have an expected poor outcome after HSCT due to patient-related (e.g. high co-morbidity index) or disease-related factors (e.g. refractory after cytoreductive therapy or TP53 mutations)

Conditioning intensity not discussed in detail, assuming general recommendations (reduced intensity in less fit patients)

Type of donors not discussed in detail: we distinguish as standard donors identical siblings or matched unrelated donors and other donors

Timing of HSCT in lower-risk MDS patients without poor-risk features

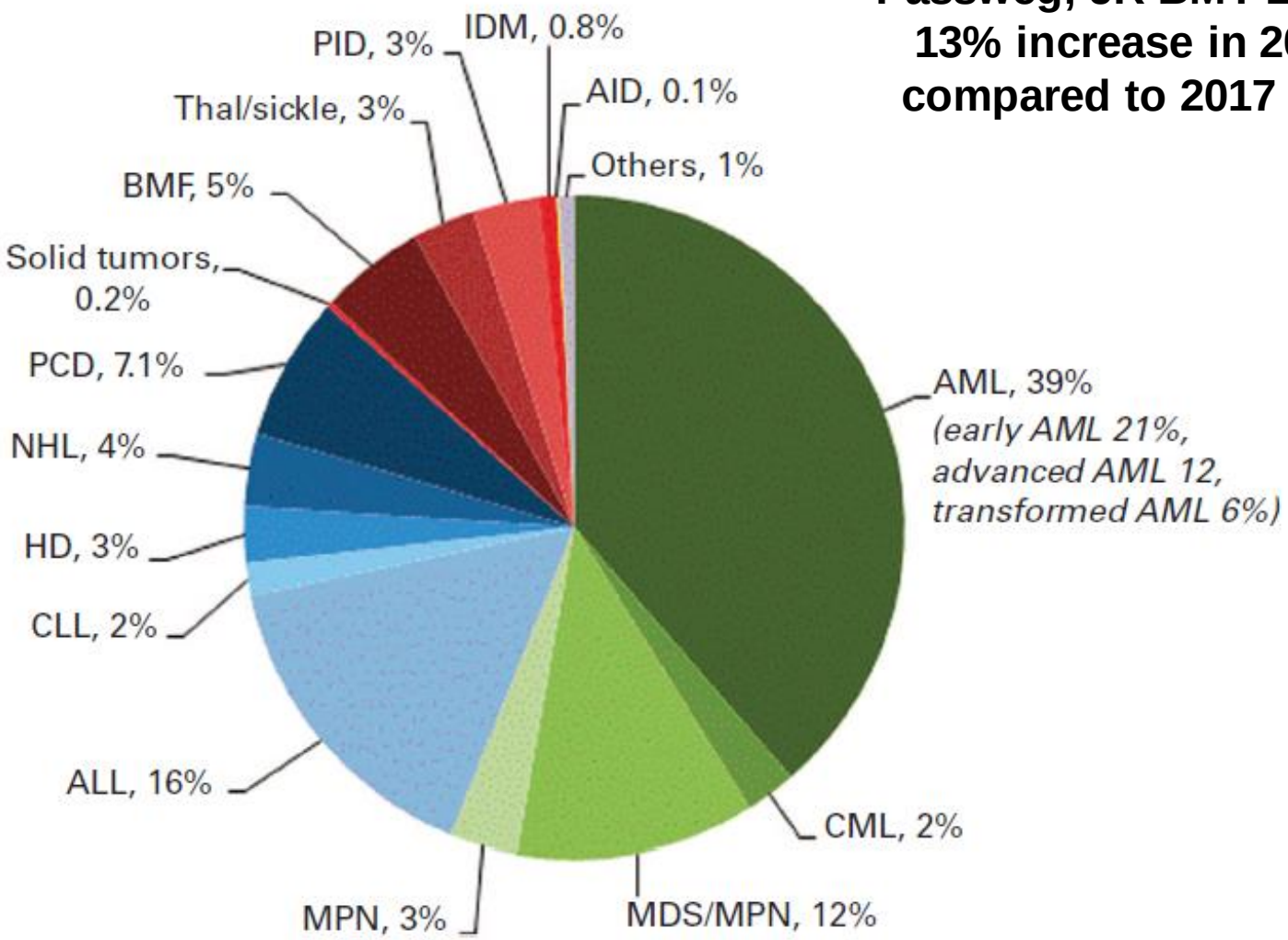
De Witte T, et al. Blood 2017; 129: 1753-62

Factors playing a role to recommend and to time a HSCT for MDS patients

- **Patient characteristics**: fitness, co-morbidity and chronic transfusion dependency/transfusion density
- **Disease characteristics** which determine response to chemotherapy and hypomethylating agents: cytogenetic (molecular) characteristics
- **Disease characteristics** which determine risk of relapse after HSCT: cytogenetic (molecular) characteristics and disease stage
- The availability of a suitable donor: 100%?
- Expected response to proposed treatment before transplantation
- Response and disease status after given treatment prior to start HSCT

De Witte T, et al. Blood 2017; 129: 1753-62

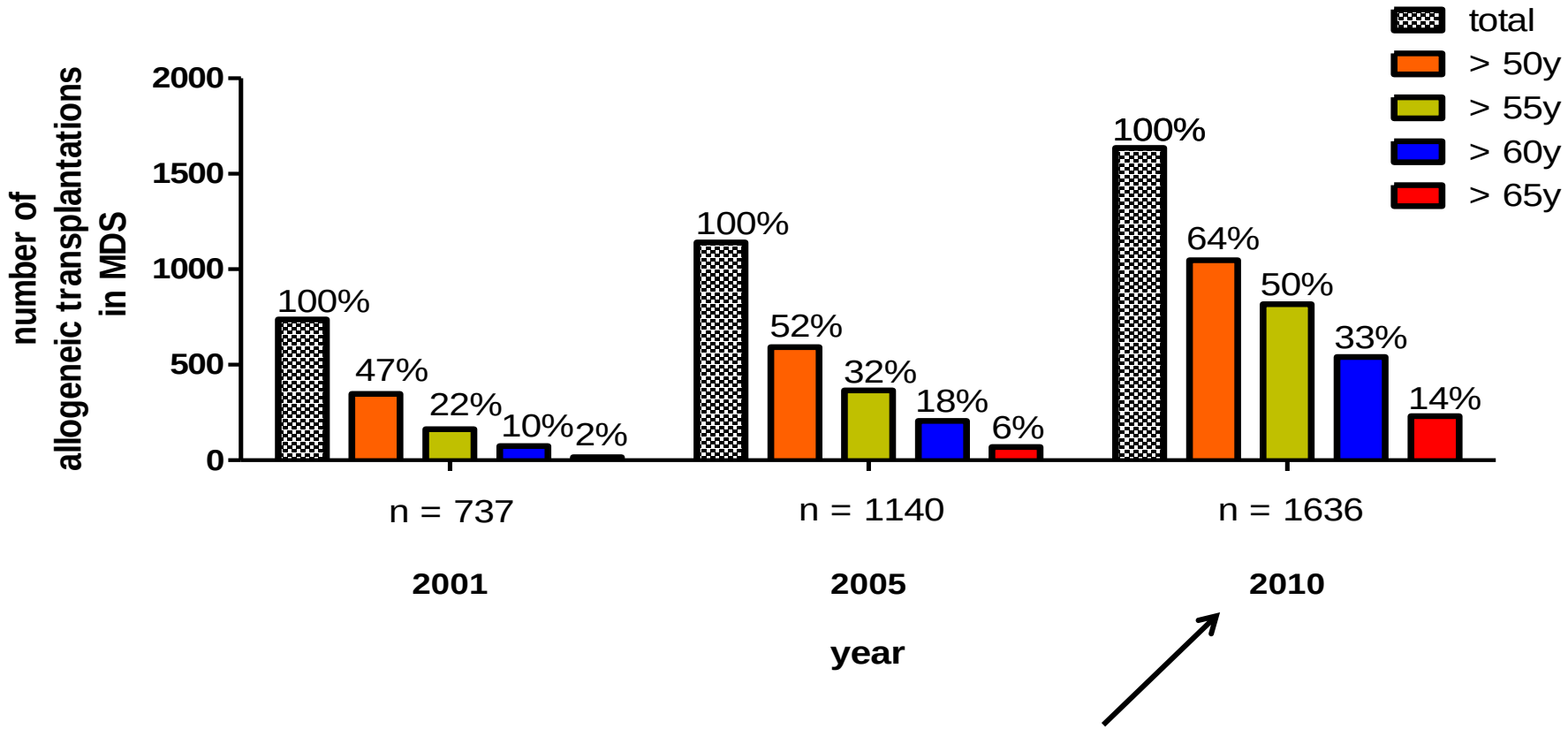
Allogeneic HSCT (16.000) in Europe (2015)



Passweg, JR BMT 2020 online: 13% increase in 2018 when compared to 2017 (2322 pts)

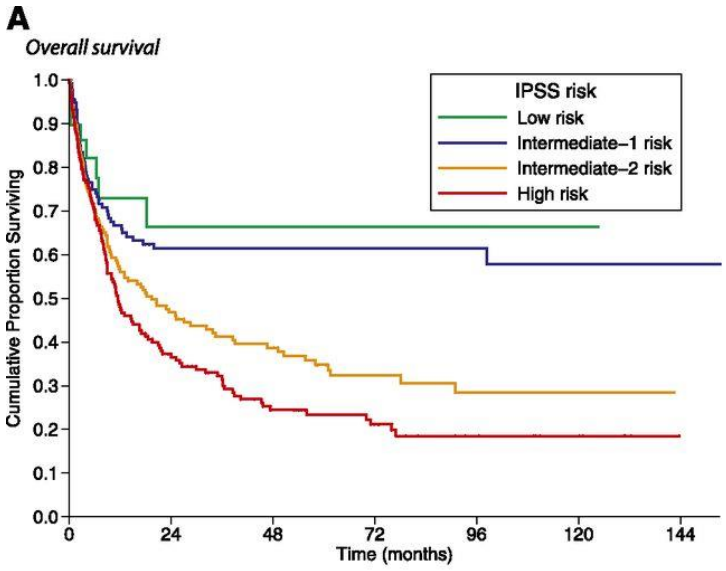
Passweg, JR BMT 2017 online; doi.1038/bmt.2017.34

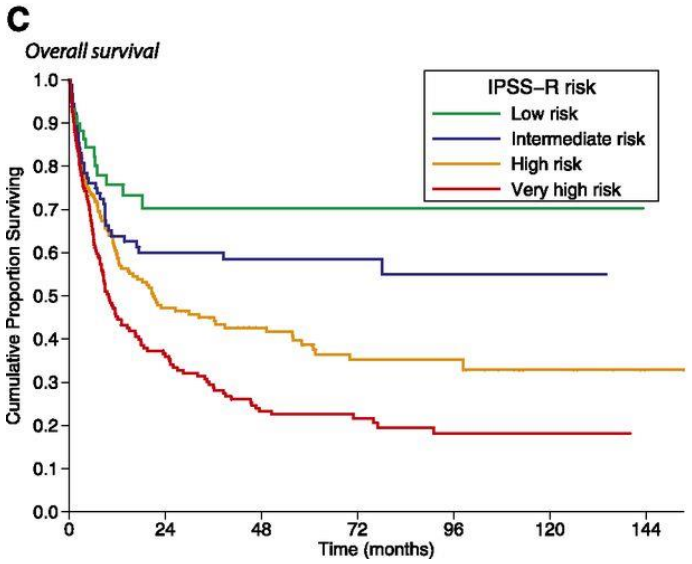
Increase of number of transplants in older MDS/sAL patients



>50% unrelated donors

Survival following HSCT in MDS patients stratified according to their pretransplant IPSS or IPSS-R risk

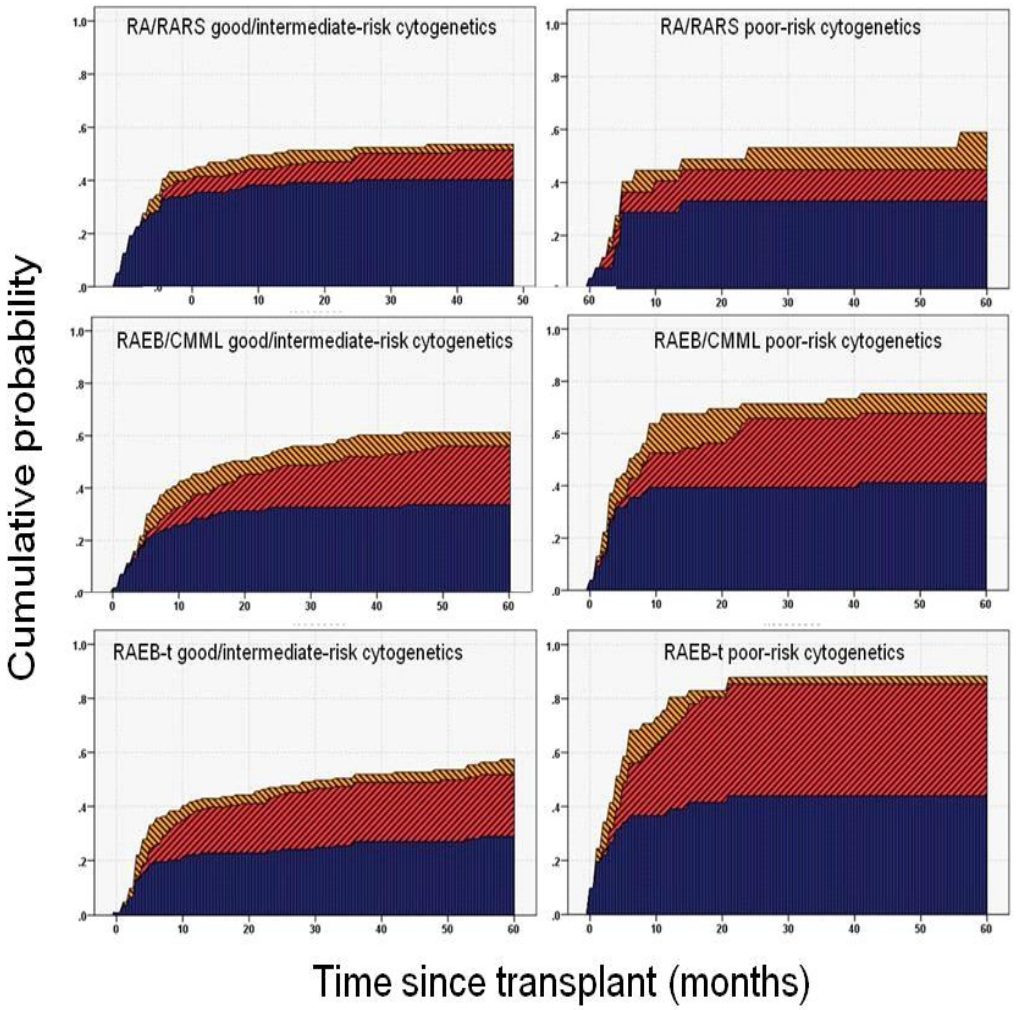




IPSS-R better model to predict outcome after HSCT

Della Porta M, et al. Blood 2014;123:2333-42

Impact of poor risk cytogenetics: more important in patients with advanced MDS



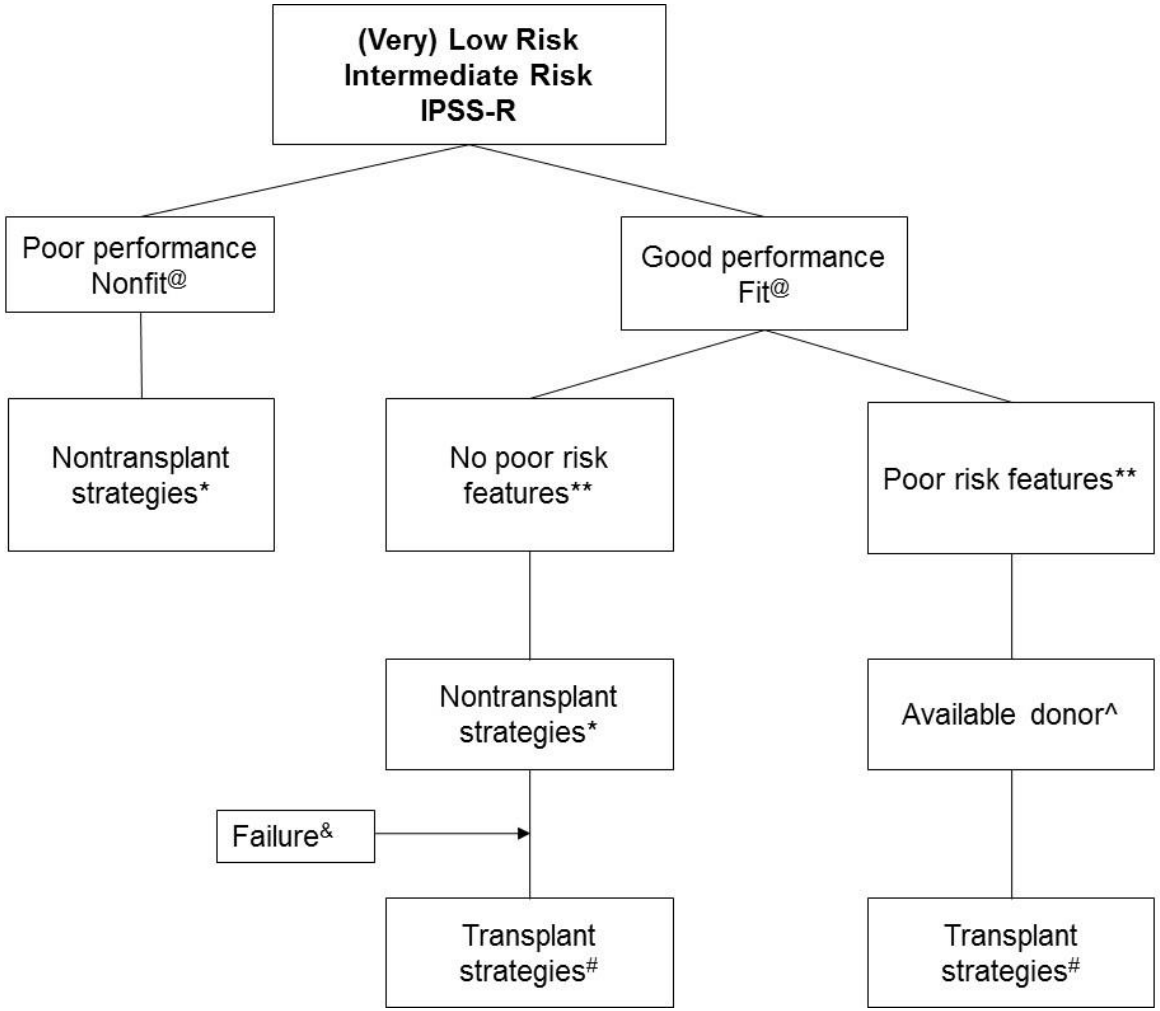
Alive after relapse
Dead after relapse
Nonrelapse death

Hazard Ratio's

RA/RARS:	**0.9 (0.5 to 1.8)**
RAEB/CMML:	**1.4 (0.9 to 2.1)**
RAEBt:	**2.5 (1.6 to 3.7)**

Onida F, et al Haematologica 2014; 99: 1582-90

Lower-risk MDS recommendations for "standard" allogeneic HSCT



De Witte T, et al. Blood 2017; 129: 1753-62

Lower-risk MDS
According to IPSS-R: Low and Intermediate Risk

Fit patients: <3 co-morbidities and good performance status (Karnofsky >60)

No upper age limit, if patients are fit, without serious co-morbidity and good Karnofsky status

Nontransplant strategies according to most recent versions published by international MDS expert groups, including ELN and NCCN

De Witte T, et al. Blood 2017; 129: 1753-62

Lower-risk MDS recommendations

Failure of nontransplant strategies: ESAs, lenalidomide and cytoreductive therapy, including HMA. Nontransplant interventions may include more than one line of nontransplant intervention, e.g. treatment with ESAs, followed by lenalidomide in patients with 5q-.

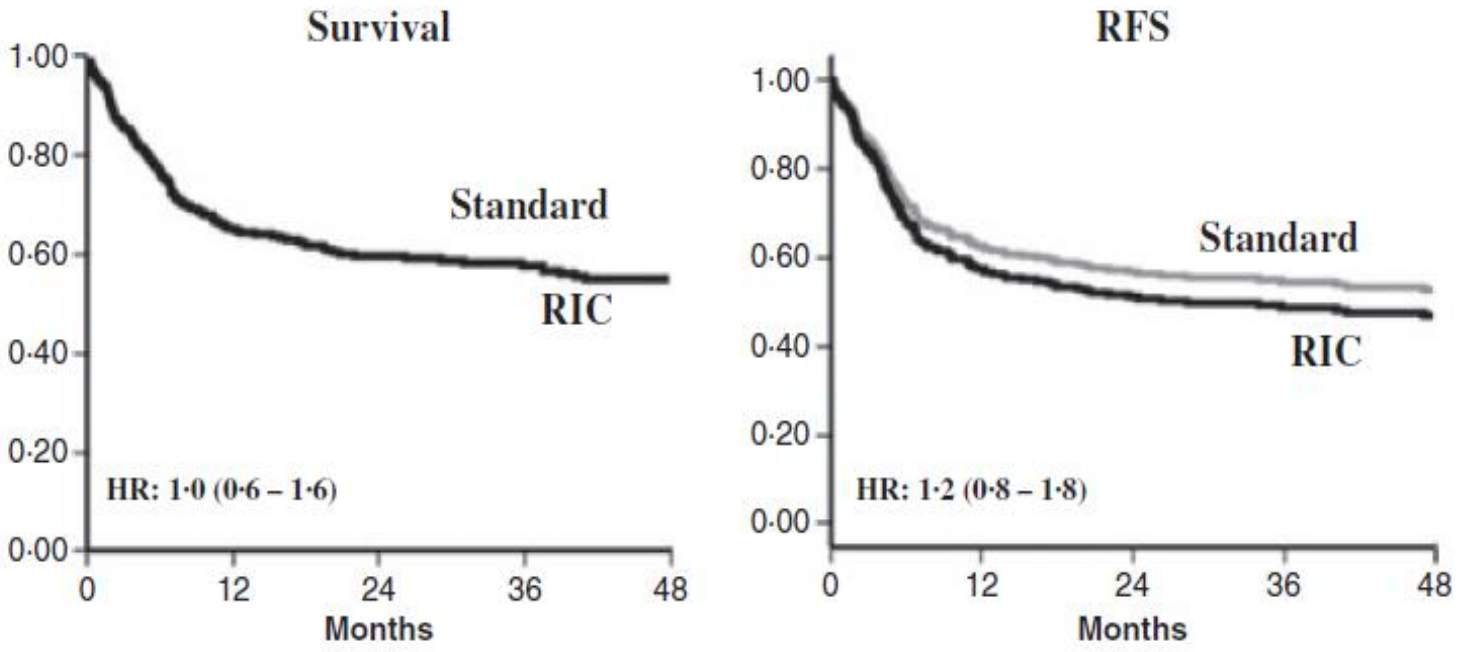
Poor risk features:

- (very) poor risk cytogenetic characteristics
- persistent blast increase (>50% increase from base line or with >15% BM blasts)
- life threatening cytopenias: neutrophil counts < 0.3 x 10^9/l; platelet counts <30 x 10^9/l)
- high transfusion intensity ≥2 units/month for 6 months
- molecular testing is generally recommended, especially in case of absence of poor risk cytogenetic characteristics or persistent blast increase

De Witte T, et al. Blood 2017; 129: 1753-62

HSCT for patients with refractory anemia with matched related and unrelated donors

When to transplant?



Delay of HSCT is associated with inferior survival

T de Witte et al. Br J Haematol 2009; 146: 627-636

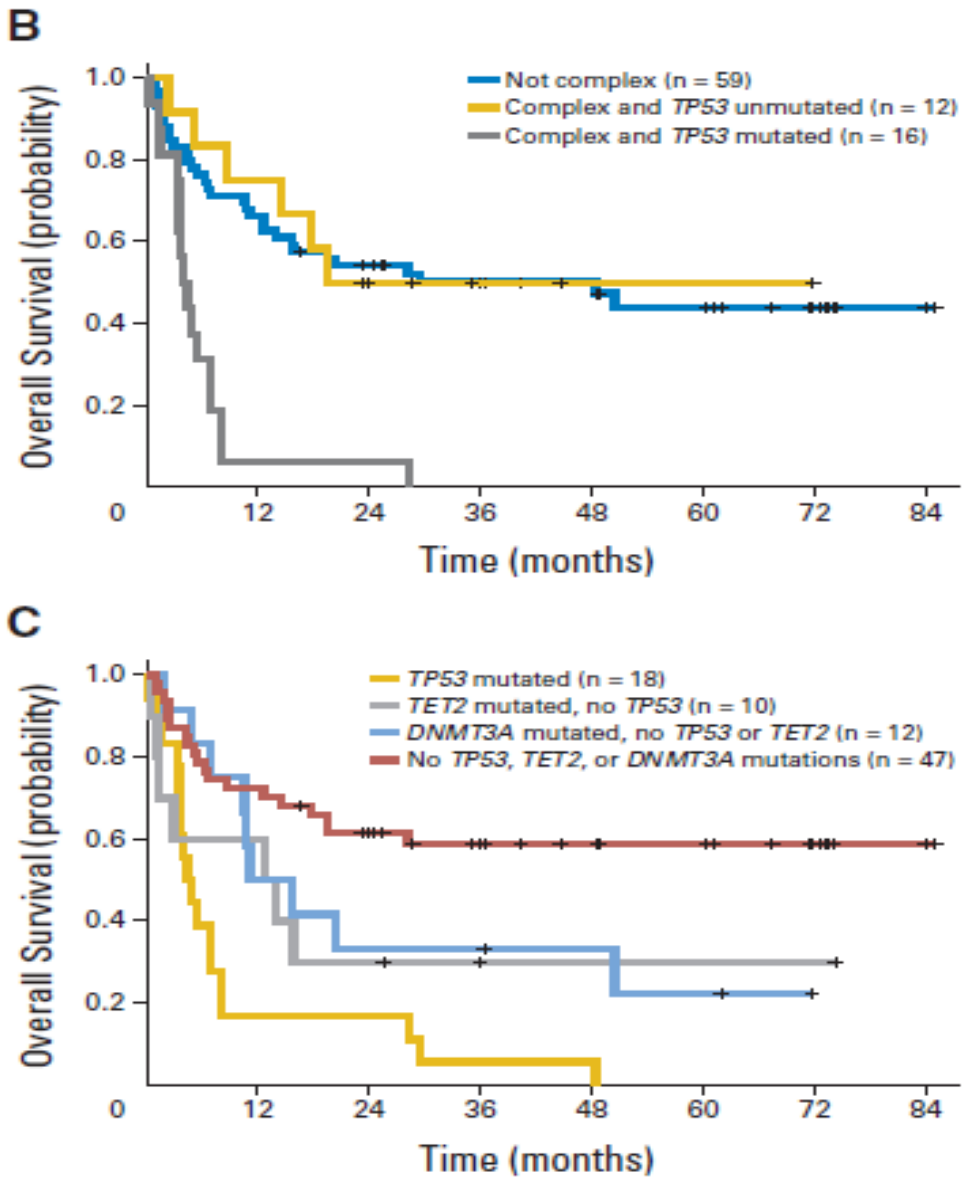
HSCT for patients with refractory anemia with matched related and unrelated donors

	Survival		RFS	
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
RIC vs. MAC	1·0 (0·6–1·6)	1·0	1·2 (0·8–1·8)	0·5
Disease duration >12 months	1·4 (1·0–1·9)	0·05	1·3 (1·0–1·8)	0·09
Age (per 10 years)	1·1 (1·0–1·3)	0·05	1·1 (1·0–1·2)	0·08
PB vs. BM	1·3 (0·9–2·1)	0·2	1·2 (0·8–1·8)	0·4
Year transplant (per year)	0·95 (0·9–1·0)	0·05	1·0 (0·9–1·0)	0·1
Unrelated donor	1·3 (0·9–1·9)	0·2	1·2 (0·8–1·7)	0·4
IPSS – low	(1)	0·6	(1)	0·6
IPSS – intermediate-1	0·8 (0·5–1·4)		0·9 (0·6–1·6)	
IPSS – Intermediate-2	0·5 (0·1–2·1)		0·5 (0·1–2·0)	

- **Disease duration of >12 months is associated with inferior survival**
- **HSCT should be preferentially performed early after diagnosis after careful analysis of prognostic variables**

T de Witte et al. Br J Haematol 2009; 146: 627-636

Contribution of gene mutations in predicting survival after HSCT



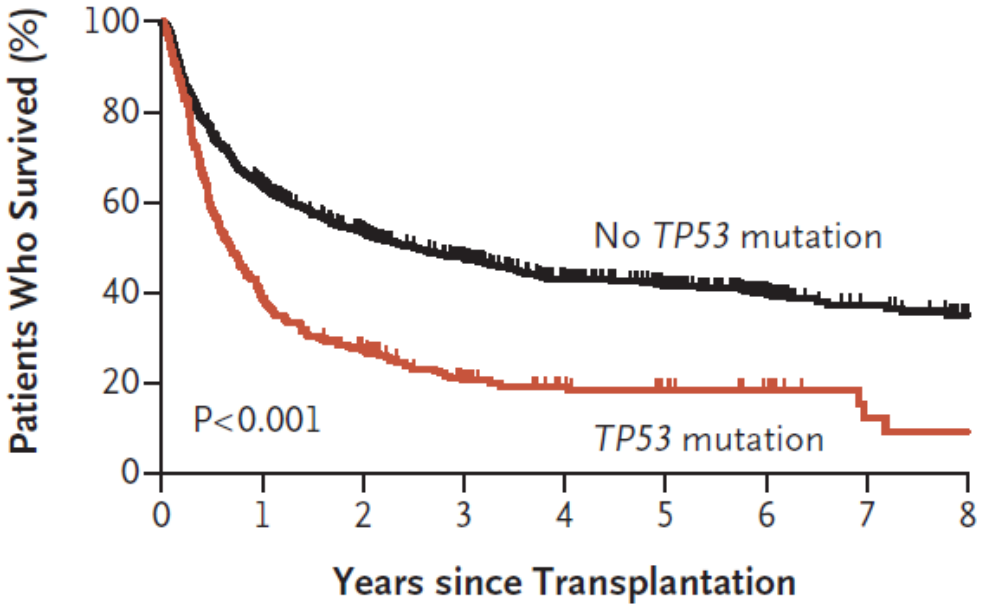
Combination TP53 and complex karyotype dismal outcome after HSCT

These patients are recommended to be treated in investigational studies

R. Bejar, et al JCO 2014; 29: 504-15

Contribution of gene mutations in predicting survival after HSCT

B **Overall Survival, According to *TP53* Mutation Status**



No. at Risk

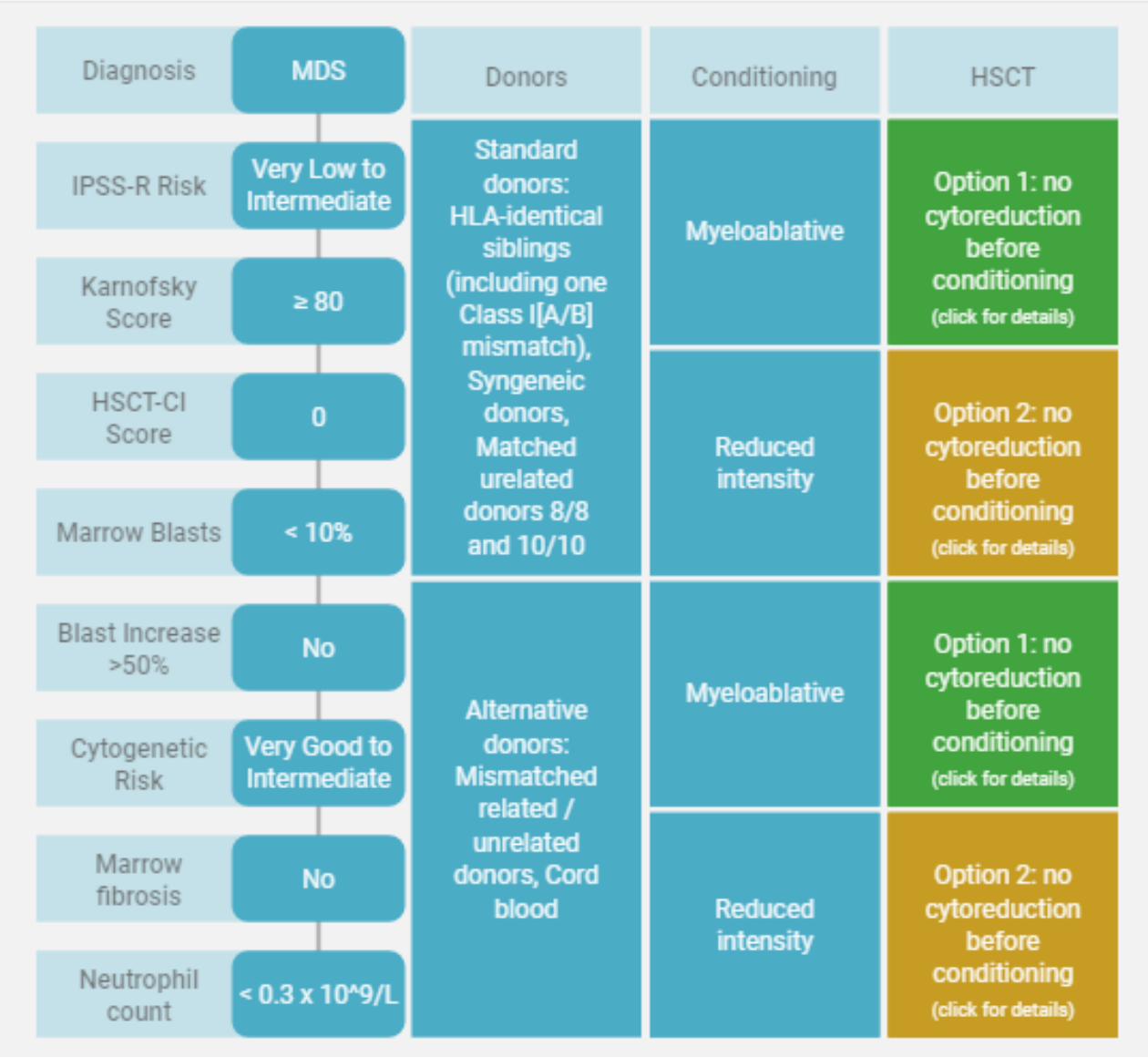
No *TP53* mutation	1224	757	529	370	261	183	109	53	32
TP53 mutation	289	109	66	39	26	20	14	6	5

TP53 mutations (19%) inferior outcome after HSCT

RAS mutations inferior outcome after RIC only

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

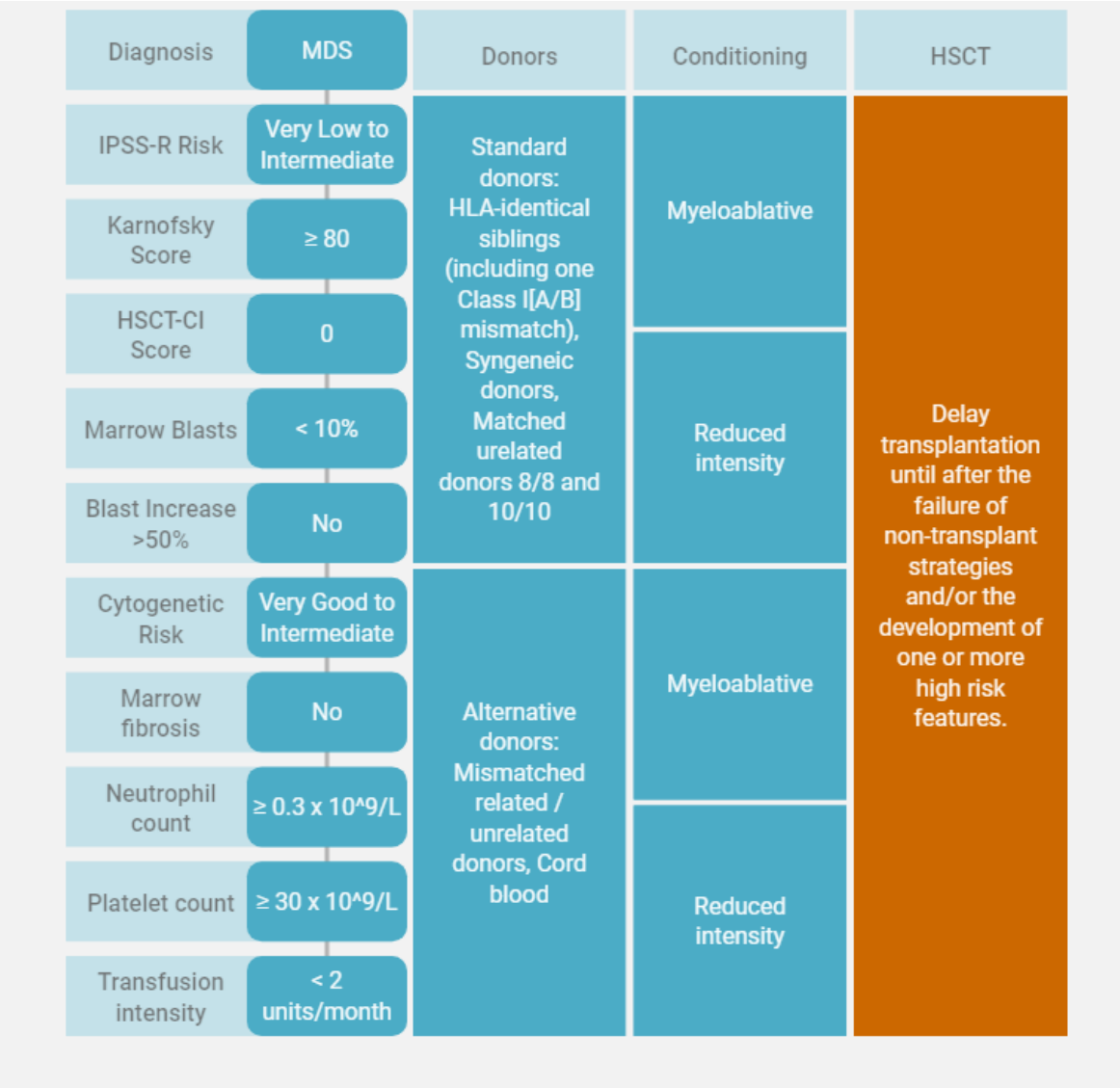
Selection of patients for HSCT, including all selection criteria and <10% marrow blasts



Standard donors: young donors are preferred in view of better results with younger donors, possibly related to reduced stem cell renewal at higher age and risk of clonal hematopoiesis at advanced age

Alternative donors, if no standard donors available: second option

Selection of patients for standard HSCT
Using all selection criteria in fit patient

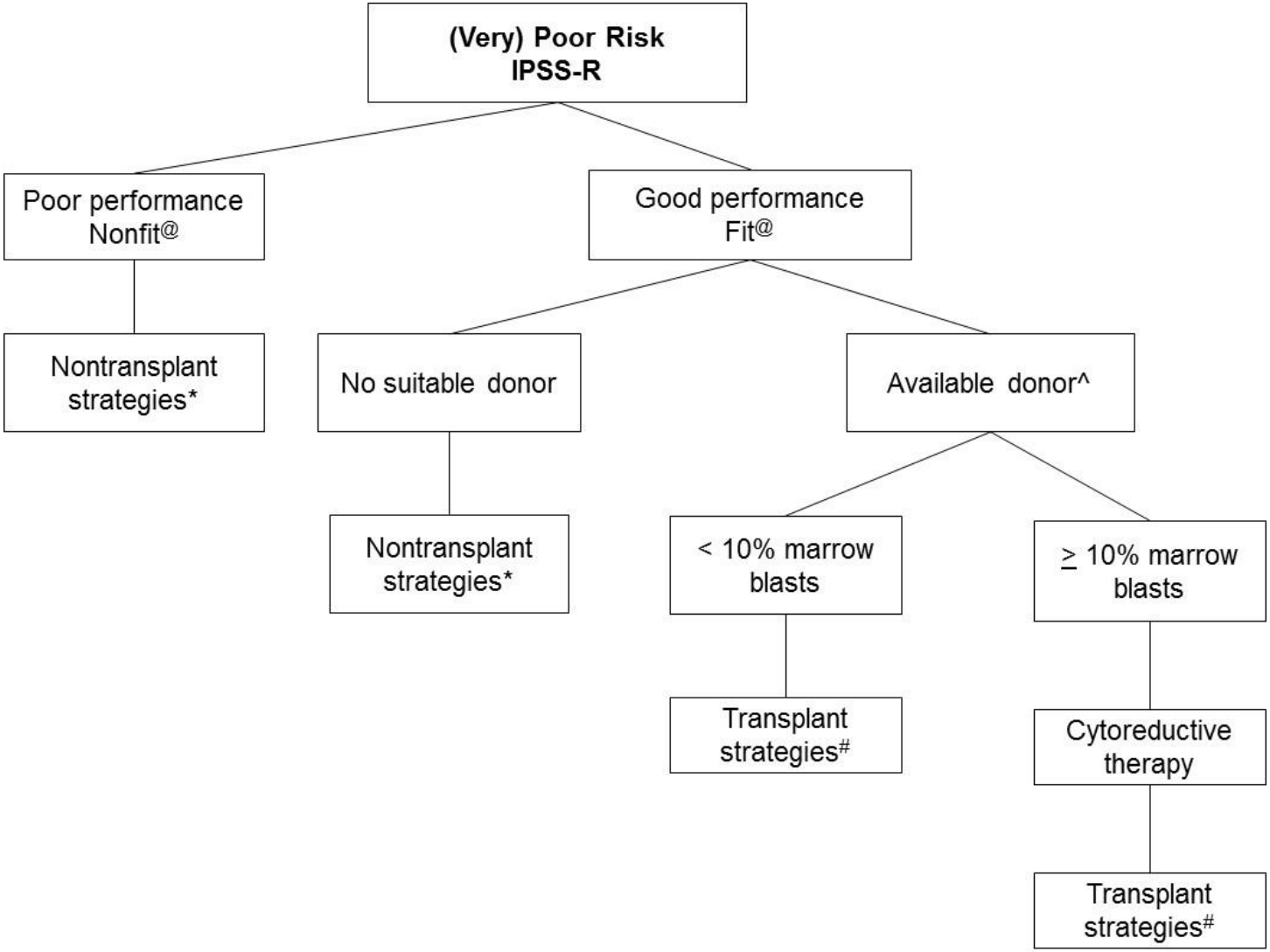


molecular testing should be seriously considered in all candidates for standard HSCT, but especially in case of absence of all nonmolecular poor risk factors

Standard : nontransplant strategies;

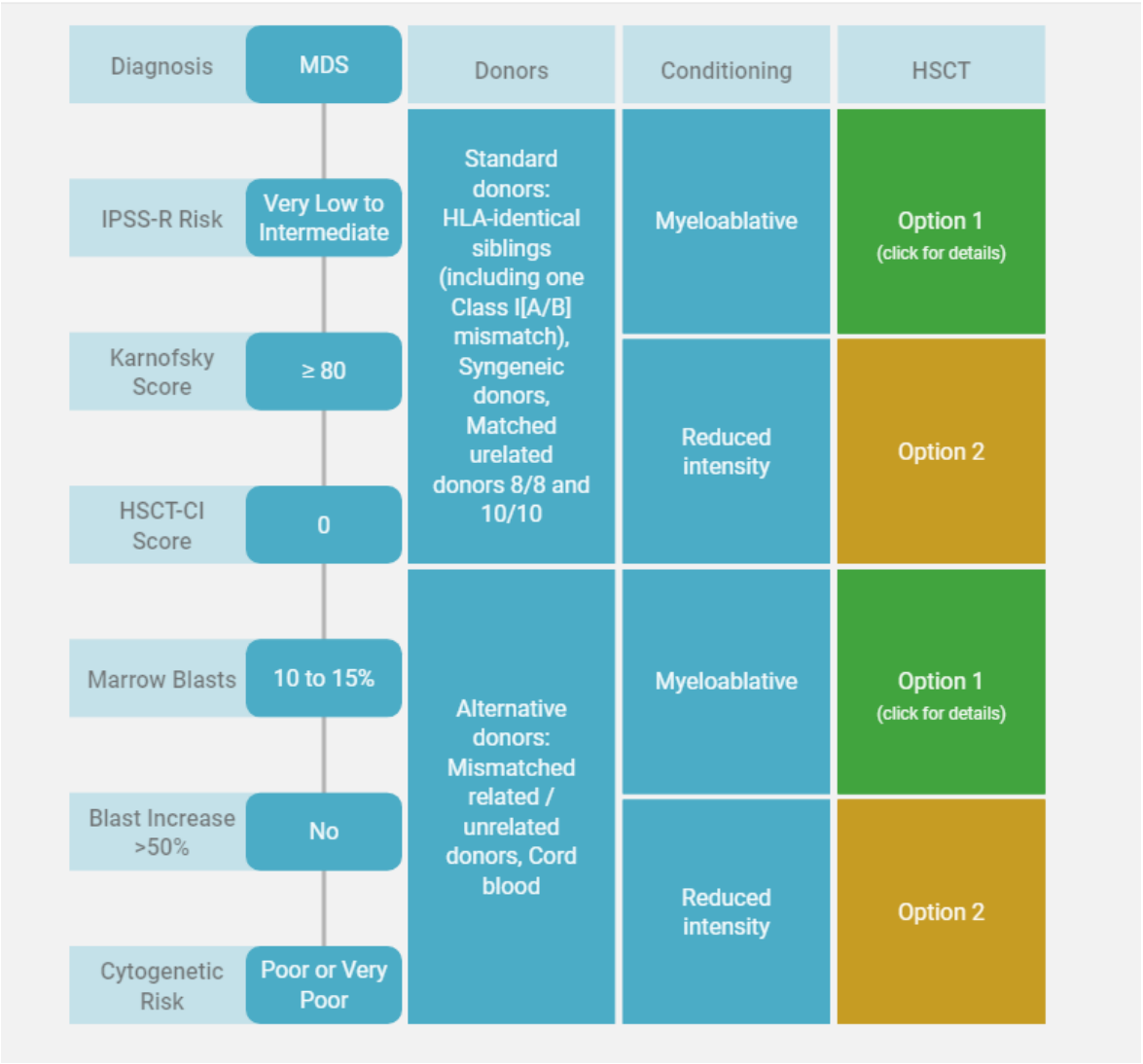
optionally: HSCT in investigational studies

Higher-risk MDS recommendations



De Witte T, et al. Blood 2017; 129: 1753-62

Selection of patients for HSCT
All selection criteria, including > 10-15% marrow blasts



Patients **may** receive cytoreductive therapy prior to the conditioning both for myeloablative and reduced intensity conditioning.

Two cytoreductive approaches possible: IC of HMA.

Selection of IC and HMA are based traditionally on age, co-morbidity. No prospective studies to support choice.

Cytoreductive therapy prior to conditioning

Intensive remission chemotherapy (IC)

- Remission induction regimens: including standard dose ara-c or higher dosage and anthracyclines
- Number of courses: 1 or 2

After remission-induction

- Consolidation therapy: no proof of value for additional consolidation courses
- HSCT recommended in:
    - CR1, CR2
    - Resistant to IC in investigational studies only

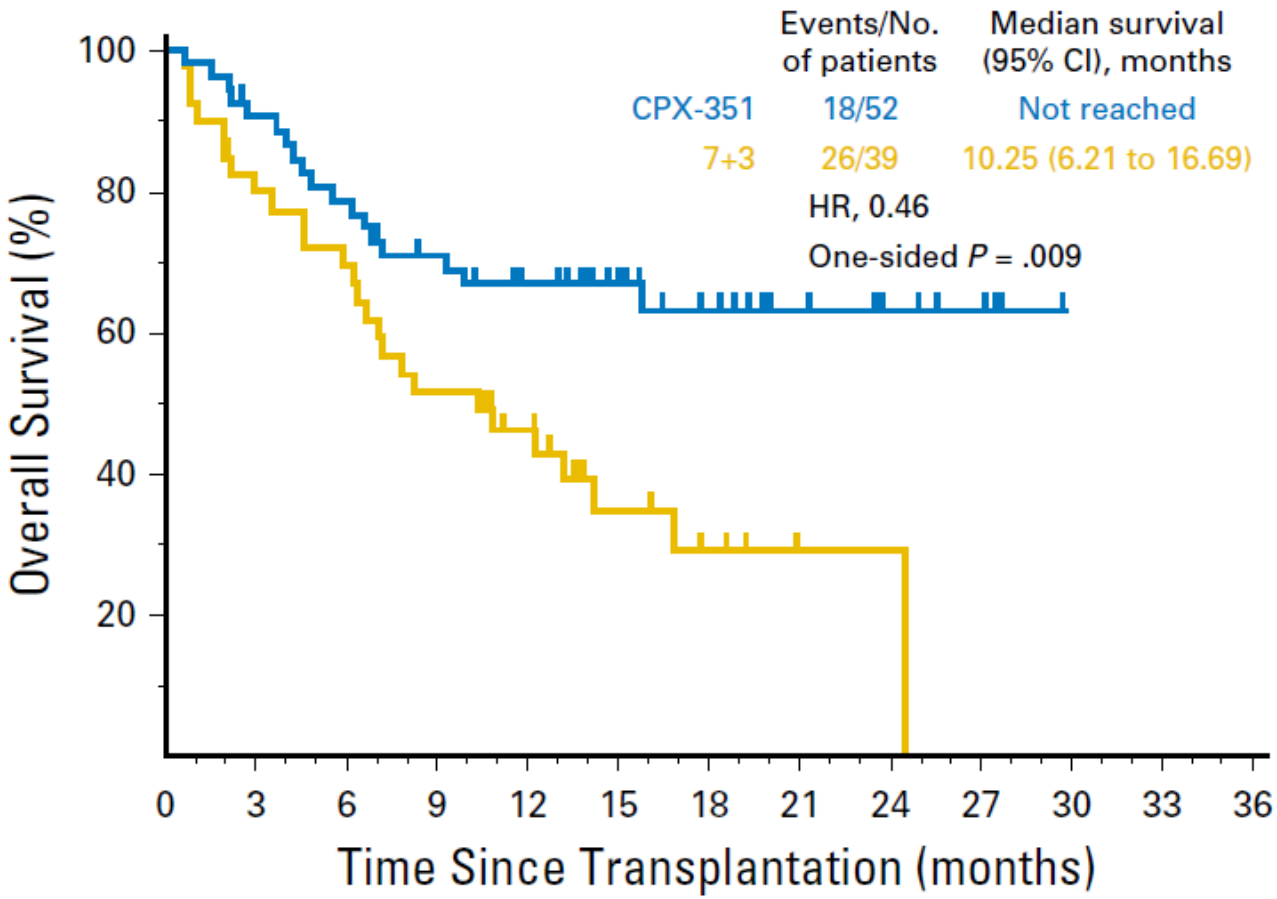
Hypomethylating agents (HMA)

- Number of courses: 4 to 6

After treatment

- HSCT recommended in:
    - CR1, PR or stable disease after 4 to 6 courses
    - Progressive disease or loss of response in investigational studies only

Prevention and treatment of relapse in a MDS patient with >15% marrow blasts by cytoreduction?



SCT not part of the protocol; survival measured from time of SCT. Interval between start treatment and SCT not provided

Lancet JE, et al. JCO 2018; 36: 284-92

Prevention and treatment of relapse in a MDS patient with >15% marrow blasts

MDS EUROPE

Post-transplant follow-up

Step 1

Monitoring of minimal residual disease (MRD) and/or mixed chimerism after transplantation

Step 2

In the event of increasing/persisting MRD or increasing autologous cells, prophylactic treatment with donor lymphocyte infusions (DLI) and/or HMA treatment (investigational)

Step 3

in the event of relapse, treatment with DLI or second HSCT (with cytoreduction in case of >15% marrow blasts) or other investigational approaches

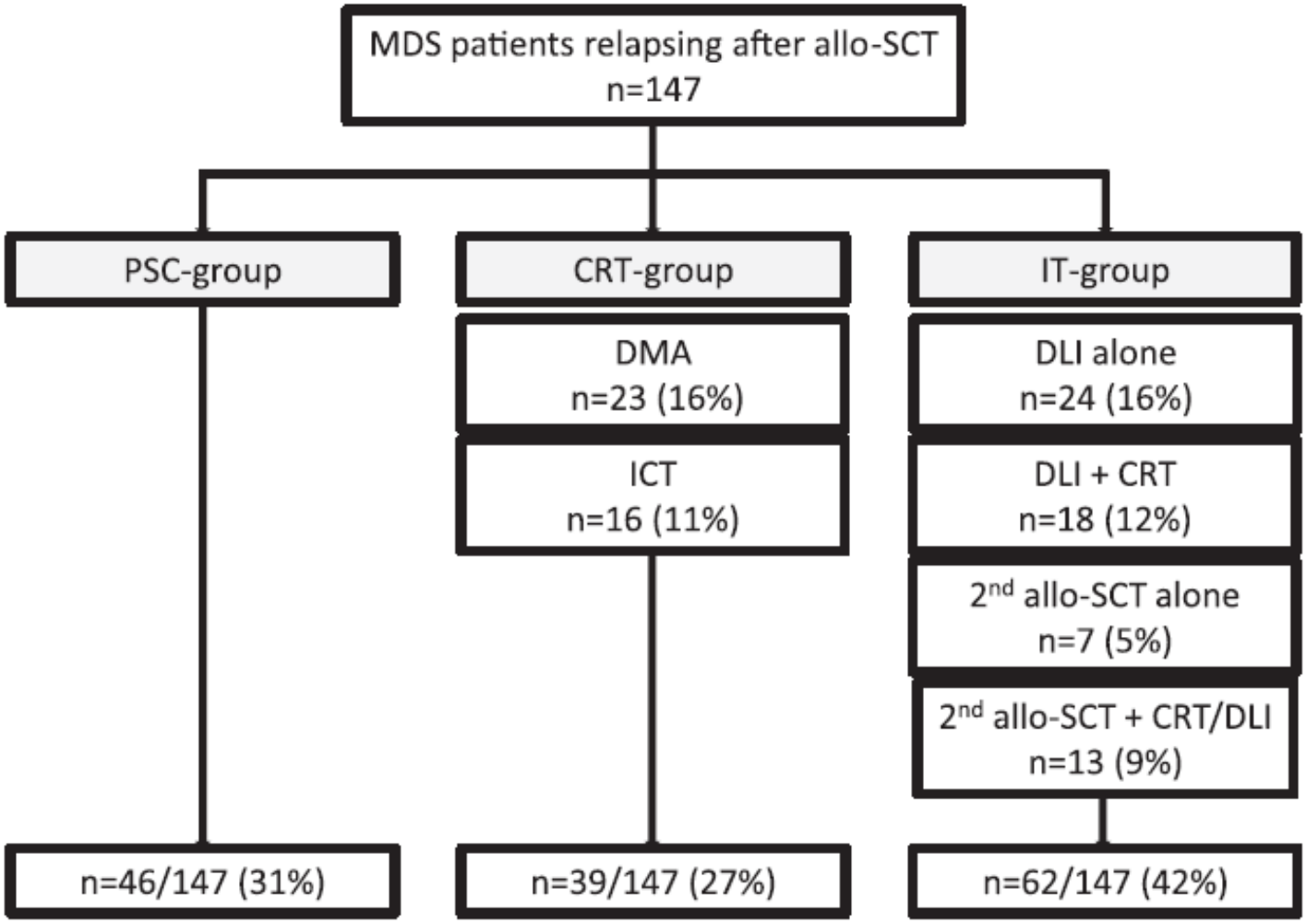
Prevention and/or treatment of iron toxicity

Treatment options for patients with relapse of MDS or MDS/MPN after HSCT

Treatment options are limited:

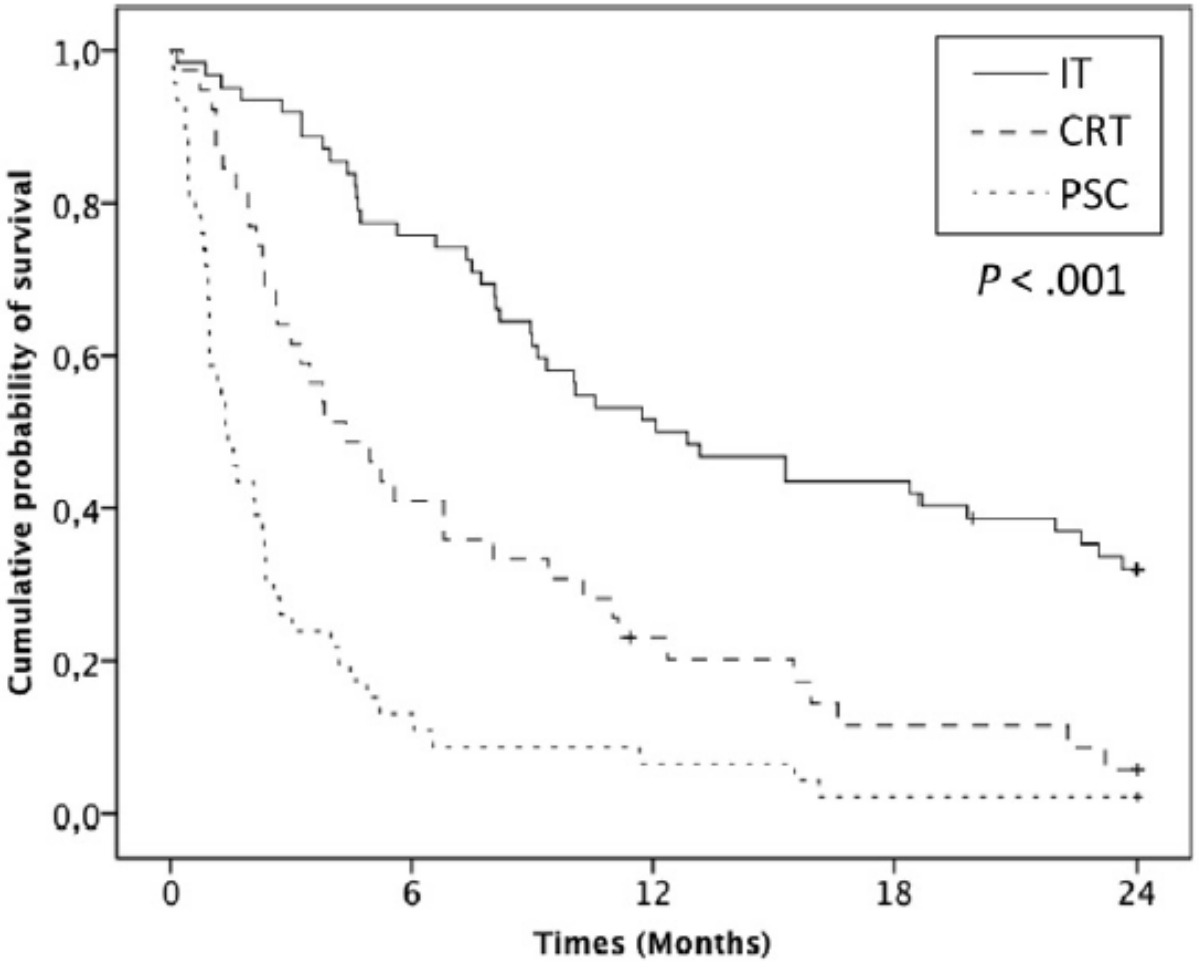
- palliative care, including supportive care
- treatment with HMA or ICT
- cellular immunotherapy after withdrawal of IS: DLI, second HSCT or a combination approach. DLI
- combination of DLI and azacitidine

Treatment options for patients with relapse of MDS or MDS/MPN after AHCT



Guieze R, et al: BBMT 2016; 22:240-7

Treatment options for patients with relapse of MDS or MDS/MPN after HSCT



Guieze R, et al: BBMT 2016; 22:240-7

Treatment options for patients with relapse of MDS or MDS/MPN after HSCT

Immunotherapy (second HSCT or DLI) for treatment of 147 patients with MDS relapse after HSCT was associated with superior survival when compared with cytoreductive therapy (23 HMA; 16 ICT) or supportive care only

Relapses within 6 months after HSCT and high tumor burden at relapse associated with poor survival

Recommendation: to offer salvage immunotherapy to patients with relapsing MDS after HSCT and a low risk profile (relapse >6 months after HCT and low tumor burden)

Guieze R, et al: BBMT 2016; 22:240-7

Conclusions

- Identification of risk factors predicting relapse after HSCT: important
- Measurement of MRD at HSCT and after HSCT: prognostic for relapse, but contribution of various methods may change
- Prevention of relapse before HSCT: early HSCT may be relevant, especially when BM blast counts <5%; cytoreduction usually applied when BM blasts are >10%, but value remains unproven
- Pre-emptive interventions are recommended in patients without complete donor chimerism or declining donor chimerism; pDLI most promising approach
- Outcome relapse after HSCT generally with short median survival of 5 months. Cellular therapies best results until now.

Prevention and treatment of transfusion-related toxicity after HSCT in MDS

No accepted method to monitor iron overload in the transplant setting.

In practice: ferritin levels are used despite some drawbacks, but LPI levels might be more relevant.

- Treatment of iron overload prior to HSCT

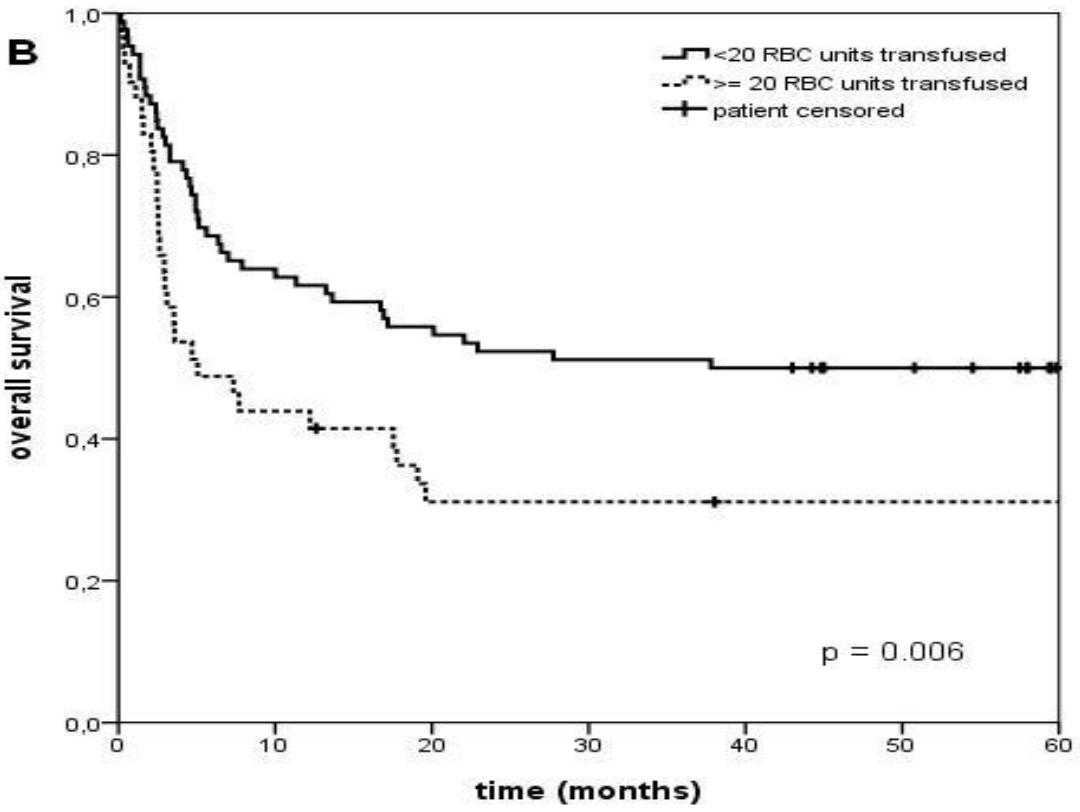
No prospective studies, but expert panel recommended appropriate iron chelation prior to HSCT in MDS patients with a RBC transfusion history of >20 units, who are candidates for HSCT

- Treatment of iron overload after HSCT

The expert panel recommended treatment of iron overload after HSCT in patients with a high transfusion burden, but the choice between phlebotomies and iron chelation remained open due to the lack of prospective studies. The treatment should start within 6 months after HSCT

De Witte T, et al. Blood 2017; 129: 1753-62

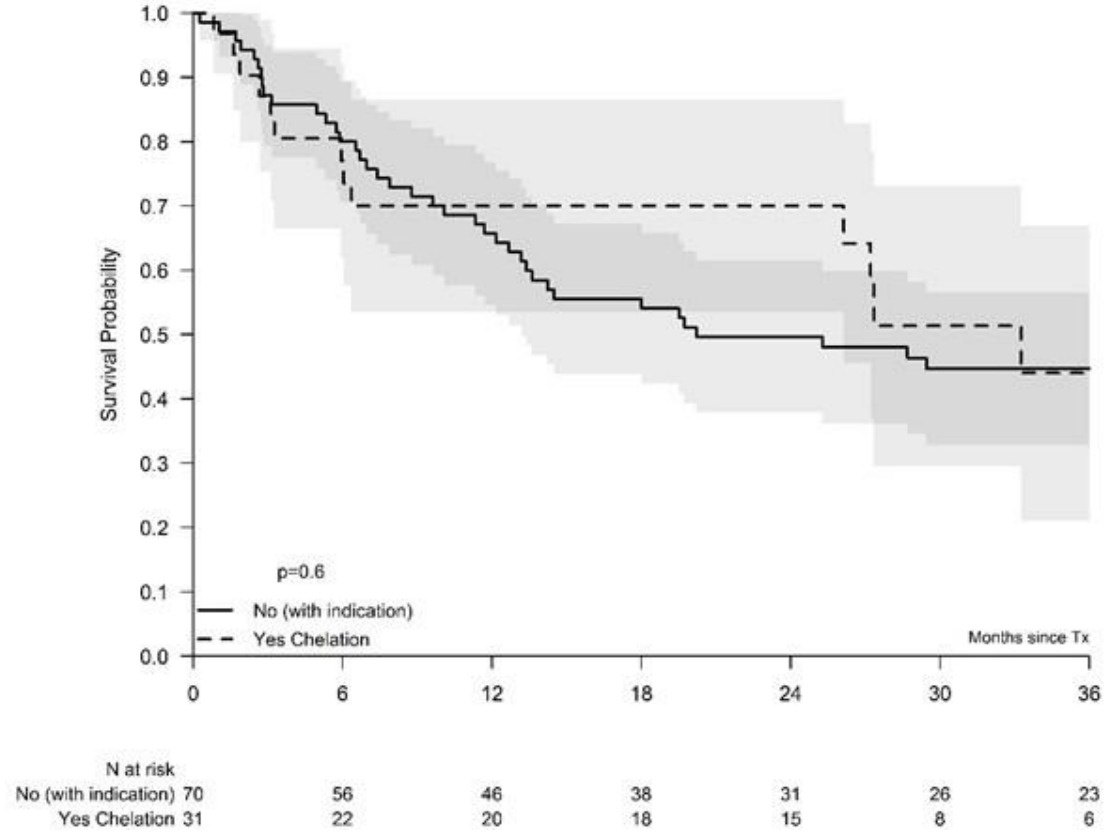
Overall survival and NRM of untreated adult MDS by RBC transfusions pre-transplant



HR for risk of NRM and RI increased in patients (n = 201) with a high transfusion-burden (HR of 1.89; P = 0.03 and HR 2.67; P = 0.03).
HR for ferritin level and comorbidity not significantly increased

Cremers E, et al: Ann Hematol 2016; 95:1971–8

Prospective observational EBMT study
Survival according to iron reduction therapy prior to HSCT

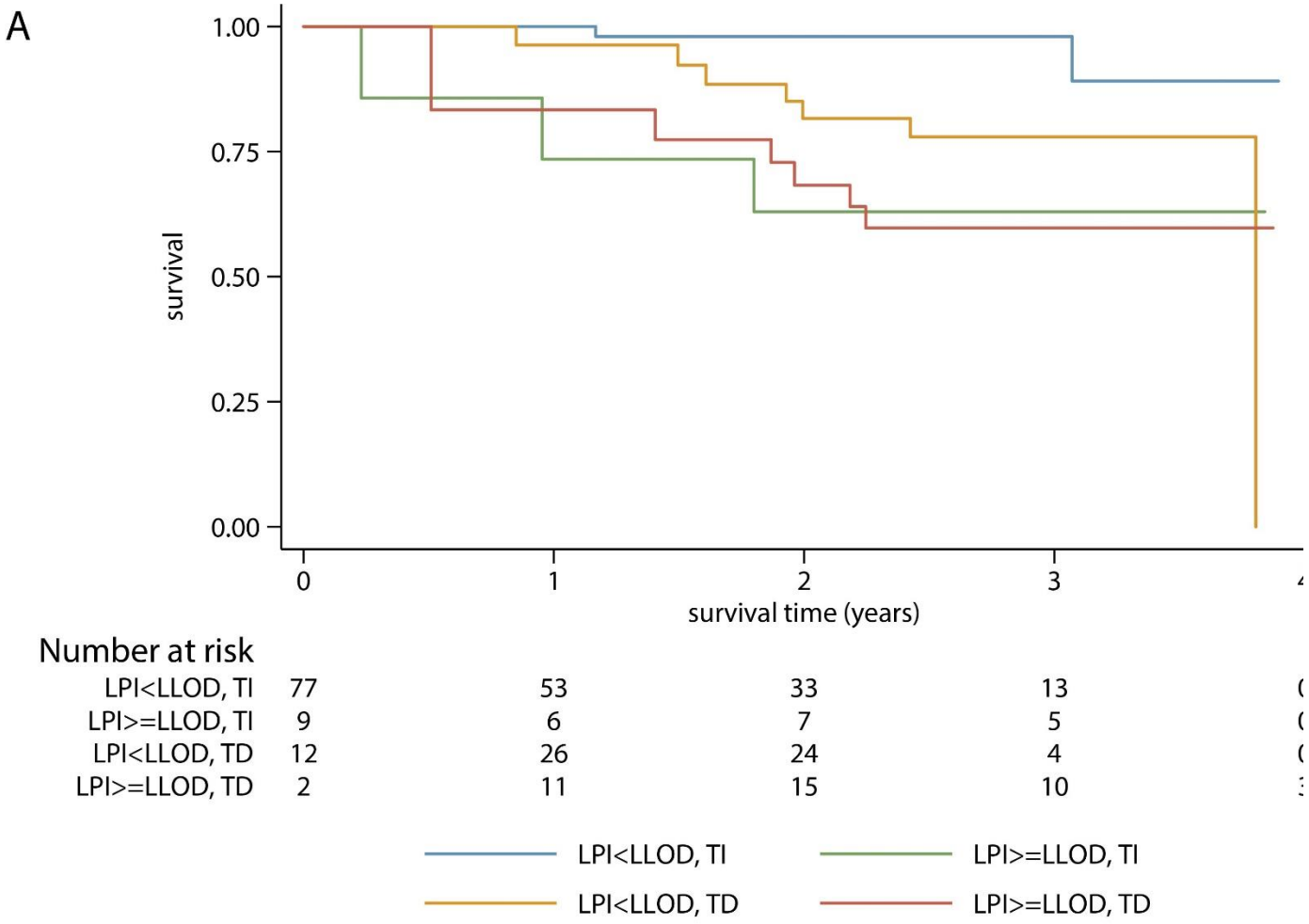


31 patients (14%) received iron chelation prior to HSCT with a median duration of 4 months

Median ferritin level at HSCT was 1598 ng/ml

Cremers E, et al: Ann Hematol 2016; 95:1971–8

LPI levels predict survival in patients with lower-risk MDS



Louise de Swart Haematologica 2018; 103:69-79

Impact baseline LPI after HSCT in AML & MDS ALLIVE study (112 patients)

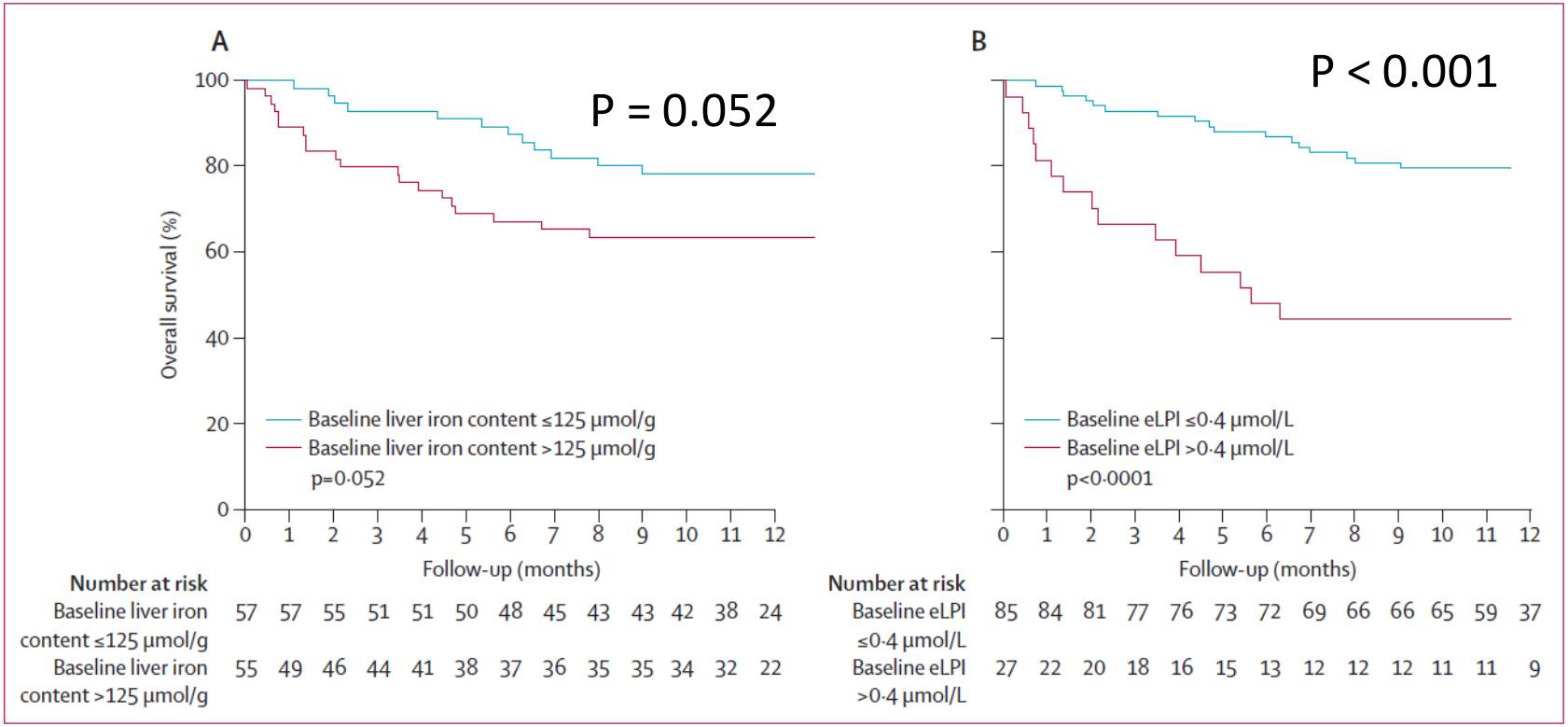
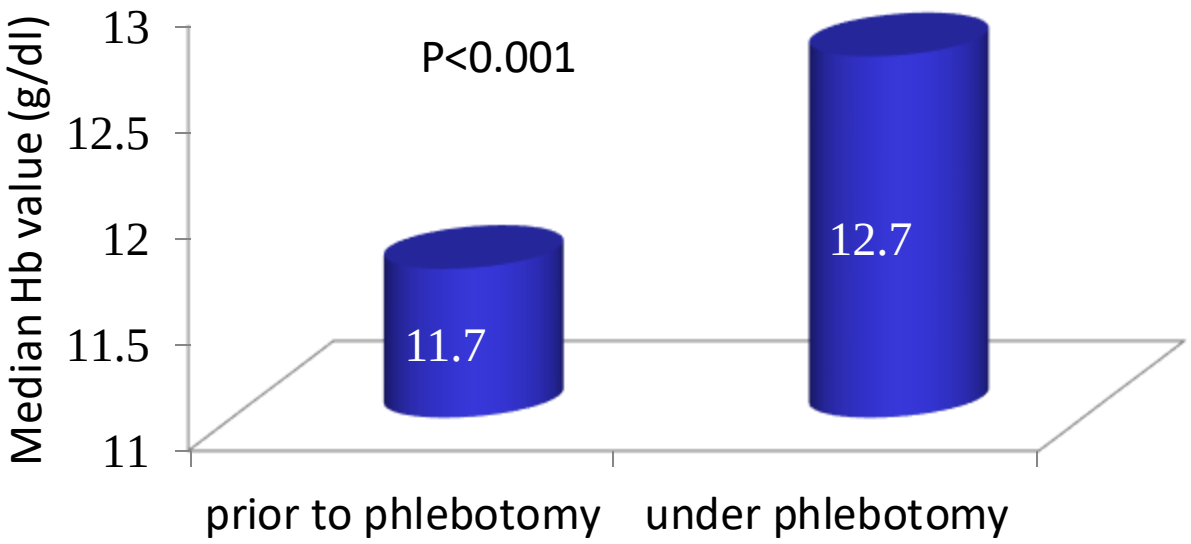


Figure 4: Exploratory post-hoc overall survival analysis
(A) Kaplan-Meier estimates for overall survival by liver iron content at baseline and (B) by eLPI concentration before the initiation of cytotoxic conditioning. p values were calculated with the log-rank test. eLPI=enhanced labile plasma iron.

Wermke M T, et al. Lancet Haemat 2018; 5: e201-10

Phlebotomy in patients with iron overload after allo-HSCT improves hemoglobin levels

Hemoglobin levels prior to and under phlebotomy



- **Phlebotomy is a convenient therapy of iron overload in survivors of HCT.**
- **A negative iron balance and a rise in hemoglobin were observed in the majority of patients.**

Phlebotomy was initiated in 61 recipients of allografts due to hematologic malignancies (median age 48 years) after a median of 18 months.

Acute leukemia & MDS 61%, Chronic leukemia 24%, Others 15%

Eisfeld et al. Am J Blood Res. 2012; 2: 243–253.

A prospective non-interventional study on the impact of transfusion burden and related iron toxicity on outcome of HSCT in MDS

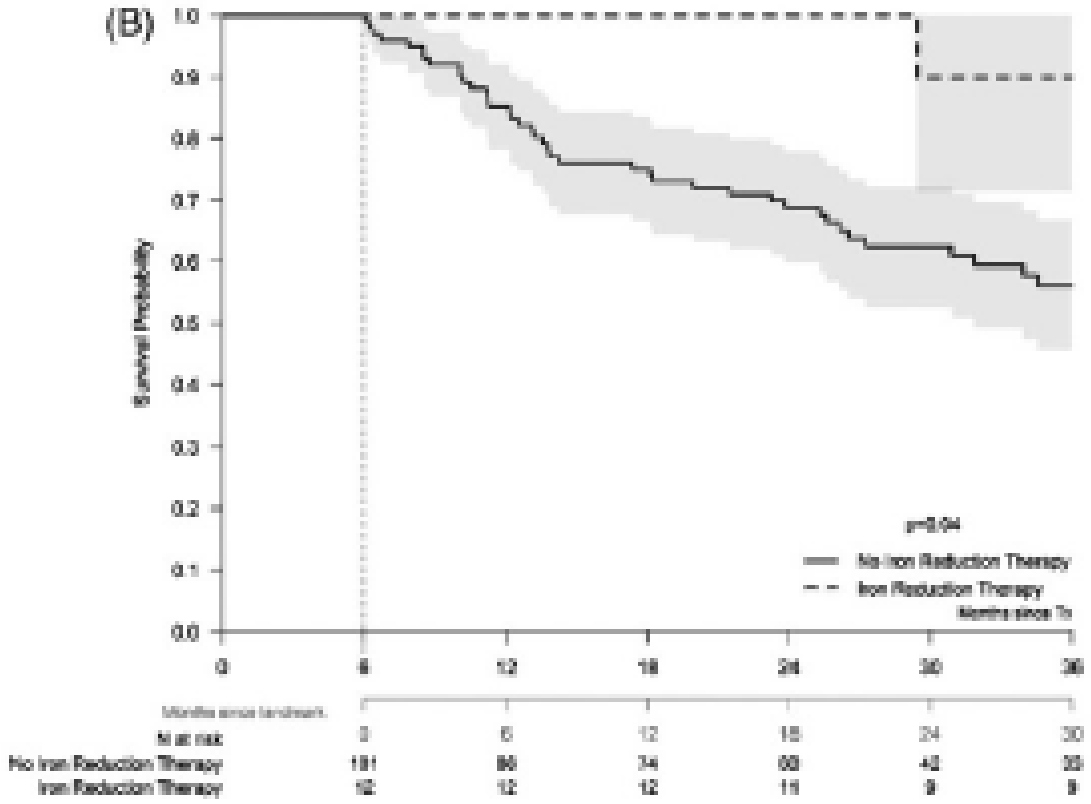
Start iron reduction treatment after HSCT	Iron reduction after HSCT	Landmark after HSCT (months)					
		0-6		0-12		12-2	
Nr of patients	No	101		77		51	
	Yes	12		27		21	
OS#	No	65% (54-75%)	0.08	75% (65-86%)	0.3	85% (79-98%	
	Yes	90% (71-100%)		81% (61-100%)		88% (73-100	
RFS#	No	56 (46-67%)	0.04	67% (55-79%)	0.3	81% (69-93%	
	Yes	90% (71-100%)		57% (58-98%)		88% (74-100	

* Control group: patients with ferritin levels above 1000 ng/ml at start comparison

Relapse-free survival of patients alive and relapse-free at 6 months after transplantation, stratified in 2 groups according to iron reduction therapy given during the first 6 months after transplantation or not.

Cremers, et Leukemia & Lymphoma 2019; 60:10, 2404-2414

A prospective non-interventional study on the impact of transfusion burden and related iron toxicity on outcome of HSCT in MDS



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Cremers, et Leukemia & Lymphoma 2019; 60:10, 2404-2414

Conclusions

- Selection of MDS patients for standard and investigational allogeneic stem cell transplantation requires intensive evaluation of patient- and disease-related factors
- Age is not the major determining selection criterium, if fitness/vitality and co-morbidities are evaluated carefully
- New effective nontransplant treatment modalities may lead to delay or reduction of allogeneic HSCT in MDS
- Molecular features are expected to increase the accuracy of selection of patients for allogeneic HSCT and may lead to better outcome after allogeneic HSCT

Conclusions

- The interactive website on recommendations for selecting and timing of allogeneic HSCT is expected to improve the implementation of high quality allogeneic HSCT in MDS

- Visit: https://mds-europe.eu

Acknowledgements:

- experts of the MDS HSCT Recommendations team
- Website team of EUMDS in York, UK: Dan Painter, Alex Smith, John Blaise