Universitätsklinikum Hamburg-Eppendorf

Risk-adapted transplant for MDS:upfront

Myelodysplastic Syndromes: Chaos and Order

October 26, 2018, Meldola, Italy

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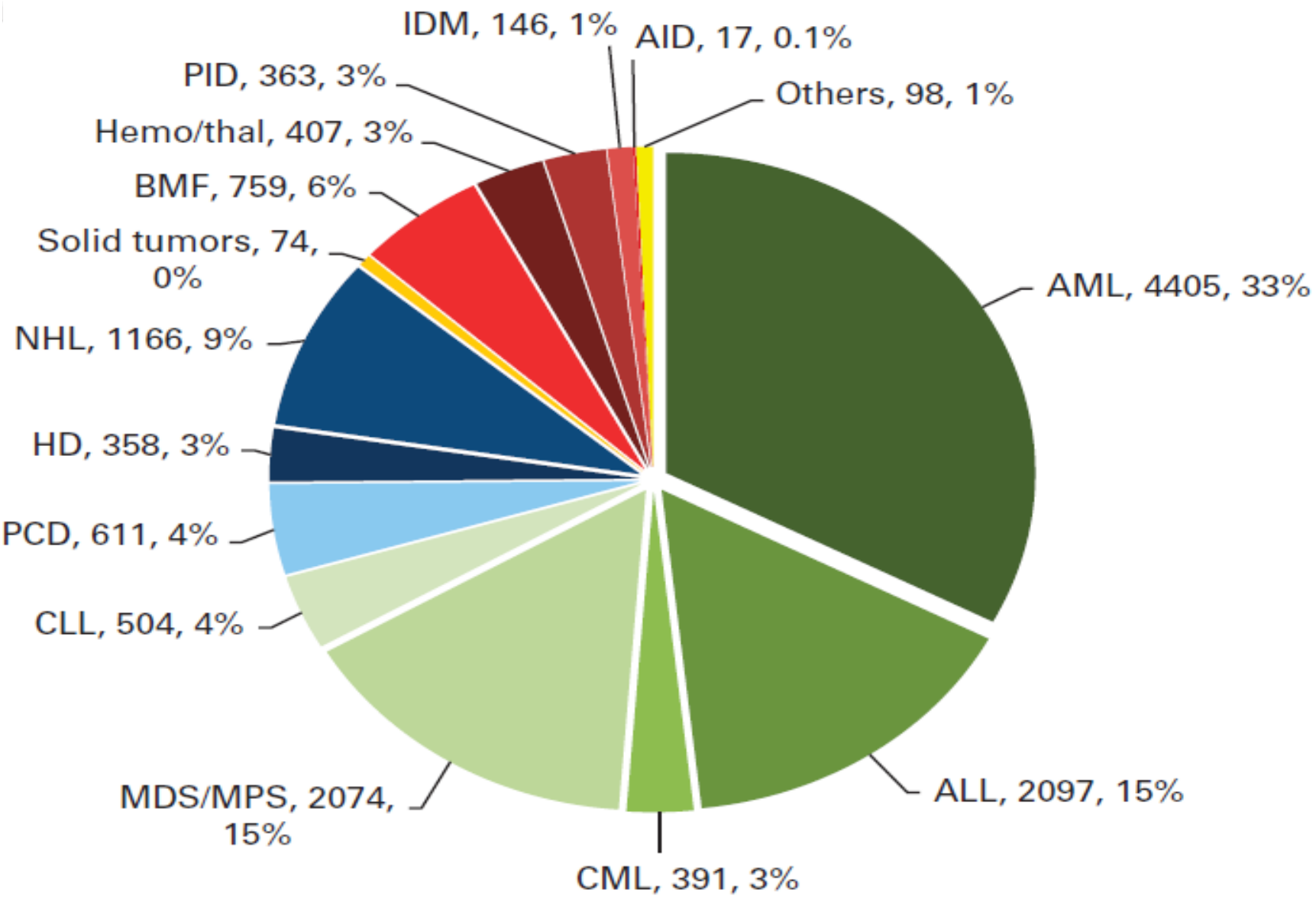
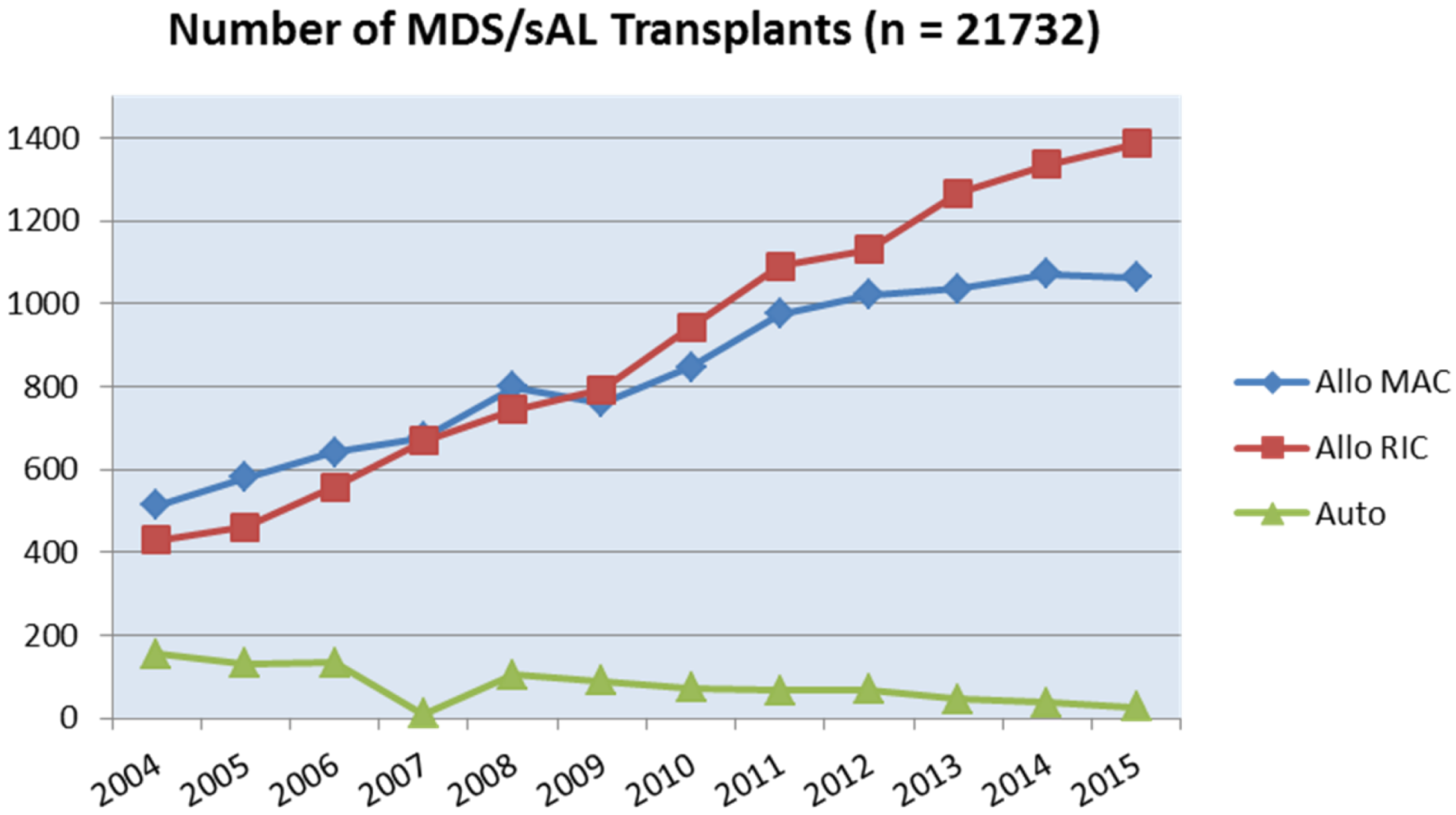
On behalf the MDS subcommittee of the CMWP (EBMT)

EBMT

Allogeneic SCT for MDS (EBMT data)

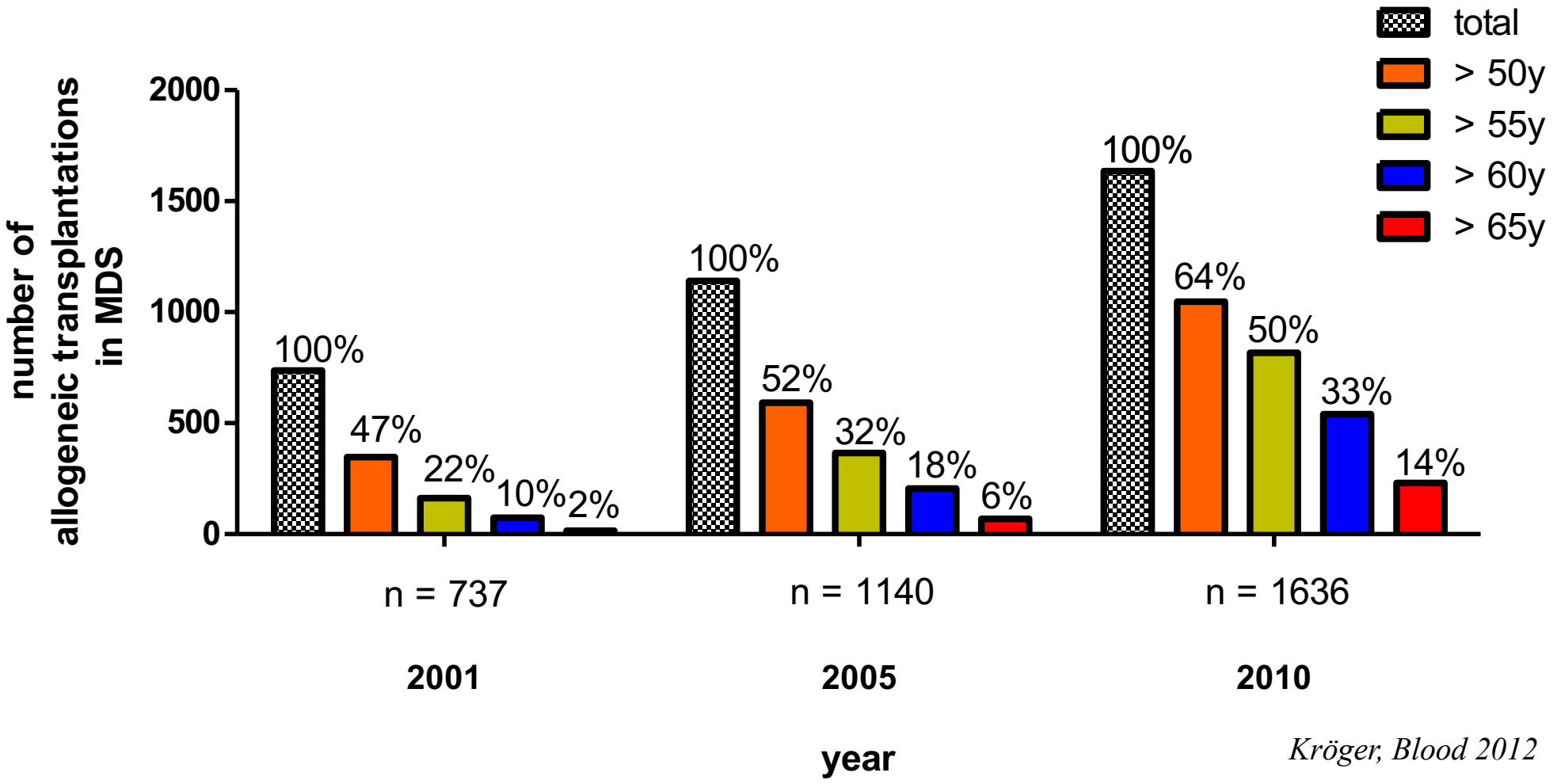


MDS transplant activity in Europe reported to EBMT



EBMT registry

Allo SCT for MDS in EBMT



Kröger, Blood 2012

Case report # 1

- 50 yr-old, female, good PS, no comorbidities, admitted due to neutropenic fever
- PB: Hb, 8.3 g/dL; WBC, 2.2 x 10^9/L (ANC, 0.35 x 10^9/L); Plt: 68 x 10^9/L
- BM: Blasts: 16%, no fibrosis
- Karyotype: 46,XX [20]
- Risk group: IPSS, int-2; IPSS-R, high
- No HLA-id sibling donor; a search for alternative donor is started

Question to case report # 1

Which would be your preferred option in this patient?

1. Wait for alternative donor availability without pre-treatment
2. Start intensive AML-type chemotherapy while waiting for the alternative donor
3. Start azacitidine while waiting for the alternative donor

Case report # 2

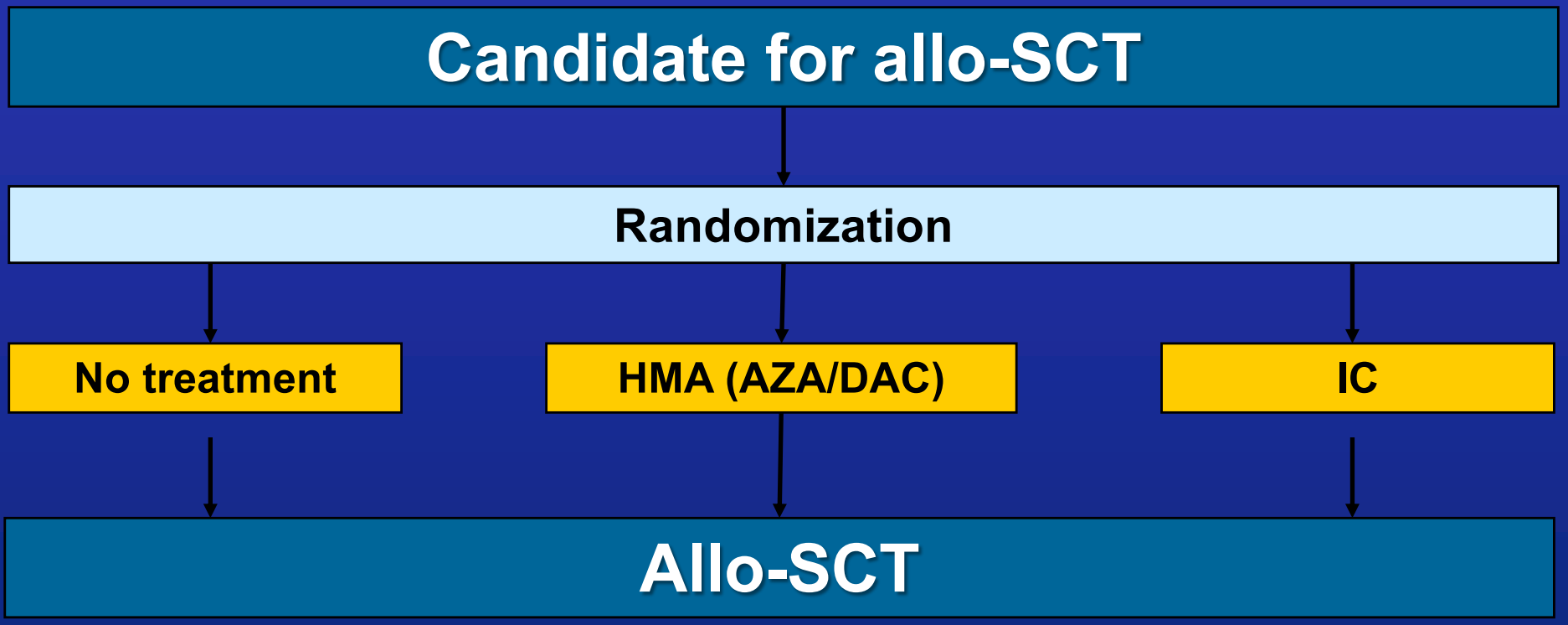
- 64 yr-old, female, no comorbidities, admitted due to neutropenic fever
- PB: Hb, 8.3 g/dL; WBC, 2.2 x 10^9/L (ANC, 0.35 x 10^9/L); Plt: 68 x 10^9/L
- BM: Blasts: 16%, no fibrosis
- Karyotype: 45,XX,-7 [12],46,XX [8]
- Risk group: IPSS, high; IPSS-R, very high
- No HLA-id sibling donor; a search for alternative donor is started

Question to case report # 2

Which would be your preferred option in this patient?

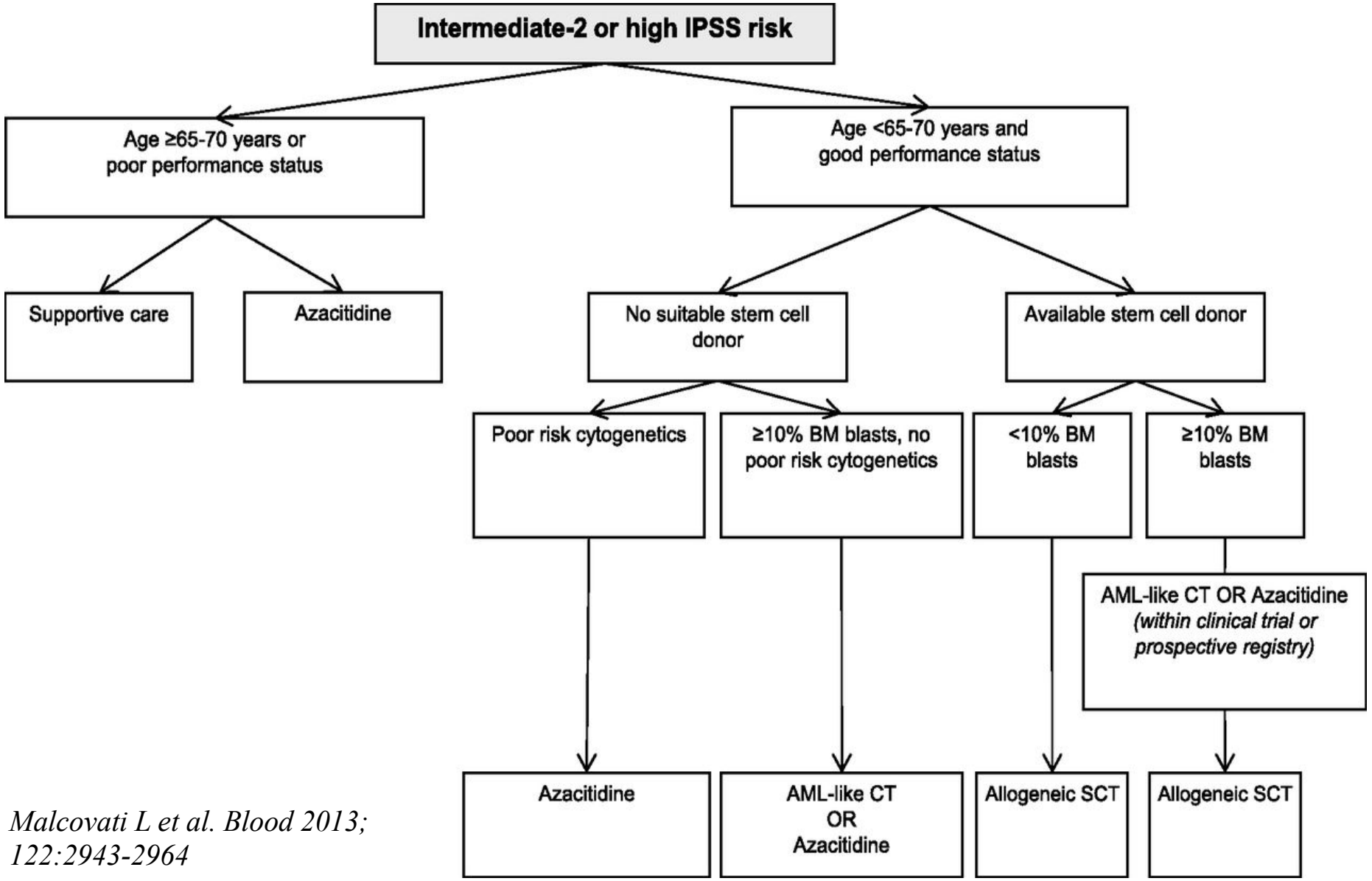
1. Wait for alternative donor availability without pre-treatment
2. Start intensive AML-type chemotherapy while waiting for the alternative donor
3. Start azacitidine while waiting for the alternative donor
4. Start azacitidine or AML-type chemotherapy. If a CR is achieved I would continue that treatment without transplant until progression

Pre-treatment
No prospective randomized trial available



Studies do not include patients who fail pre-treatment or progress without pre-treatment and are not referred to transplantation: potential bias

Therapeutic algorithm for adult pts with primary MDS + intermediate-2 or high IPSS score (ELN)



Malcovati L et al. Blood 2013; 122:2943-2964

Pre-treatment
Main reasons for preconditioning therapy

- Lower the burden of disease
  - Aim: To reduce relapse risk and improve survival
  - Classical indications:
    - Excess of blasts (usually > 10%; > 5% if RIC)
    - Poor-risk cytogenetics
- Logistics
  - Aim: To stabilize the disease while waiting for the transplant
  - Classical indication:
    - Search for an alternative donor (MUD/Haplo)

Pre-treatment
Disadvantages of preconditioning therapy

- Prevent the patient from reaching the transplant or increase NRM after SCT
  - Death or serious adverse events
    - Intensive chemotherapy (~ 20 – 30%)
    - Hypomethylating drugs (unknown, likely < 15%)
- Failure to reduce burden of disease
  - Refractory disease or progression
    - Intensive chemotherapy (~ 25 – 30%)
    - Hypomethylating drugs (> 40%)

Reducing Risk of Relapse after allogeneic SCT for MDS

AML-like induction-chemotherapy in RAEB-T/sAML prior HLA-identical sibling stem cell tranplantation

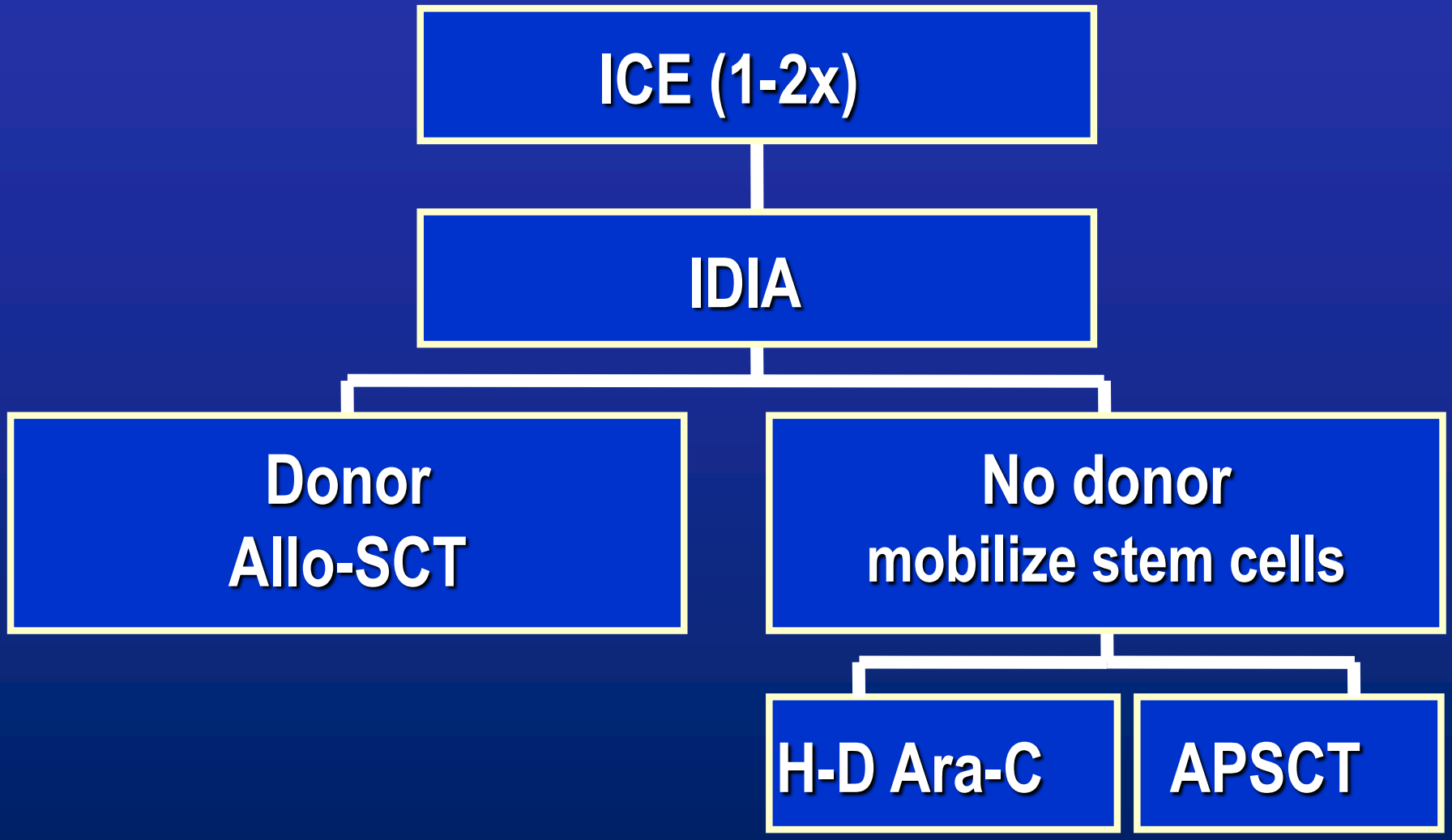
Retrospective registry data from EBMT

	DFS	*Relapse*	*TRM*
Without induction chemotherapy (n=111)	32%	43%	32%
In 1.CR after induction chemotherapy (n=230)	44%	30%	37%
Induction chemotherapy but without CR (n=440)	29%	42%	45%

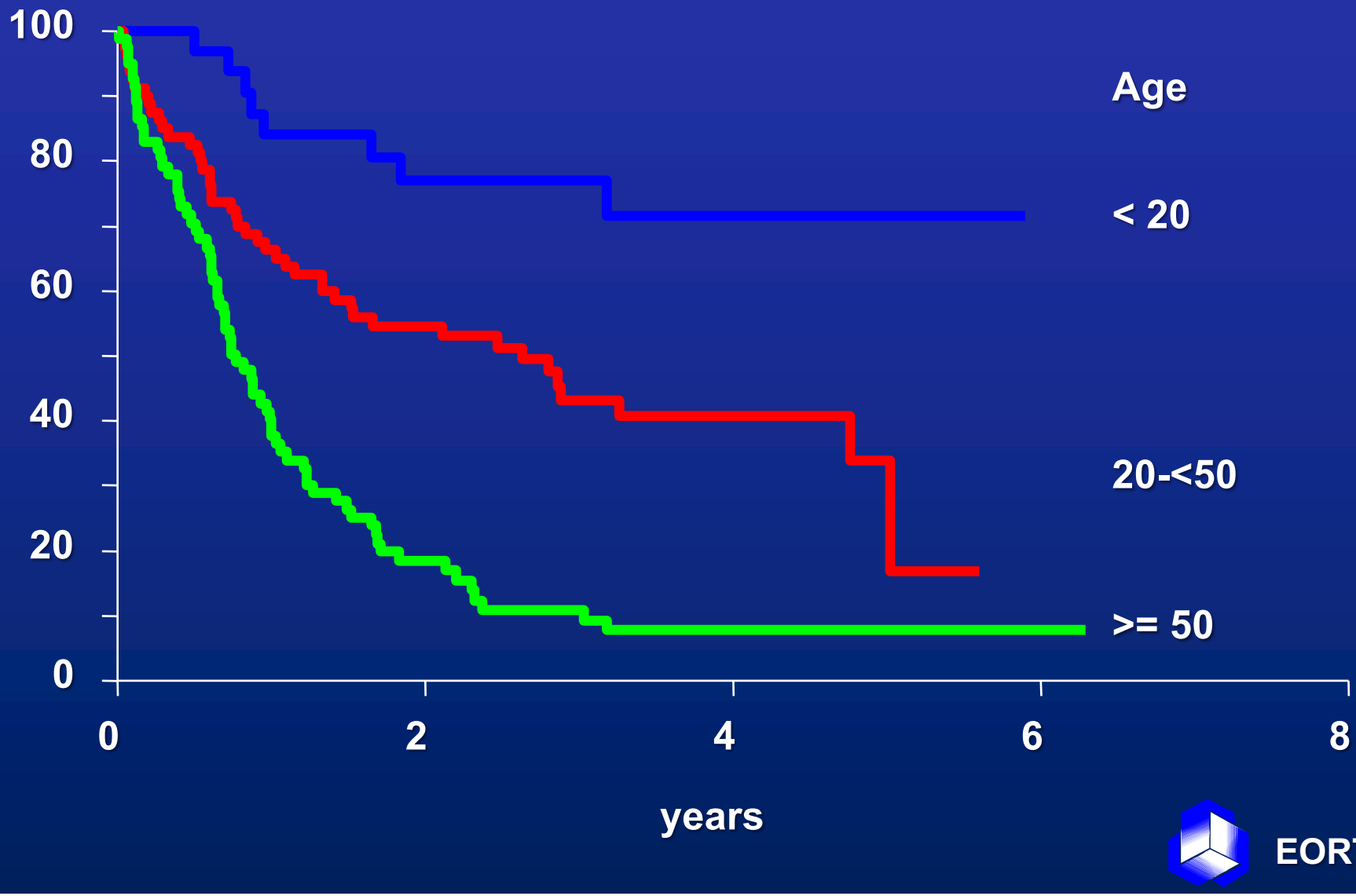
(unpublished results)

EBMT

Postremissionstherapy in poor MDS/sAML
CRIANT- Study (EORTC)

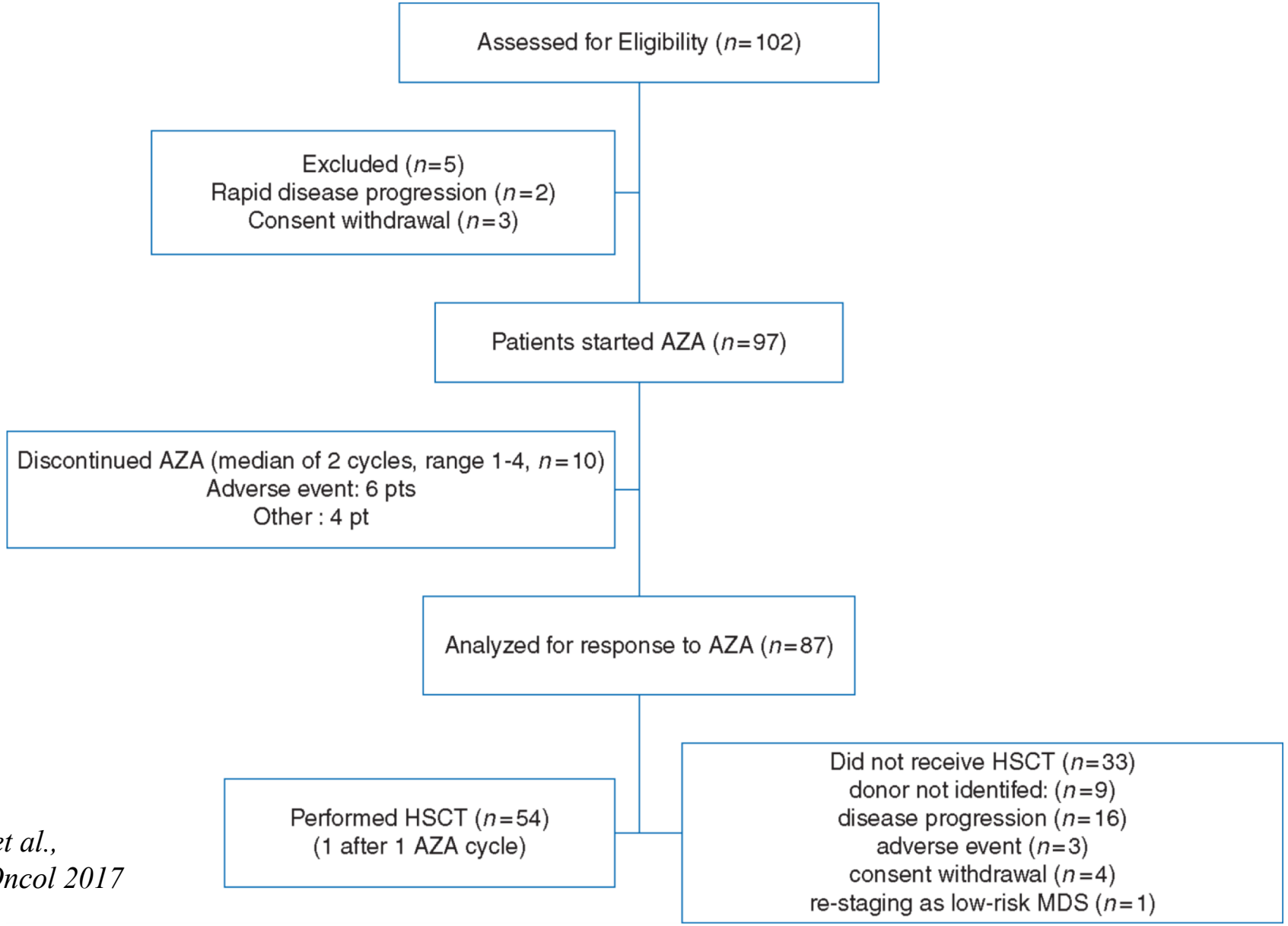


CRIANT: Survival according age



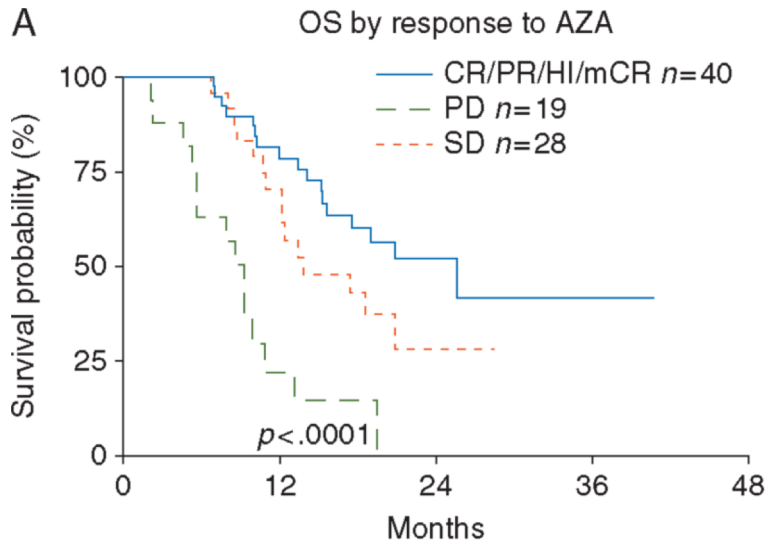
EORTC LG

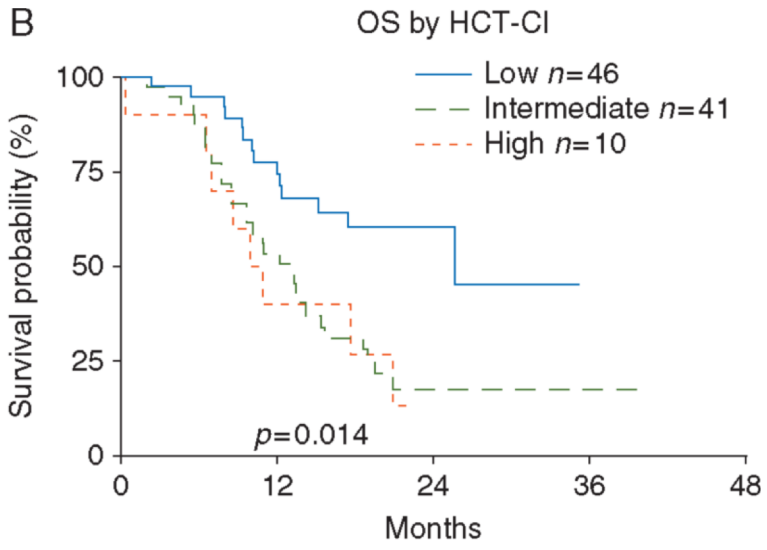
5- Azacytidine for bridging to allogeneic SCT: MDS/AML

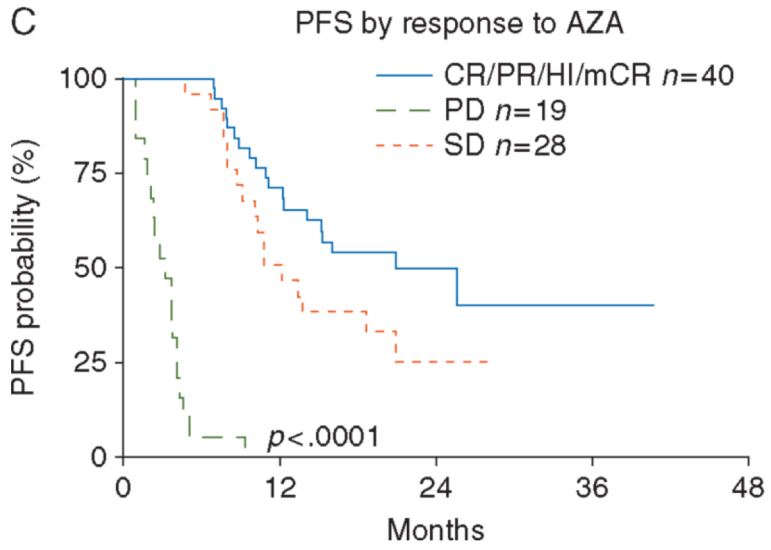


Voso et al.,
Ann Oncol 2017

5- Azacytidine for bridging to allogeneic SCT: MDS/AML







Prospective Vidaza-allo study

MDS (age 55-70 years) IPSS: intermediate II or high risk
(and intermediate I with high risk cytogenetic)

Registration

5-Azacytidine (Vidaza®) 7x75 mg/m² s.c. (q28d)
4 cycles plus donor search (HLA-identical sibling or matched unrelated donor (10/10)

After 4 (max 6) cycles of Vidaza®

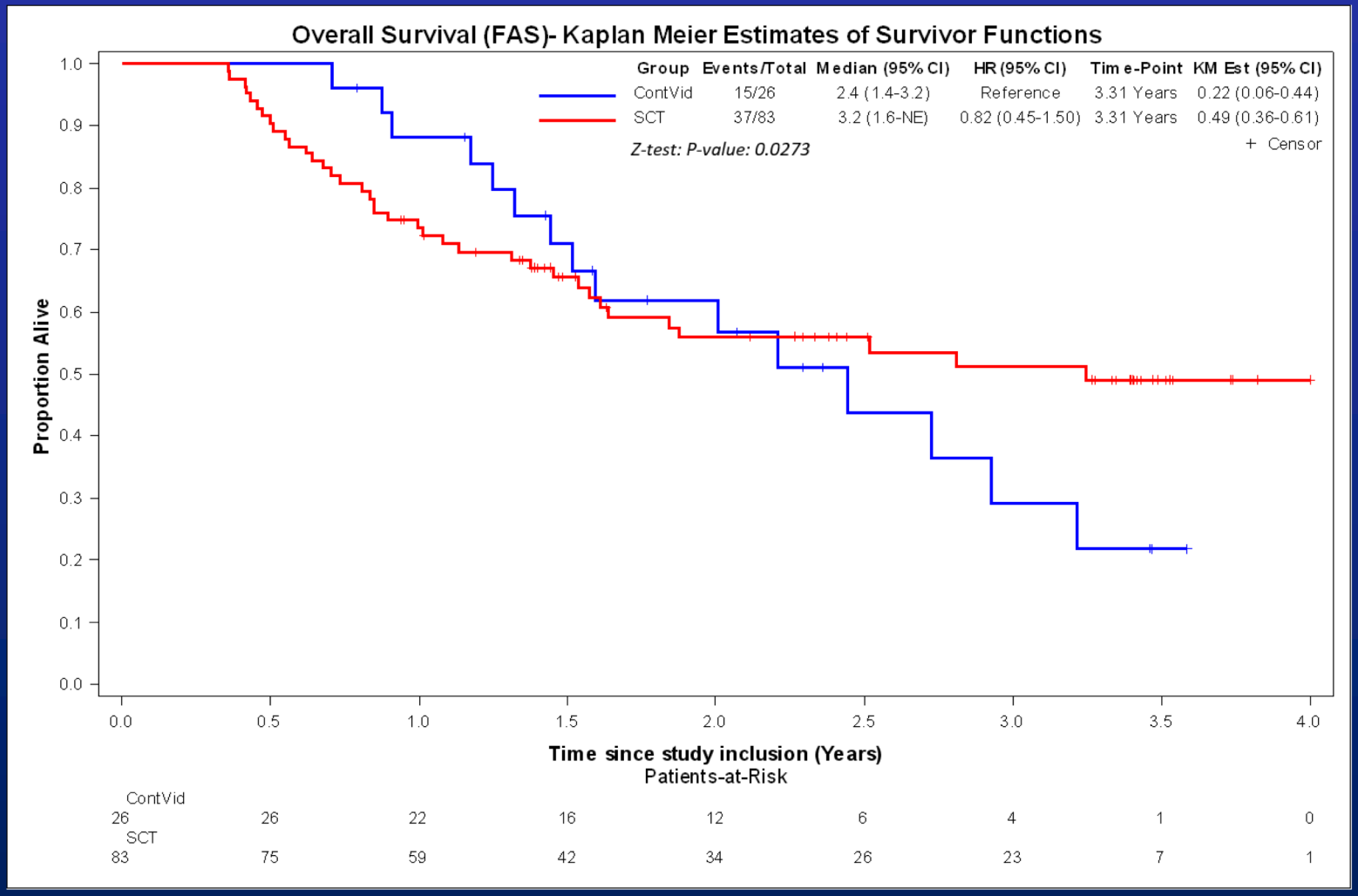
No donor available:
Continue with Vidaza® treatment until progress or unacceptable toxcities

Donor available:
Allogeneic stem cell transplantation after reduced intensity conditioning*

possible RIC regimen:
- Busulfan 8 mg/kg (or Busilvex 6,4 mg/kg) plus Fludarabine (150 mg/m²)
- FLAMSA plus Busulfan 8 mg/kg (or Busilvex 6,4 mg/kg) plus Fludarabine (60 mg/m²)

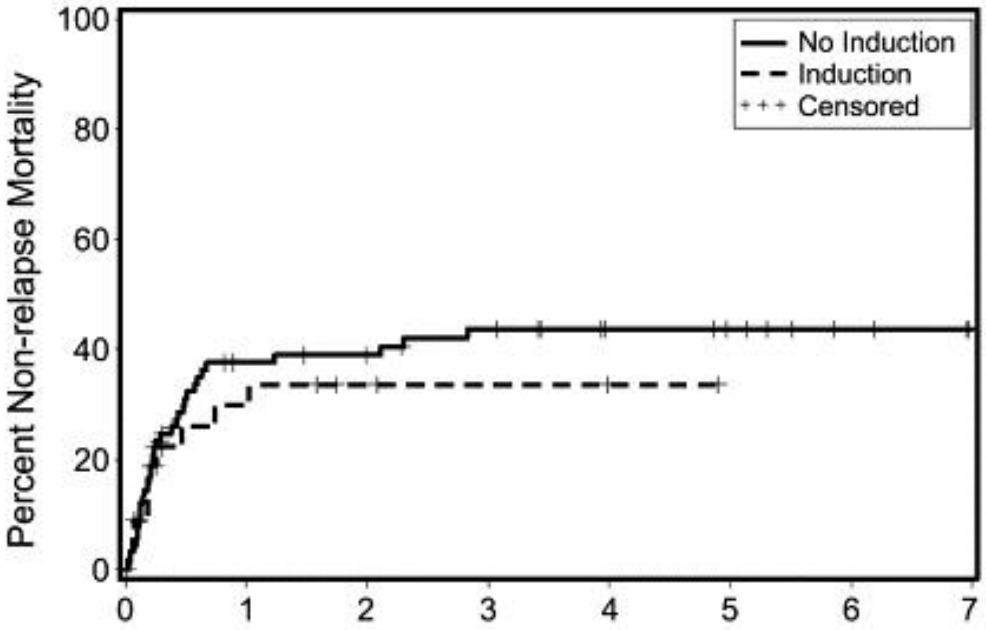
Prospective Vidaza-allo study

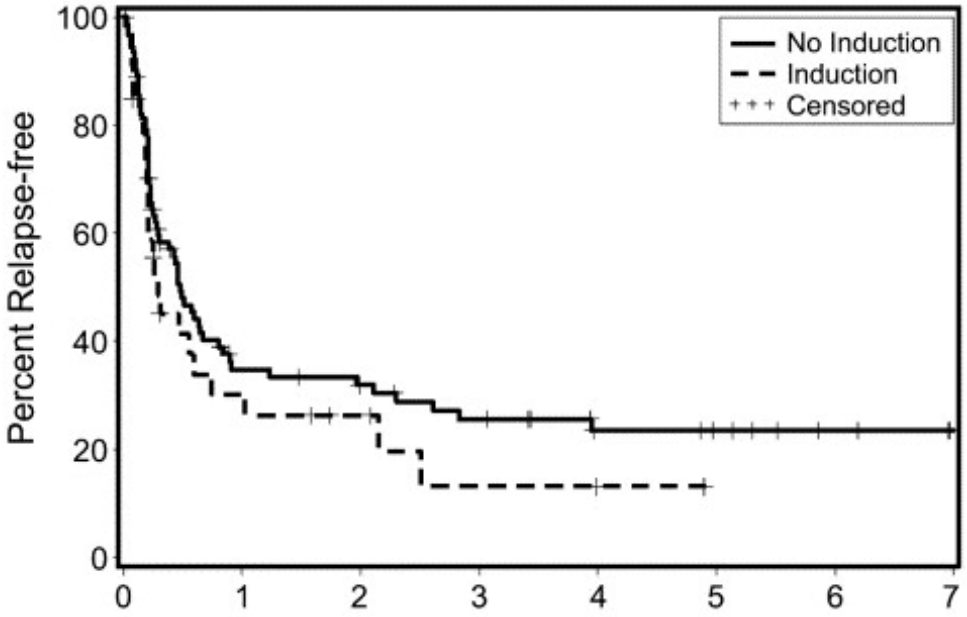
Between June 2011 and November 2016 190 patients with a median age of 63 years (range, 55 to 72y) from 14 German centers were included
43% (n= 81) could not be selected after 5 Aza induction for one of the treatment arm because of progressive disease (n=25; 31%), mortality (n=14; 17%), inclusion or exclusion criteria not fulfilled (n=18, 22%),



Pre-treatment
IC versus no treatment

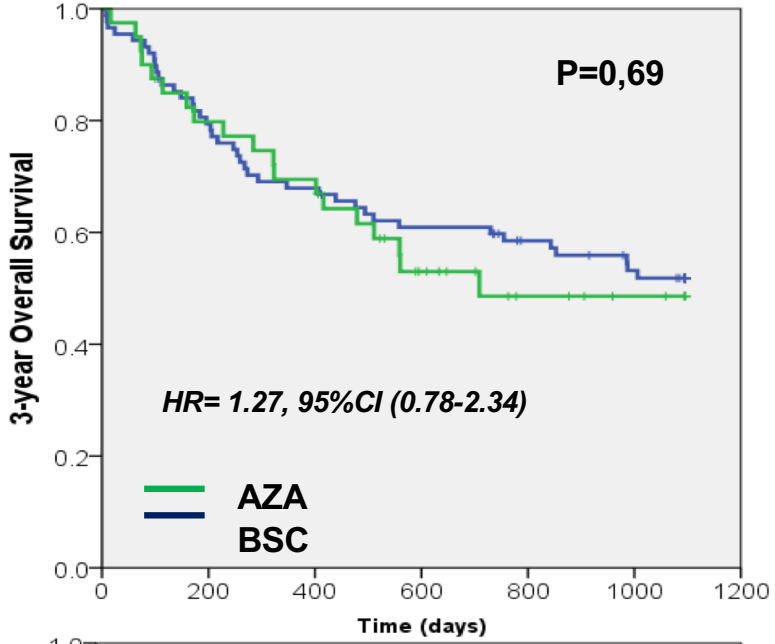
- 125 patients: IC (n = 33), no IC (n = 92)
- All received myeloablative conditioning
- No differences in RR, NRM, and RFS

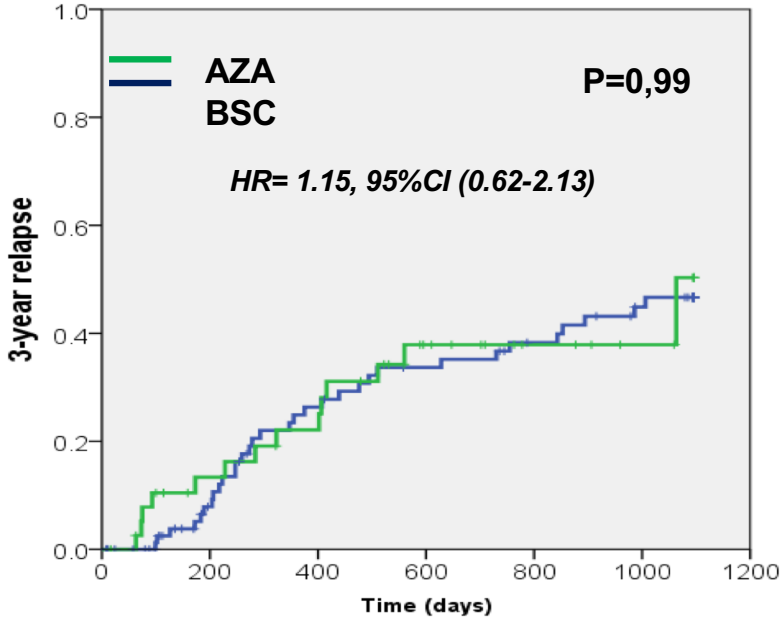


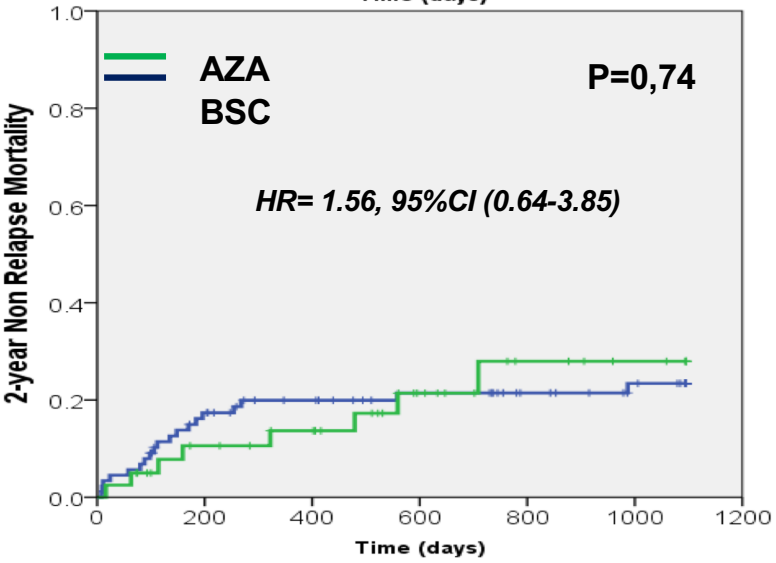


Scott BL et al. Biol Blood Marrow Transplant 2005;11:65-73

Pre-treatment
Azacitidine versus no treatment





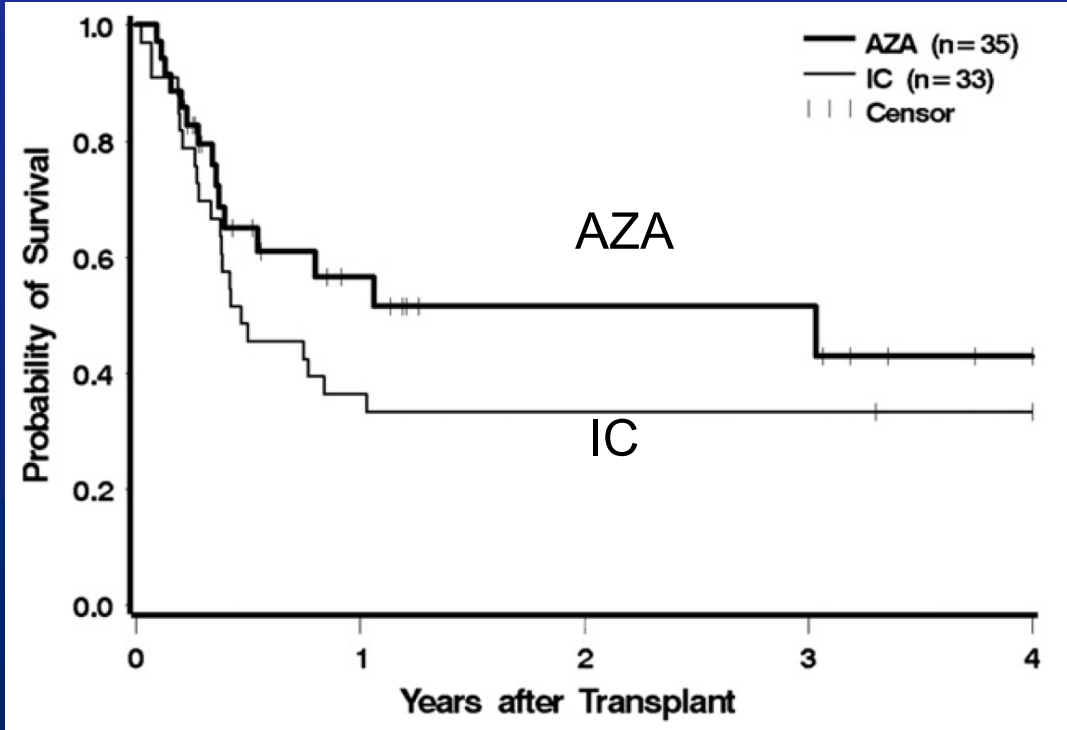


- 128 patients; AZA (n = 40), BSC (n = 88)
- All received RIC
- RD (n = 78), and URD (n = 50)
- AZA group older (P < .001), higher IPSS (P = .003), and more often URD (P < .001)

Damaj G et al. BBMT 2014;20:1349-1355.

Pre-treatment
Azacitidine versus intensive chemotherapy

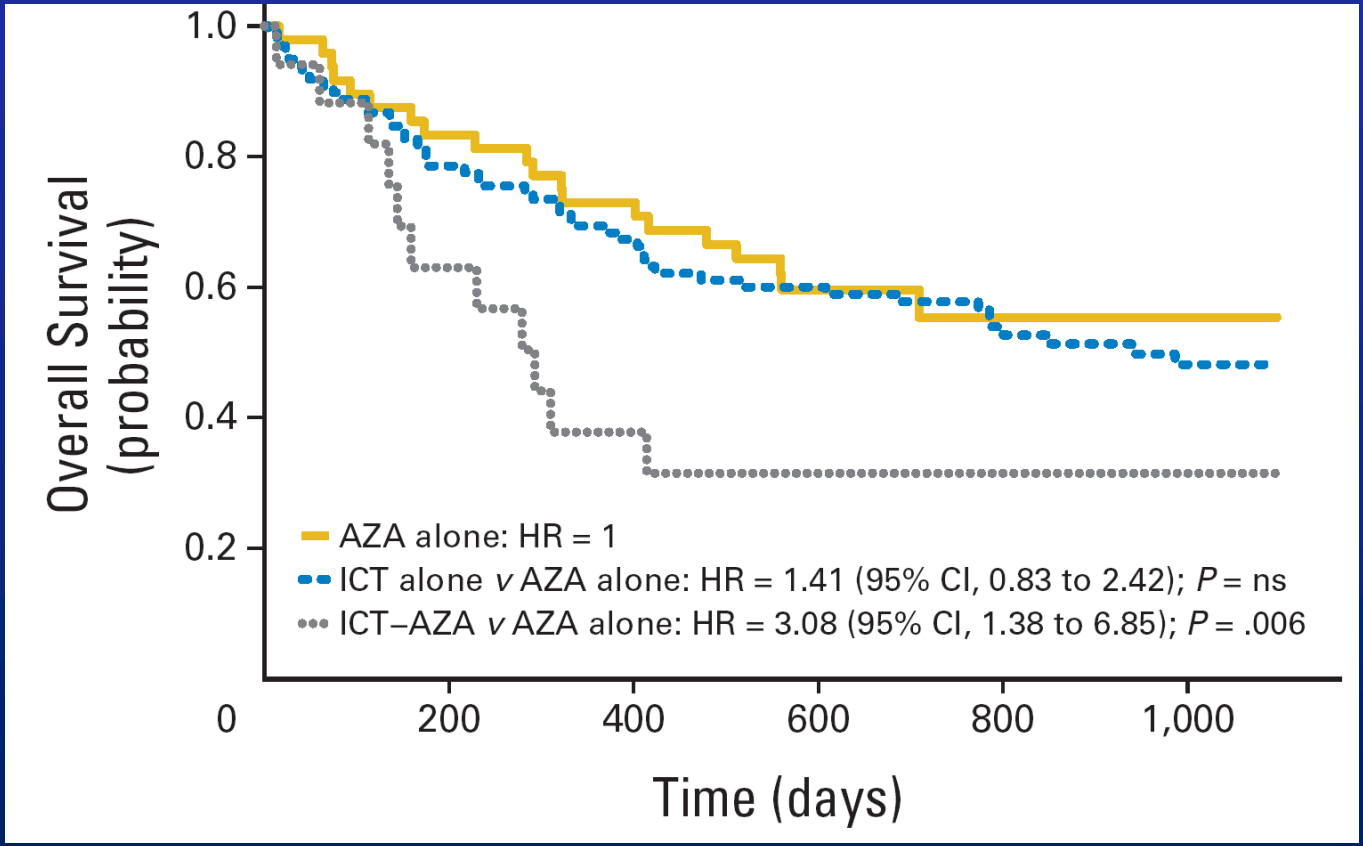
- 68 pts: IC (n = 33, all myeloablative), AZA (n = 35, 60% RIC)
- AZA patients were older (median age, 60 y vs 47 y), had less advanced disease, and had more frequently an URD (P = .002)
- No significant differences in RR, NRM, and OS were evident in multivariate analysis



Gerds AT, et al. Biol Blood Marrow Transplant 2012;18:1211-8.

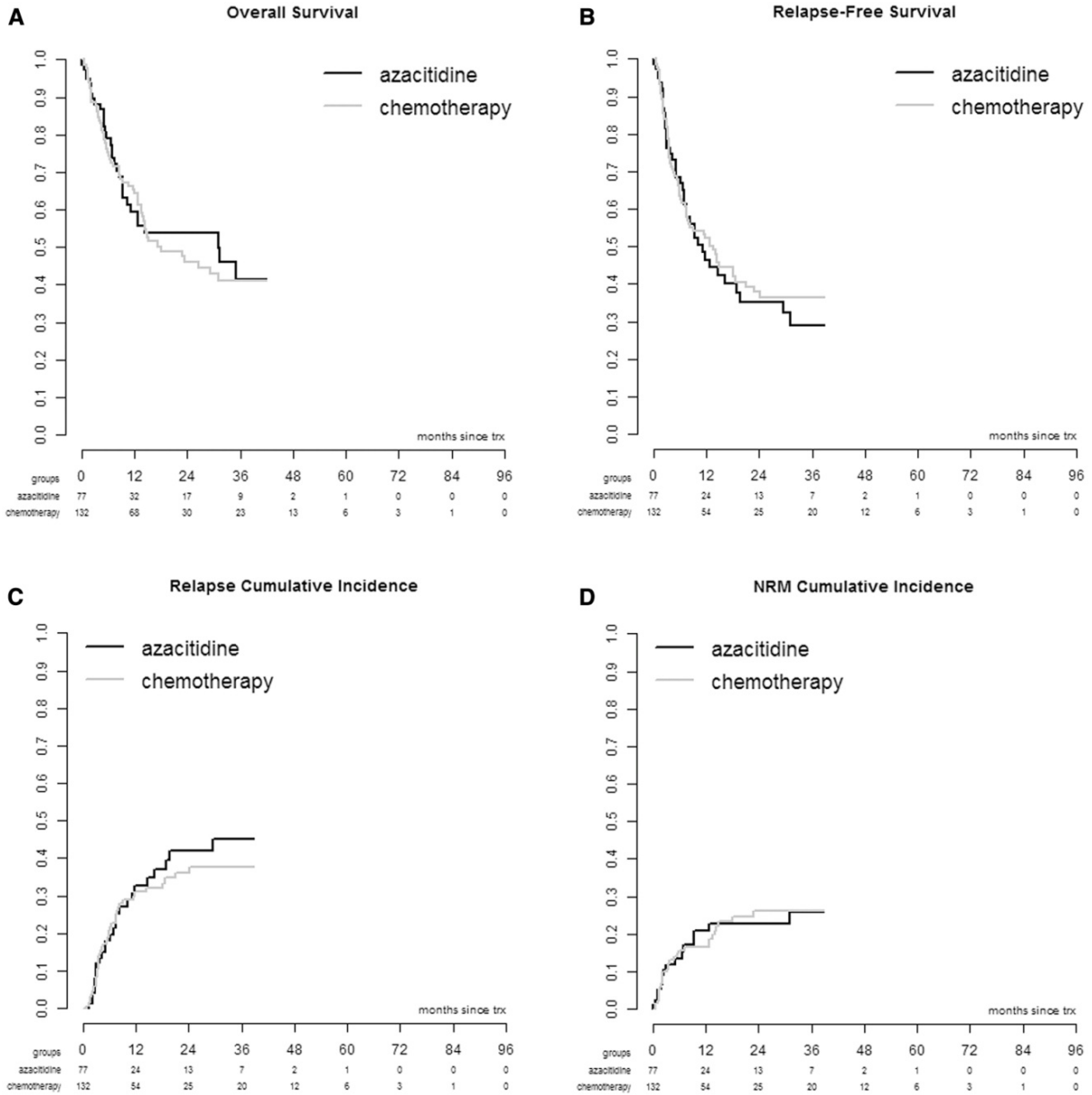
Pre-treatment
Azacitidine versus intensive chemotherapy

- 163 pts (AZA, 48; ICT, 98; AZA-ICT, 17)
- Donors: siblings, 75; MUD, 88
- Conditioning: RIC, 130; MAC, 33



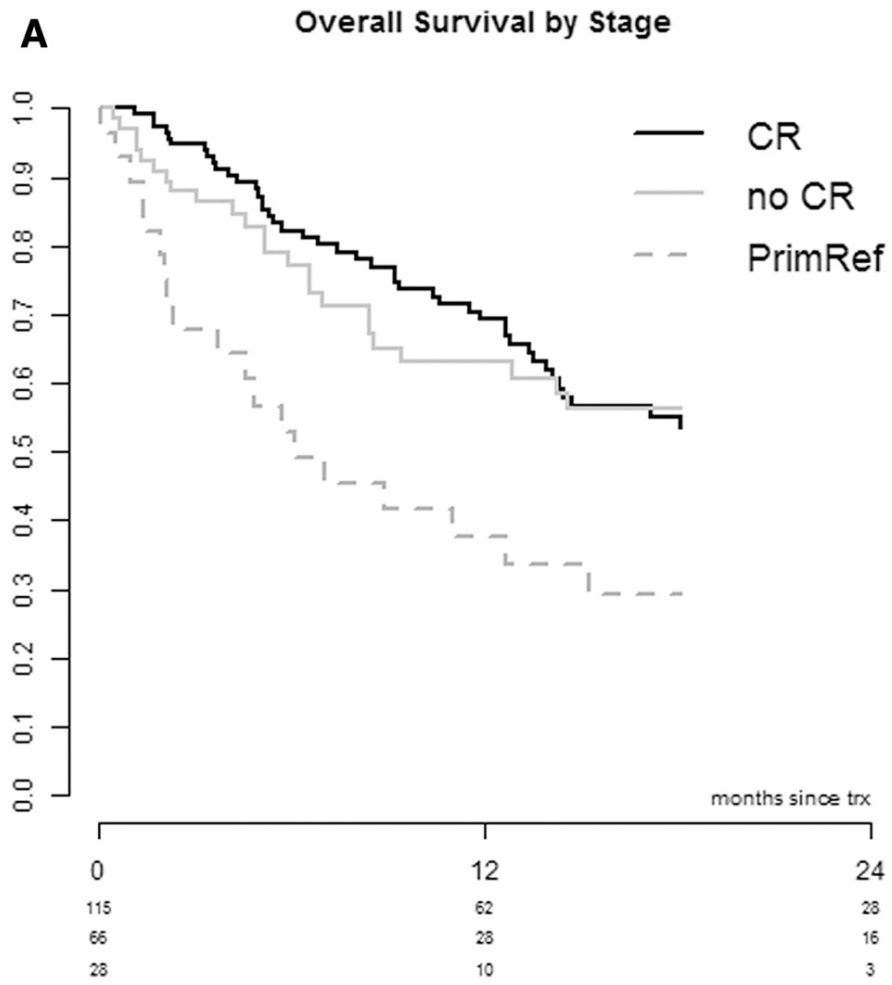
Damaj G, et al. J Clin Oncol 2012; 30: 4533-40.

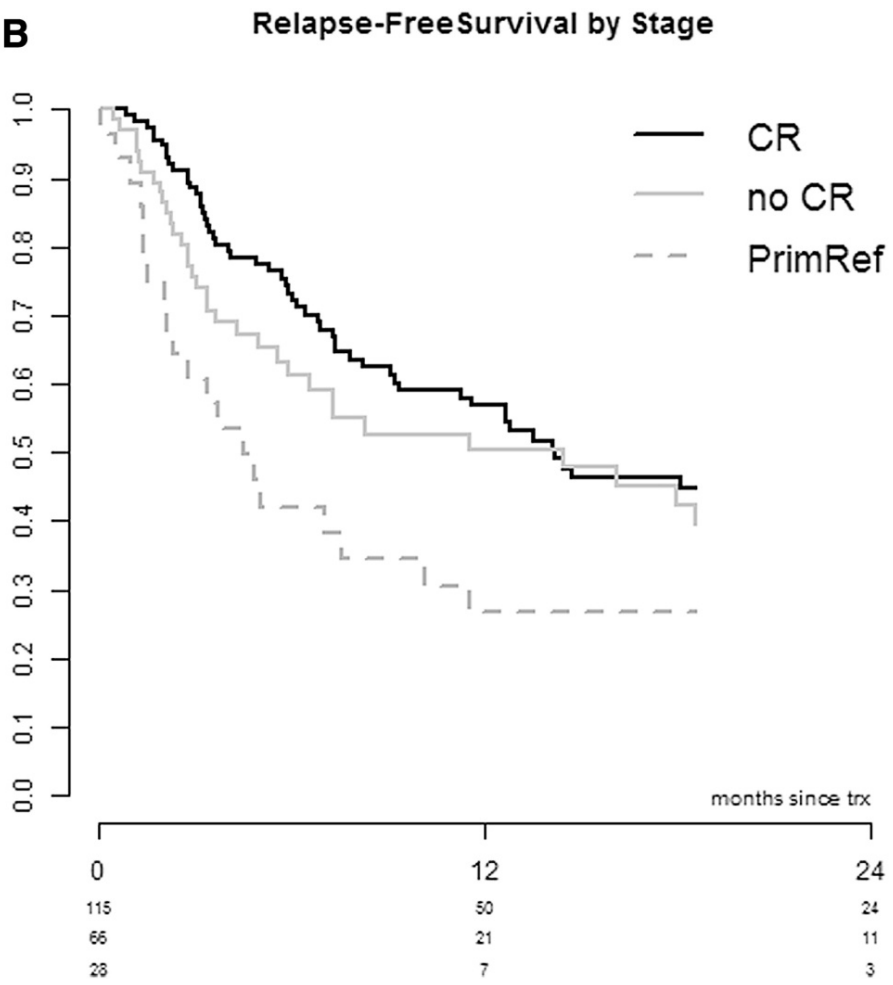
Pre-treatment
Azacitidine vs intensive chemotherapy (EBMT)



V. Potter et al Biology of Blood and Marrow Transplantation 2016 22, 1615-1620

Pre-treatment
Azacitidine vs intensive chemotherapy (EBMT)

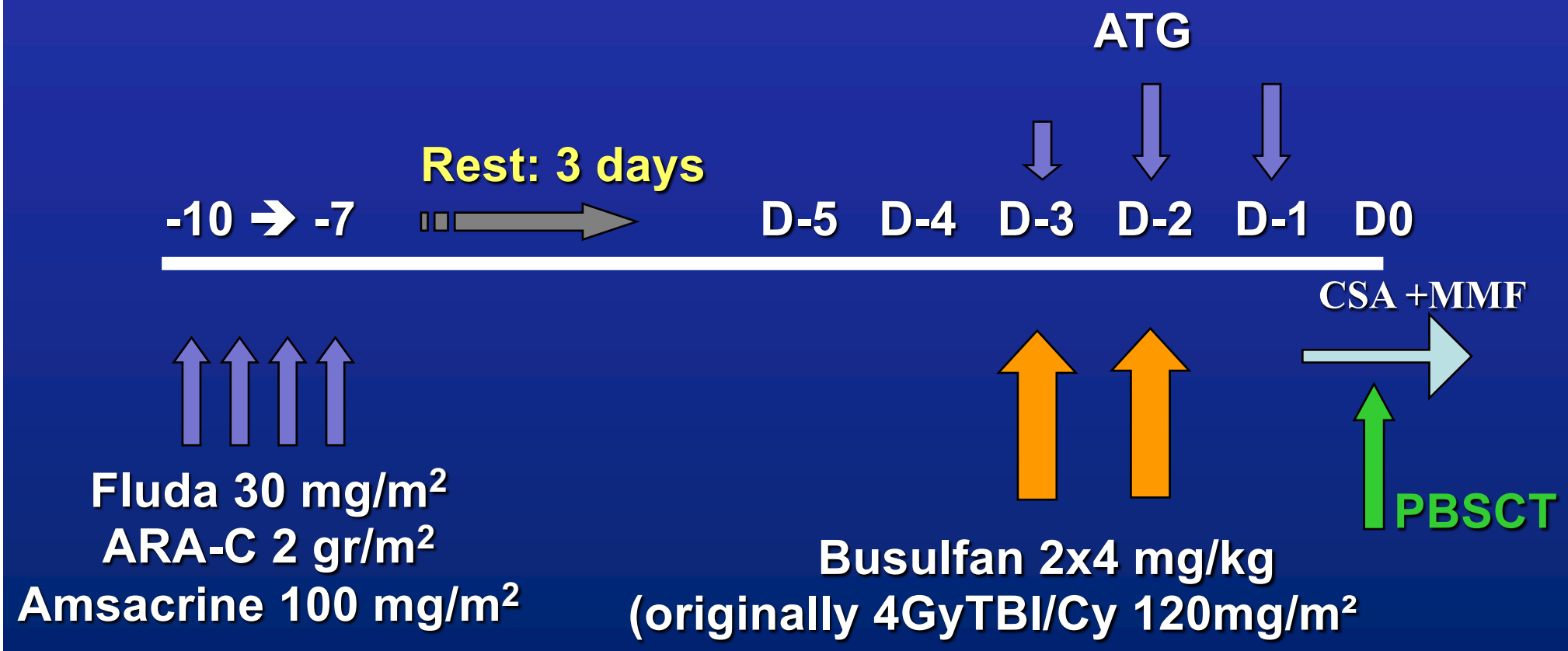




V. Potter et al Biology of Blood and Marrow Transplantation 2016 22, 1615-1620

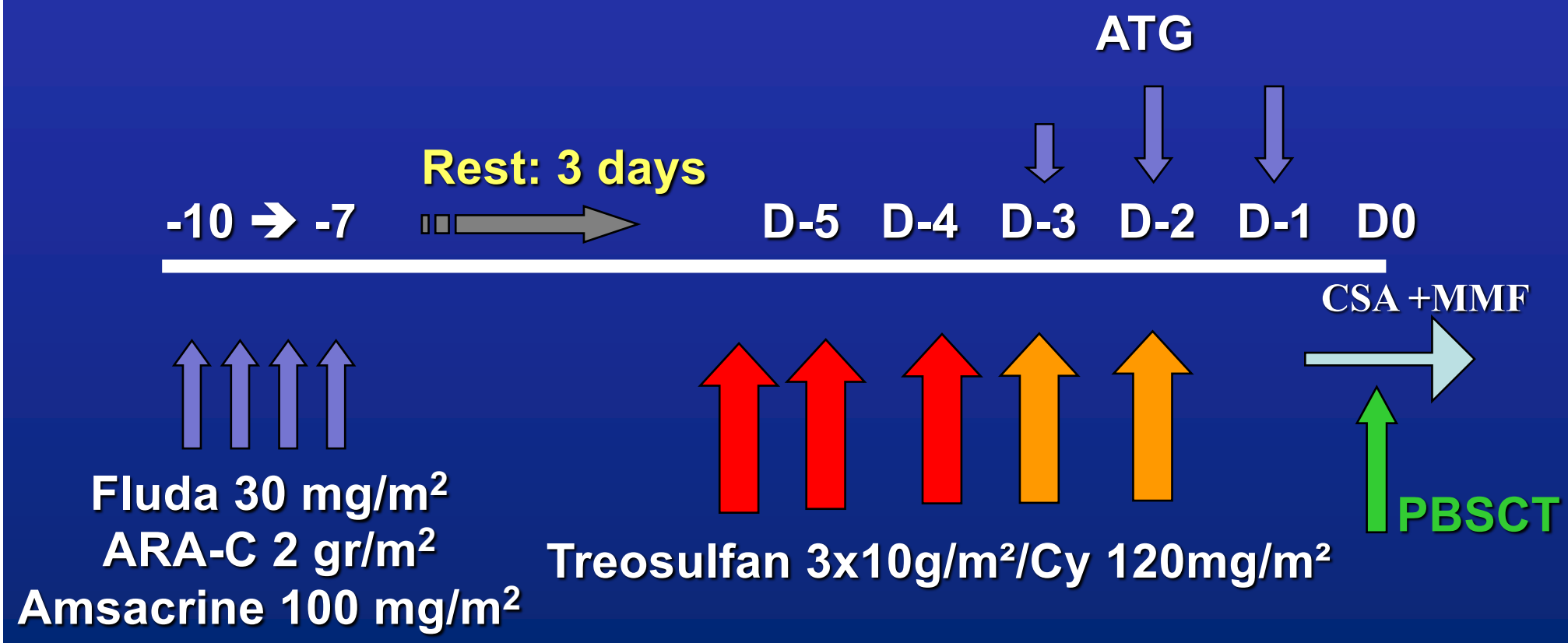
Induction followed by immediate conditioning

FLAMSA protocol



adapted from H.J Kolb

Induction followed by immediate conditioning



Chemnitz et al., 2011

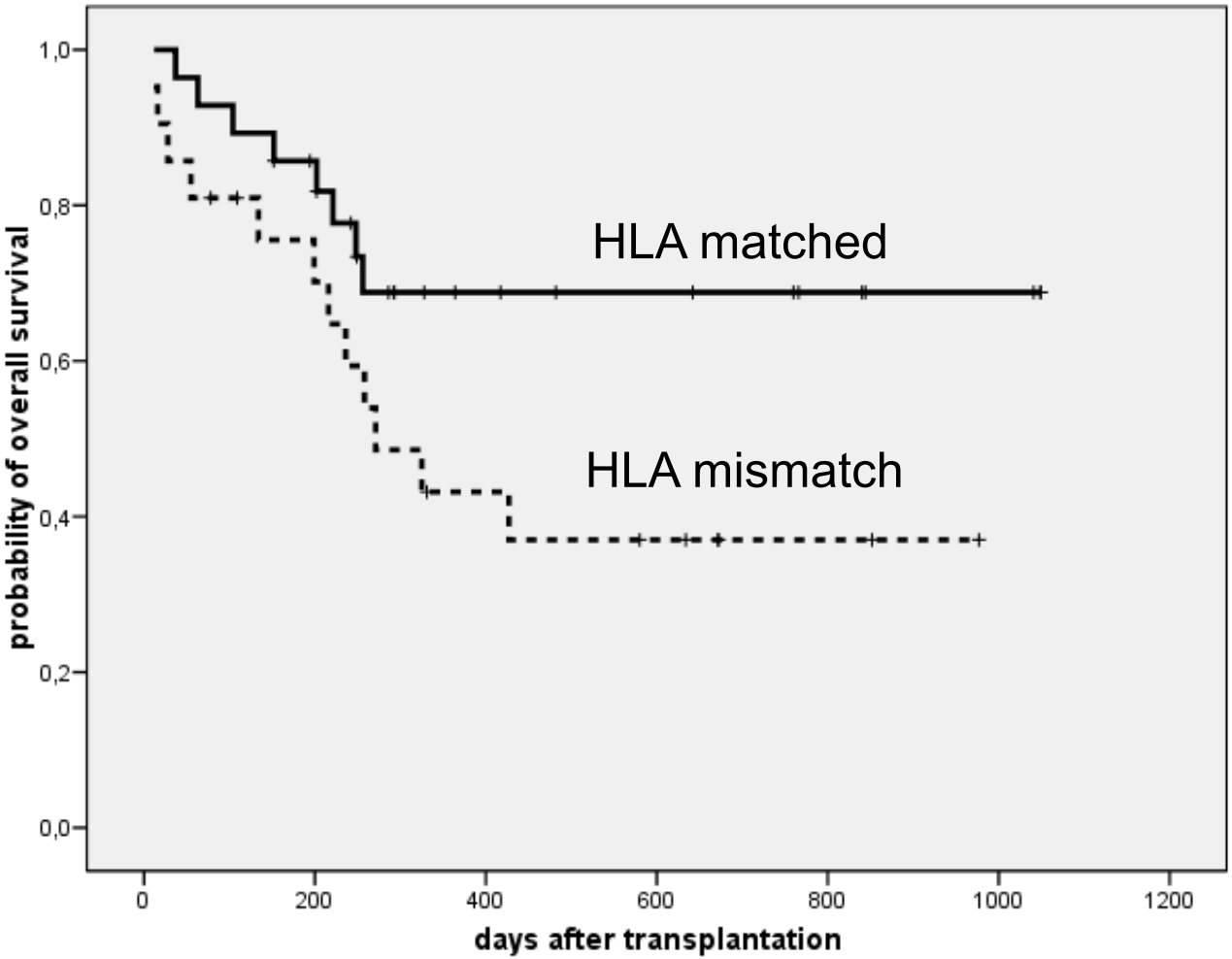
Sequential chemotherapy followed by reduced intensity conditioning

Amsacrine/fludarabine/ARA-C followed by busulfan (8 mg/kg) and fludarabine (60 mg/m^2) and ATG

- n = 77
- MDS (n = 36), CMML (n =11), sAML (n = 15)
- Median age: 61 years (r, 26 - 73)
- Donor: MUD (n = 65), related (n = 12)
- HLA 10/10: n= 46 MMUD: n=31
- Median blasts at SCT: 12% (r, 0 – 60)

Kröger et al. (unpublished)

Sequential chemotherapy followed by reduced intensity conditioning



Kröger et al. unpublished

Case report # 1

- 50 yr-old, female, good PS, no comorbidities, admitted due to neutropenic fever
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- BM: Blasts: 16%, no fibrosis
- Karyotype: 46,XX [20]
- Risk group: IPSS, int-2; IPSS-R, high
- No HLA-id sibling donor; a search for alternative donor is started

My personal choice:
I would wait for MUD, then sequential conditioning (FLAMSA)

Case report # 2

- 62 yr-old, female, no comorbidities, admitted due to neutropenic fever
- PB: Hb, 8.3 g/dL; WBC, 2.2 x 109/L (ANC, 0.35 x 109/L); Plt: 68 x 109/L
- BM: Blasts: 16%, no fibrosis
- Karyotype: 45,XX,-7 [12],46,XX [8]
- Risk group: IPSS, high; IPSS-R, very high
- No HLA-id sibling donor; a search for alternative donor is started

My personal choice:
I would wait for MUD, then sequential conditioning (FLAMSA))

Pre-treatment
Azacitidine vs intensive chemotherapy

- Data do not allow definite recommendations on the best type of pre-treatment
- Subsets of patients who could benefit from pre-treatment cannot be properly defined
- Decision should be made on an individual basis
  - Characteristics of the disease (blasts, cytogenetics)
  - Characteristics of the patient (age, comorbidity)
  - Characteristics of the transplant (conditioning, alternative donor)
  - Patient's choice