EBMT

Chronic Malignancies Working Party

FACULTE DE MEDECINE
Université de Lille
HENRI WAREMBOURG

Université de Lille

CHU LILLE

Risk adapted transplant:

Remission-induced transplant

Ibrahim Yakoub-Agha, MD, PHD

MYELODYSPLASTIC SYNDROMES: CHAOS AND ORDER

October 26, 2018

IRST, Meldola

EBMT

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No conflict of interest

Myelodysplastic Syndrome is a heterogeneous group of …….

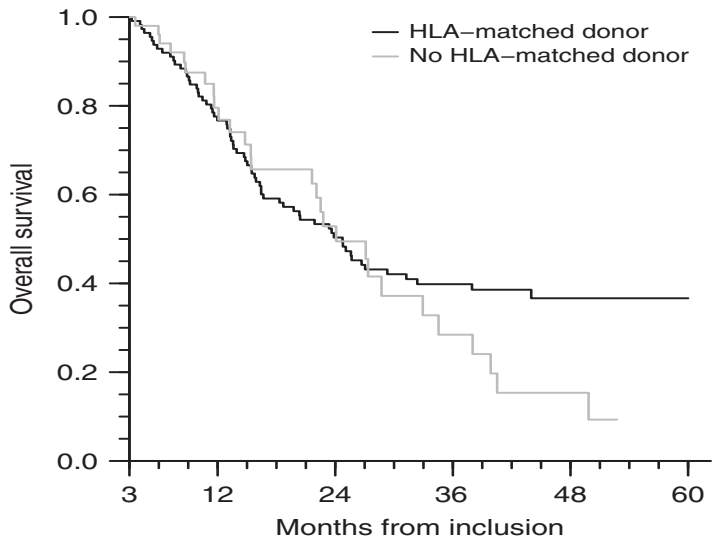
Allogeneic stem cell transplantation is the only curative treatment for patients with MDS…..*

* Every single article dealing with allo-HCT in MDS patients.

ORIGINAL ARTICLE

HLA-matched allogeneic stem cell transplantation improves outcome of higher risk myelodysplastic syndrome A prospective study on behalf of SFGM-TC and GFM

M Robin[1,2,3], R Porcher[4,5], L Adès[6], E Raffoux[7], M Michallet[8], S François[9], J-Y Cahn[10], A Delmer[11], E Wattel[8], S Vigouroux[12], J-O Bay[13], J Cornillon[14], A Huynh[15], S Nguyen[16], M-T Rubio[17], L Vincent[18], N Maillard[19], A Charbonnier[20], RP de Latour[1,2,3], O Reman[21], H Dombret[2,6], P Fenaux[2,6] and G Socié[1,2,3]



Robin et al, Leukemia 2015

Nevertheless,

* Every single article dealing with allo-HCT in MDS patients.

Nevertheless, this approach is still associated with potentially life-threatening complications such as conditioning-regimen toxicity, graft-versus-host disease (GVHD) and relapse*

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Nevertheless, this approach is still associated with potentially life-threatening complications such as conditioning-regimen toxicity, graft-versus-host disease (GVHD) and

post-transplant relapse*

* Every single article dealing with allo-HCT in MDS patients.

Management of myelodysplastic syndromes (MDS)

- Therapeutic approaches include:

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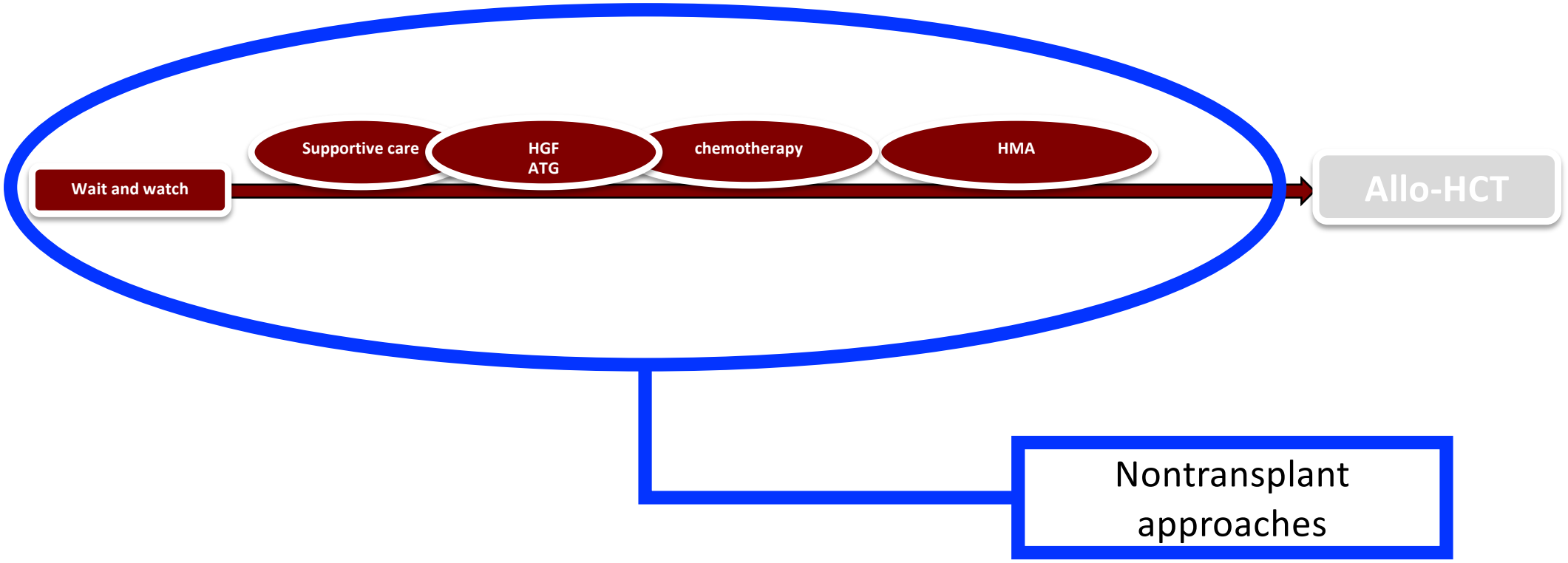
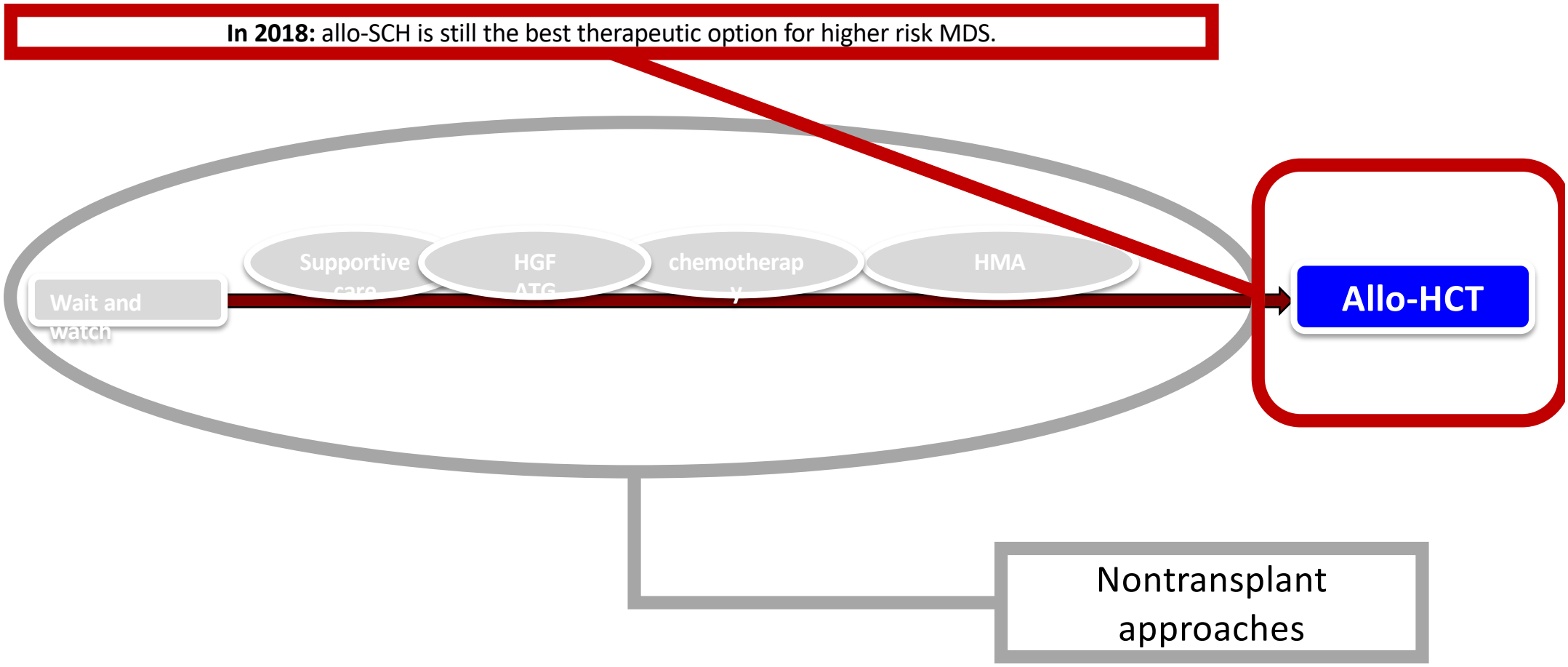


Management of myelodysplastic syndromes (MDS)

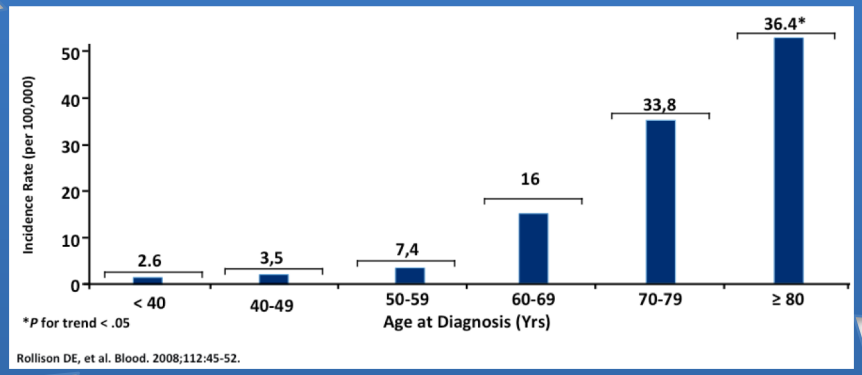


Management of myelodysplastic syndromes (MDS)

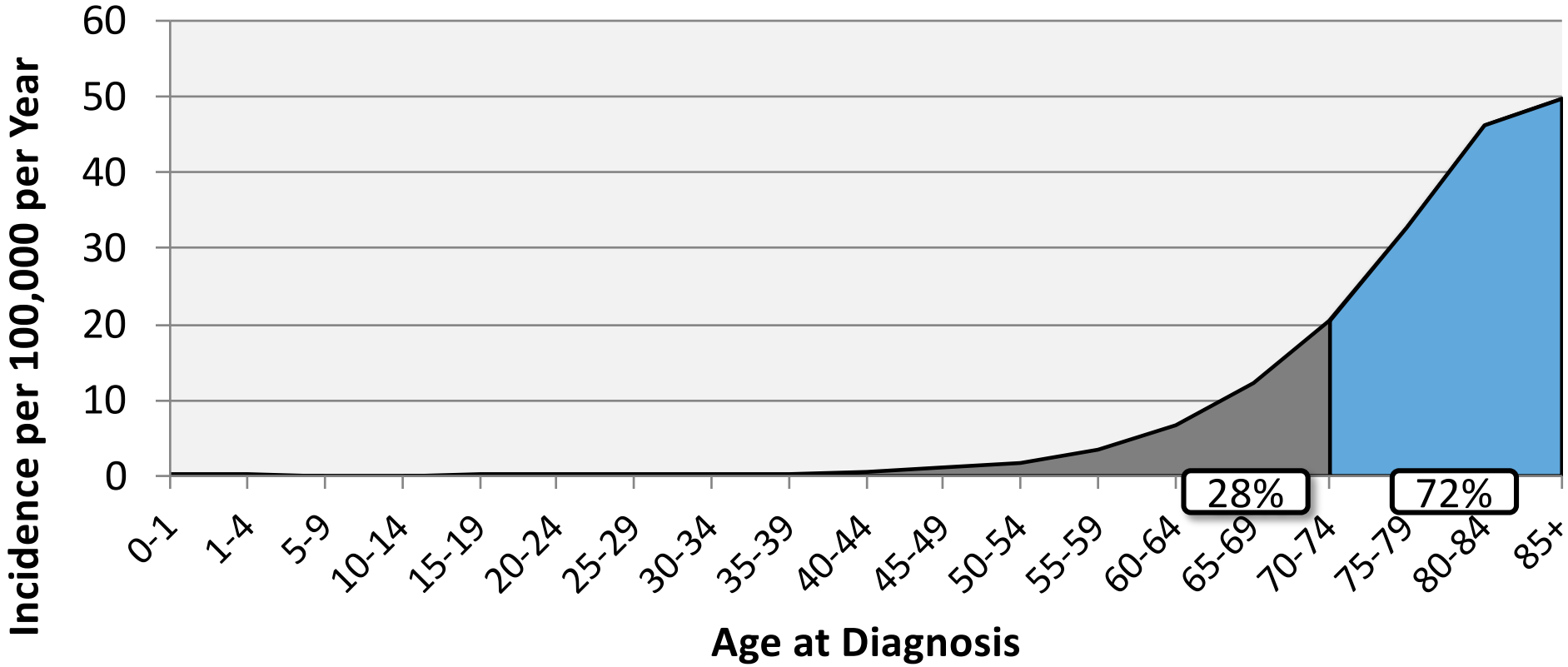
Epidemiology

Confirmed diagnosis of MDS

C d diagnosis of MDS



Age-Specific (Crude) SEER Incidence Rates of MDS (M &F) 2000-2009



Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2009), National Cancer Institute, DCCPS,

Transplant-related Mortality: *impact of the age?*

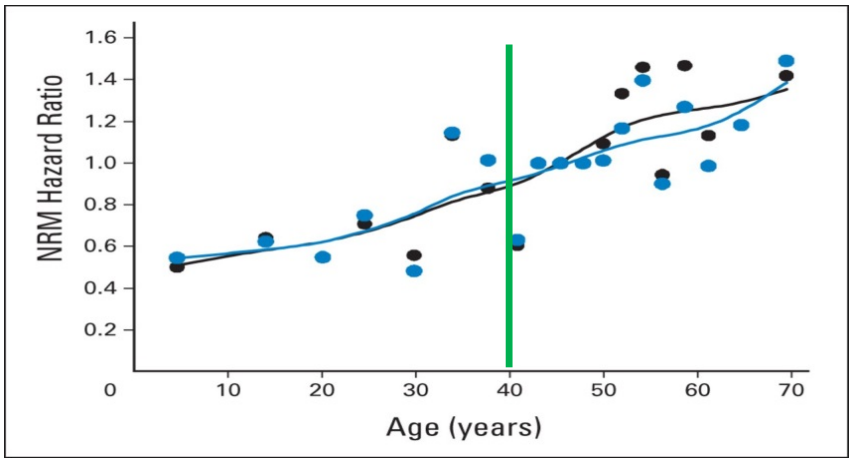


Table 3. Cumulative Incidence and HR for Nonrelapse Mortality Stratified by Regimen Intensity and Age

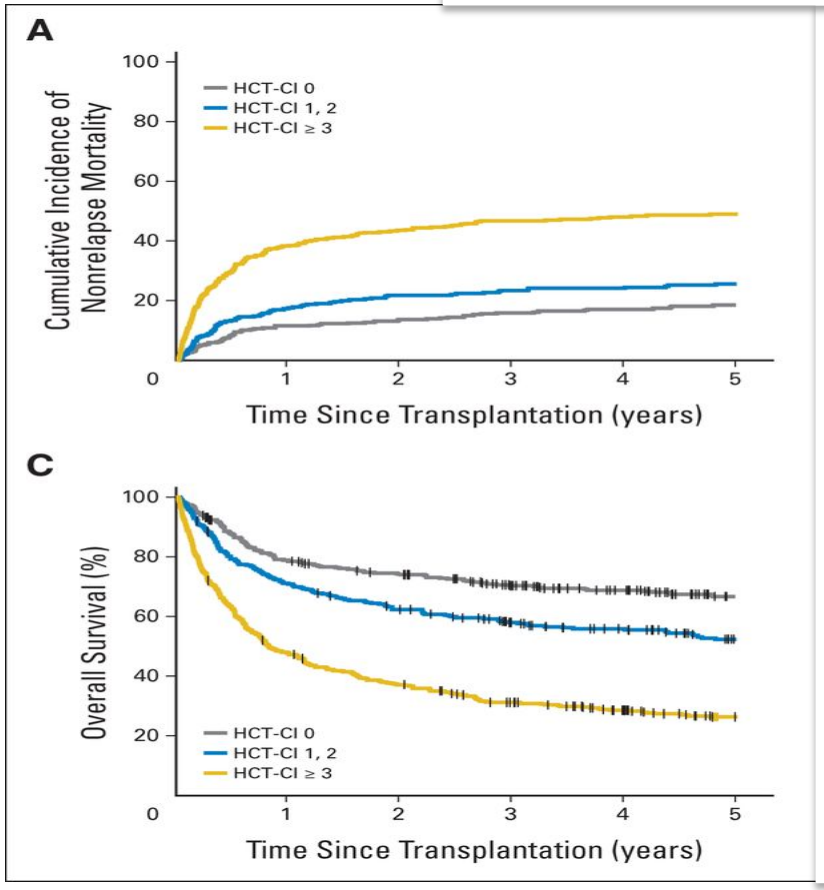
Age Group by Regimen Intensity (years)	Cumulative 2-Year Incidence (%)	Univariable			Multivariable*		
		HR	95% CI	*P*	HR	95% CI	*P*
Myeloablative							
0-39	21	1.0			1.0		
≥ 40	32	1.58	1.3 to 1.9	< .001	1.35	1.1 to 1.6	.004
Reduced intensity							
0-39	24	1.0			1.0		
≥ 40	34	2.02	1.3 to 3.0	< .001	1.52	1.0 to 2.4	.07
Nonmyeloablative							
0-39	16	1.0			1.0		
≥ 40	23	1.68	1.0 to 2.8	.04	2.01	1.1 to 3.6	.02

Abbreviations: ATG, antithymocyte globulin; CMV, cytomegalovirus; HCT-CI, hematopoietic cell transplantation–comorbidity index; HR, hazard ratio; KPS, Karnofsky performance status.

*Cox regression models were adjusted for diagnosis category, disease risk, HCT-CI risk group, donor type, stem-cell source, KPS percentage, No. of prior regimens, use of ATG, and CMV serology status.

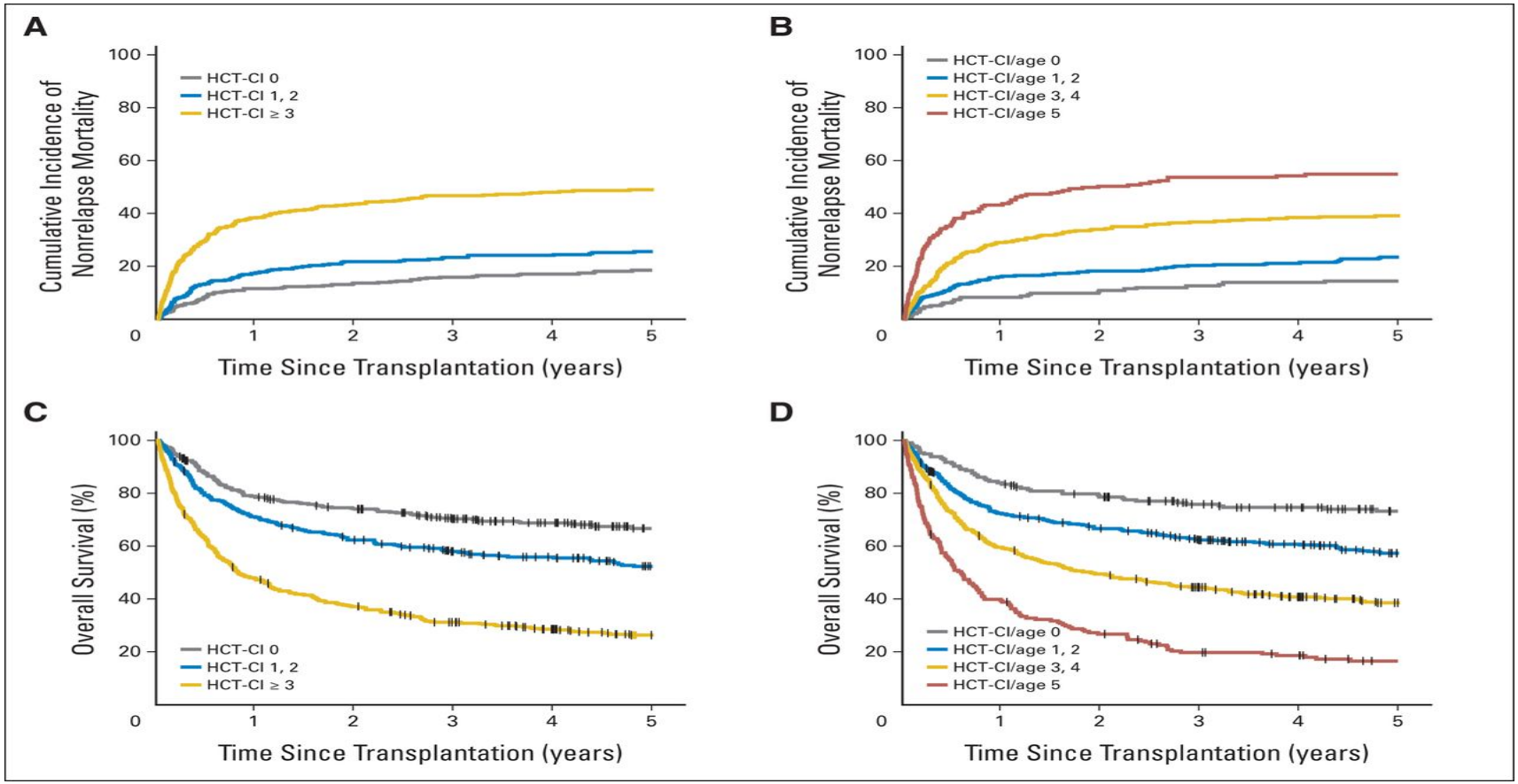
Sorror et al, JCO 2014

Comparisons of outcome stratifications by the hematopoietic cell transplantation–comorbidity index (HCT-CI) and the



Mohamed L. Sorror et al. JCO 2014;32:3249-3256

Comparisons of outcome stratifications by the hematopoietic cell transplantation–comorbidity index (HCT-CI) and the composite comorbidity/age index (HCT-CI/age).



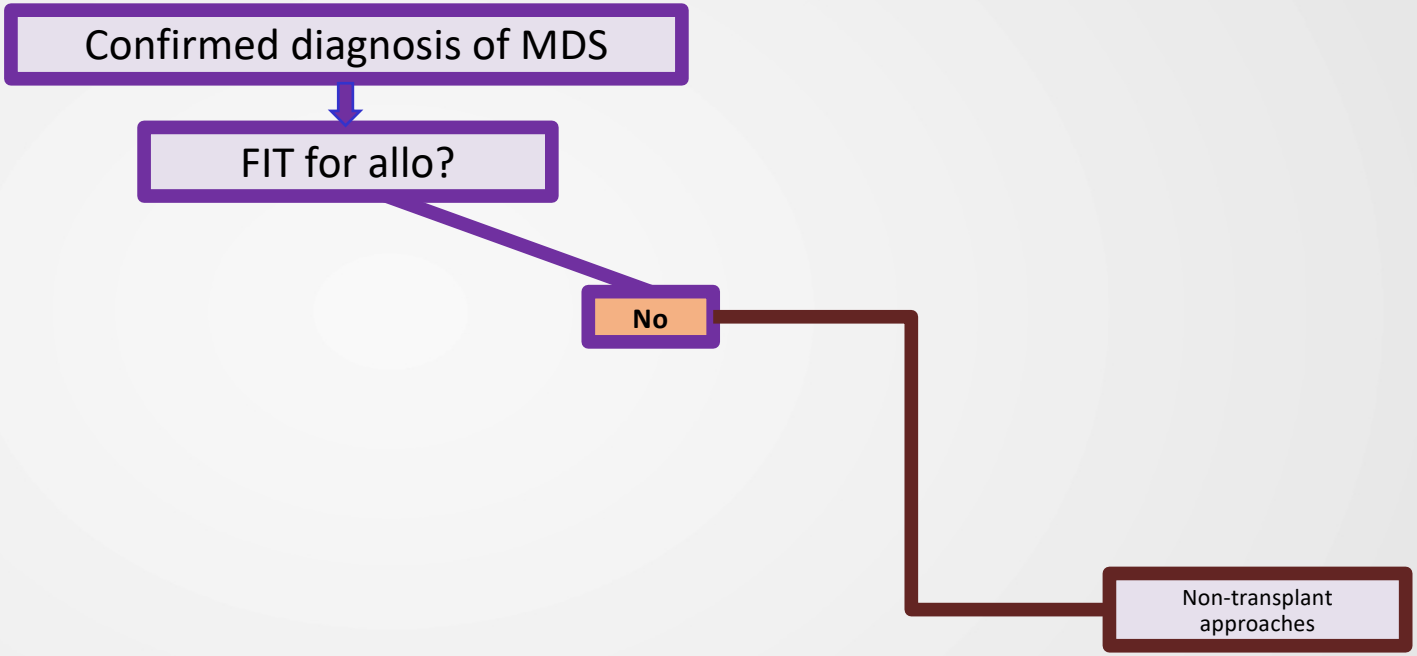
Mohamed L. Sorror et al. JCO 2014;32:3249-3256

« Fit patient »

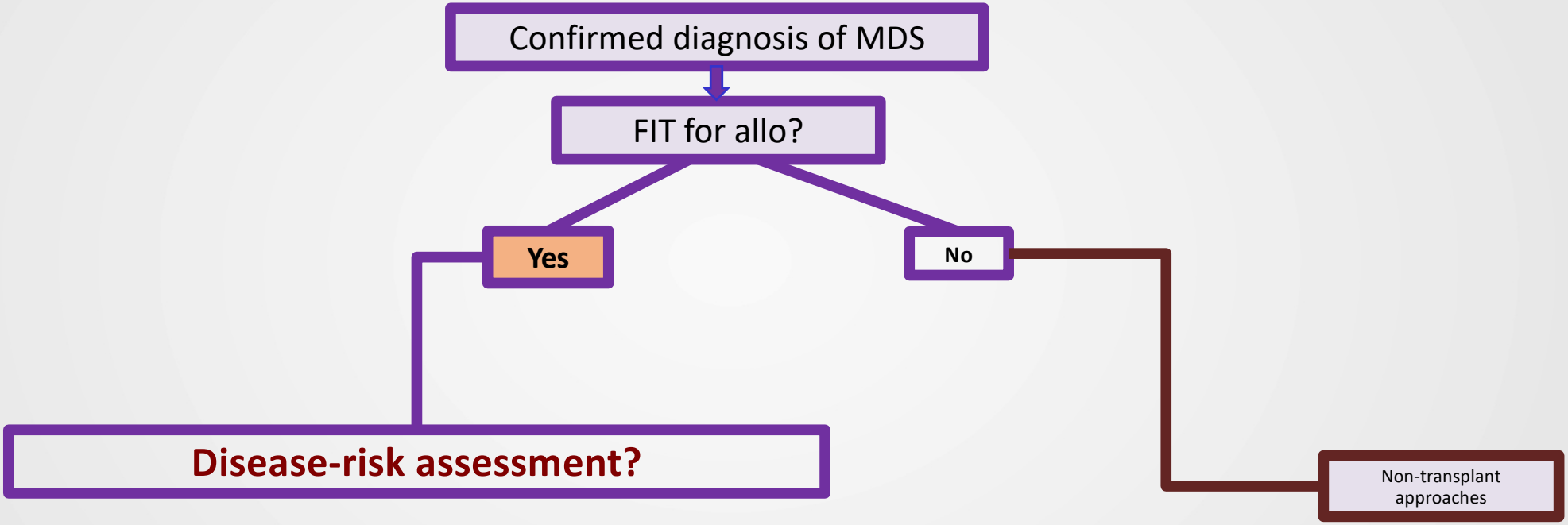
- Patient aged < 70 years (reasonable) *
- Age-adjusted/CI < 5 **

* Dewitt et al, Blood 2017

**Sorror et al, JCO 2014



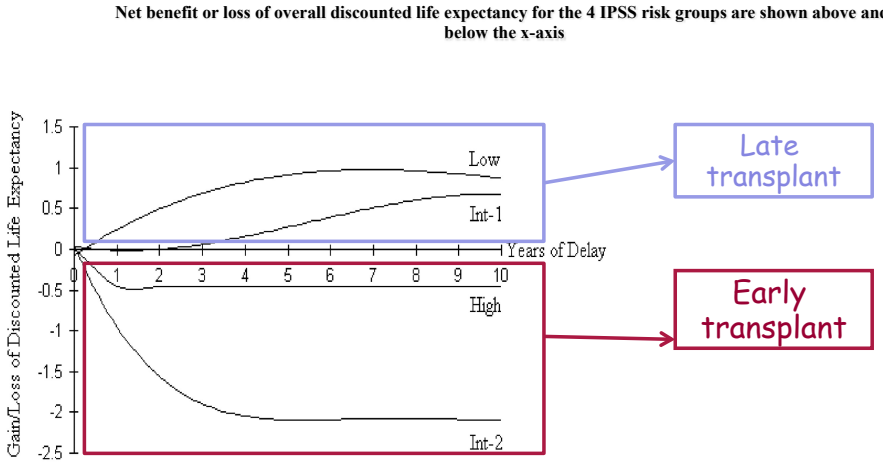
Adapted from Dewitt et all, blood 2017


Confirmed diagnosis of MDS
FIT for allo?
Yes
No
Disease-risk assessment?
Non-transplant approaches

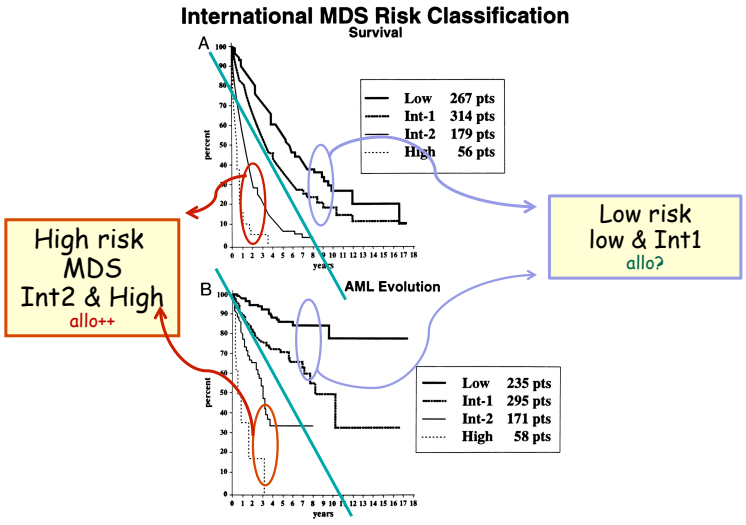
What scoring system to use?

- The ELN* and the National Comprehensive Cancer Network (NCCN)** formulated the general recommendation for allo-HCT at diagnosis based on IPSS.

* Malcovati, *et al* 2013, ** Greenberg, *et al* 2013



Cutler, C. S. et al. Blood 2004;104:579-585



Greenberg, P. et al. Blood 1997;89:2079-2088

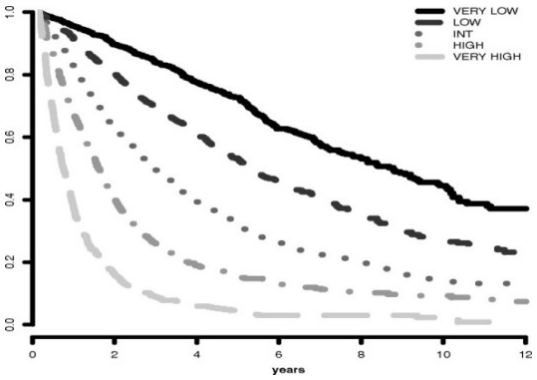
What scoring system to use?

- The ELN* and the National Comprehensive Cancer Network (NCCN)** formulated the general recommendation for allo-CST at diagnosis based on IPSS.

- More recentely, an international expert panel from of the EBMT, ELN, BBT Clinical Trial Group and the International MDS Foundation, adjusted this general recommendation to the IPSS-R risk score.***

* Malcovati, *et al* 2013,
** Greenberg, *et al* 2013
*** Dewitt et al, Blood 2017

Survival based on IPSS-R prognostic risk-based categories.



IPSS-R Risk category (% IPSS-R pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
VERY LOW (19)	≤1.5	8.8	Not reached
LOW (38)	>1.5-≤3.0	5.3	10.8
INT (20)	>3.0-≤4.5	3	3.2
HIGH (13)	>4.5-≤6.0	1.6	1.4
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Peter L. Greenberg et al. Blood 2012;120:2454-2465

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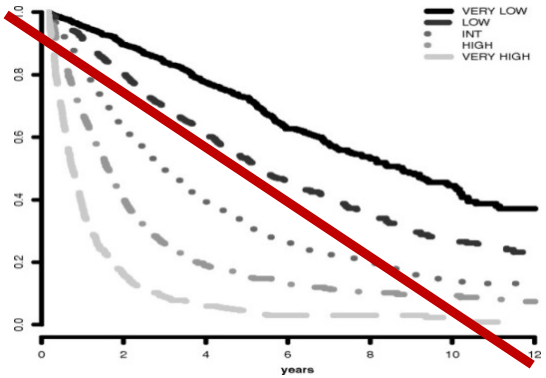

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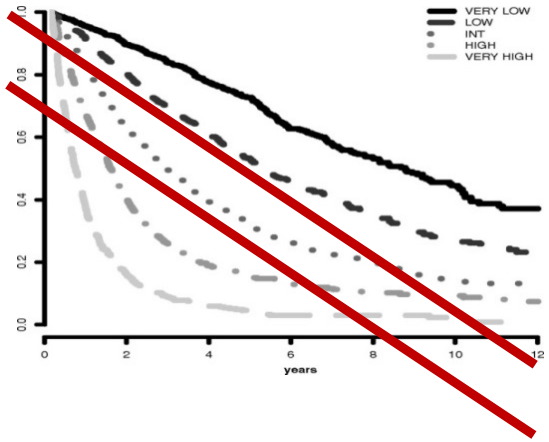

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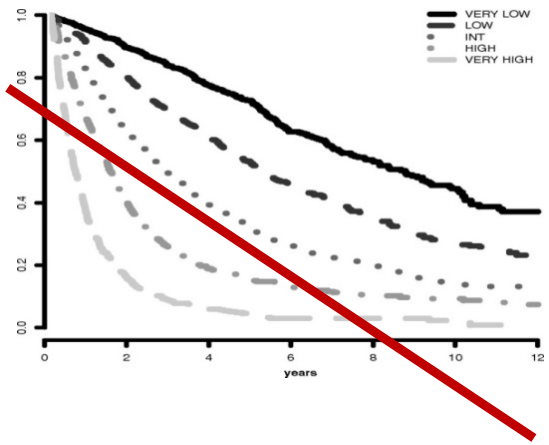

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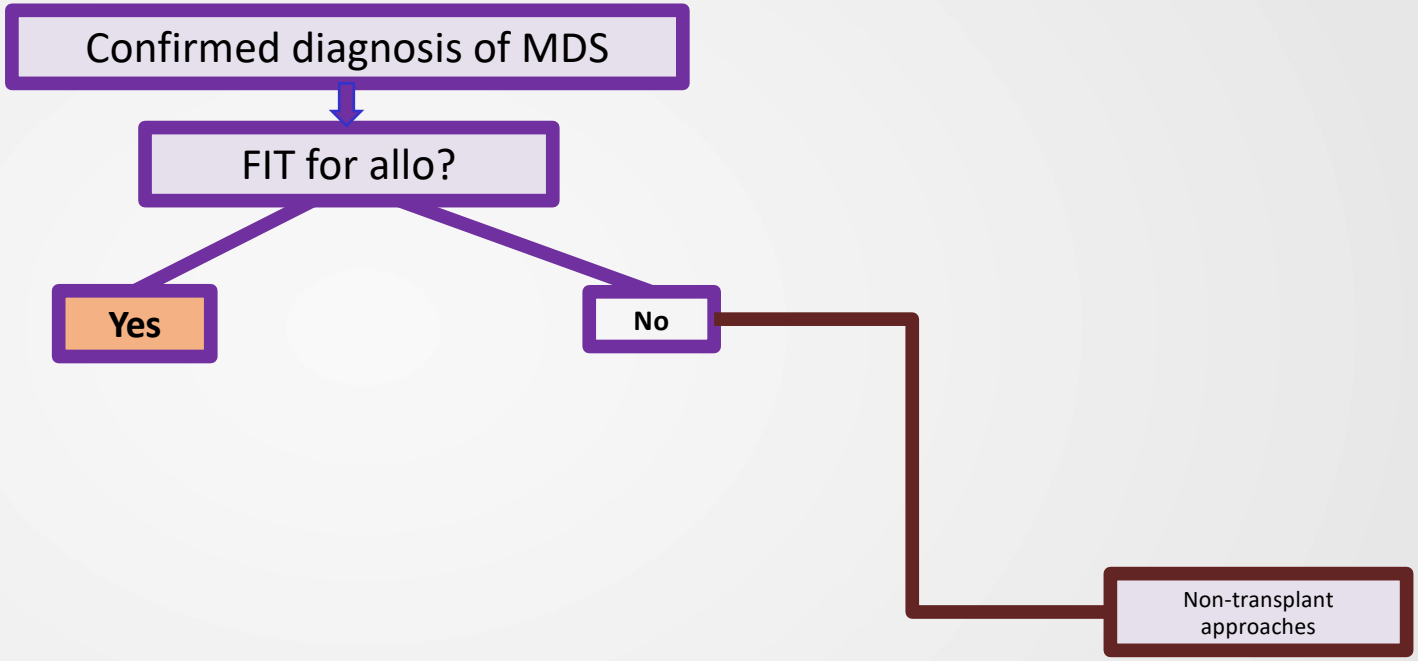
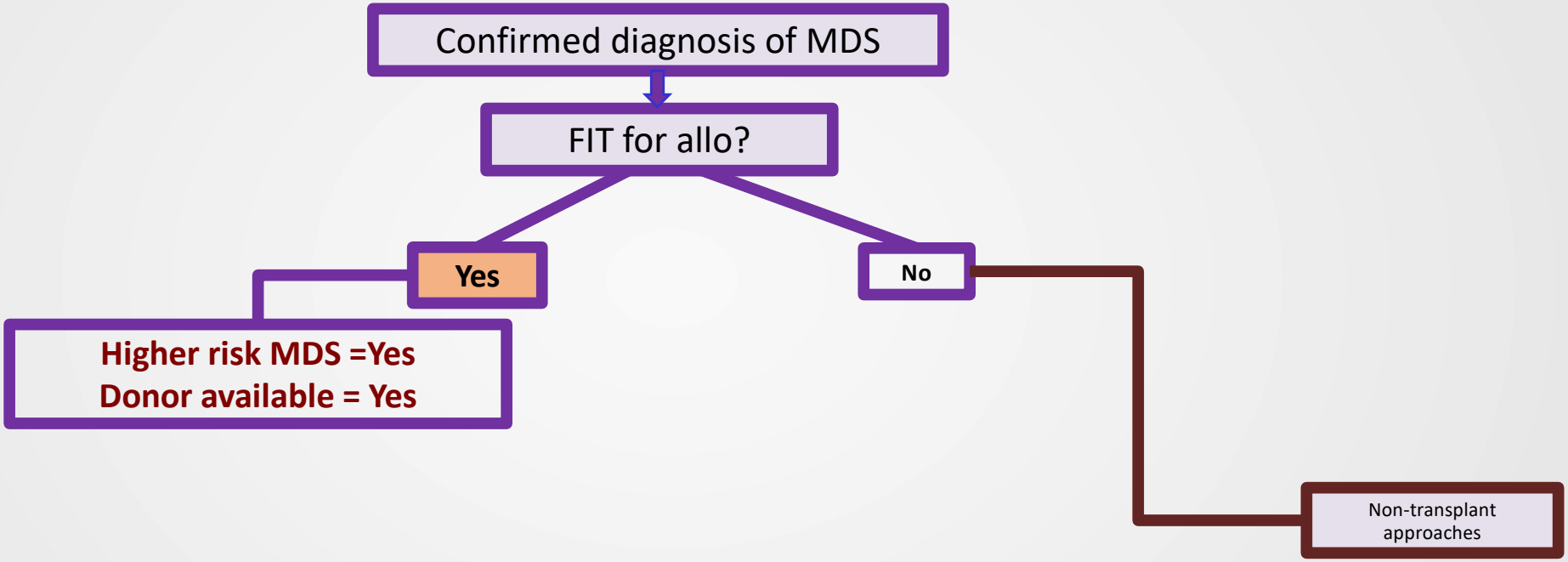
blood


Confirmed diagnosis of MDS
FIT for allo?
Yes
No
Non-transplant approaches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Donor available = Yes
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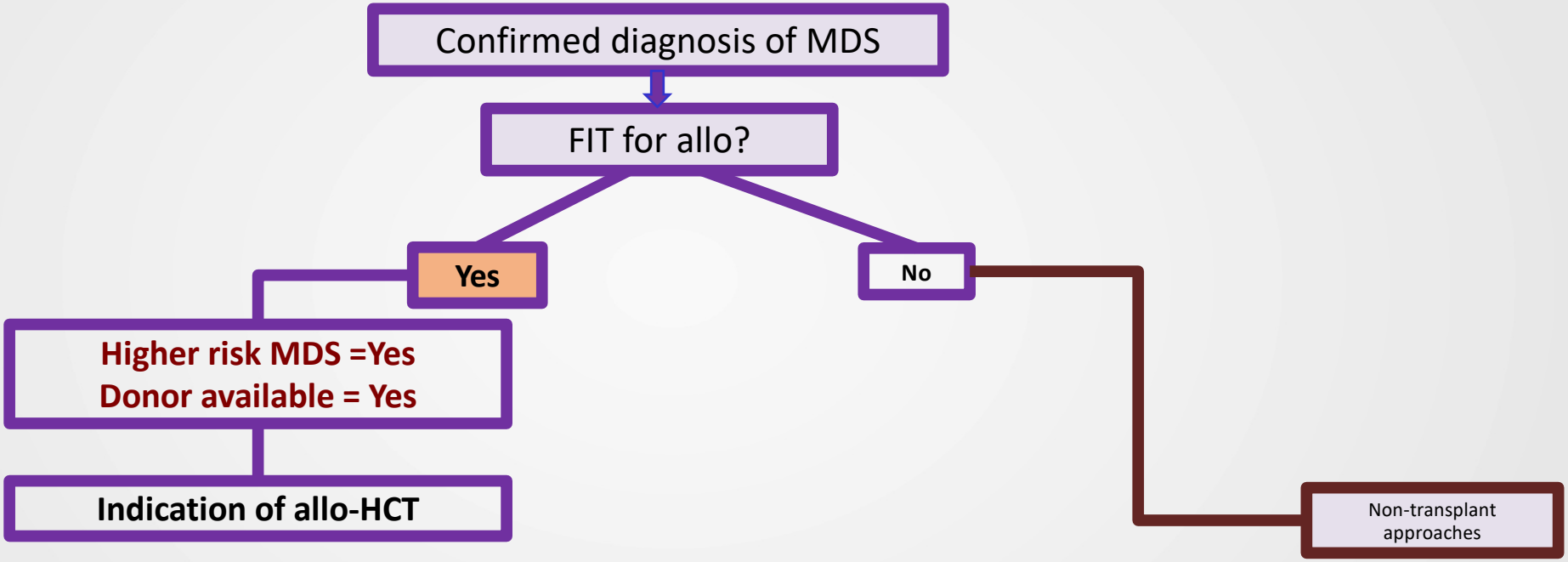
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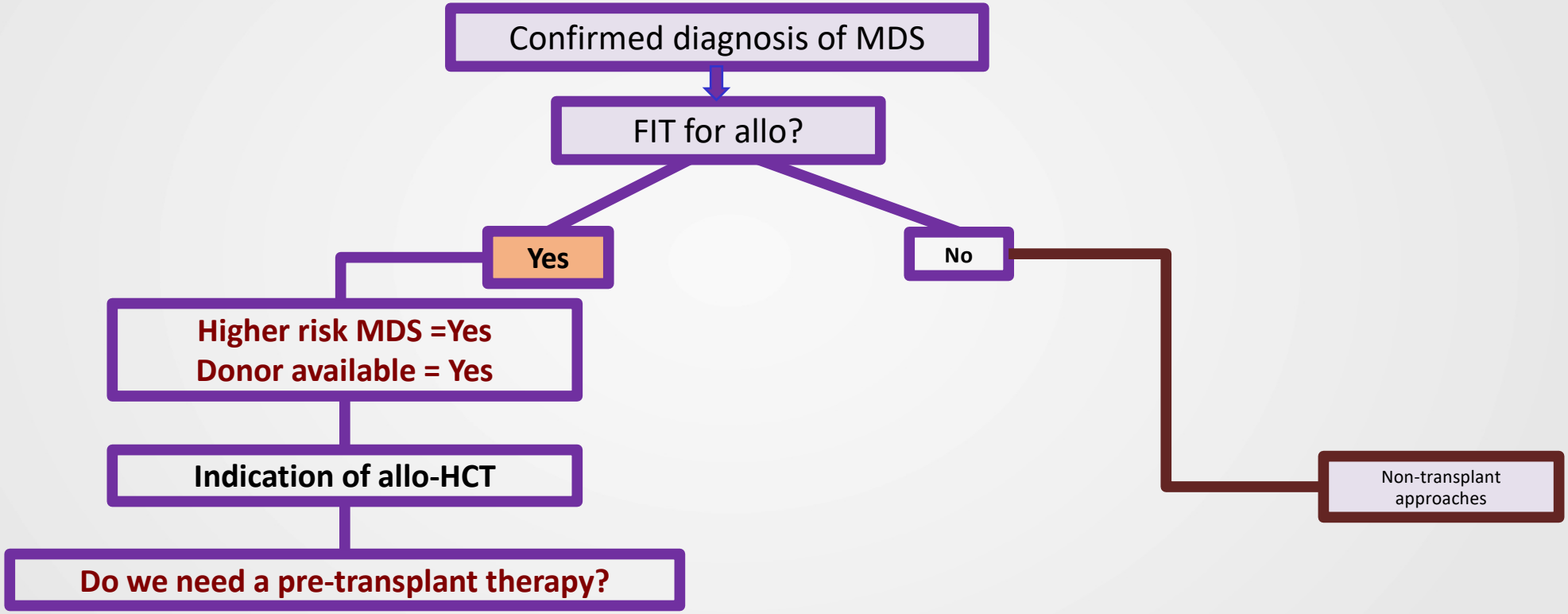
Non-transplant approaches


Confirmed diagnosis of MDS
FIT for allo?
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Indication of allo-HCT
Do we need a pre-transplant therapy?
Non-transplant approaches

Why Pre-transplant Therapy?

- **"Buy time" prior to transplant ("bridging")**

- **Cytoreduction**
  - **Lower risk of post-transplant relapse in responders**
  - **Lower MDS burden – time for donor cells to exert GvL effect**

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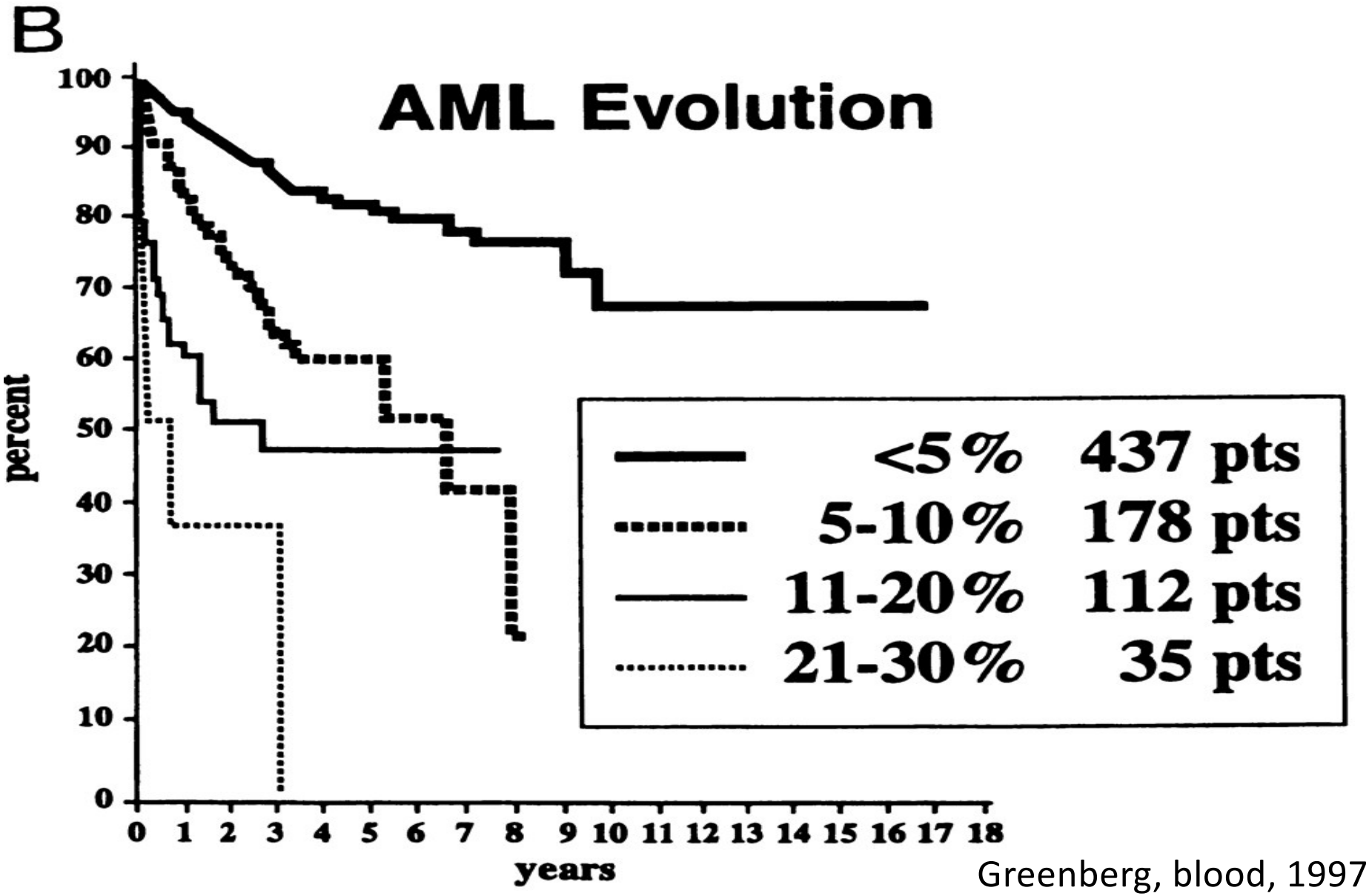
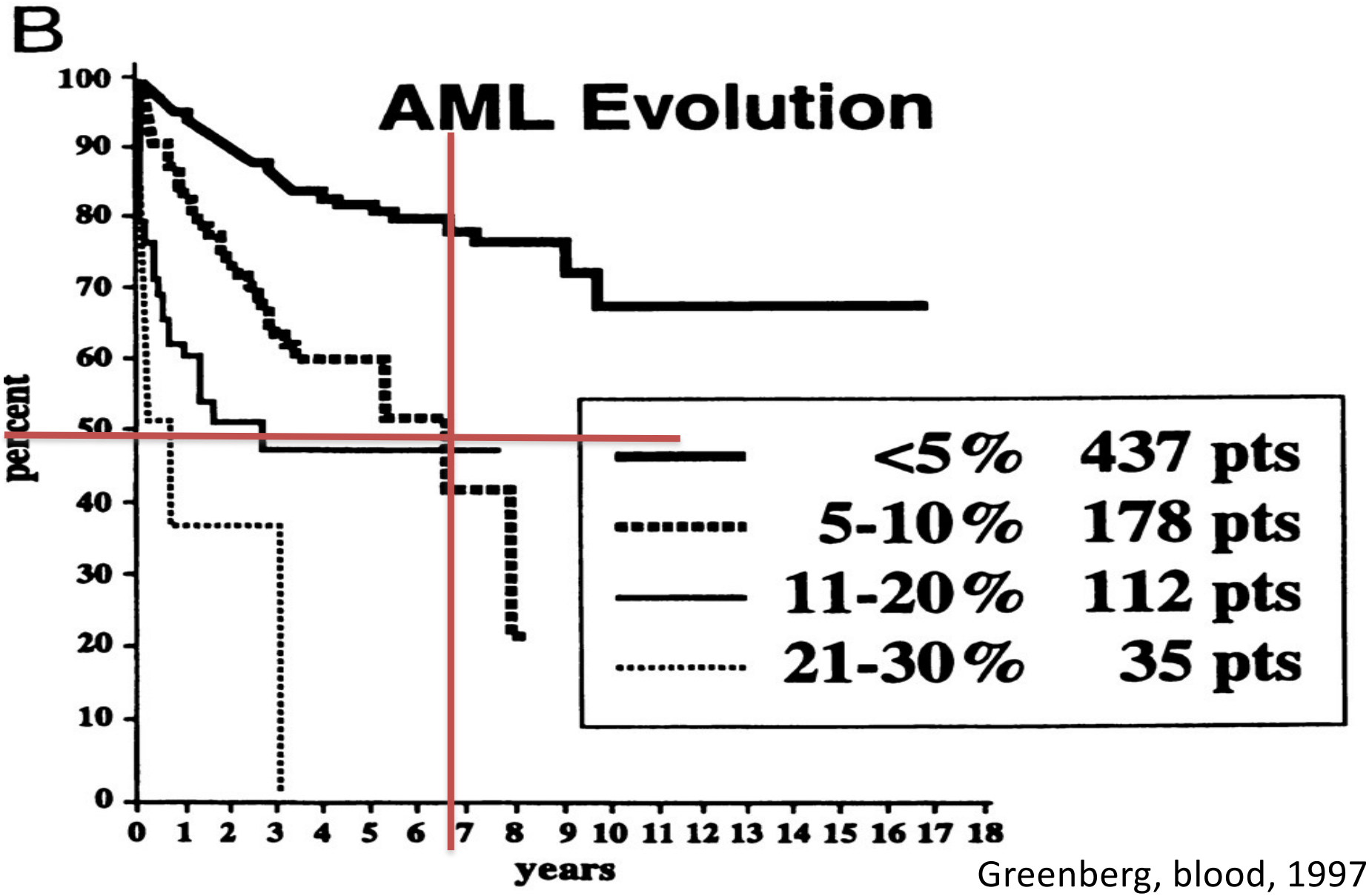


Greenberg, blood, 1997



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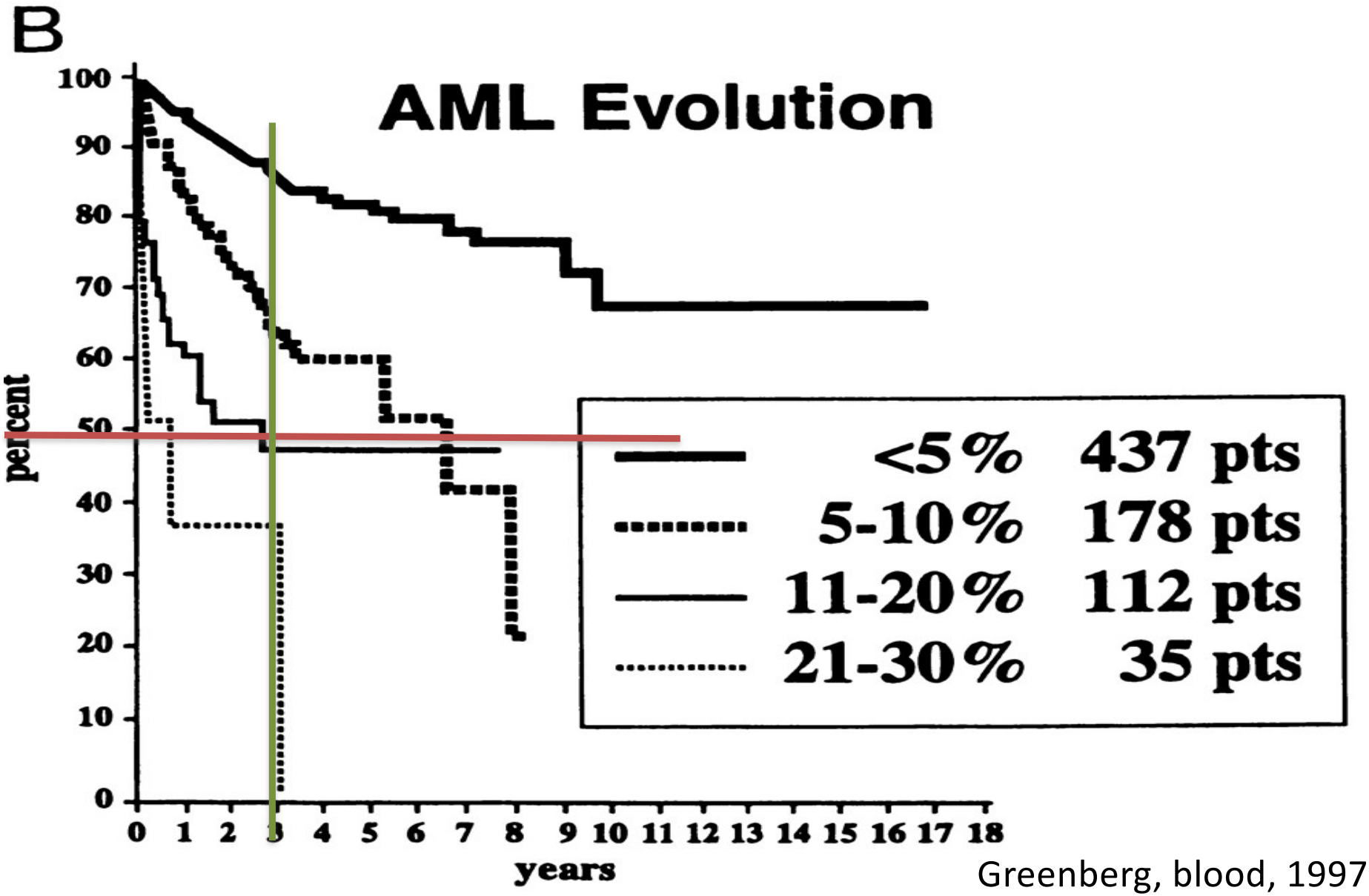

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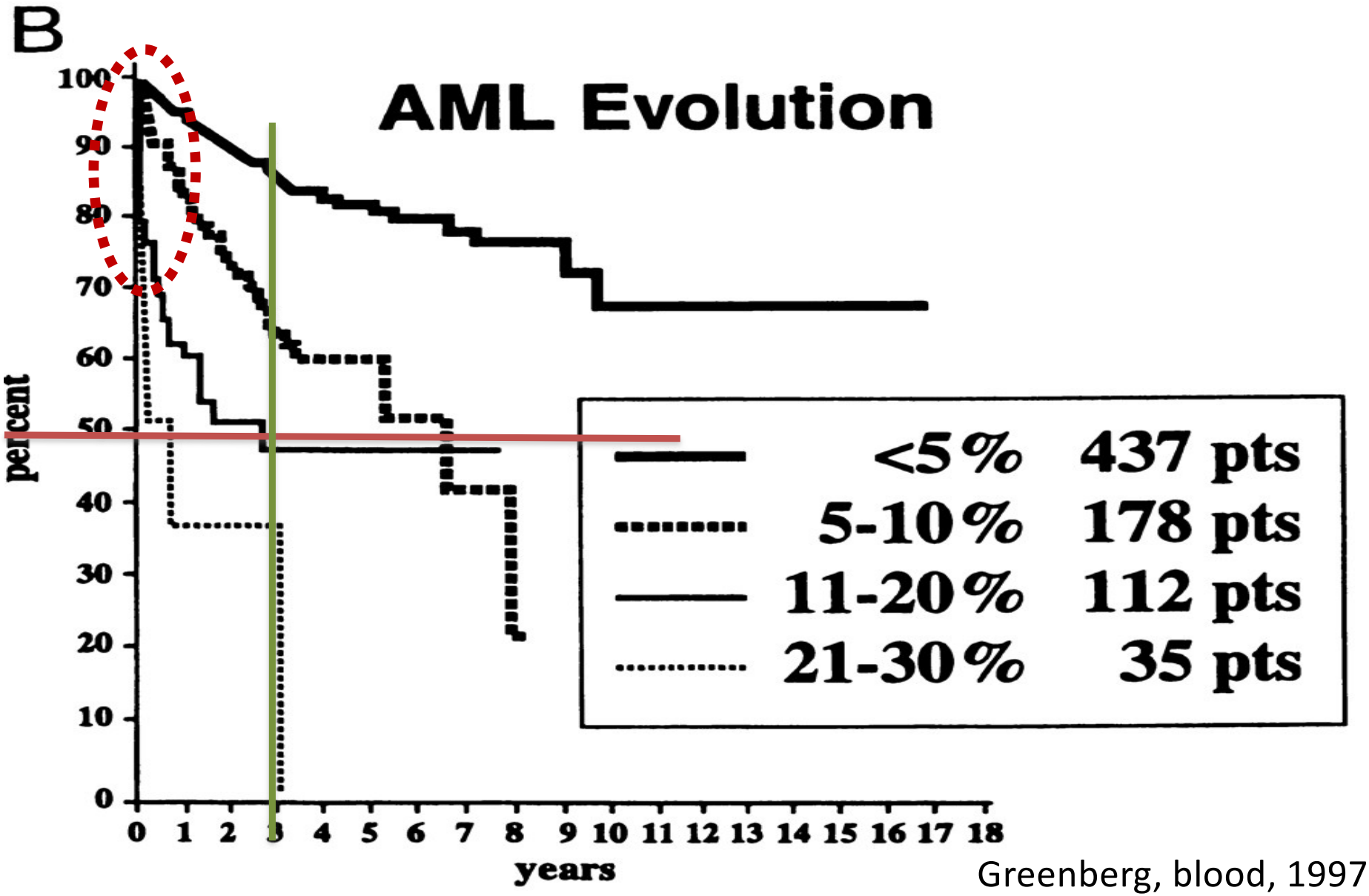

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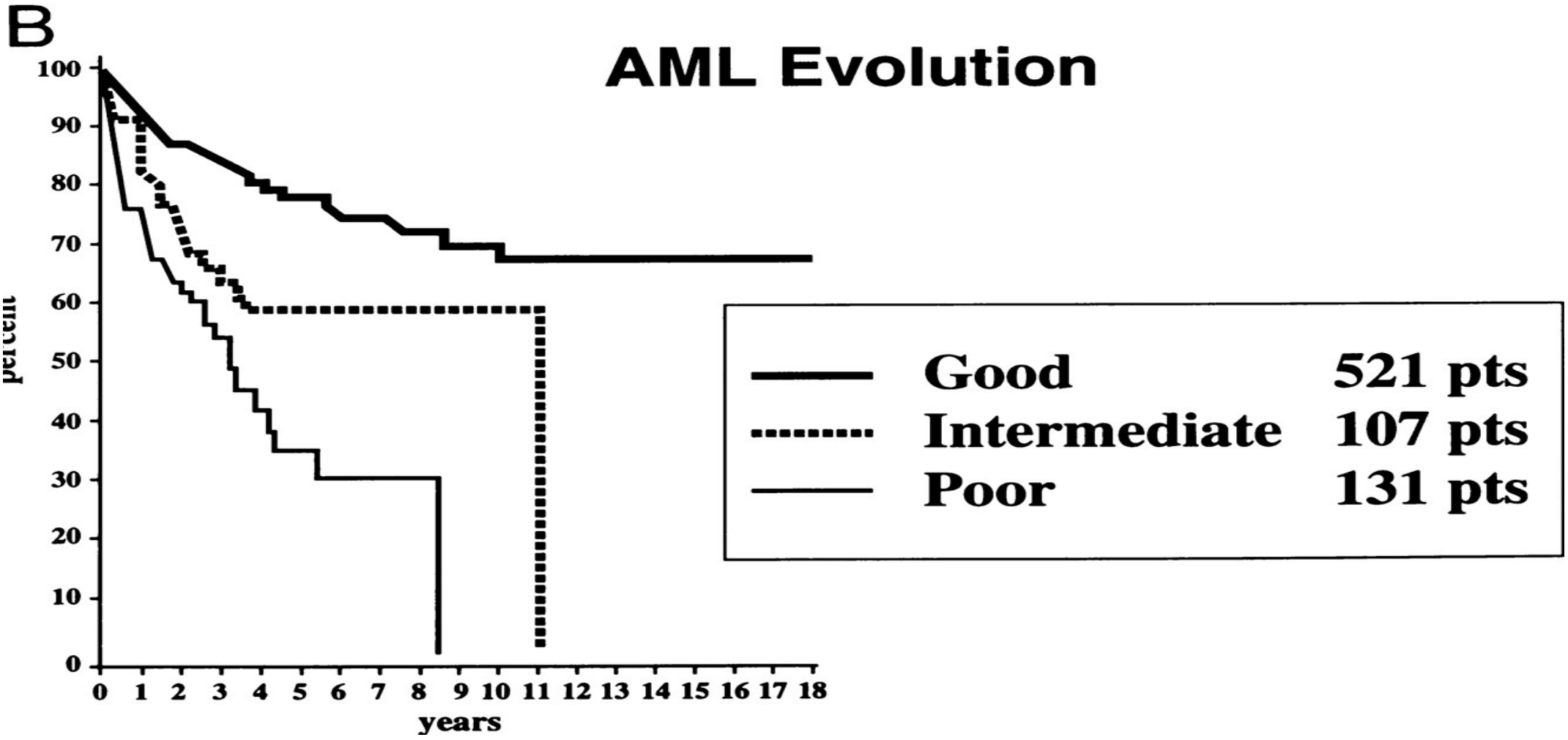

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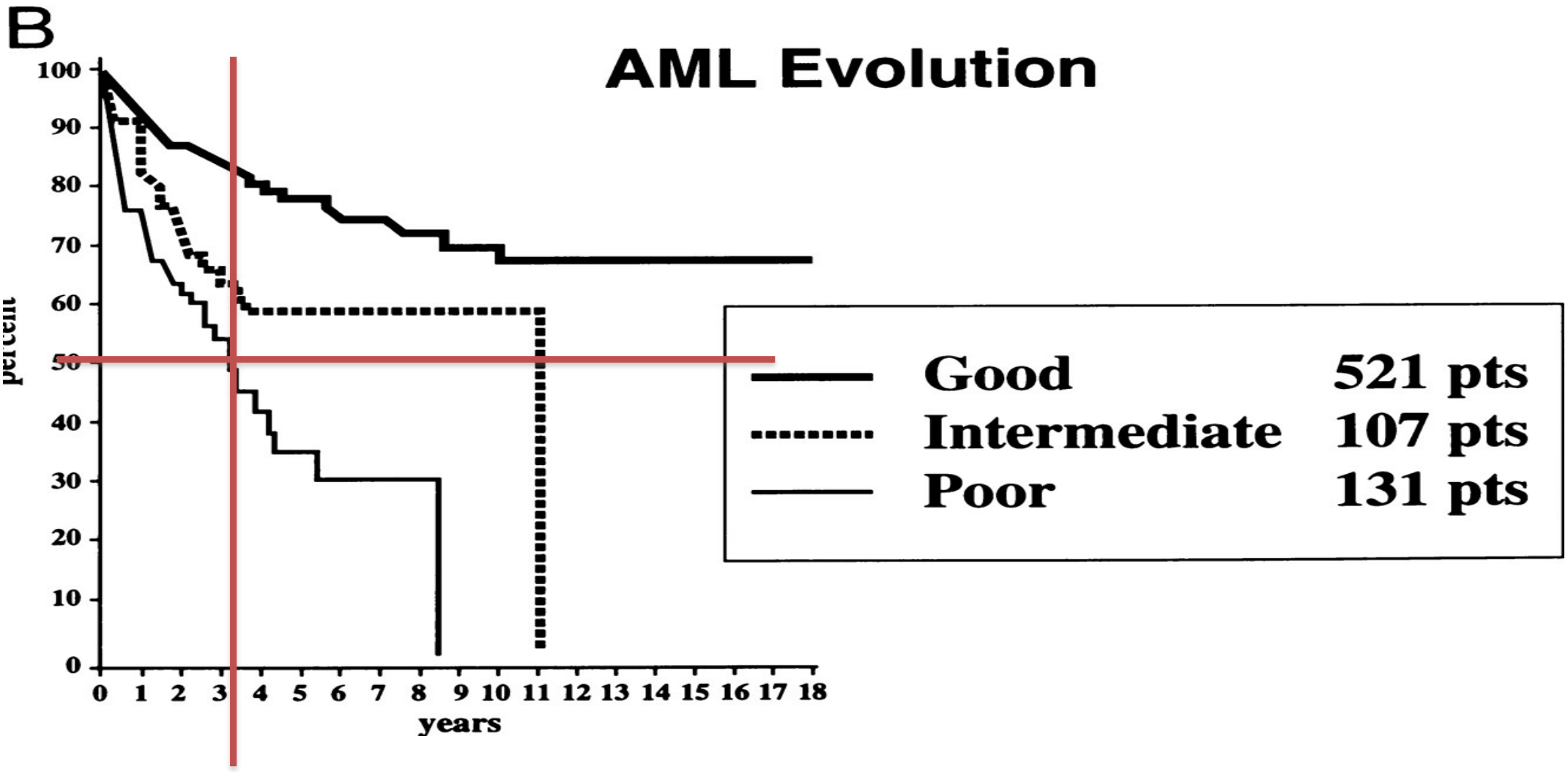

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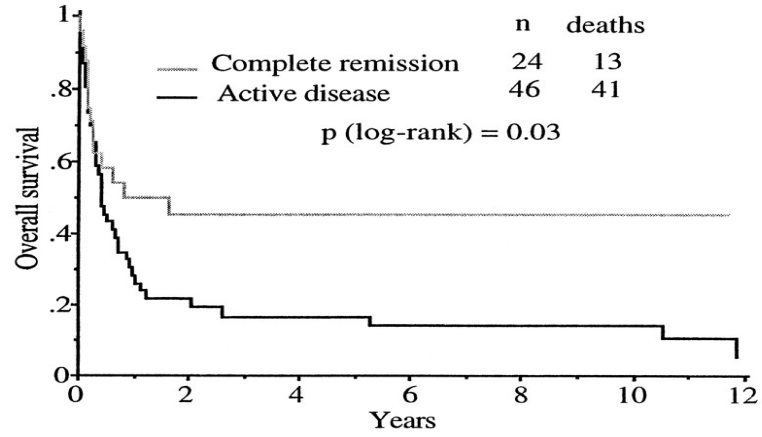
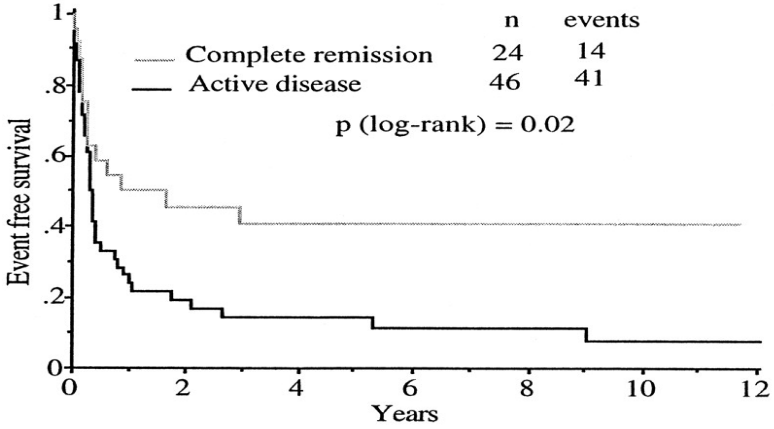
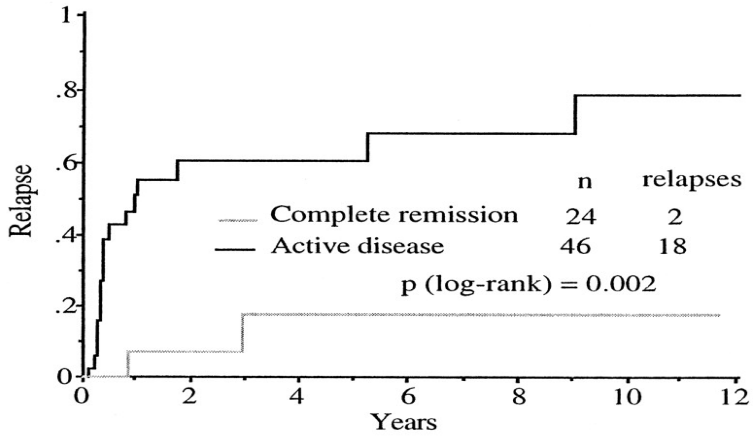
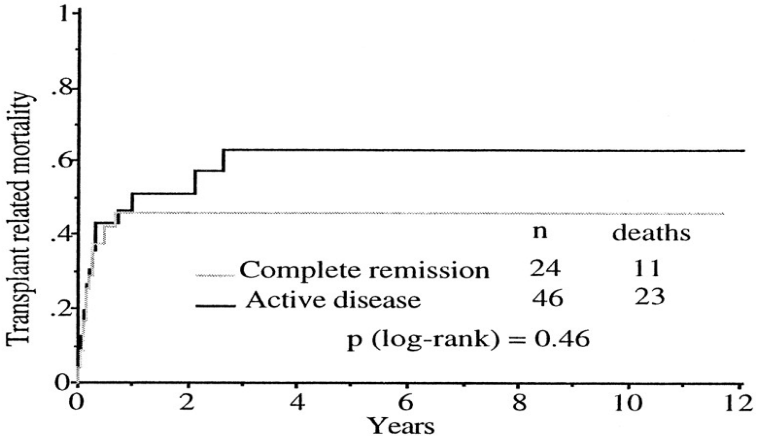


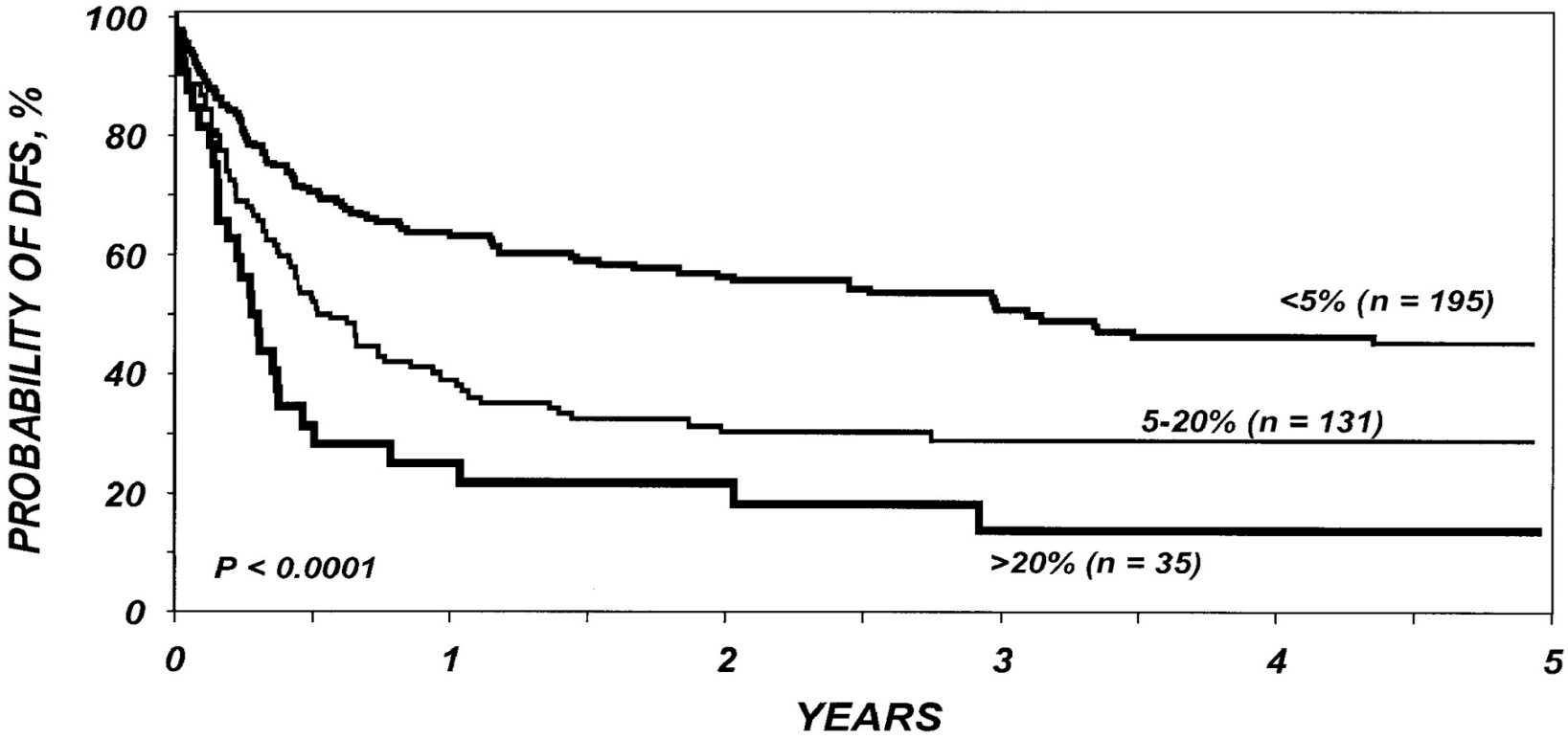






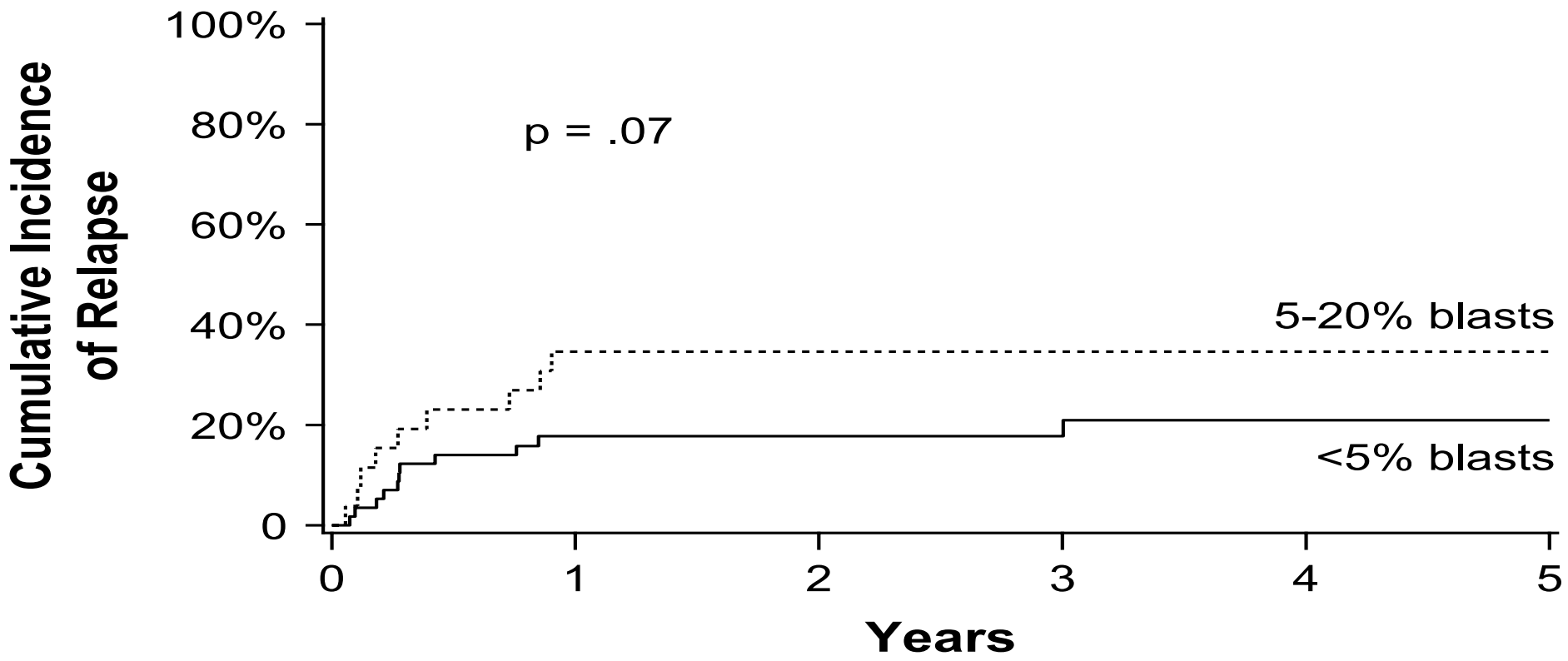
Yakoub-Agha I et al. JCO 2000;18:963

Allo-SCT for MDS and Blasts %



Sierra, Blood 2002

Pre-HCT Disease Burden and Post-transplant Relapse



Warlick E, et al. Biol Blood Marrow Transplant. 2009 Jan;15(1):30-8.

We need CR before transplant ➔

What bridging therapy to use?

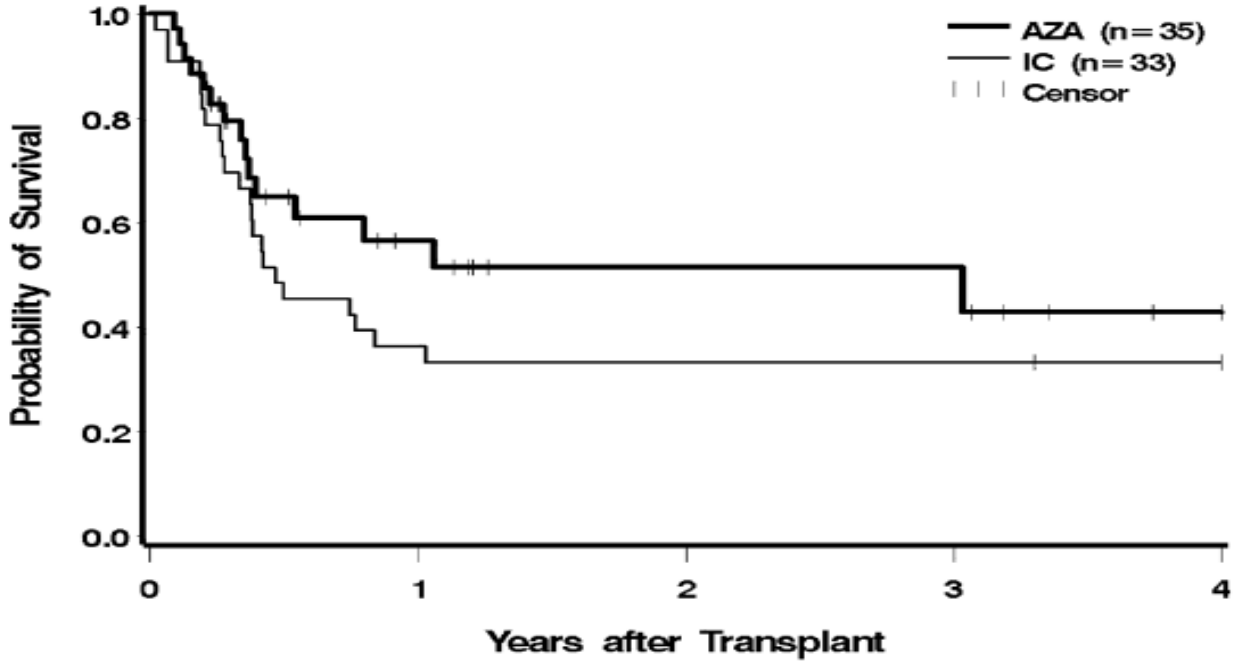
- **Induction-type chemotherapy (ICT)**
- **Hypomethylating agents (HMA)**

Pre-Transplant Therapy with Azacitidine Versus Induction Chemotherapy and Post-Transplant Outcome in Patients with MDS

Aaron T. Gerds, M.D.[1,2], **Ted A. Gooley, Ph.D.**[1,2], **Elihu H. Estey, M.D.**[1,2], **Frederick R. Appelbaum, M.D.**[1,2], **H. Joachim Deeg, M.D.**[1,2], and **Bart L. Scott, M.D.**[1,2]

[1]Fred Hutchinson Cancer Research Center, Seattle, Washington

[2]University of Washington School of Medicine, Seattle, Washington



Biol Blood Marrow Transplant. 2012 August ; 18(8): 1211–1218.

JOURNAL OF CLINICAL ONCOLOGY

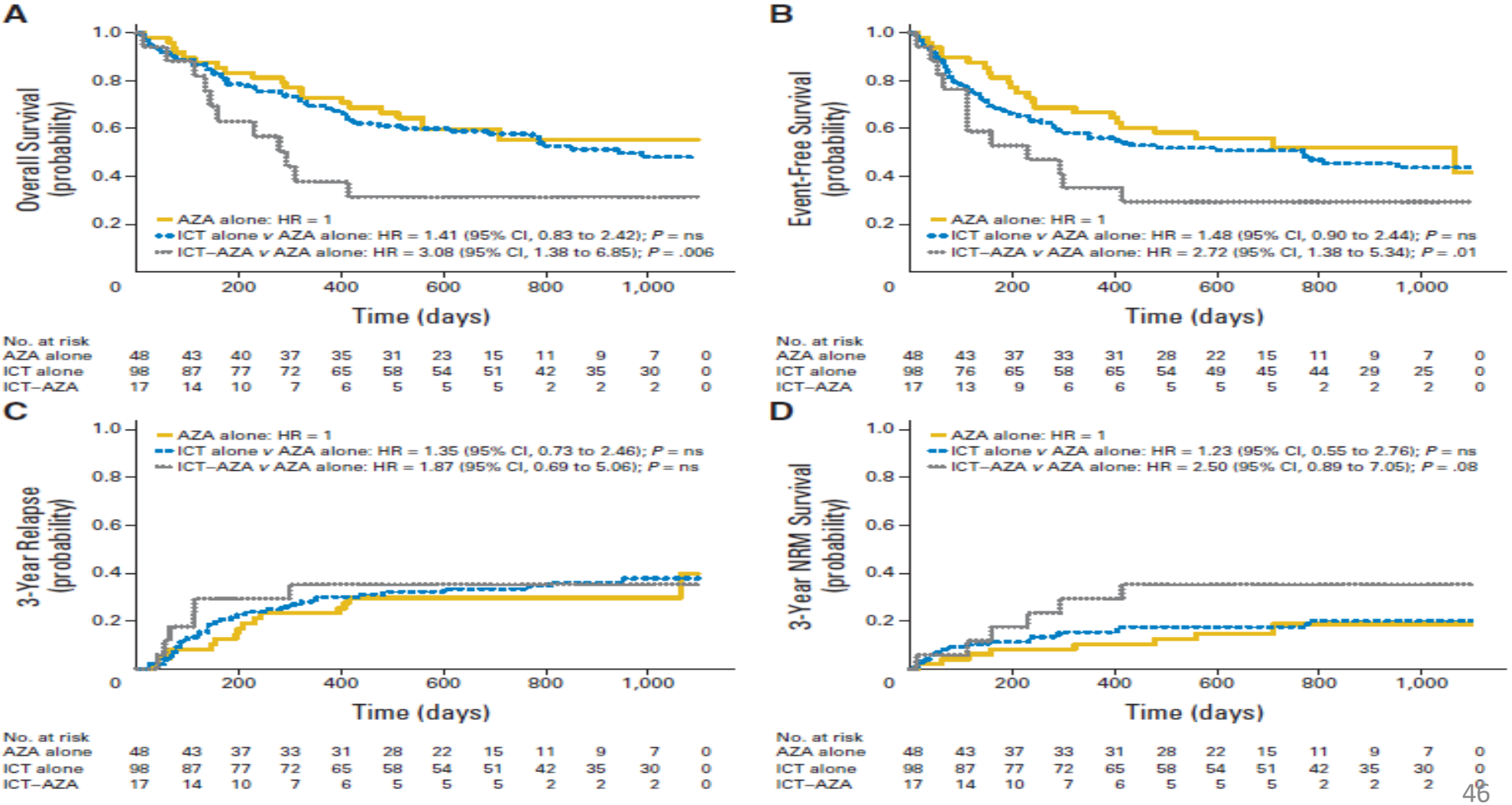
ORIGINAL REPORT

Impact of Azacitidine Before Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes: A Study by the Société Française de Greffe de Moelle et de Thérapie-Cellulaire and the Groupe-Francophone des Myélodysplasies

Gandhi Damaj, Alain Duhamel, Marie Robin, Yves Beguin, Mauricette Michallet, Mohamad Mohty, Stephane Vigouroux, Pierre Bories, Alice Garnier, Jean El Cheikh, Claude-Eric Bulabois, Anne Huynh, Jacques-Olivier Bay, Faeyzeh Legrand, Eric Deconinck, Nathalie Fegueux, Laurence Clement, Charles Dauriac, Natacha Maillard, Jérôme Cornillon, Lionel Ades, Gaelle Guillerm, Aline Schmidt-Tanguy, Zora Marjanovic, Sophie Park, Marie-Thérèse Rubio, Jean-Pierre Marolleau, Federico Garnier, Pierre Fenaux, and Ibrahim Yakoub-Agha

JCO.2012.44.3499

OUTCOME


A
Overall Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
AZA alone: HR = 1
ICT alone v AZA alone: HR = 1.41 (95% CI, 0.83 to 2.42); P = ns
ICT–AZA v AZA alone: HR = 3.08 (95% CI, 1.38 to 6.85); P = .006
200
400
600
800
1,000
Time (days)
No. at risk
AZA alone 48 43 40 37 35 31 23 15 11 9 7 0
ICT alone 98 87 77 72 65 58 54 51 42 35 30 0
ICT–AZA 17 14 10 7 6 5 5 5 2 2 2 0
B
Event-Free Survival (probability)
AZA alone: HR = 1
ICT alone v AZA alone: HR = 1.48 (95% CI, 0.90 to 2.44); P = ns
ICT–AZA v AZA alone: HR = 2.72 (95% CI, 1.38 to 5.34); P = .01
Time (days)
No. at risk
AZA alone 48 43 37 33 31 28 22 15 11 9 7 0
ICT alone 98 76 65 58 65 54 49 45 44 29 25 0
ICT–AZA 17 13 9 6 6 5 5 5 2 2 2 0
C
3-Year Relapse (probability)
AZA alone: HR = 1
ICT alone v AZA alone: HR = 1.35 (95% CI, 0.73 to 2.46); P = ns
ICT–AZA v AZA alone: HR = 1.87 (95% CI, 0.69 to 5.06); P = ns
Time (days)
No. at risk
AZA alone 48 43 37 33 31 28 22 15 11 9 7 0
ICT alone 98 87 77 72 65 58 54 51 42 35 30 0
ICT–AZA 17 14 10 7 6 5 5 5 2 2 2 0
D
3-Year NRM Survival (probability)
AZA alone: HR = 1
ICT alone v AZA alone: HR = 1.23 (95% CI, 0.55 to 2.76); P = ns
ICT–AZA v AZA alone: HR = 2.50 (95% CI, 0.89 to 7.05); P = .08
Time (days)
No. at risk
AZA alone 48 43 37 33 31 28 22 15 11 9 7 0
ICT alone 98 87 77 72 65 58 54 51 42 35 30 0
ICT–AZA 17 14 10 7 6 5 5 5 2 2 2 0

We need CR before transplant ➔

What bridging therapy to use?

- **Induction-type chemotherapy (ICT)**
- **Hypomethylating agents (HMA)**

Value of chemotherapy before allogeneic hematopoietic stem cell transplantation from an HLA-identical sibling donor for myelodysplastic syndrome

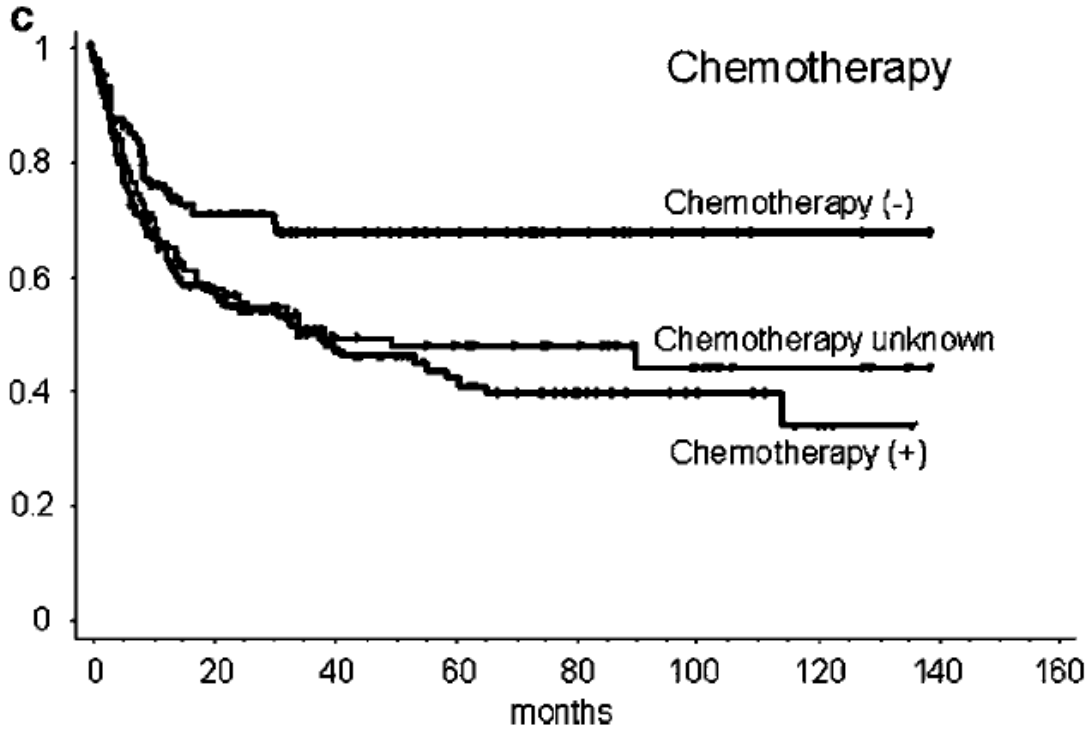
K Nakai[1], Y Kanda[2], S Fukuhara[1], H Sakamaki[3], S Okamoto[4], Y Kodera[5], R Tanosaki[6], S Takahashi[7], T Matsushima[8], Y Atsuta[9], N Hamajima[9], M Kasai[10] and S Kato[11]

Leukemia (2005) 19, 396–401

		History of previous chemotherapy		
	Total	*Presence*	*Absence*	P-*value*
Age (years)				
⩽40	136	94	42	0.38
>40	147	94	53	
Sex				
Male	171	116	55	0.61
Female	112	72	40	
FAB				
RA	61	29	32	<0.0001
RAEB	58	29	29	
RAEBt	70	55	15	
CMML	25	19	6	
LT	69	56	13	
Karyotype				
Good	131	84	47	0.004
Intermediate	60	31	29	
Poor	41	32	9	
Unknown	51	41	10	
TBI				
Presence	173	115	58	>0.99
Absence	110	73	37	
Stem cell				
BM	218	144	74	0.88
PB	65	44	21	

LT = leukemic transformation.

Overall Survival



Nakai et al,**Leukemia (2005) 19**, 396–401

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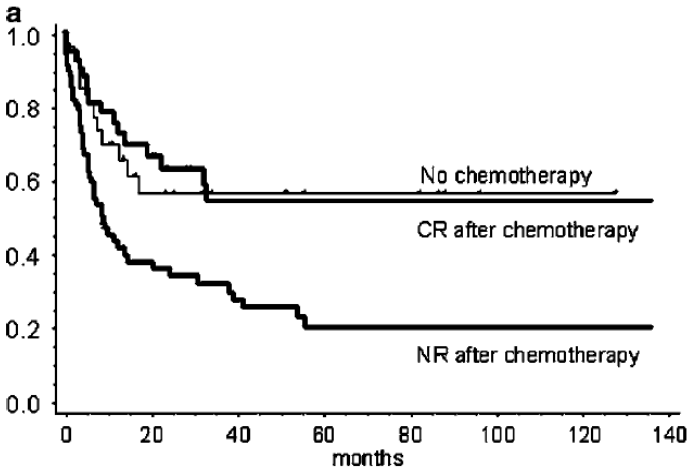
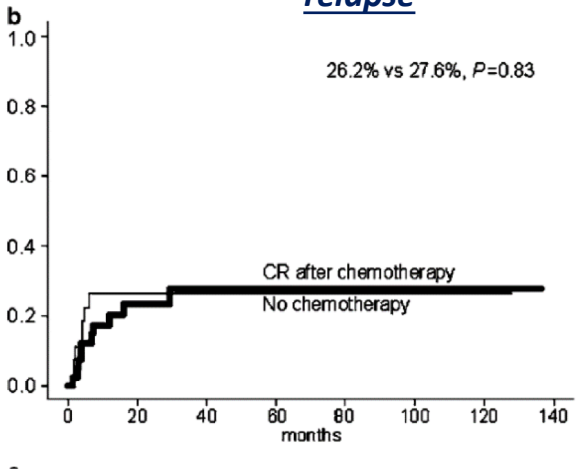
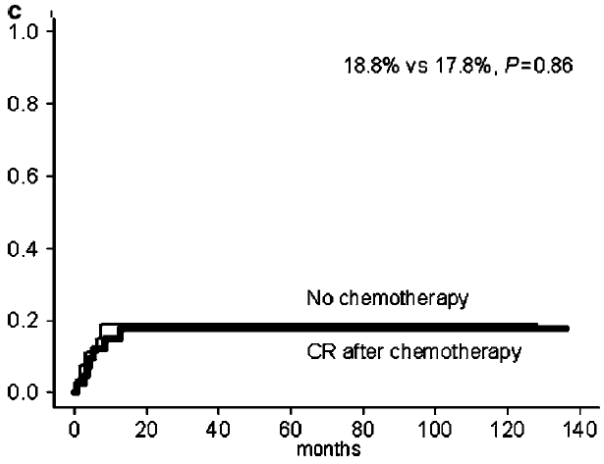


Cumulative incidence of relapse



Non-relapse mortality



Nakai et al, **Leukemia (2005) 19**, 396–401

Prognostic factors in adult de novo MDS treated by intensive chemotherapy. P. Fenaux, Br J Haematol. 1991

CR rate according to FAB

RAEB-T (> 19% of marrow blasts) at diagnosis : 69%

other FAB subtypes : 19% (P = 0.008)

DFS according to karyotype

normal : median 16.5 months

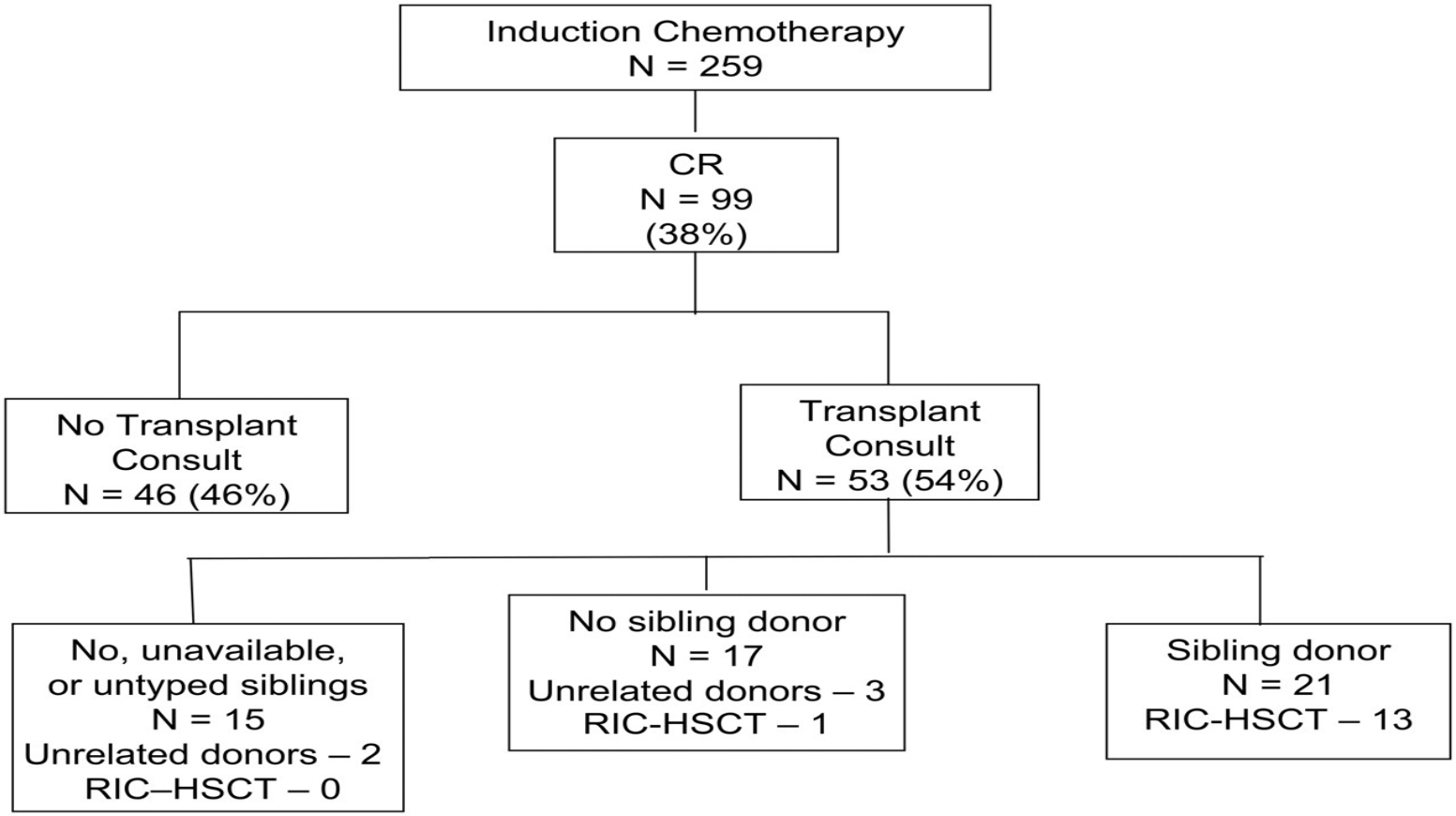
abnormal : median 4 months (P = 0.018).

15 RAEB-T at diagnosis and normal karyotype

- CR rate of 80%
- median actuarial DFS of 18 months,.

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

High-risk MDS and AML, > 50 years old



Estey E et al. Blood 2007;109:1395-1400

blood
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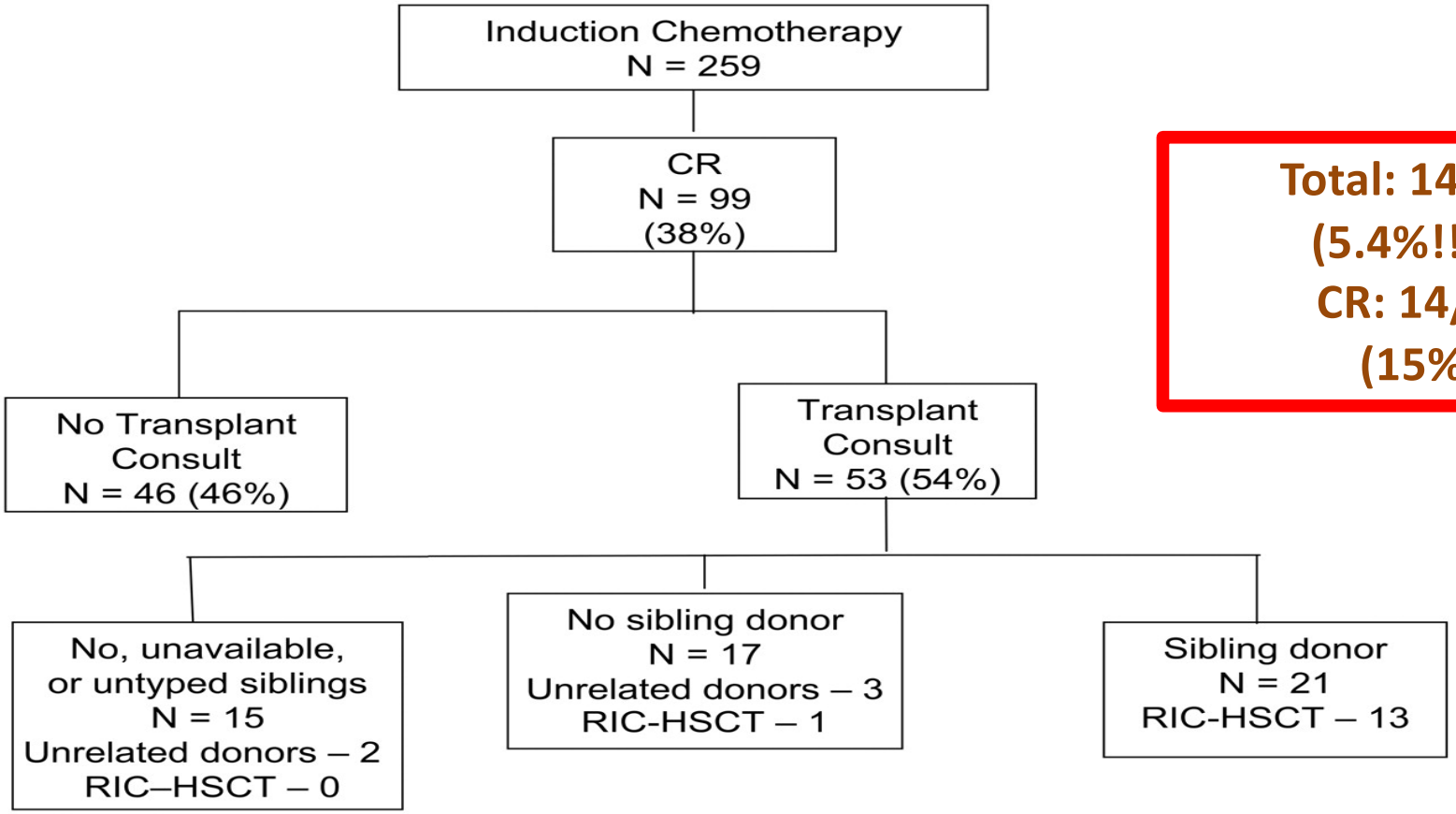

Total: 14/259
(5.4%!!!!!)
CR: 14/99
(15%)

Estey E et al. Blood 2007;109:1395-1400

Induction-type chemotherapy

- Is less effective in patients with complex karyotype and those with few MB.
- Is associated with considerable morbidity and mortality.
- Could be helpful in young patients with proliferation features

Induction-type chemotherapy is not for everybody!

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Induction-type chemotherapy is not for everybody!

- Is less effective in patients with complex karyotype and those with few MB.
- Is associated with considerable morbidity and mortality.
- **Could be helpful in young patients with proliferation features without poor-risk cytogenetic**

decision-making algorithm based on disease characteristics and patient age and comorbidities. ***In the absence of prospective trial.***

Patient condition	Disease characteristics		ICT	HMA	Up-front allo-SCT
	Cytogenetics*	Marrow blasts %			
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		5-10	possible		
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ICT: induction-type chemotherapy; HMA: hypomethylating agents; allo-SCT: allogeneic stem cell transplantation: *as assessed by IPSS: NI: not indicated; BO: best option; **: if patient can undergo allo-SCT rapidly within less than 3 months.

I. Yakoub-Agha and J. Deeg, BBMT, 2014

We need CR before transplant ➔

What bridging therapy to use?

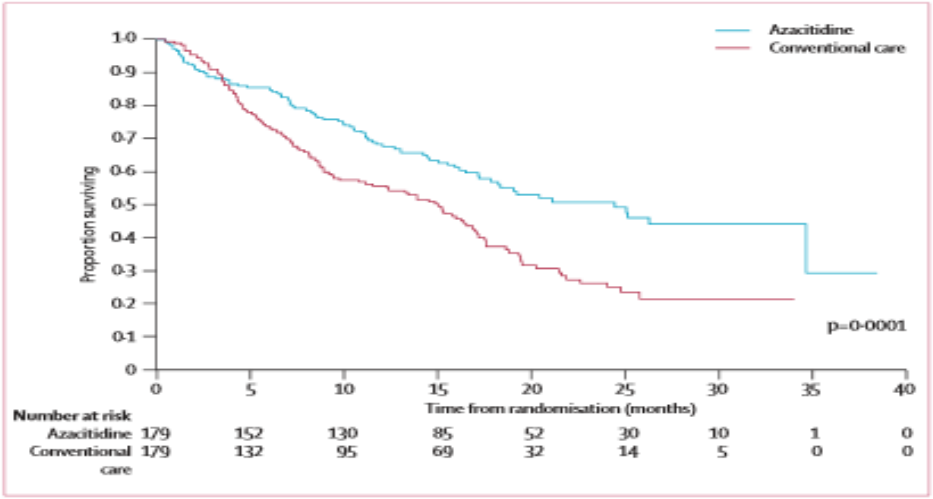
- **Induction-type chemotherapy (ICT)**
- **Hypomethylating agents (HMA)**

Hypomethylating agents (HMA)

- Broad spectrum: The DNA methyltransferases inhibitors (azacitidine and decitabine) have anti-tumor activity against a broad range of malignancies

- Effective : Administration of the HMA, is associated with only mild toxicity and has been shown to delay progression to AML and, in the case of azacitidine, to extend survival by 9.5 months as compared to conventional care.

- Well tolerated: even in elderly.



Fenaux et al, lancet oncol, 2012

HMA and Ch 5 and 7 abnormalities

Superior Outcome With Hypomethylating Therapy in Patients With Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome and Chromosome 5 and 7 Abnormalities

Farhad Ravandi, MD; Jean-Pierre Issa, MD; Guillermo Garcia-Manero, MD; Susan O'Brien, MD; Sherry Pierce, BSN; Jianqin Shan, PhD; Gautam Borthakur, MD; Srdan Verstovsek, MD; Stefan Faderl, MD; Jorge Cortes, MD[1]; and Hagop Kantarjian, MD

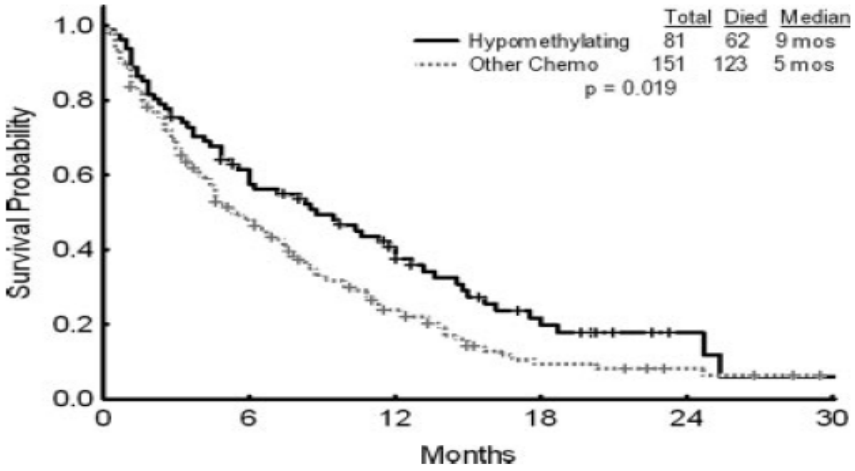


FIGURE 2. Overall survival by treatment strategy is shown. Chemo indicates chemotherapy.

Cancer December 15, 2009

HMA and response rates

Table 1 Phase III trials of azacitidine as a single agent

Study	CALGB 9221 No. (%)	Updated CALGB No. (%)	AZA-001 No. (%)
No. patients	99	99	179
CR	7 (7)	10 (10)	30 (17)
PR	16 (16)	1 (1)	21 (12)
HI	37 (37)	36 (36)	87 (49)
OR	60 (60)	47 (47)	138 (78)

Abbreviations: CR, complete remission; PR, partial remission; HI, hematological improvement; OR, overall response.

Vigil et al Drug Design, Development and Therapy 2010:4 221–229

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Vigil et al Drug Design, Development and Therapy 2010:4 221–229

Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine

*Raphael Itzykson,[1] *Sylvain Thépot,[1,2] Bruno Quesnel,[3] Francois Dreyfus,[4] Odile Beyne-Rauzy,[5] Pascal Turlure,[6] Norbert Vey,[7] Christian Recher,[8] Caroline Dartigeas,[9] Laurence Legros,[10] Jacques Delaunay,[11] Célia Salanoubat,[12] Sorin Visanica,[13] Aspasia Stamatoullas,[14] Francoise Isnard,[15] Anne Marfaing-Koka,[16] Stephane de Botton,[17] Youcef Chelghoum,[18] Anne-Laure Taksin,[19] Isabelle Plantier,[20] Shanti Ame,[21] Simone Boehrer,[1,2] Claude Gardin,[1] C. L. Beach,[22] Lionel Adès,[1,2] and Pierre Fenaux,[1,2] on behalf of the Groupe Francophone des Myelodysplasies (GFM)

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vas good in 31%, inter-
nd poor in 47%. Patients
a median of 6 cycles

(1-52). Previous low-dose cytosine arabinoside treatment ($P = .009$), bone marrow blasts > 15% ($P = .004$), and abnormal karyotype ($P = .03$) independently predicted lower response rates. Complex karyotype predicted shorter responses ($P = .0003$). Performance status ≥ 2, intermediate- and poor-risk cytogenetics, presence of circulating blasts, and red blood cell transfusion dependency ≥ 4 units/8 weeks (all $P < 10^{-4}$) independently predicted poorer overall survival (OS). A prognostic score based on those factors discriminated 3

groups with median
15.0 and 6.1 mon
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tain complete or par
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In conclusion, routine
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117(2):403-411)

BLOOD, 13 JANUARY 2011 • VOLUME 117, NUMBER 2

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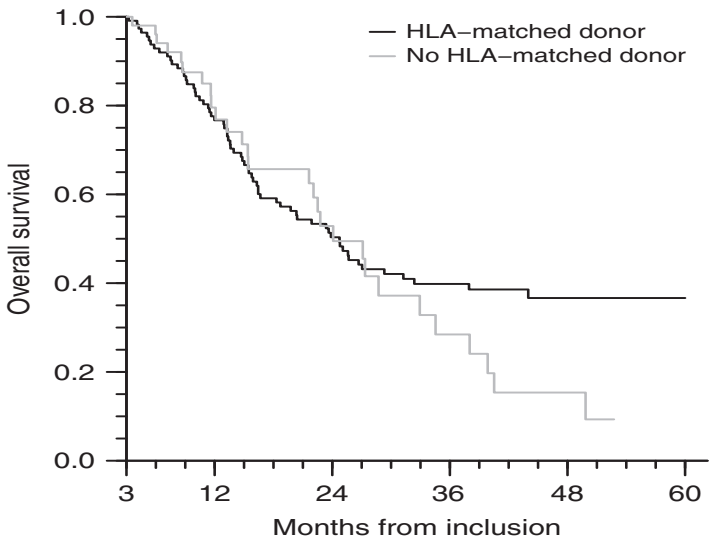
117(2):403-41

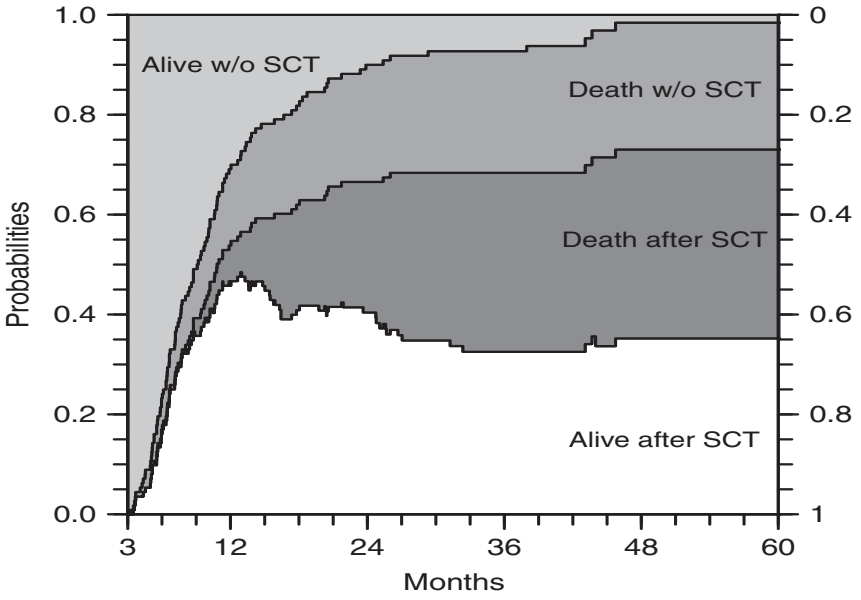
ORIGINAL ARTICLE

HLA-matched allogeneic stem cell transplantation improves outcome of higher risk myelodysplastic syndrome A prospective study on behalf of SFGM-TC and GFM

M Robin[1,2,3], R Porcher[4,5], L Adès[6], E Raffoux[7], M Michallet[8], S François[9], J-Y Cahn[10], A Delmer[11], E Wattel[8], S Vigouroux[12], J-O Bay[13], J Cornillon[14], A Huynh[15], S Nguyen[16], M-T Rubio[17], L Vincent[18], N Maillard[19], A Charbonnier[20], RP de Latour[1,2,3], O Reman[21], H Dombret[2,6], P Fenaux[2,6] and G Socié[1,2,3]



No. at risk:										
HLA−matched donor	112	85	63	50	39	33	23	14	8	5
No matched donor	50	29	21	15	8	6	3	2	0	0



Robin et al, Leukemia 2015

Hypomethylating agents (HMA)

- HMA are effective and well tolerated
- HMA are less effective in patients with > 15% of MB
- Short responses to HMA in patients with complex karyotype
- Toxicity?

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- Short responses to HMA in patients with complex karyotype
- Toxicity? Before and after transplant

decision-making algorithm based on disease characteristics and patient age and comorbidities. ***In the absence of prospective trial.***

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	Cytogenetics*	Marrow blasts %			
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		5-10	possible	**BO**	
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	High risk	< 5	No	possible	
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ICT: induction-type chemotherapy; HMA: hypomethylating agents; allo-SCT: allogeneic stem cell transplantation: *as assessed by IPSS: NI: not indicated; BO: best option; **: if patient can undergo allo-SCT rapidly within less than 3 months.

I. Yakoub-Agha and J. Deeg, BBMT, 2014

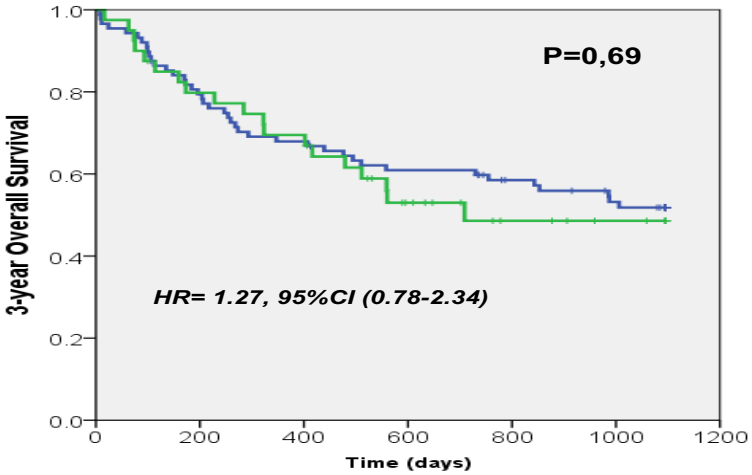
Upfront Allogeneic Stem Cell Transplantation after Reduced-Intensity/Nonmyeloablative Conditioning for Patients with Myelodysplastic Syndrome: A Study by the Société Française de Greffe de Moelle et de Thérapie Cellulaire

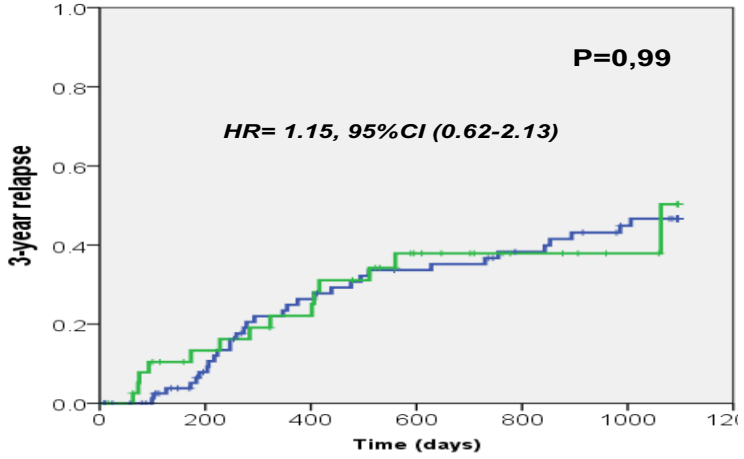
Gandhi Damaj [1], Mohammad Mohty [2], Marie Robin [3], Mauricette Michallet [4], Patrice Chevallier [5], Yves Beguin [6], Stephanie Nguyen [7], Pierre Bories [8], Didier Blaise [9], Natacha Maillard [10], Marie Therese Rubio [2], Nathalie Fegueux [11], Jerome Cornillon [12], Aline Clavert [13], Anne Huynh [14], Lionel Adès [15], Anne Thiébaut-Bertrand [16], Olivier Hermine [17], Stephane Vigouroux [18], Pierre Fenaux [15], Alain Duhamel [19], Ibrahim Yakoub-Agha [20,*]

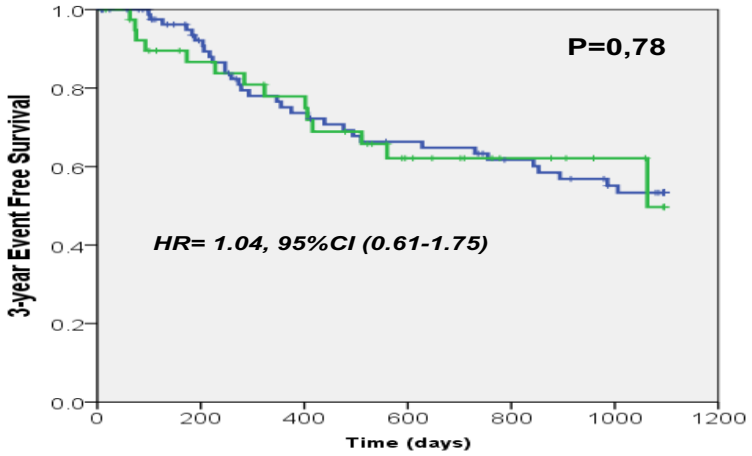
Damaj et al, BBMT, 2014

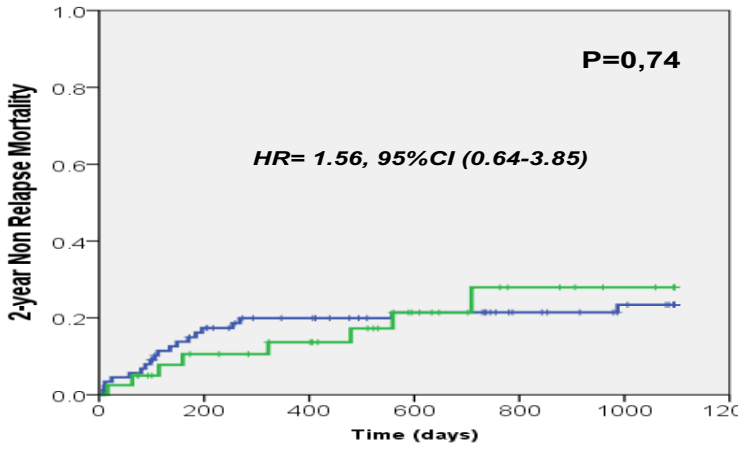
AZA versus BSC

BSC
AZA









Damaj et al, BBMT 2014

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Fit patients (without comorbidities)	< high risk	< 5	No	**BO**	possible
		5-10	possible	**BO**	possible
		> 10	**BO**	possible	possible
	High risk	< 5	No	possible	**BO****
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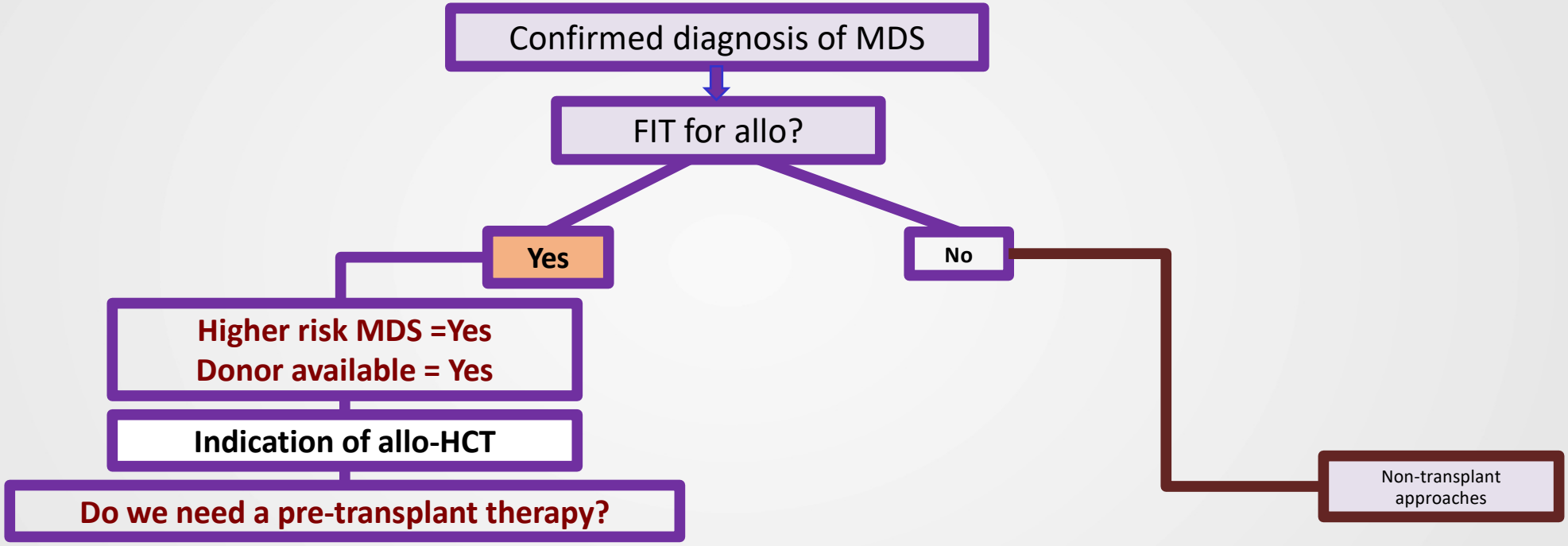
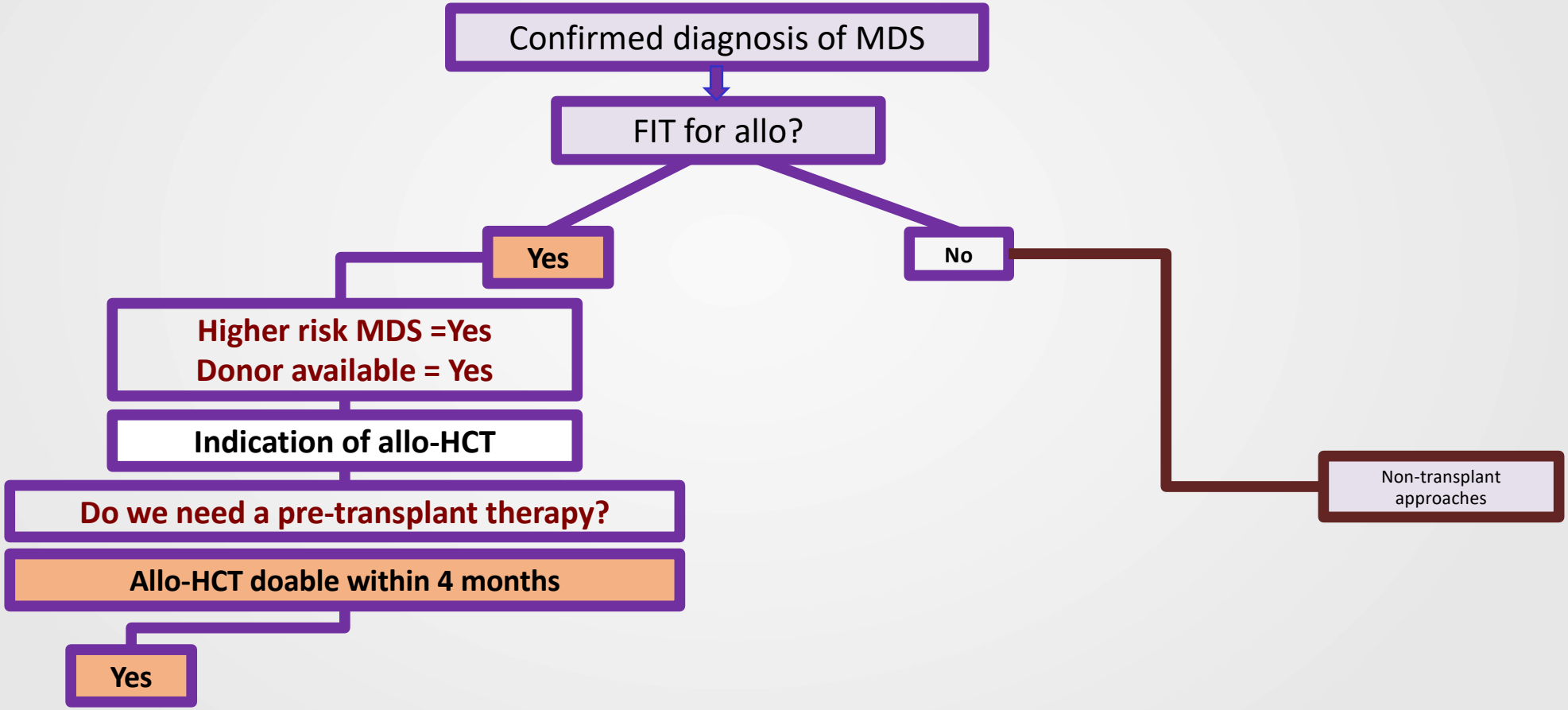
**: if patient can undergo allo-SCT rapidly within less than 4 months.

I. Yakoub-Agha and J. Deeg, BBMT, 2014



Adapted from I. Yakoub-Agha and J. Deeg, BBMT, 2014



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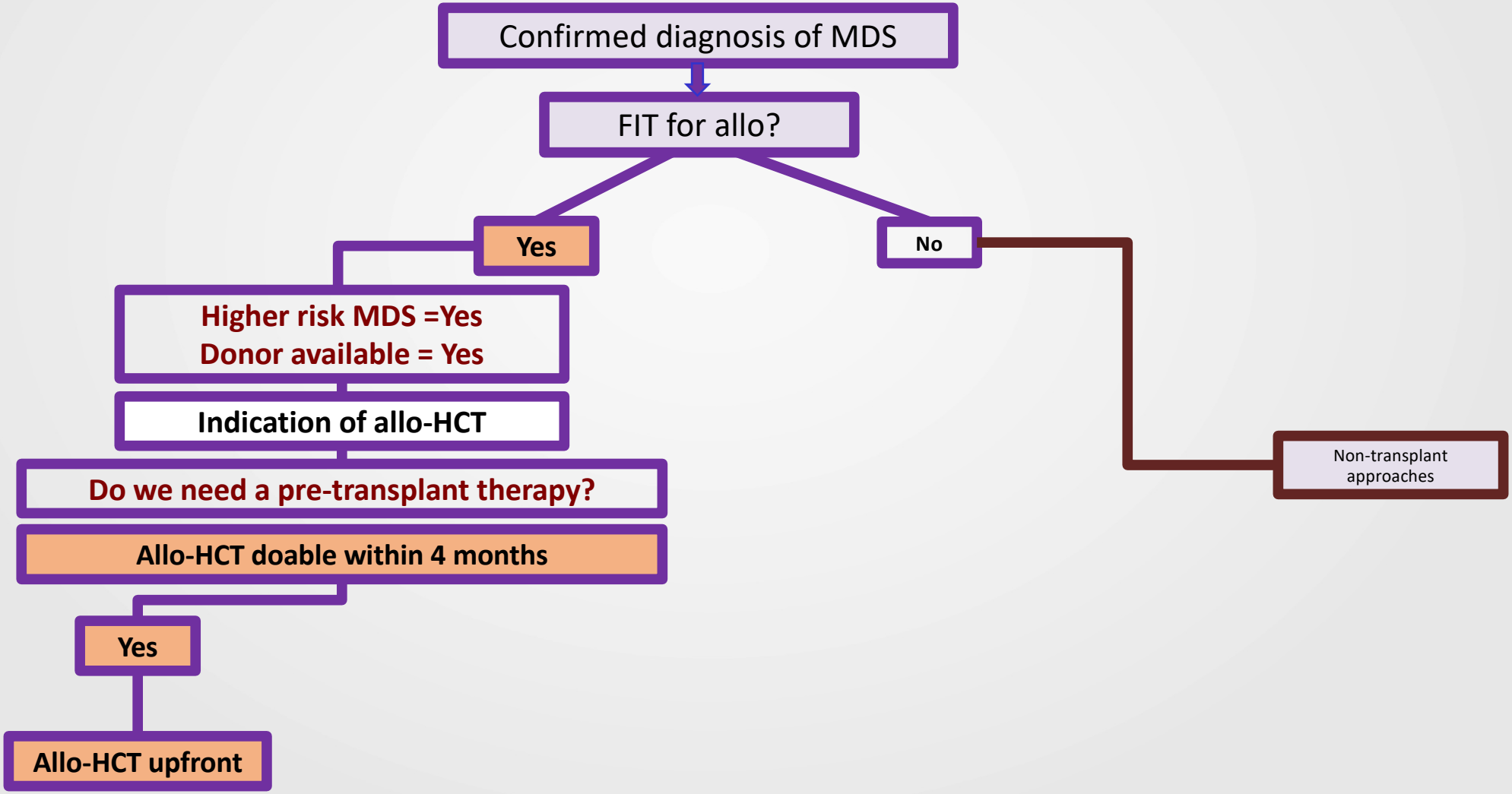

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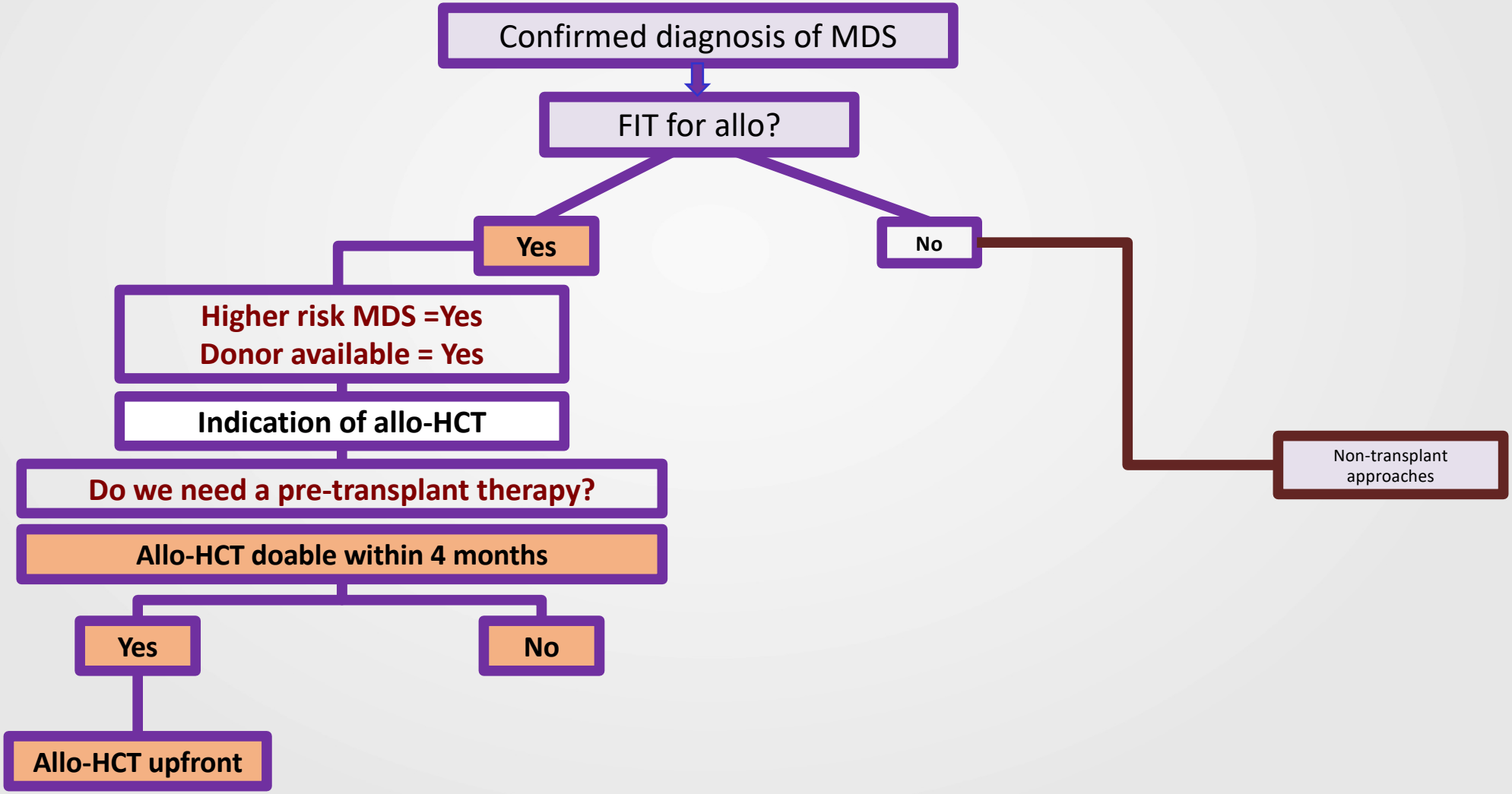

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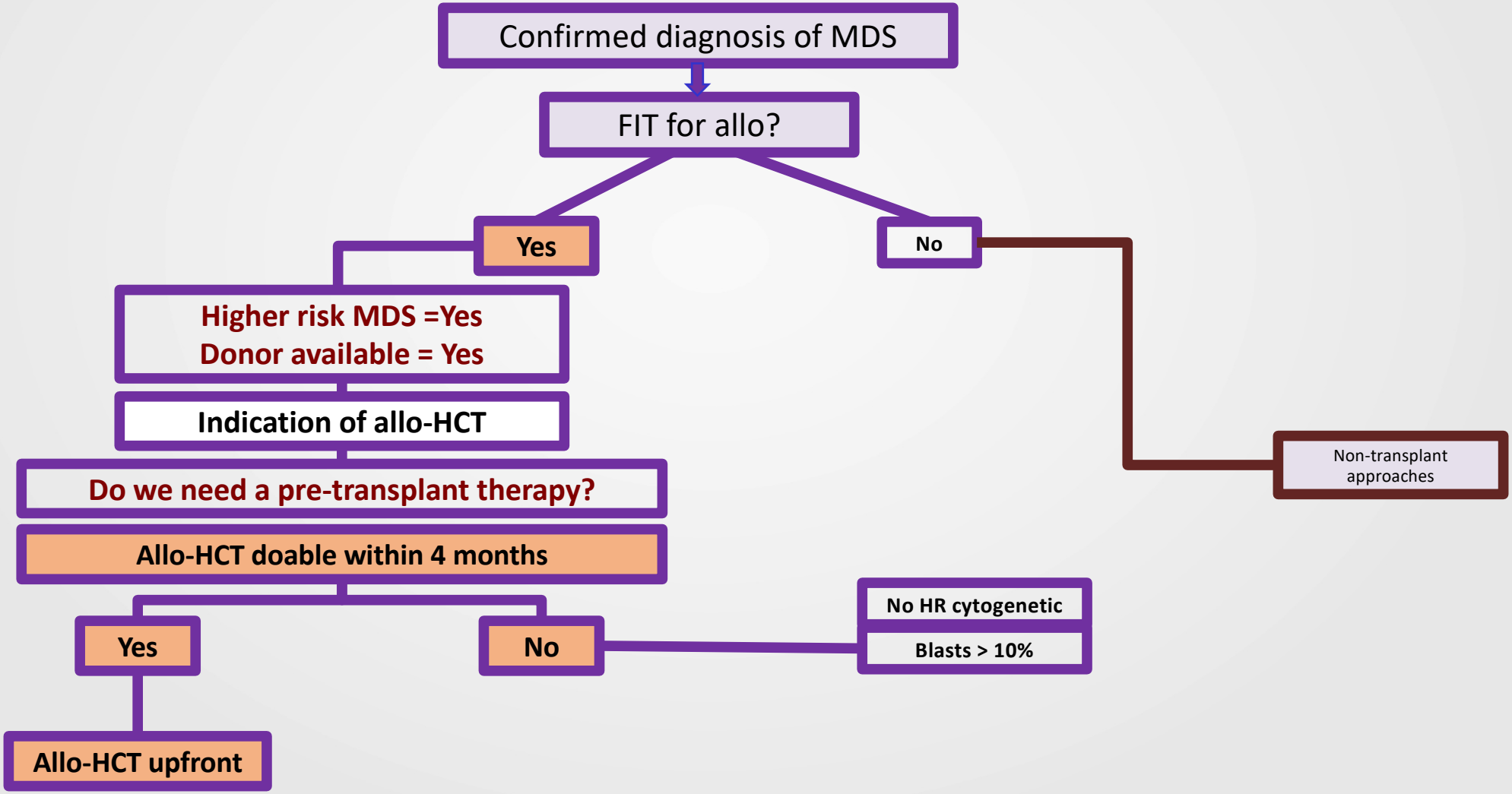

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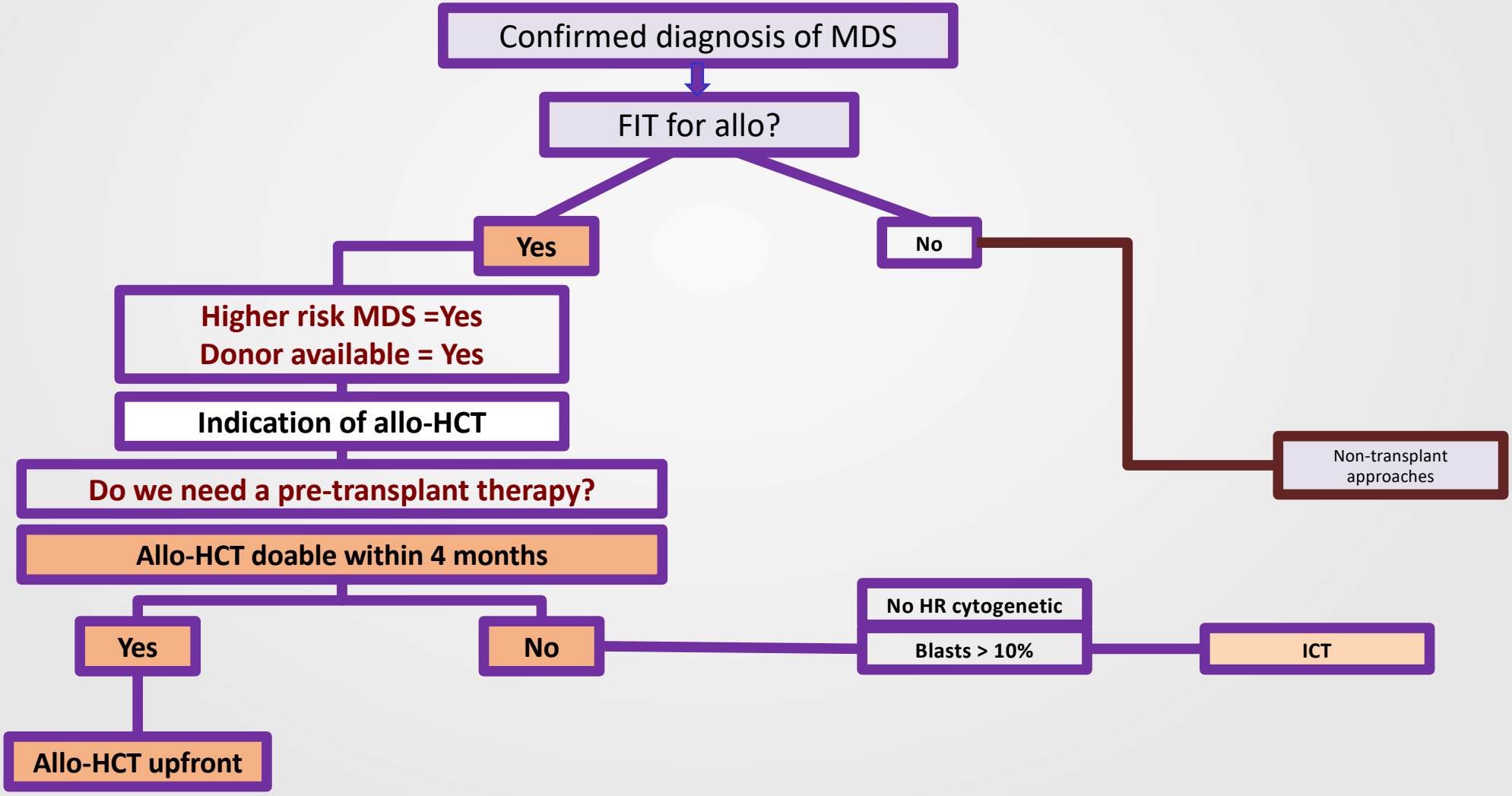

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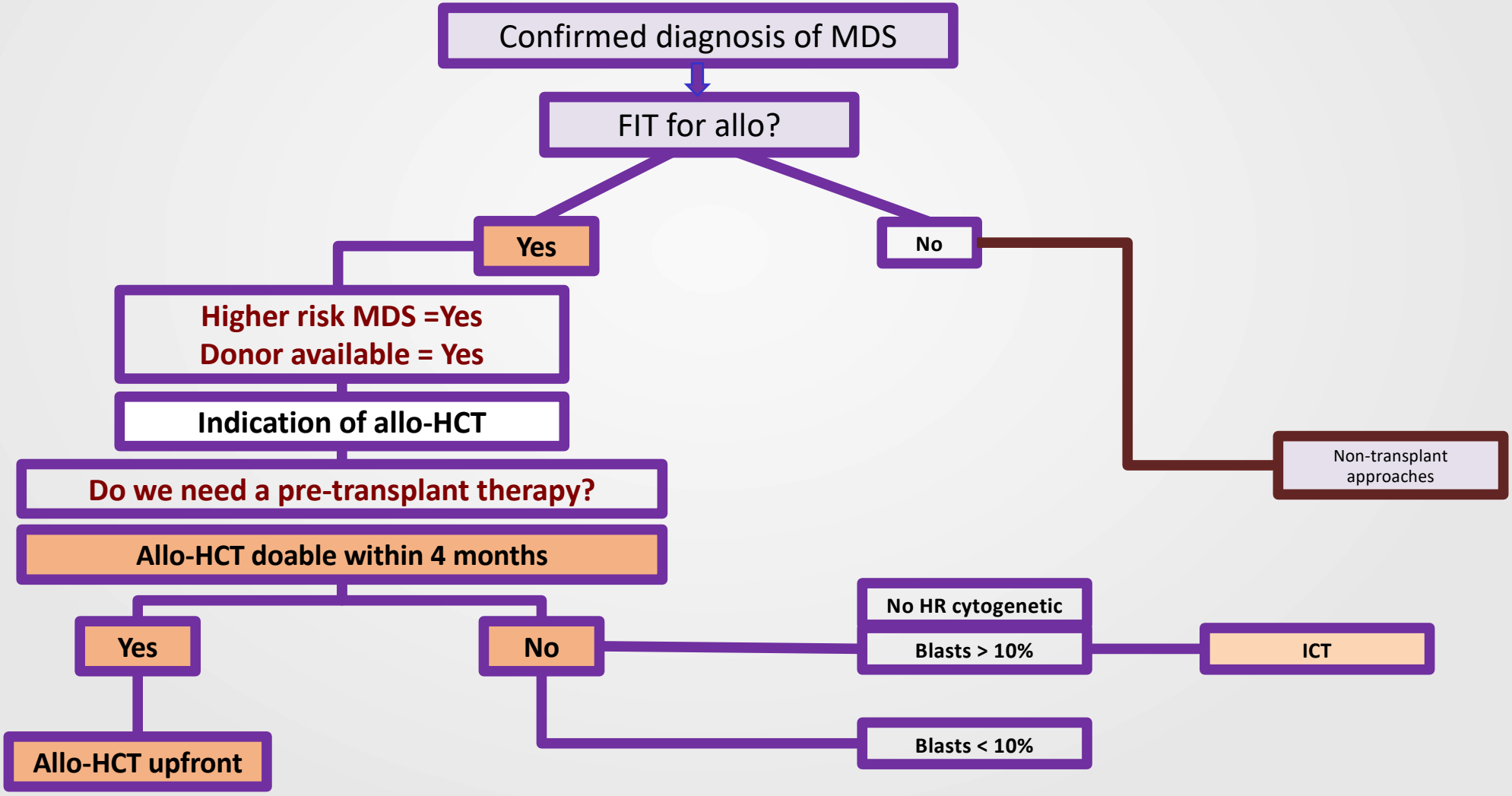

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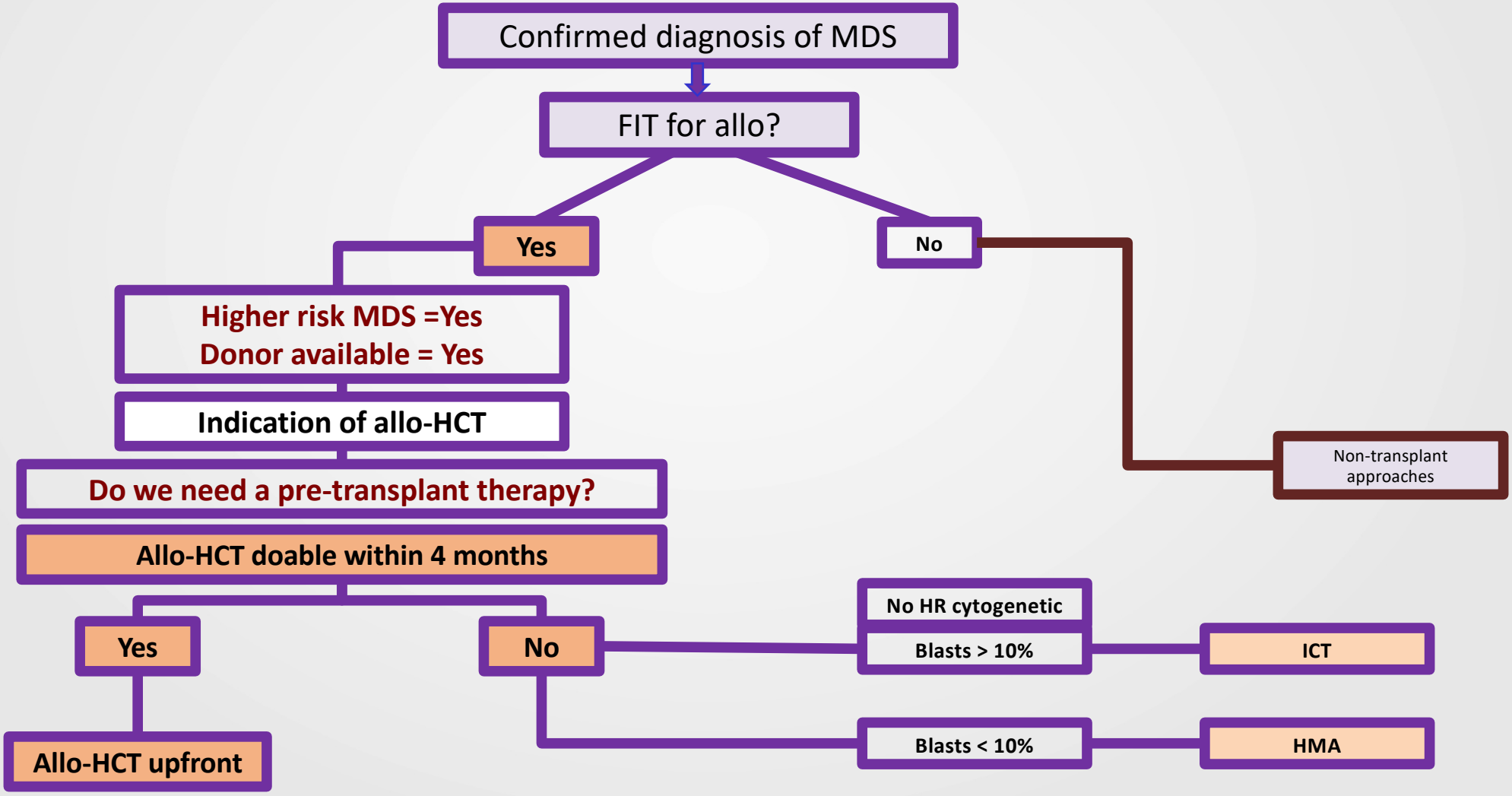

Adapted from I. Yakoub-Agha and J. Deeg, BBMT, 2014

CONCLUSION

- The ideal strategy to discern the post-HCT benefit of pretransplant cytoreductive therapy, and to identify the optimal agent, would be in the form of a randomized prospective study.

Thank you