Conditioning for allos

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Internal Medicine II

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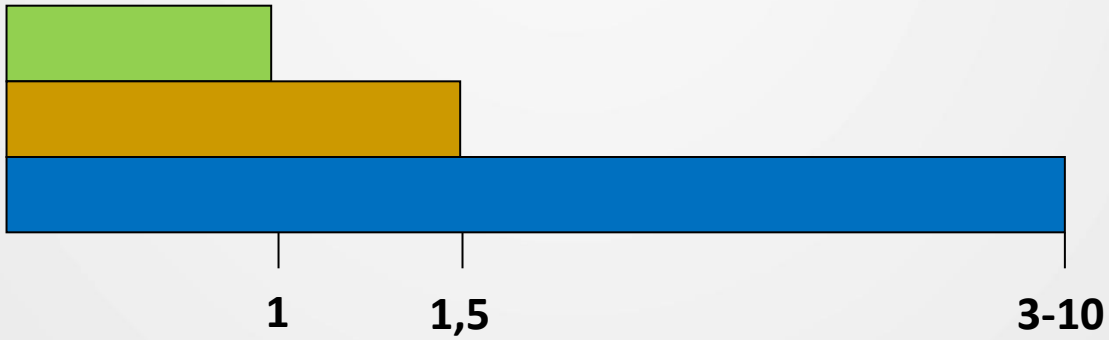
Agenda

- Rational for high dose chemotherapy
- What is a myeloablative conditioning regimen?
- Comparative trials of HD-therapy and ASCT vs conventional chemotherapy
- Dose-adapted high dose regimens in Auto SCT?
- Conditioning for allo SCT
  MAC-RIC-NMA
- Why do we need NMA/RIC?
- Comparative trials RIC vs MAC

Rational of High Dose Chemotherapy and Autologous Stem Cell Transplantation

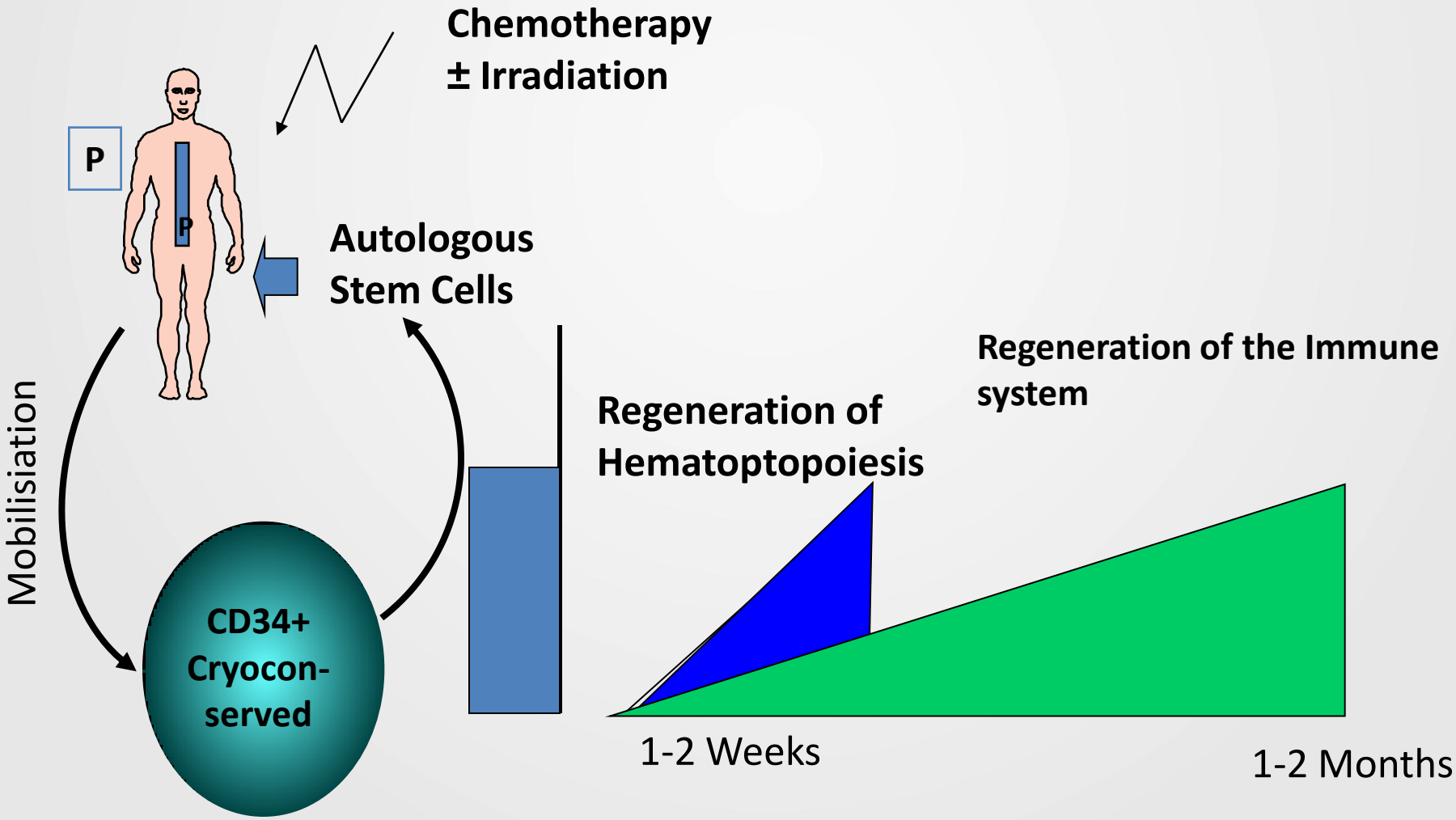
- **Intensification of the Chemo(radio)therapy**



→ **Overcoming Resistence of Tumor cells**

→ **Significant Increase in Response Rates**

Scheme of an Autologous Stem Cell Transplantation



What is a myeloablative Regimen?
HD - Chemotherapy for Multiple Myeloma

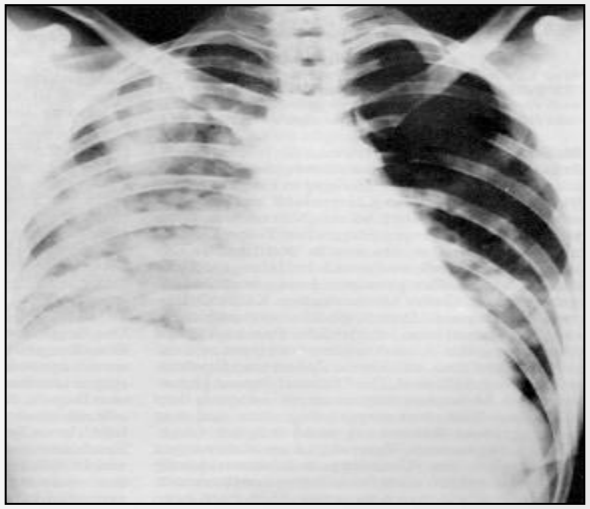
Melphalan 100 - 140 mg/m²

Mc Elwain 1983

Response Rate : > 70% (CR 20%)

TRM : 15 - 25 %

Compared to MP: Response Rate 40%, CR 3-4%



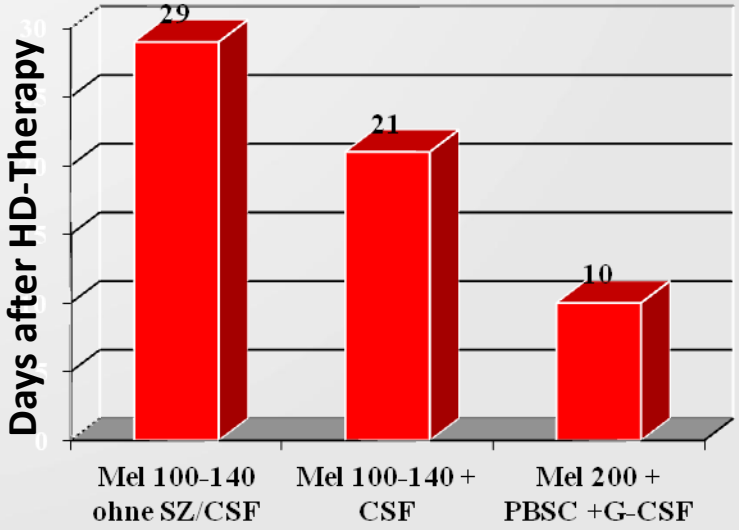
Hematopoietic reconstitution

HD - Chemo (Mel200) with Stem Cell Support:

Unpublished Würzburg Results

Response Rate : > 95 % (CR > 50%)

TRM : < 0,5%



Conventional vs High Dose Chemotherapy for younger patients with NOMM

Standard dose CTX

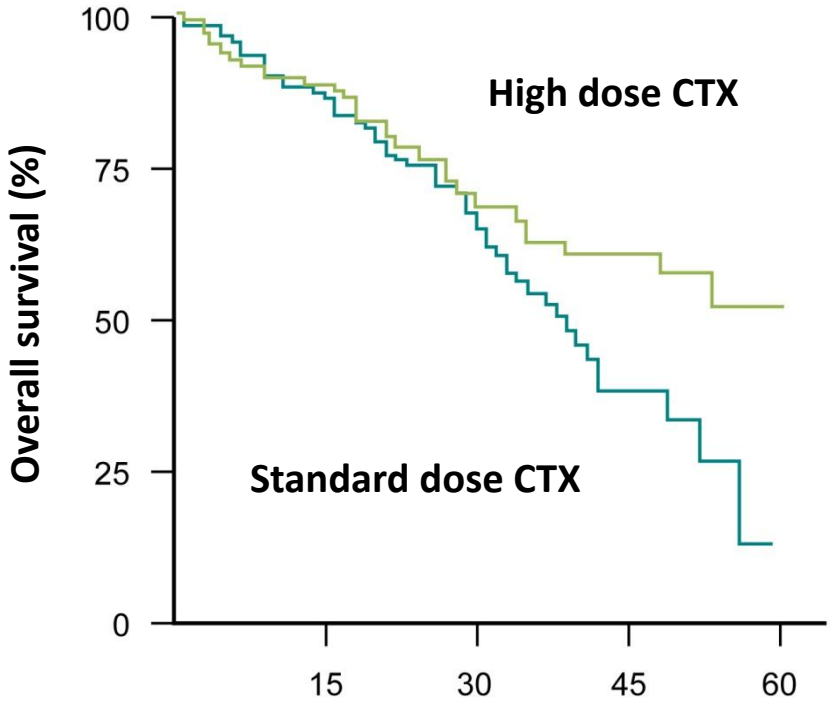
VMCP/BVAP 18x

High dose CTX

VMCP/BVAP 4-6x
Cy 4
TBI/Mel 140

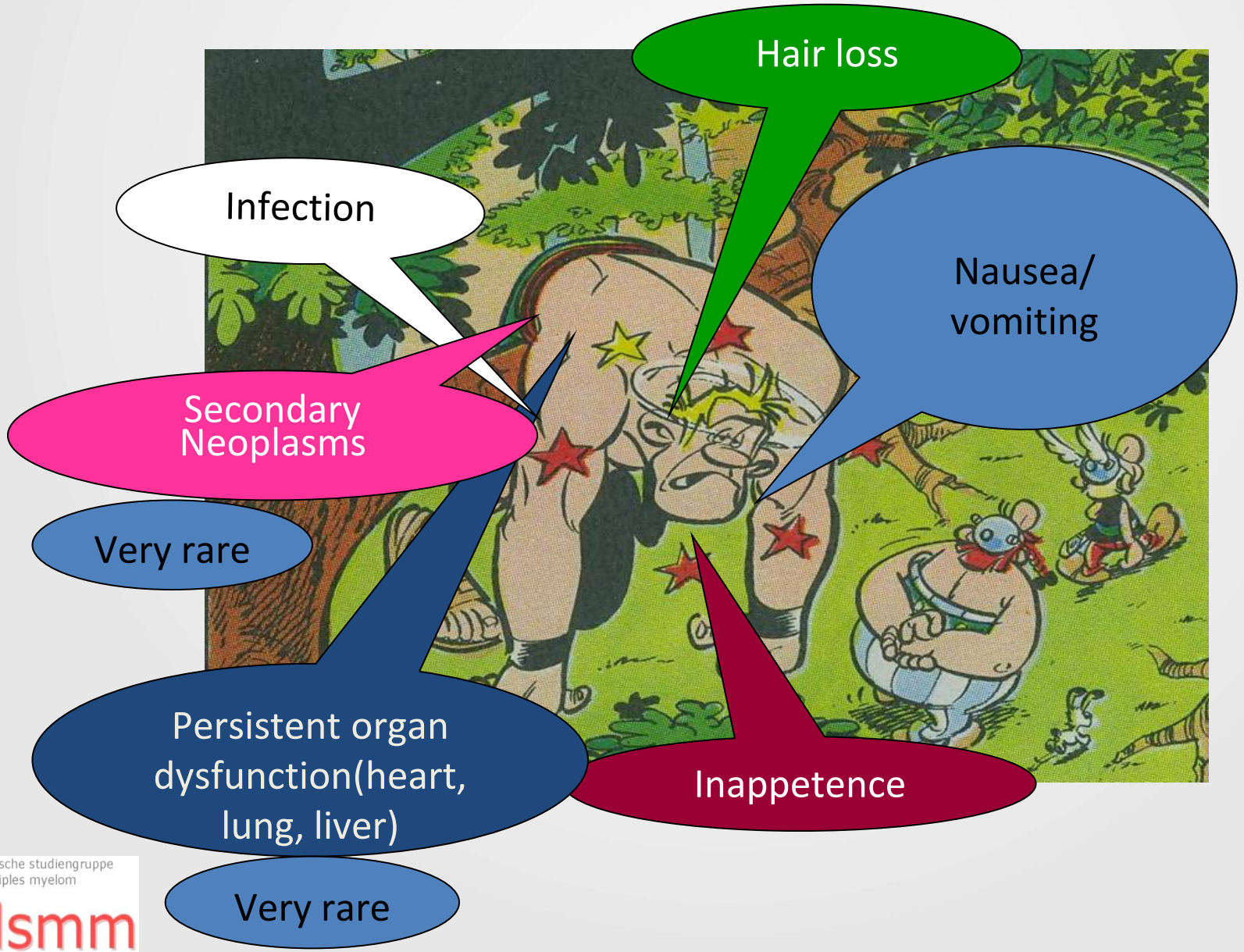
ORR

	CR	PR	PD
Standard dose CTX	5 %	52 %	25 %
High dose CTX	22 %	59 %	12 %



Attal et al., NEJM, 1996

Side Effects of a Myeloablative Regimen



deutsche studiengruppe multiples myelom
dsmm
doing studies on multiple myeloma

Myelom Zelle

Infections

- Increased susceptibility to infection already at the time of diagnosis
- With induction therapy the susceptibility to infection increased by 100%
- During neutropenia after high-dose therapy 4x↑ risk of infection
- After discharge: increased susceptibility to infection for further 6-8 weeks
  → *ACV/Cotrim*
- After the end of treatment: Susceptibility to infection is largely dependent on the quality of response

GI-Toxicity

- Nausea / vomiting:
  - Food intake ↓: 50-80% !
  - Duration: 3 (median) days

- Constipation / diarrhea: 60%
  - Duration 3-4 days
  - Significantly more severe with TBI

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Myelom Zelle

Late effects of transplantation

secondary tumors

MDS, acute leukemias: very rare (<1%)

Exception: intensive pretreatment with Mel before Tx

Other secondary tumors in patients with myeloma

regardless of the therapy

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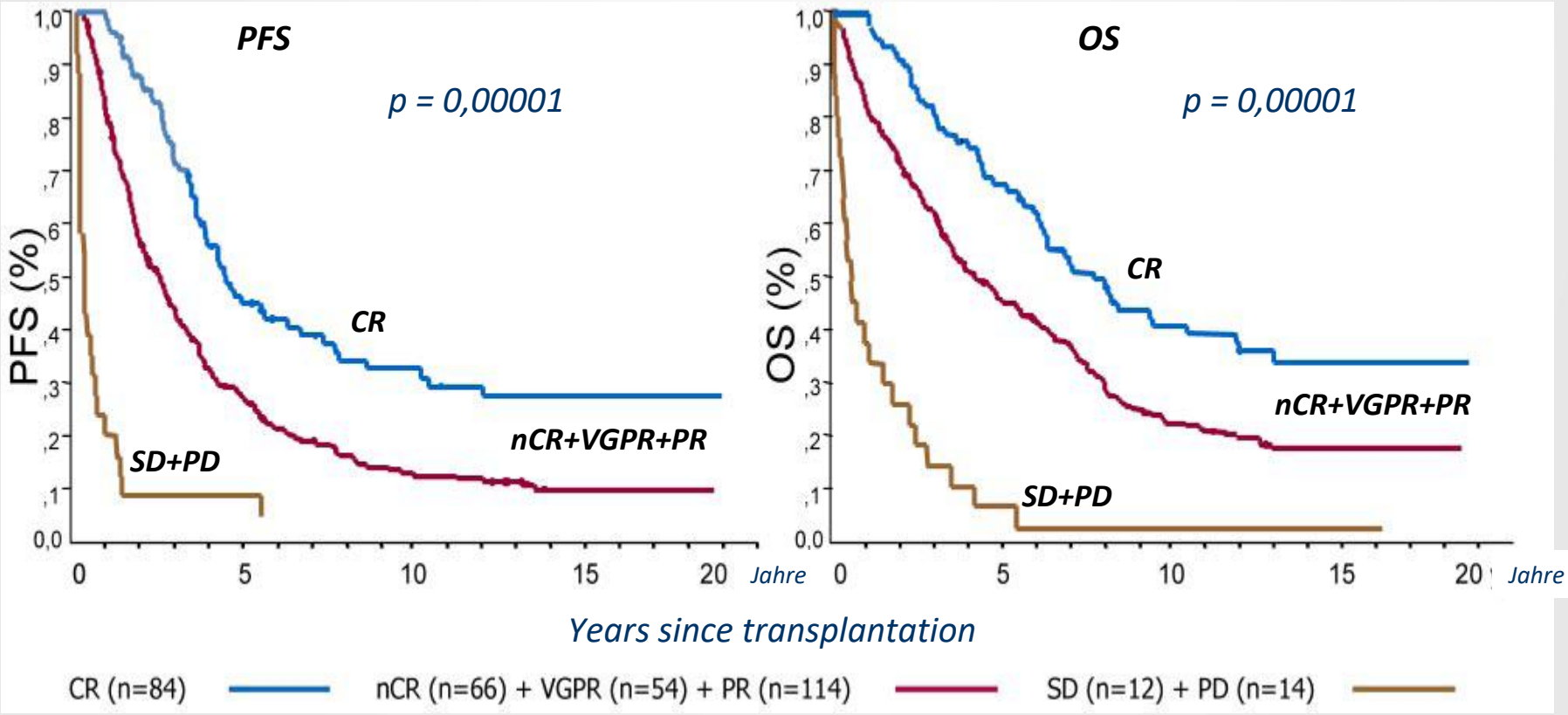
doing studies on multiple myeloma

Myelom Zelle

Long-term disease control only after HD-Therapy

Quality of Response determines PFS/OS after Auto-SCT

CR vs. nCR/VGPR/PR vs. SD/PD (n = 344)



- **Landmark-study: plateau in OS and PFS after 11 years for patients with CR (35%)**
- **Afer 17 years 35 % of the patients alive with CR and 11% of the patients with nCR+VGPR+PR**

Martinez-Lopez J et al., Blood 2011

Intensification with Tandem Transplantation

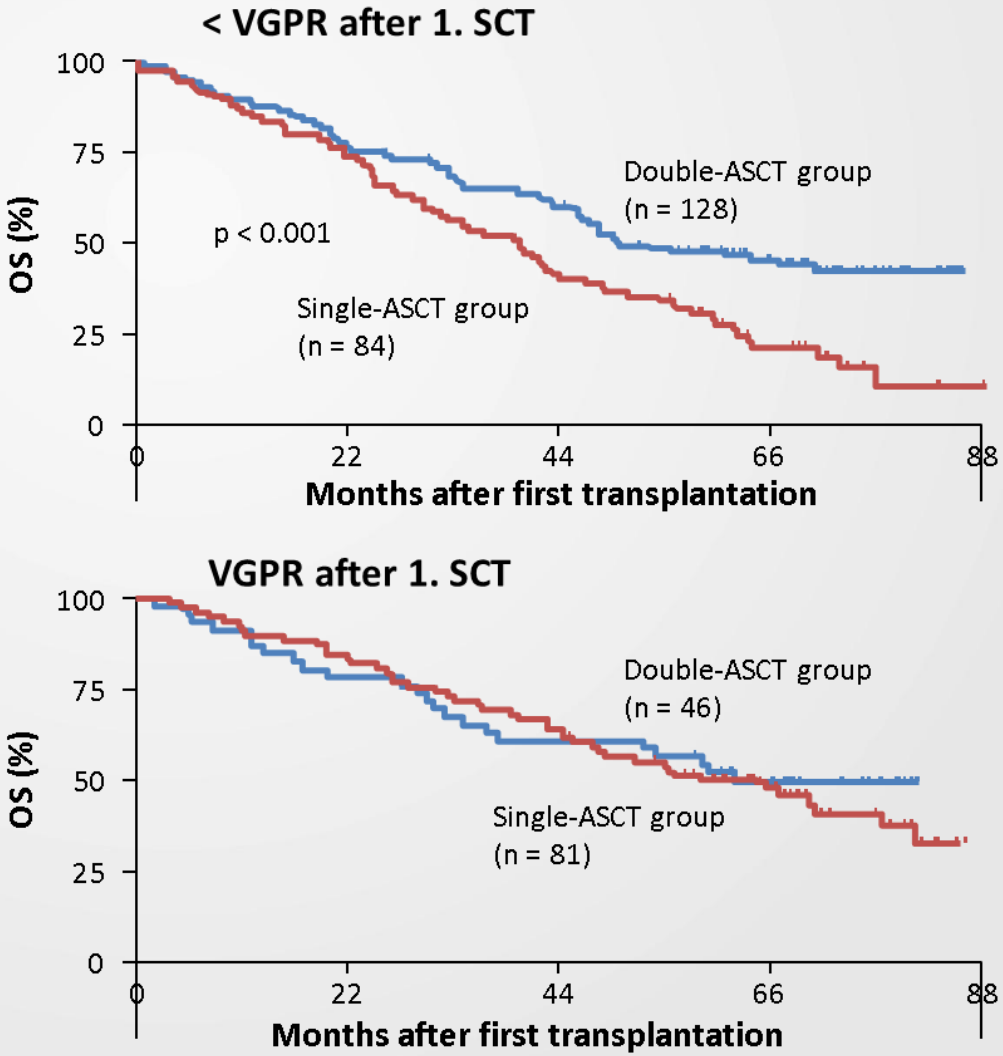
- Comparison between Single and Tandem Transplantation
- In the era prior to the novel agents
- In the era of the novel agents

IFM 94: Single - vs Tandem-SCT

- EFS after 7 years
  - 10 % vs 20 % (p = 0.03)
- OS after 7 years
  - 21 % vs 42 % (p = 0.01)
- Tandem-SCT improves OS, esp. In pts. <VGPR after 1st SCT

  OS after 7 years – 11 % vs 43 % (p < 0.001)

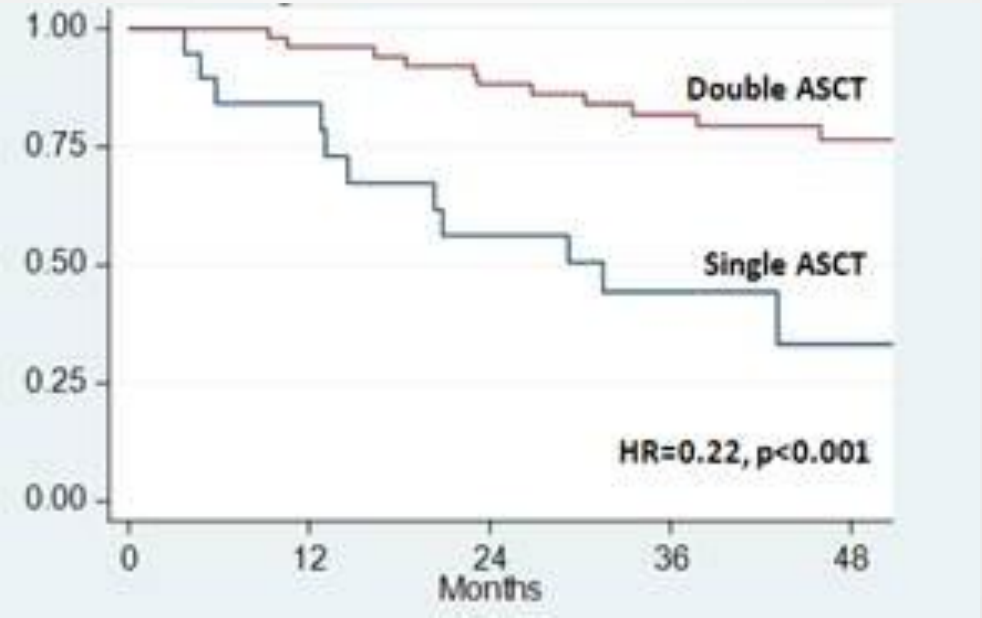
  (Post-hoc subgroup analysis)



Attal M et al., N Engl J Med. 2003

Double vs single ASCT after bortezomib-based induction: OS data

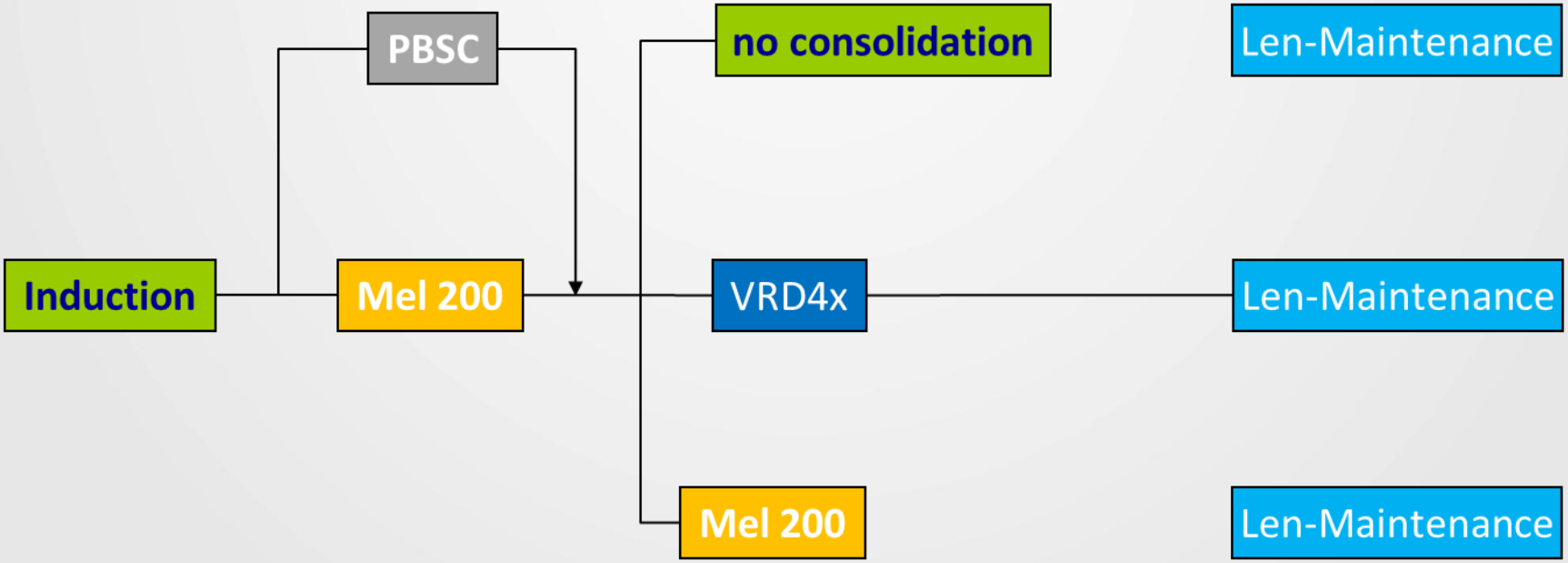
- Pts with 2 adverse variables who received double ASCT had significantly longer OS compared to pts who received single ASCT
- OS benefit with double ASCT particularly relevant for pts who failed CR after bortezomib-based induction therapies and who had high-risk cytogenetics or ISS 3



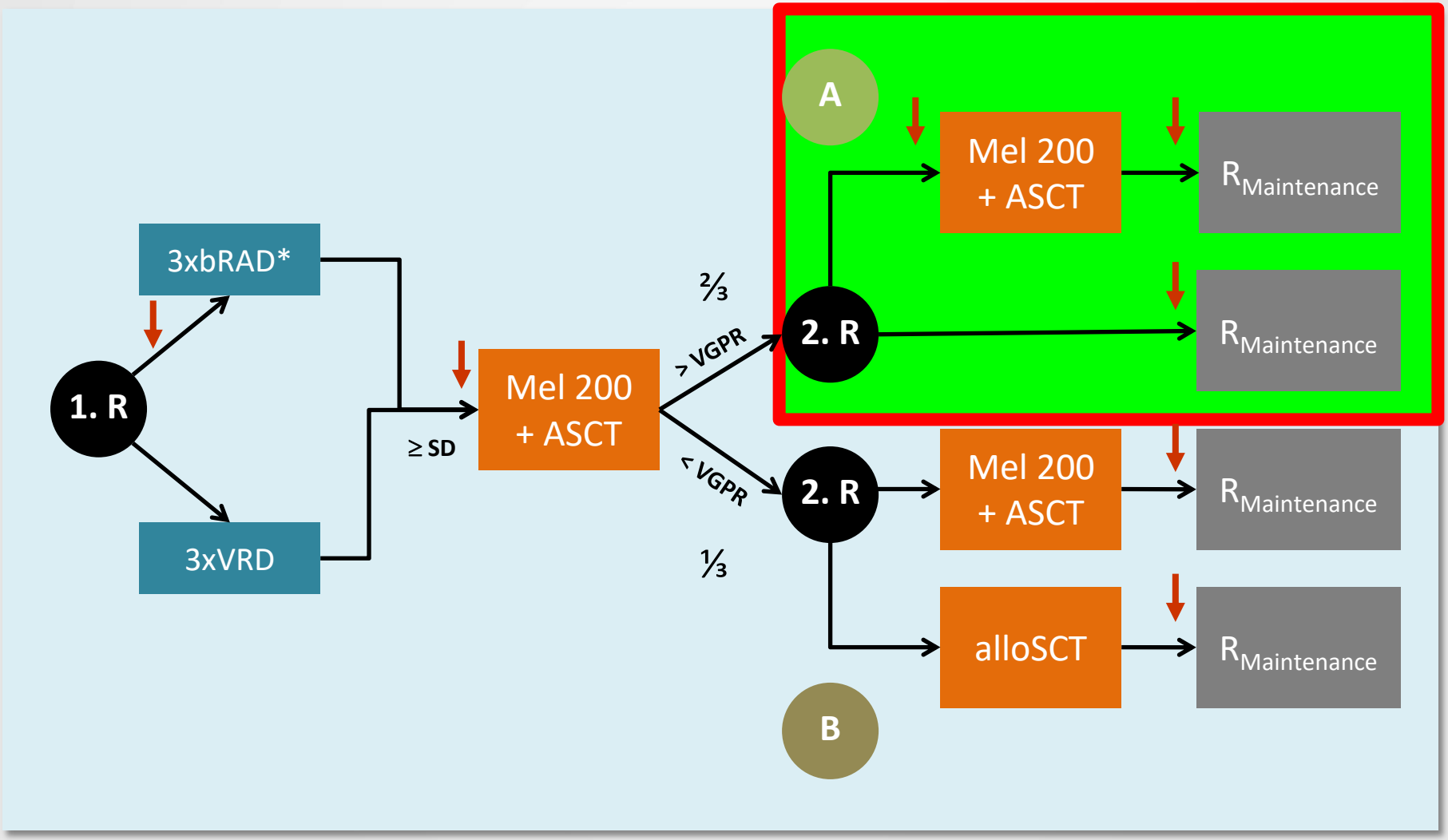
Median OS 67 vs 31.5 months, P<0.001

Cavo et al. ASH 2013 (Abstract 767), oral presentation

US Trial
CTN/IBMTR-Study



DSMM XIV: Role of second ASCT in pts with at least VGPR after the first ASCT



Analysis of molecular response with immunophenotyping/PCR

EudraCT NUMMER: 2009-016616-21

Age Limit/Intensity of HD-Therapy in elderly Patients ?

Background:

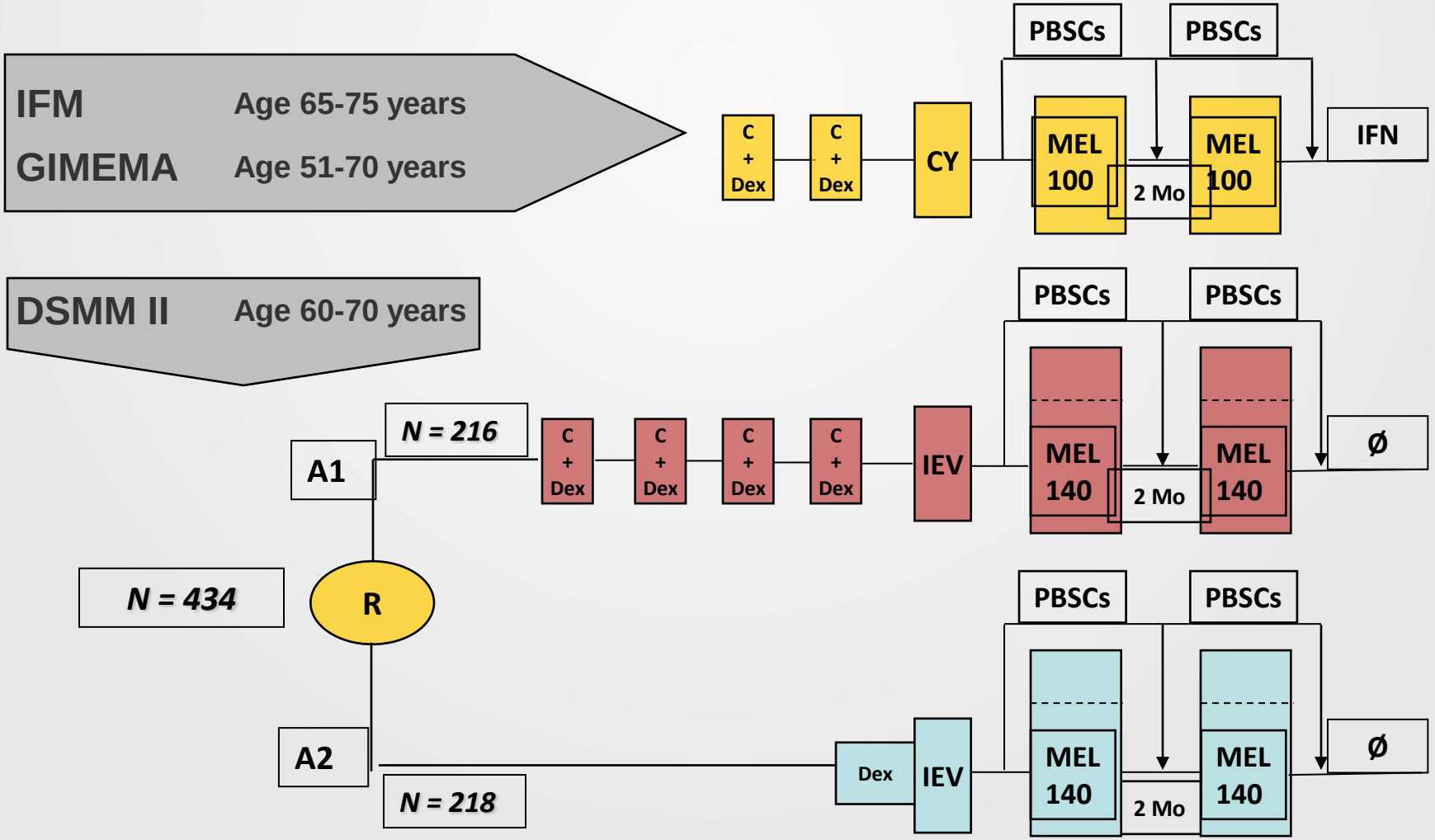
- HD-Melphalan controversially discussed for the elderly patient
  - More toxicity (?)
  - Lower efficacy (?)
  - Do novel combinations replace ASCT in the elderly patient ?

DSMM II – MM 60-70 yrs

Results on:

- 549 Patients
- 5,3 yrs median follow-up

Age-adapted HD-Therapy for elderly MM patients



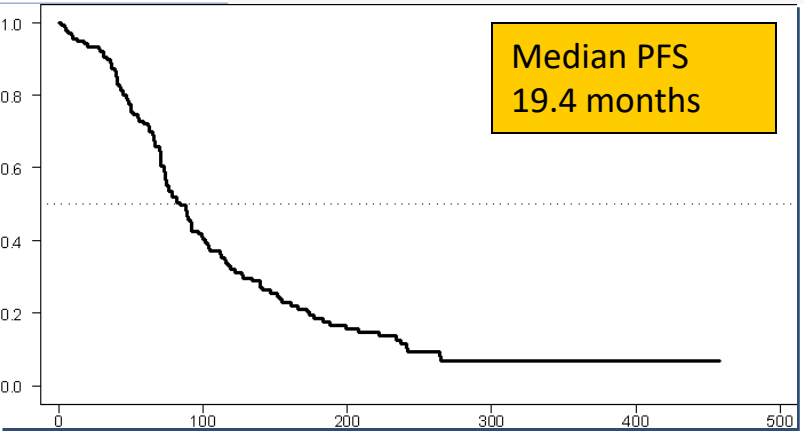
DSMM II – Non-hematological Toxicity NCI-Grades 3/4

Age 60-64 vs. 65-70 years

	1. HD-Melphalan		2. HD-Melphalan	
	Induction A1	No Induction A2	Induction A1	No Induction A2
Infection	33 % vs. 35 %	45 % vs. 42 %	30 % vs. 36 %	38 % vs. 30 %
Mucositis	11 % vs. 10 %	18 % vs. 13 %	4 % vs. 6 %	10 % vs. 4 %

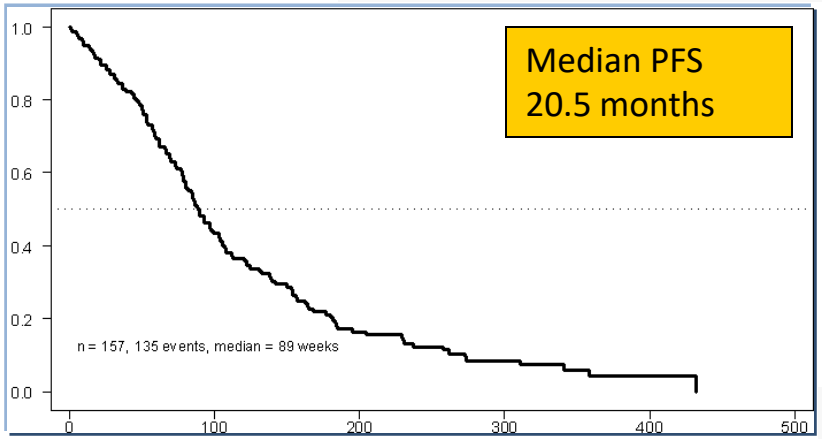
Progression-free survival (PFS)

Age 60-63 years N = 138



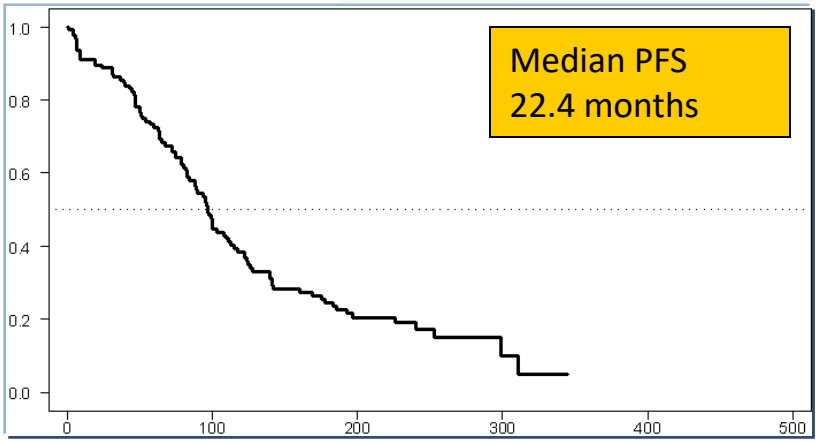
Weeks

Age 64-66 years N = 125



Weeks

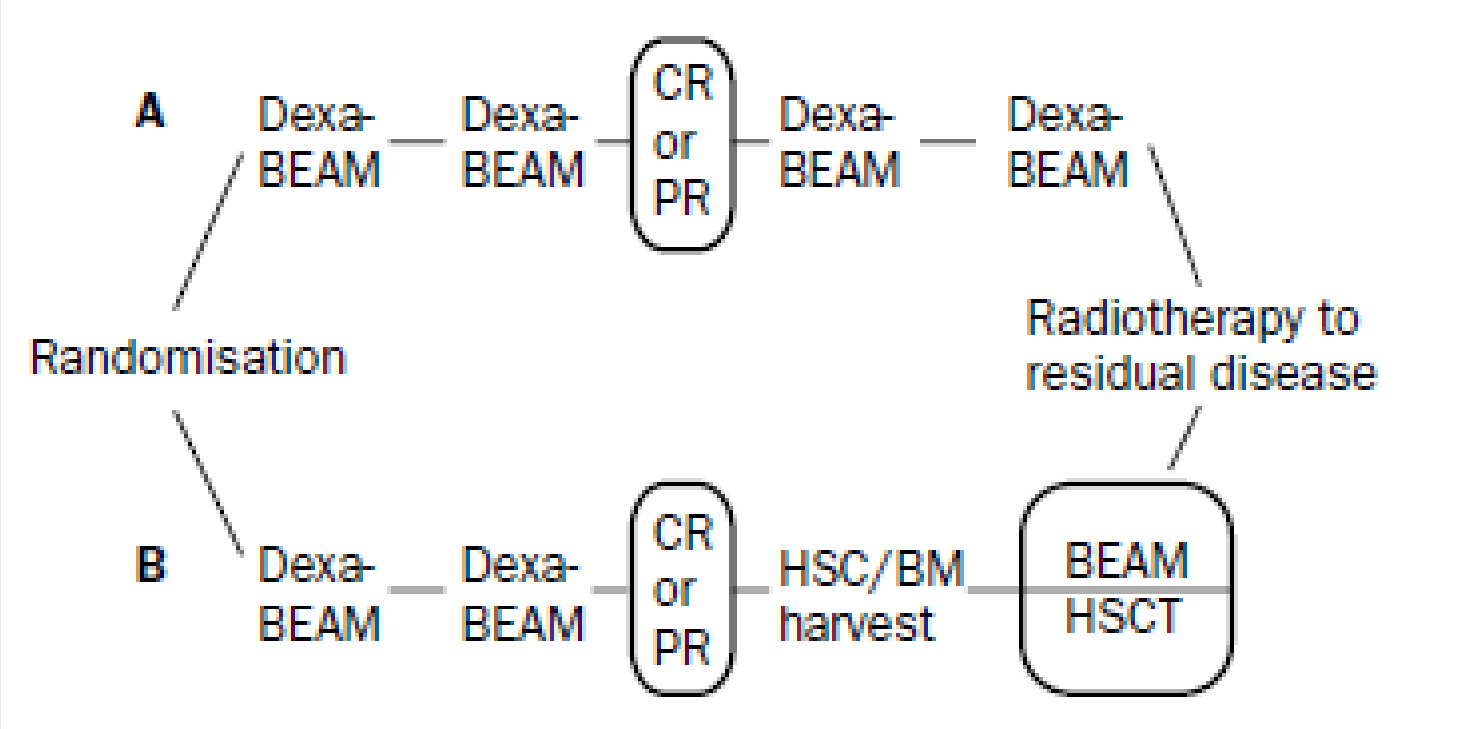
Age 67-70 years N = 157



Weeks

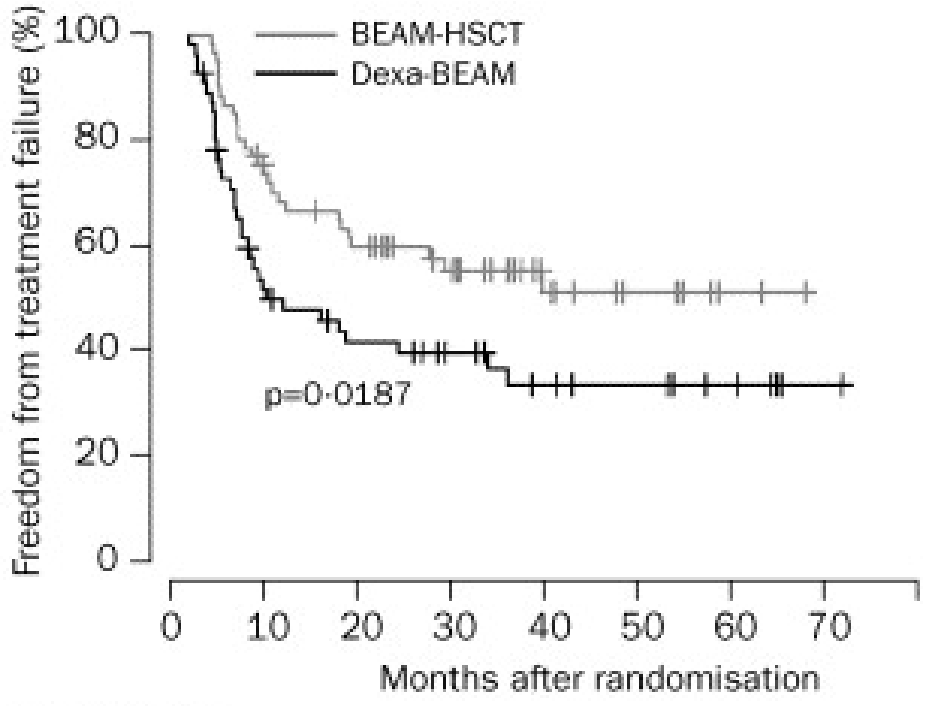
DSMM II

Aggressive conventional chemotherapy compared with high-dose chemotherapy with HSCT for relapsed chemosensitive Hodgkin's disease



Schmitz N et al. Lancet 2002

Aggressive conventional chemotherapy compared with high-dose chemotherapy with HSCT for relapsed chemosensitive Hodgkin's disease

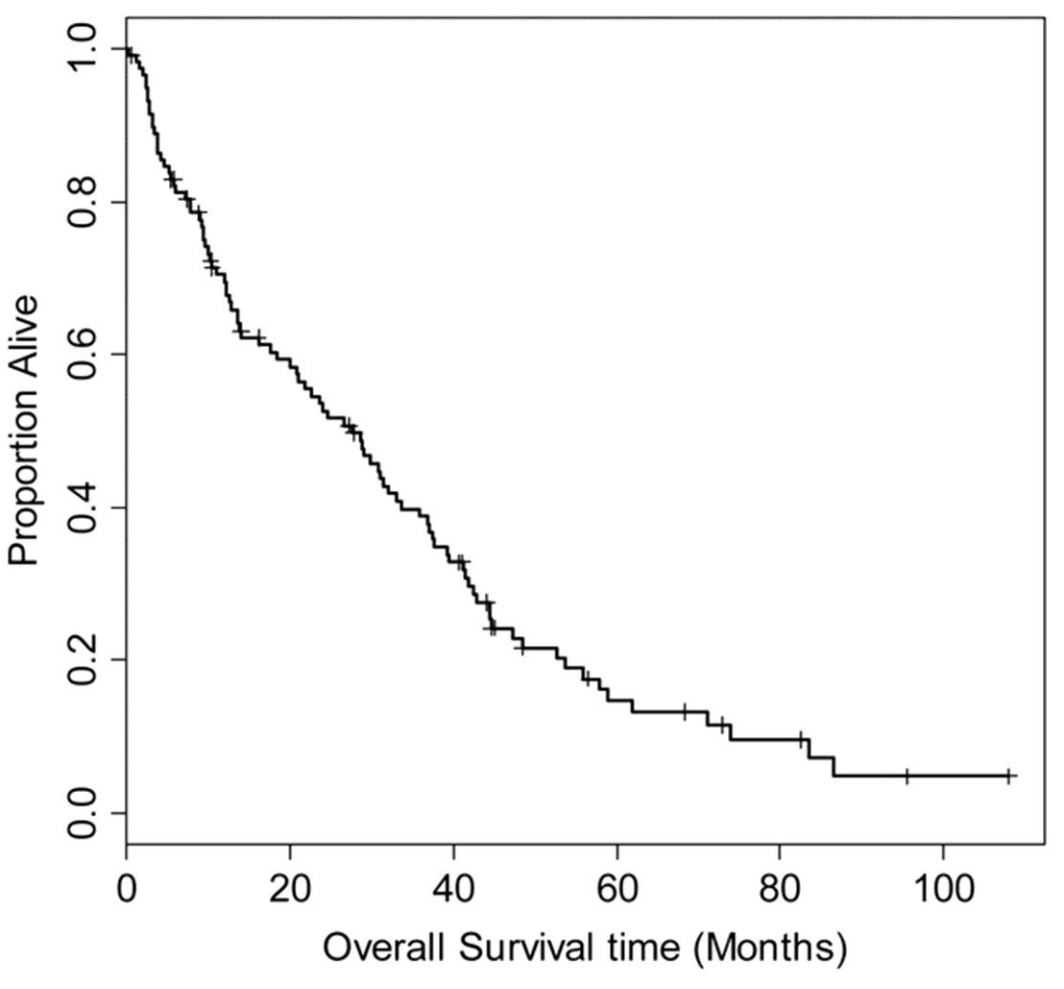


- High Dose Therapy followed by Auto-SCT standard of care for medically fit patients with relapsed HD
- 70% of these patients can be salvaged in first relapse

but: in early relapse only 40%
in refractory disease only 20-35%
} long term survival after ASCT

Schmitz N et al. Lancet 2002

Overall survival of 118 patients from date of relapse after auto SCT for relapsed or refractory Hodgkin lymphoma



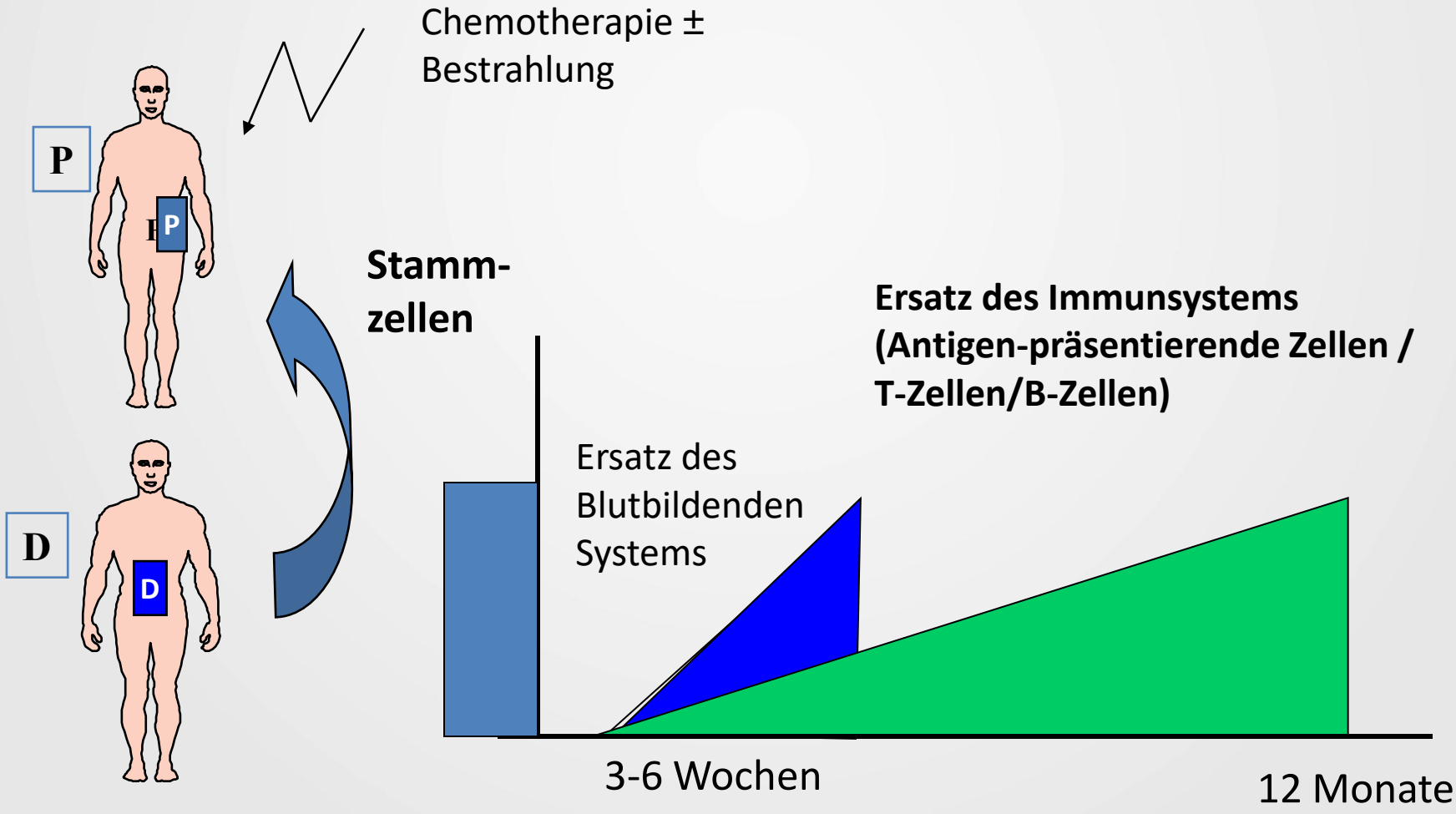
Crump, M. Hematology 2008

Recent results with reduced-intensity allogeneic transplantation for Hodgkin lymphoma (HL)

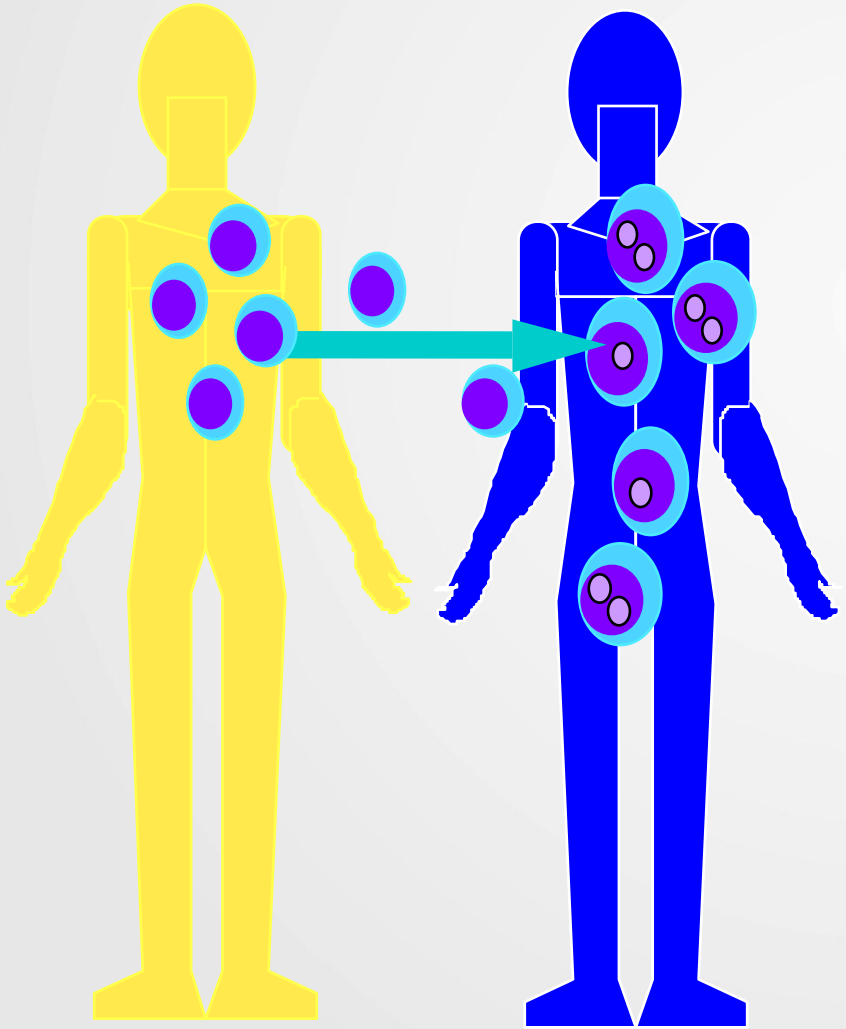
Author	n	Prior ASCT	Prior regimens (median)	TRM, % (time point)	PFS, % (time point)	OS, % (time point)
Peggs	49	44	5	16 (2 y)	32 (4 y)	56 (4 y)
Sureda	89	55	85% ≥3	23 (1 y)	18 (3 y)	35 (3 y)
Alderlini	40	30	5	22 (18 m)	55 (18 m)	61 (18 m)
Armand	36	34	4	15 (3 y)	22 (3 y)	56 (3 y)
Alvarez	40	29	55% ≥3	25 (1 y)	32 (2 y)	48 (2 y)

Crump, M. Hematology 2008

Scheme of the allogeneic Stem Cell Transplantation



Self Tolerance → Alloimmune reaction



Donor

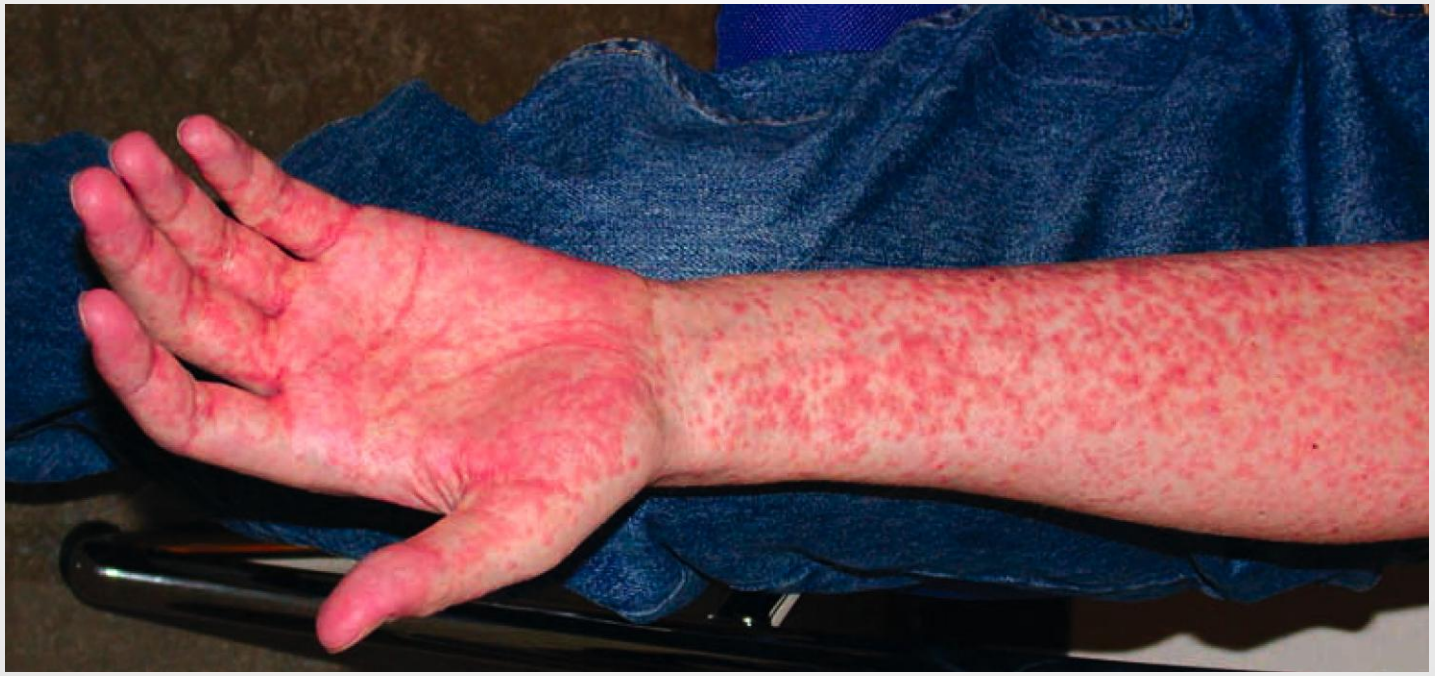
Patient
(immunosuppressed)

Donor T Cells

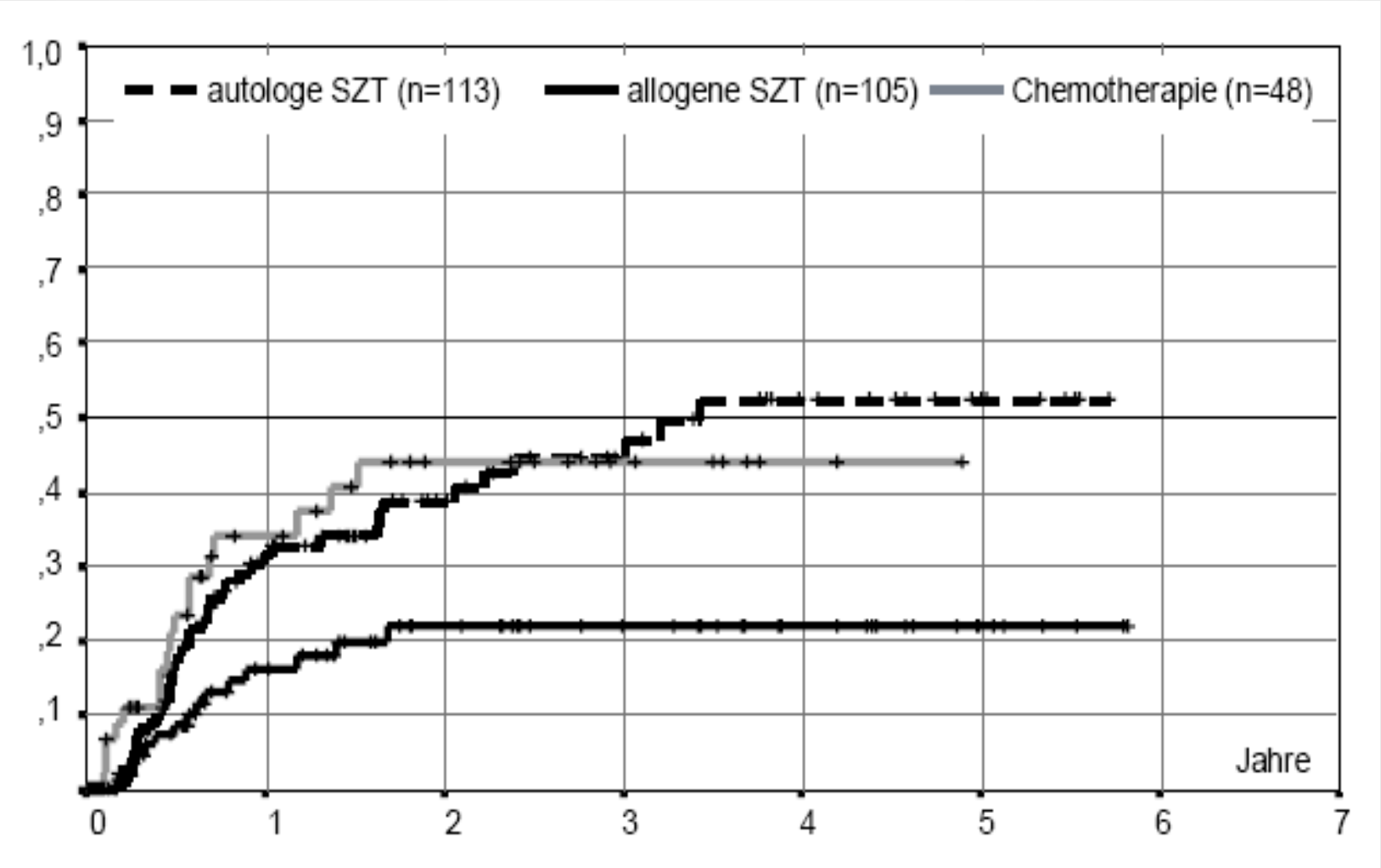
Novel (Patient-specific)-Antigens = Target antigens of the Donor T cells -> GvHD

But also: **residual Tumor cells = Targets for the transfered donor-derived immune system -> Transplantat-vs Tumor reaction**

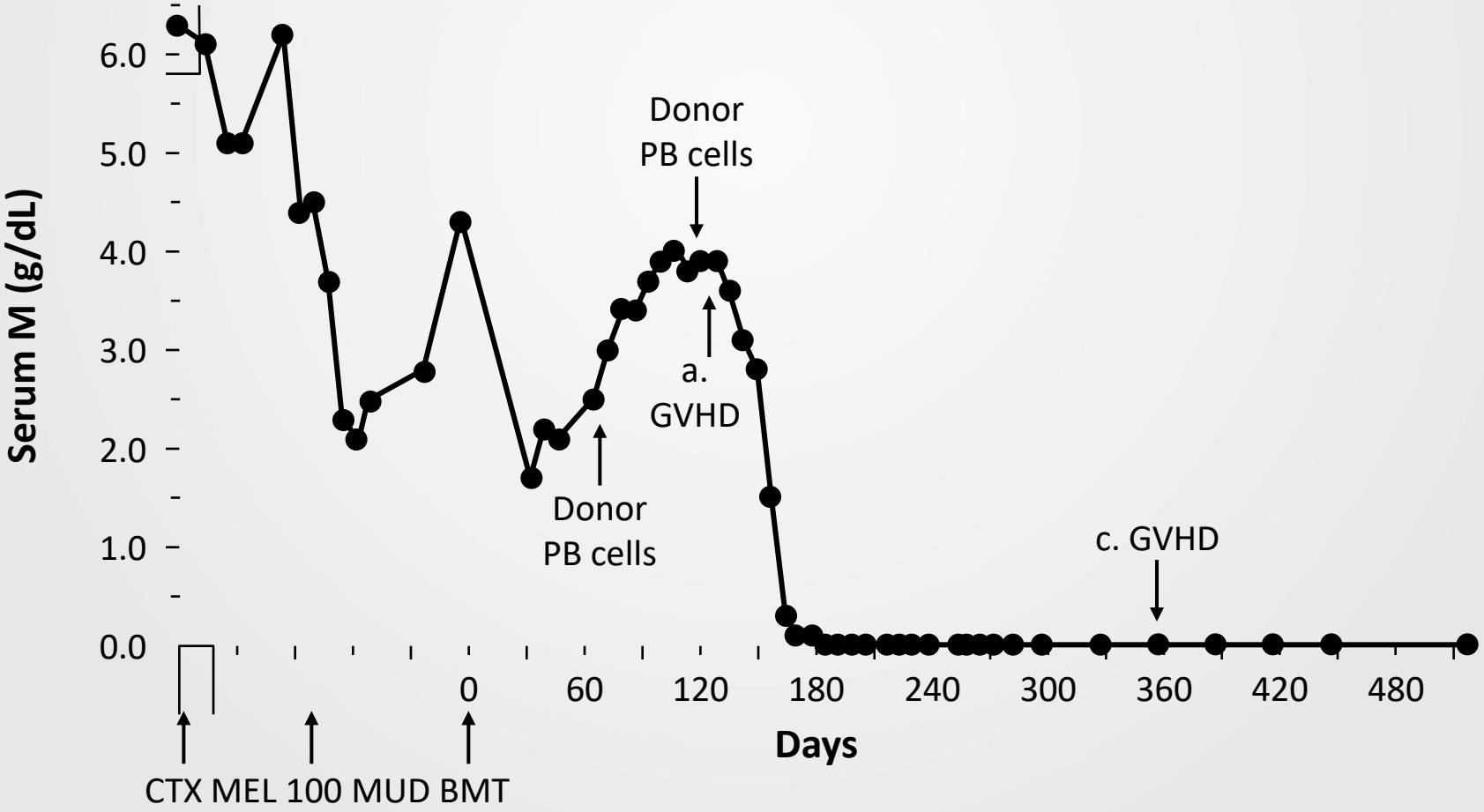
Graft-versus-Host Disease



Relapse Risk of Patients with AML



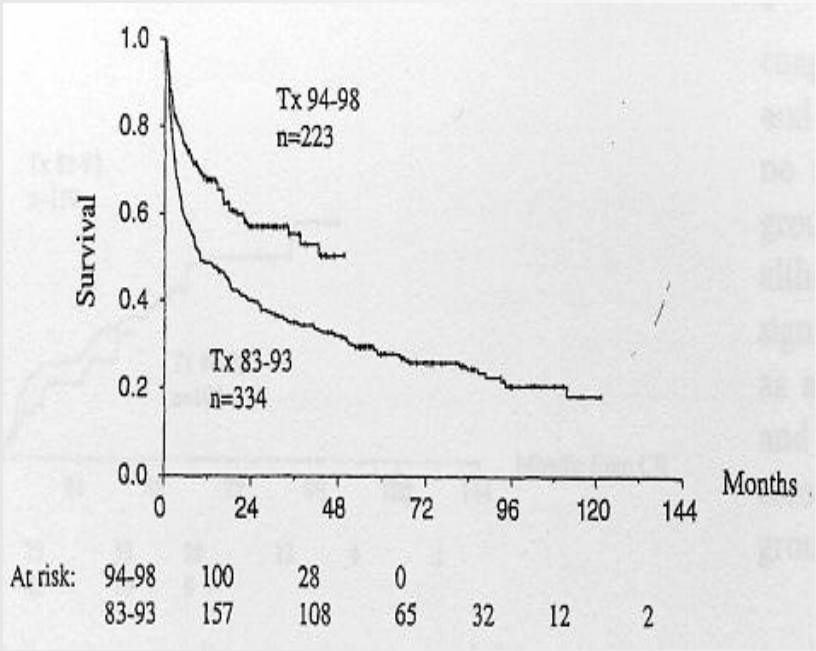
Graft-versus Myeloma Effect



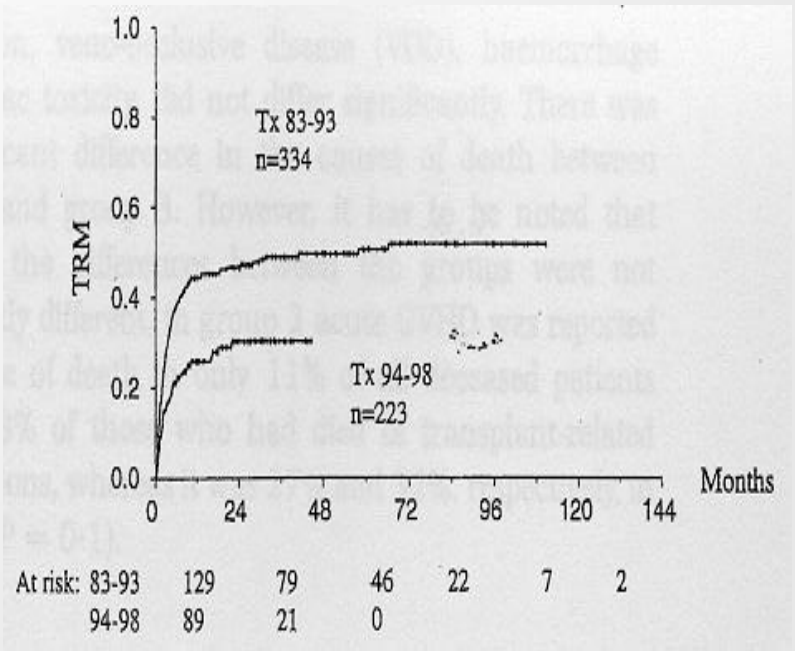
Tricot G, et al. Blood. 1996;87:1196-8

Outcome after Allo-SCT

Survival



TRM



G. Gahrton et al. 2001

Different Modalities of Allo-SCT

Non-myeloablative Conditioning

TBI

2 Gy

CSA/MMF

Classical Conditioning

TBI

Cy

120mg/kg

12 Gy

CSA/MTX

- *Advantage:*
  - *Organ Toxicity (TRM of 30% → < 15%)*
  - *upper age limit ↑ (> 60 J)*
- *Disadvantage:*
  - *Tumor Reduction by Conditioning Therapy*

Conditioning Therapy for Allo-SCT
Goals

1. Induce an intensive immunosupression of the recipient to allow engraftment of the hematopoetic and immune system of the donor and to prevent primary graft failure

2.Anti-leukemic activity – to eradicate as many malignant cells as possible

3. Inducing myeloablation to create „space“ for the transplanted donor-derived stem cells

But: preclinical models and clinical observation have shown that:
The main anti-leukemic activity of allogeneic stem cell transplantation is induced by the graft-versus Tumor effect and that myeloablation is not Essential for a successful engraftment

Intensity of the Conditioning

1. Standard conditioning = Myeloablative Regimens
High dose alkylating agents +/- TBI
Irreversible eradication of the hematopoetic system of the recipient

2. Non-myeloablative regimens induce only minimal hematotoxicity and could be applied without a stem cell support
-> autologous reconstitution
But: sufficient to induce engraftment of the donor-derived hematopoetic system which replaces the recipient`s hematopoetic system

3. Reduced intensity regimens
Does not fall in the category of 1. and 2.
Intensity of chemotherapy and/or irradiation should be reduced by at least 30% when compared to a myeloablative regimen
But due to a prolonged pancytopenia stem cell support is essential

MAC (Myeloablative Conditioning)

1. Definition of MA regimen: a combination of agents expected to produce profound pancytopenia and myeloablation within 1-3 weeks from administration; pancytopenia is long lasting, usually irreversible, and in most instances fatal, unless hematopoiesis is restored by hemopoietic stem cell infusion
2. The combinations of Bu-Cy or Cy-TBI are considered to be an MA conditioning regimen. Further intensification: by addition of melphalan (MEL), thiotepa (THIO), etoposide (VP16), and dimethylbusulfan.
3. MA regimens usually produce rapid engraftment of donor cells, which may be followed in a proportion of patients, by graft-versus-host disease (GVHD).

Bacigalupo A, et al, Biol Blood Marrow Transplant, 2009

NMA (Non-myeloablative) Conditioning

1. Definition of NMA regimen: a regimen that will cause minimal cytopenia and does not require stem cell support.
2. Examples of NMA regimens include: Flu-Cy, TBI 2 Gy, TBI 1 Gy, total lymphoid radiation (TLI), and antithymocyte globulin (ATG). NMA typically cause minimal cytopenia, and little early toxicity, but are immunosuppressive to the extent that, when followed by granulocyte-colony stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSCs), they usually result in full engraftment of donor lymphohemopoietic SCs.
3. However, NMA also require a large number of donor T lymphocytes and donor $CD34^{+}$ cells, to facilitate donor engraftment. It is therefore the combination of *immunoablation* and large numbers of donor cells that constitute the essence of NMA programs. These transplants are followed by low early toxicity, despite older patient age and greater number of patients with comorbidity. TRM is lower after NMA compared to MA regimens. Acute GVHD (aGVHD) after NMA is delayed, and may develop after day 100, at a time when chronic GVHD (cGVHD) is usually diagnosed after an MA regimen.

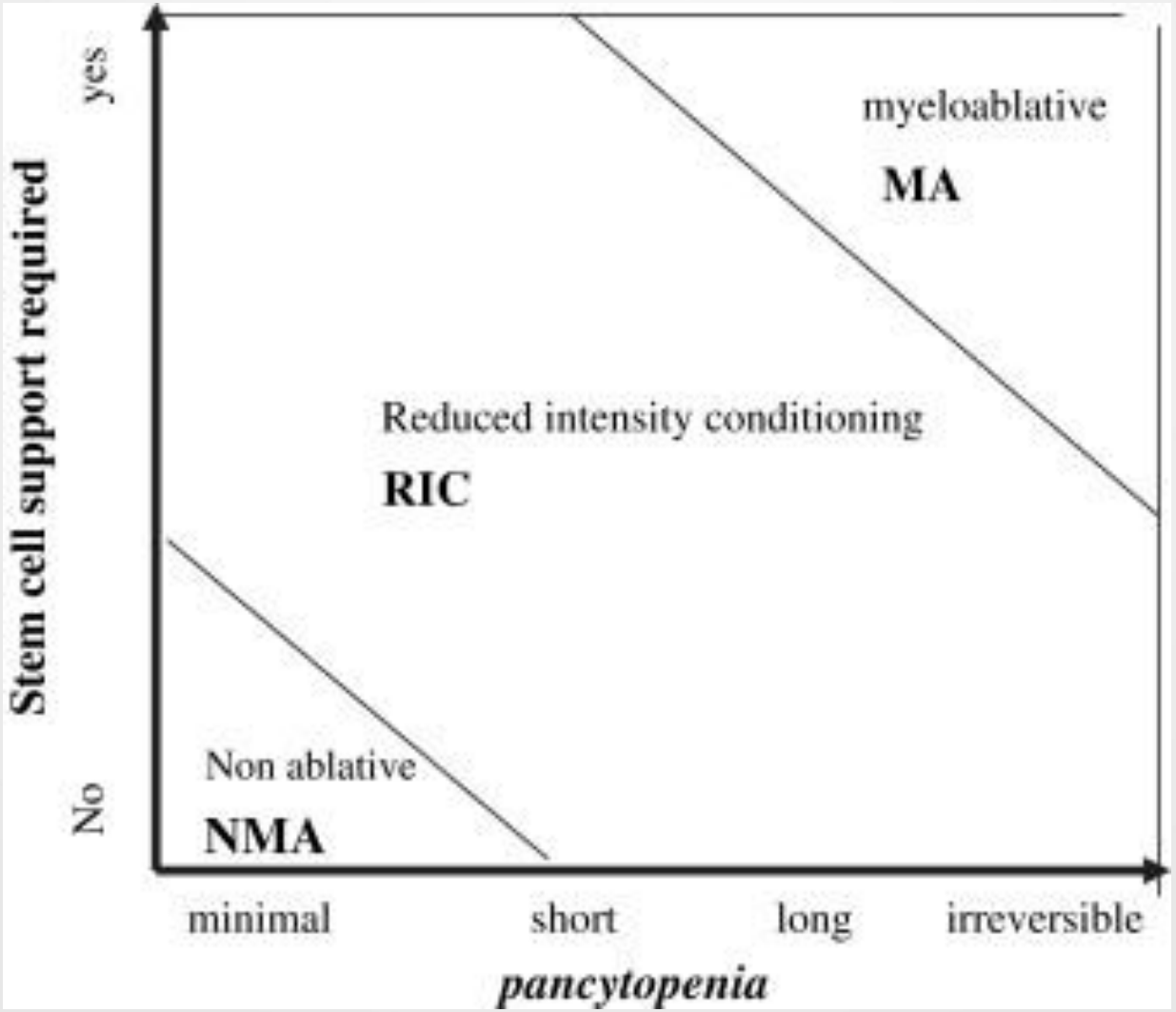
Bacigalupo A, et al, Biol Blood Marrow Transplant, 2009

RIC (Reduced Intensity Conditioning

1. A conditioning regimen that does not fulfill MA or NMA is defined as an *RIC regimen.*
2. An intermediate category of regimens that do not fit the definition for MA or NMA. *RIC regimens differ from NMA*: they cause cytopenia, which may be prolonged, and do require stem cell support.
3. *RIC regimens differ from MA conditioning*, because the dose of alkylating agents or TBI is reduced by at least 30%. Most often these regimens combine Flu with an alkylating agent, melphalan (Mel), Bu, thiotepa in reduced doses, or Flu with reduced-dose TBI. TRM is reduced after RIC regimens, as shown by several registry-based studies comparing RIC and MA regimens.

Bacigalupo A, et al, Biol Blood Marrow Transplant, 2009

Intensity of the Conditioning and impact on duration of aplasia or need for stem cell support



Bacigalupo A, et al, Biol Blood Marrow Transplant, 2009

Myeloablative and Nonmyeloablative Regimens

Myeloablative (MA)
TBI ≥5 Gy single dose or ≥8 Gy fractionated
Bu >8 mg/kg orally or intravenous equivalent
Nonmyeloablative (NMA)
TBI ≤2 Gy± purine analog
Flu + Cy ± ATG
Flu +AraC + Ida
Cladribine + AraC
TNI + ATG
Reduced Conditioning
Neither myeloablative nor non-myeloablative

Bacigalupo A, et al, Biol Blood Marrow Transplant, 2009

GvT to Treat Relapse (Response to DLI)

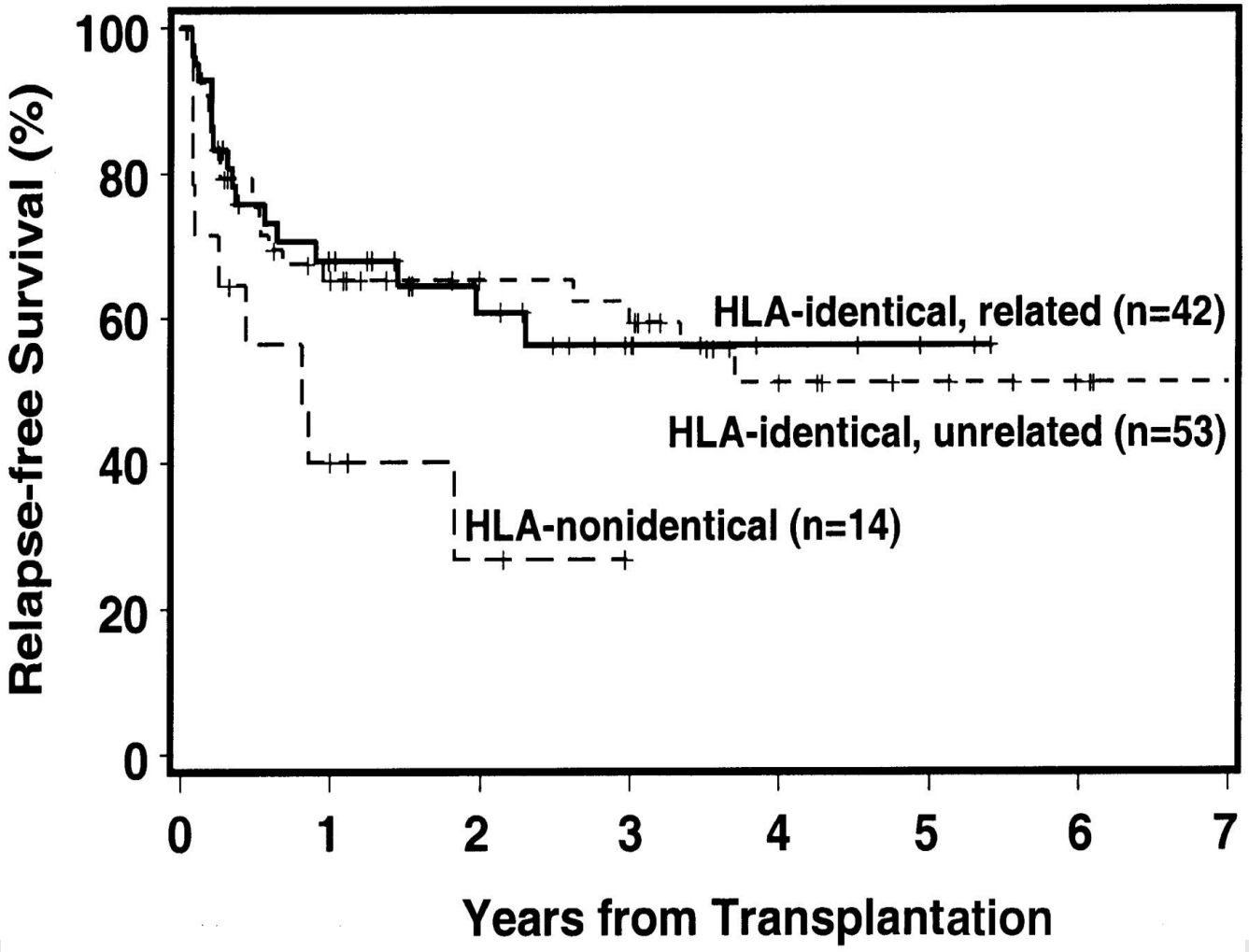
CML	**Up to 80% molecular remissions**
Hodgkin‘s disease	79% responses
CLL	~ 50% responses
Myeloma	Responses in up to 50% → only patients in CR long-term disease control
AML	Responses in 15-30% Cure 20%
High grade lymphoma	Remission 0-30%
ALL	Remission rate 0-20% OS << 15%

Porter D, 2011

Why do we need RIC/NMA-Conditioning AlloSCT for MDS

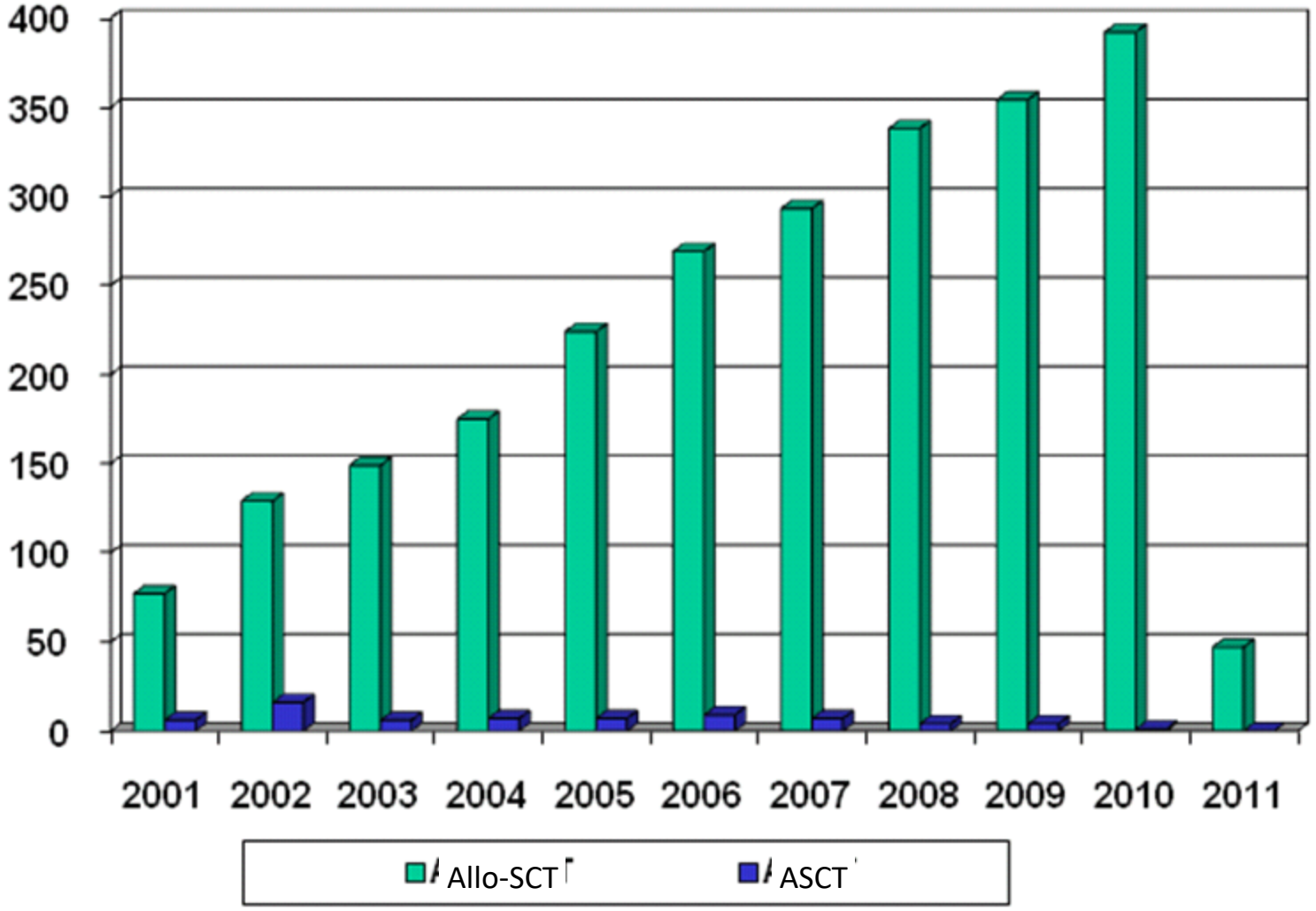
- **IPSS intermediate-2 or high risk**
  - Age < 75 years
- **IPSS intermediate-1**
  - Individual decision with the patients
- **IPSS low risk**
  - Only in high selected patients

MDS:
PFS after Allo SCT



Deeg et al, Blood 2002;100:1201-1207

Allo-SCT for cMPS (non-CML)



Allo SCT for CMF

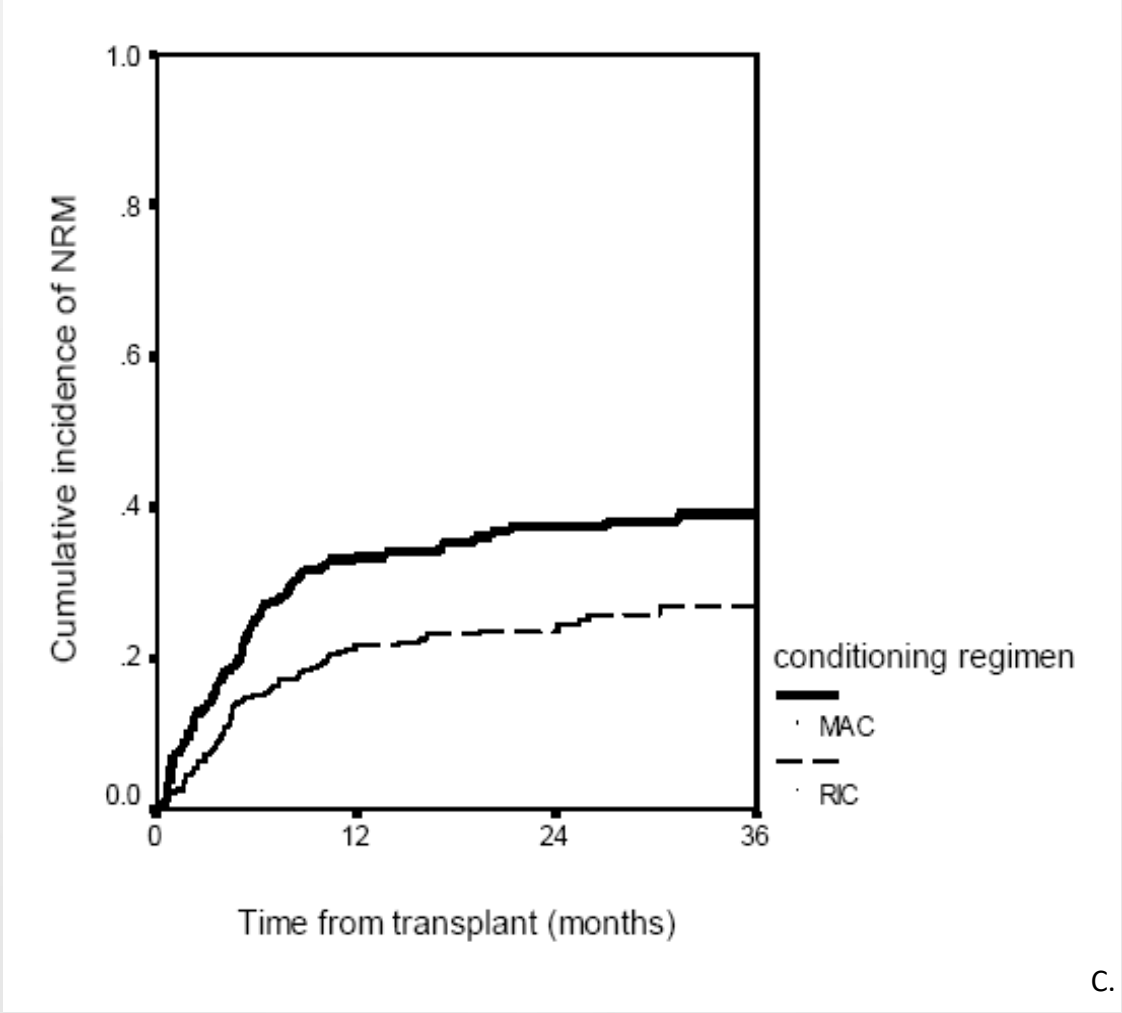
- Deeg et al. 2003: 56 Pat., MAC – Allo SCT
  Age: 43 years (10 – 66 years)
  3 yrs OS: 58%
- Anderson et al. 2001: 21 Pat.
  2 yrs OS: 61%
- Rondelli et al. 2005: 20 Pat., RIC-Allo-SCT (Flu-Bu – up to age 70 yrs)
  31 Mo. OS: 83% !!

→ Recommendation: Intermediate or High Risk Patients
up to age 70-75 years
allo-SCT but RIC or NMA, not MAC!

Comparison of MAC vs RIC Allo SCT

Conv. Allo-SCT vs. RIC-Allo-SCT for MM

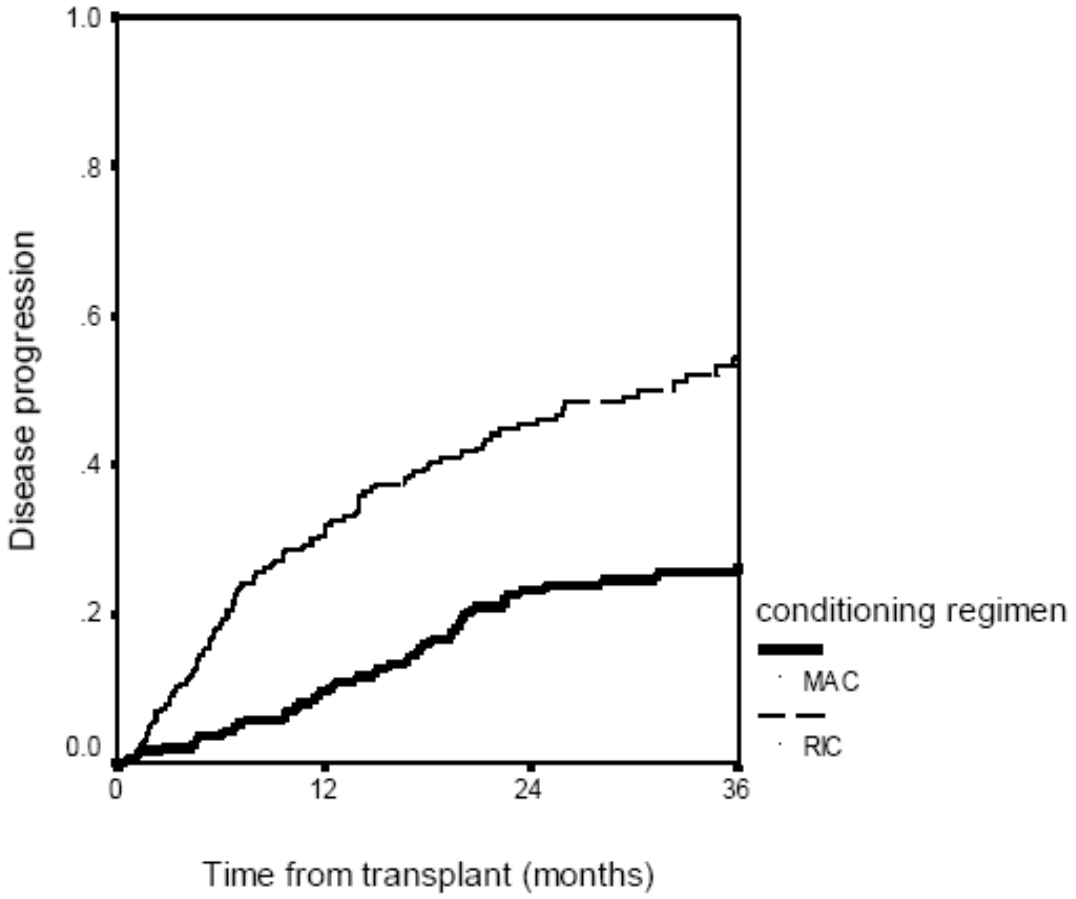
Non-relapse Mortality



C. Crawley Blood et al. 2007

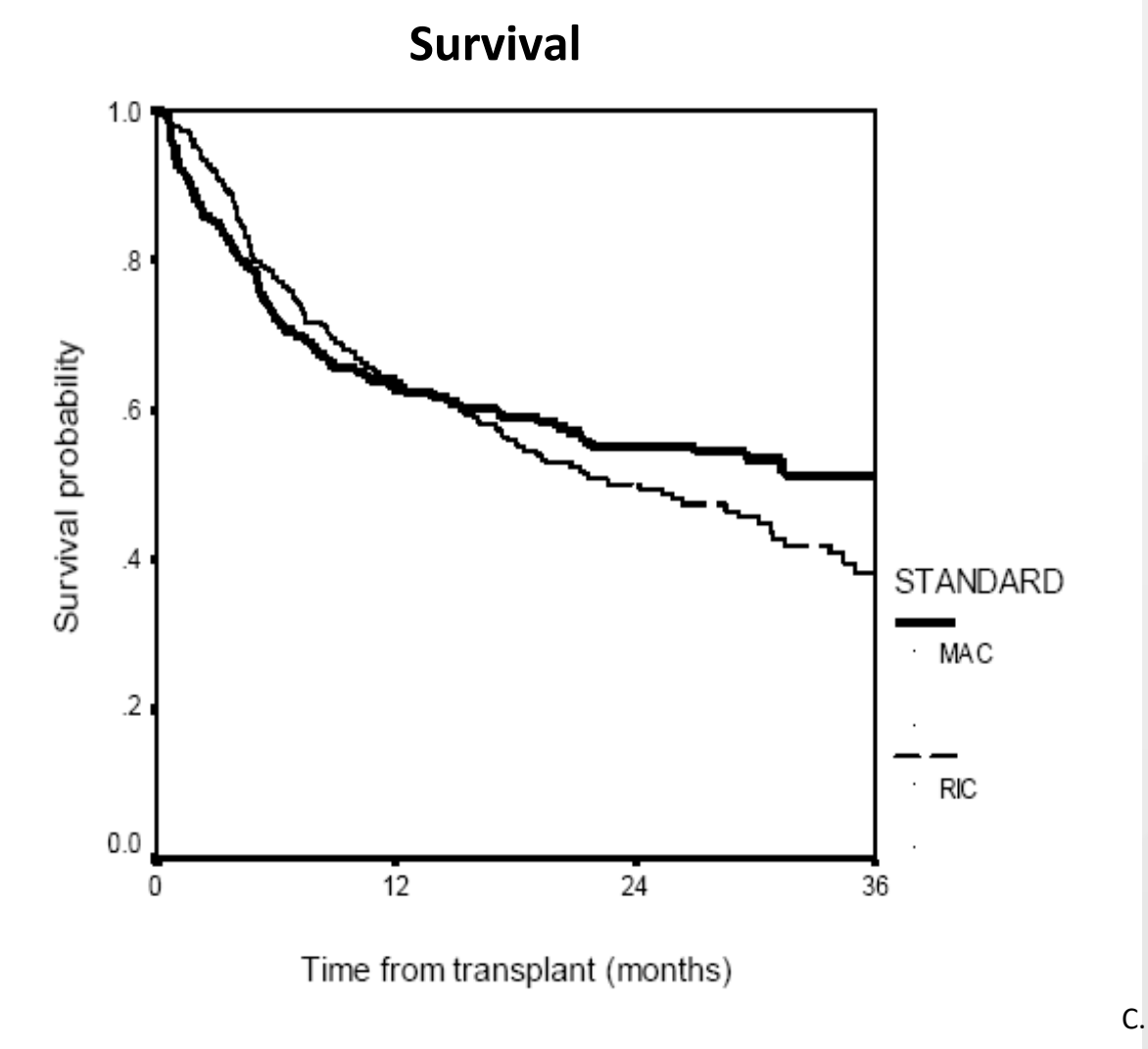
Conv. Allo-SCT vs. RIC-Allo-SCT for MM

Disease Progression



C. Crawley Blood et al. 2007

Conv. Allo-SCT vs. RIC-Allo-SCT for MM



C. Crawley Blood et al. 2007

MM-URD allo-SCT in AML: RIC vs. MAC: Conclusions

- There was no differences in RI after RIC vs. MAC regimens in both <50 and ≥50 year group after MM-URD allo-SCT
- Study shows no significant outcome difference between RIC and MAC regimens after MM-URD allo-SCT in patients **younger than 50 y**ears.
- **Data support superiority of RIC regimen in patients ≥50 year receiving transplant from MM-URD**
- Inherent limitations of a retrospective registry based study

Do we need intensified Conditioning Regimens? Yes – if there is little GvT

Allogeneic haematopoietic stem-cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma*

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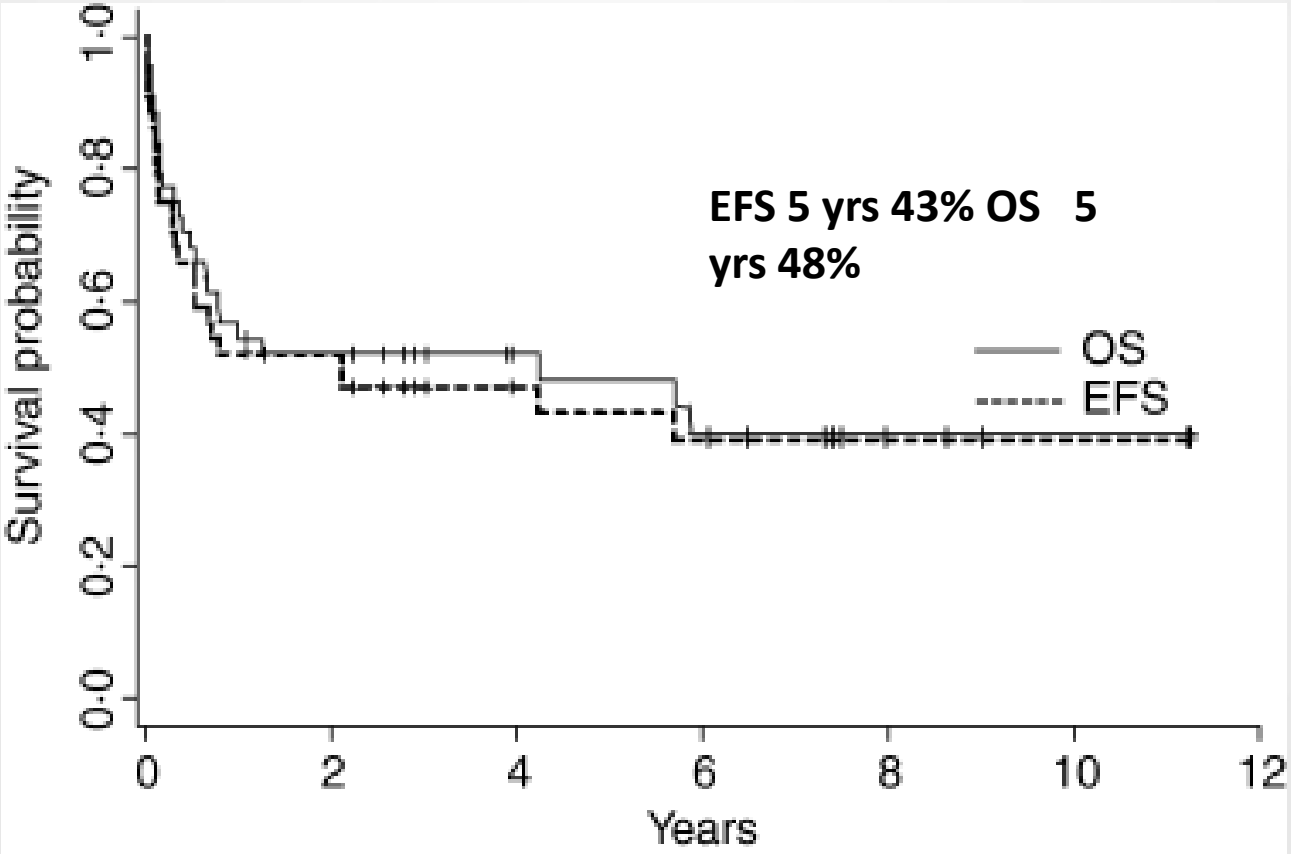
12 Gy

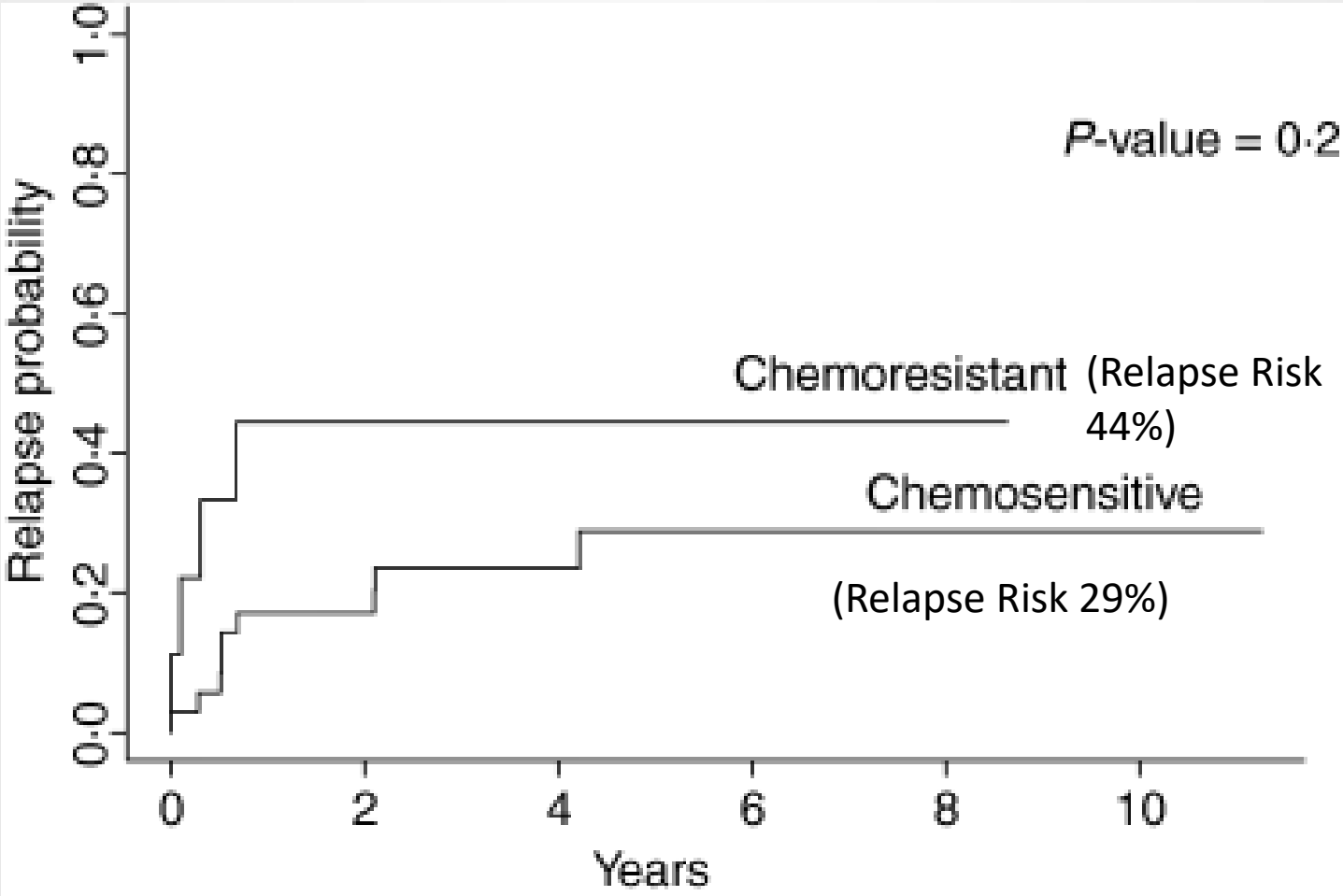
150 mg/kg Cyclo

CSA/short course MTX

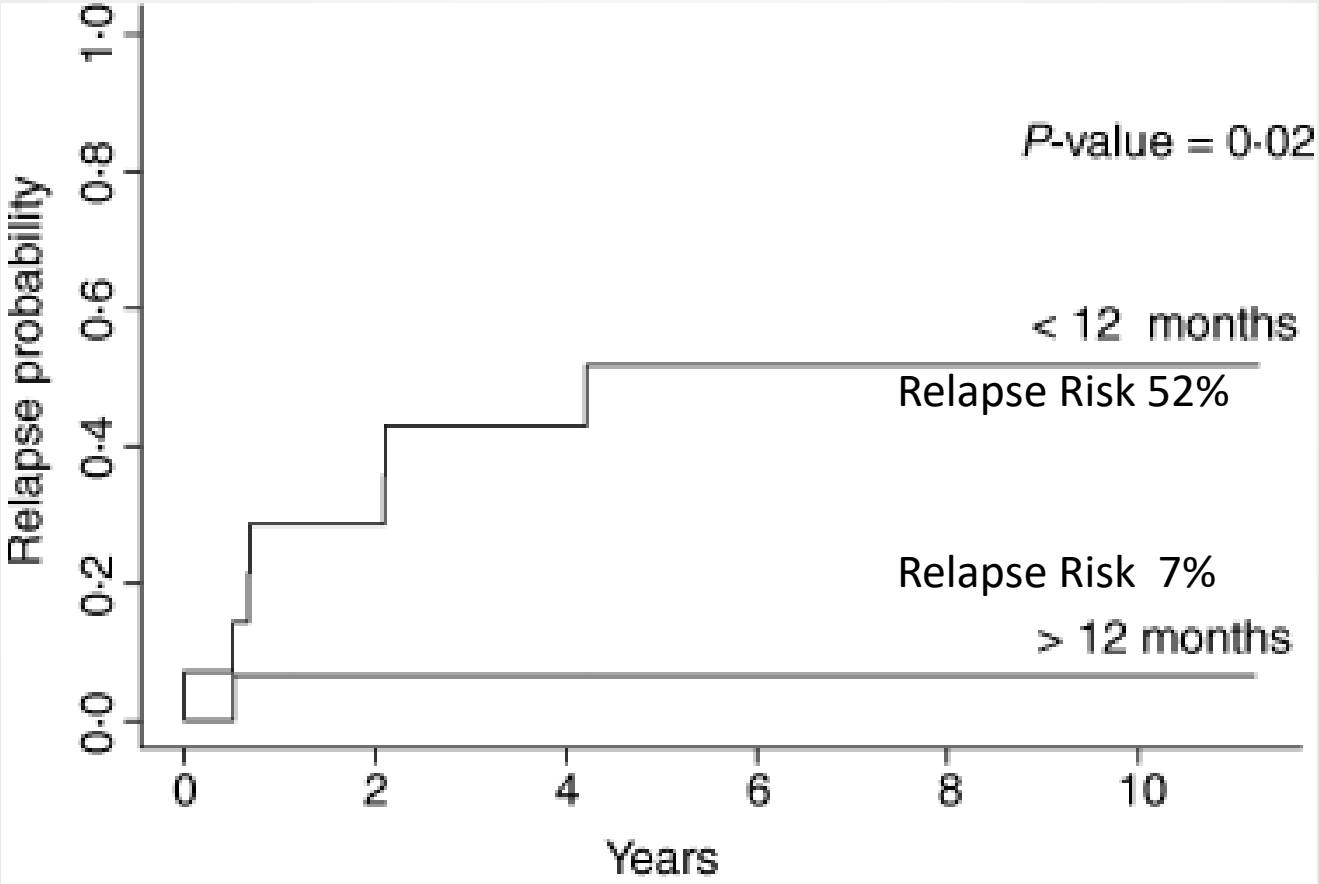
EFS and OS for the entire group (n=44)



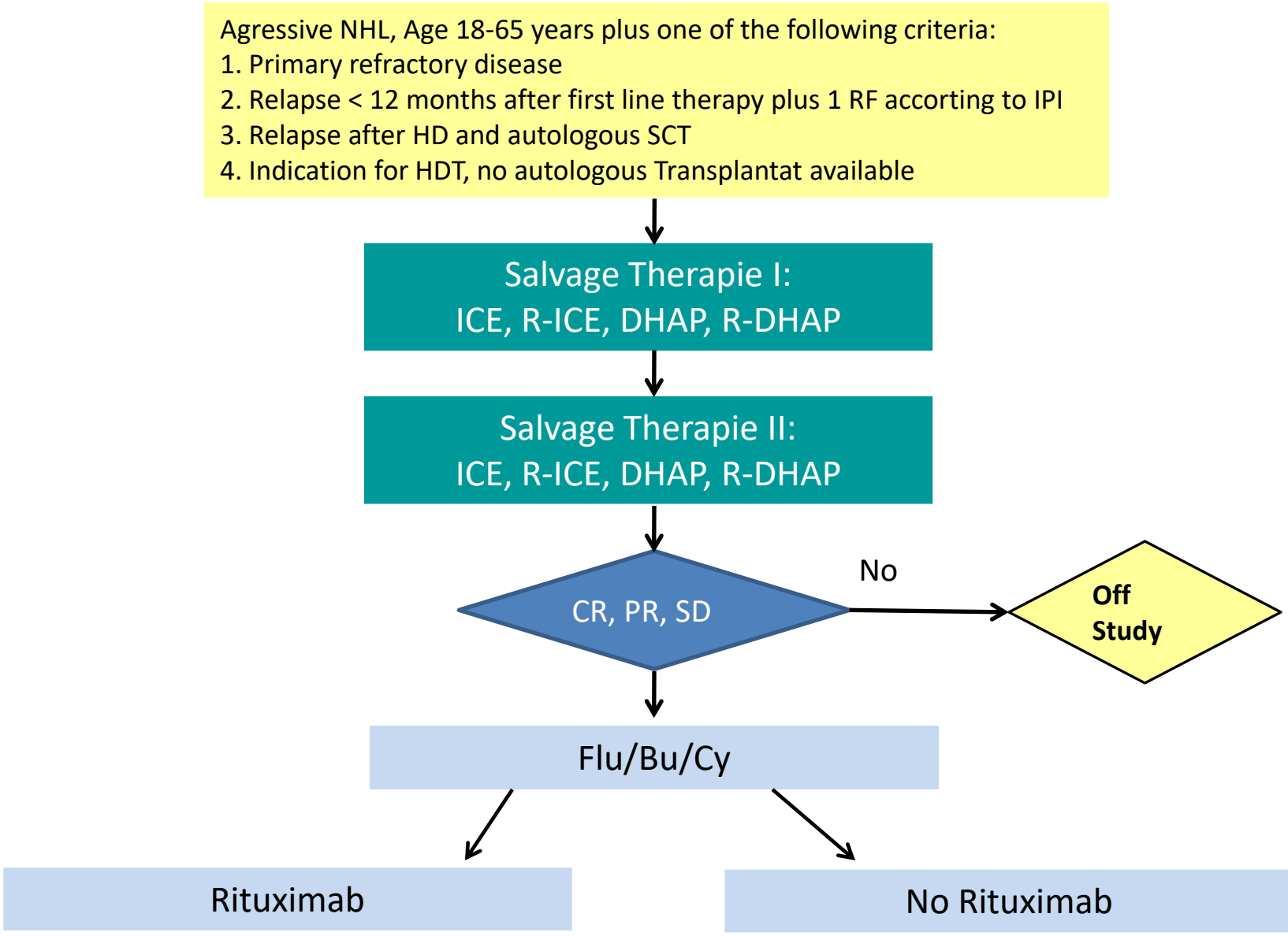
Cumulative incidence of relapse



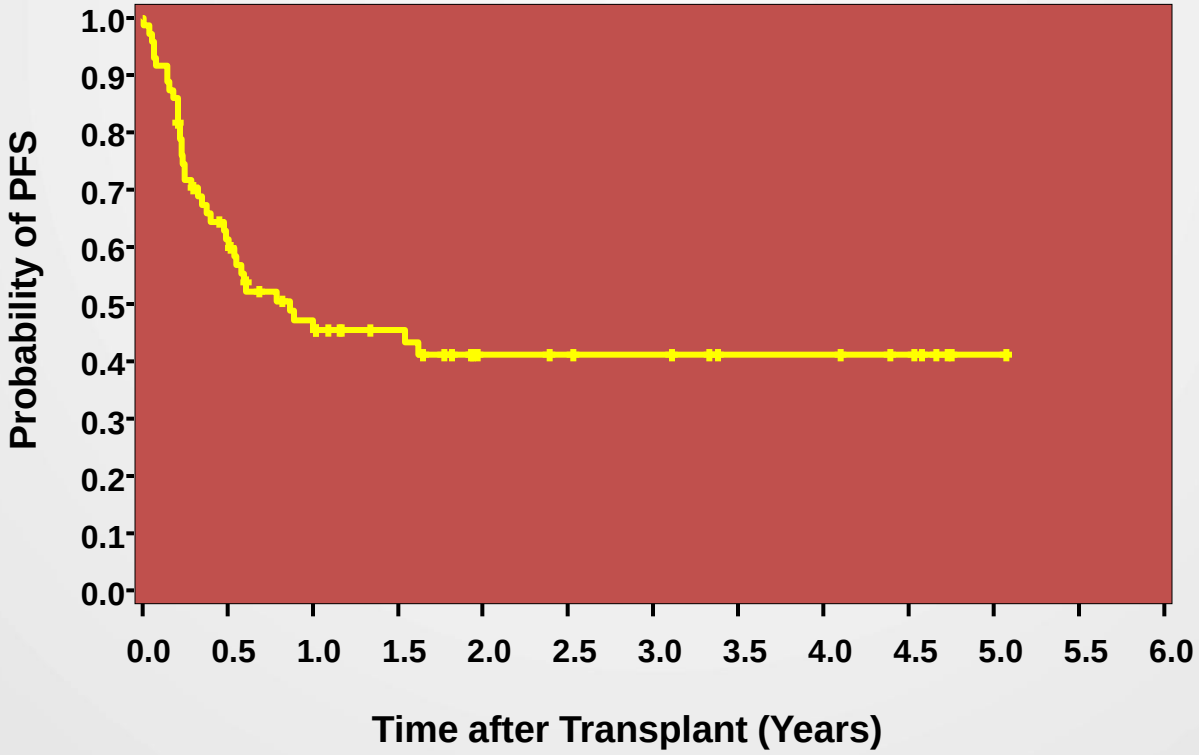
Cumulative incidence of relapse according to time to relapse after initial therapy



Current Protocol of the DSHNL for Allo-SCT for high grade NHL



Aggressive B-NHL - Relapse
Results of allo SCT – DSHNHL R3
Progression Free Survival, n=81



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Thanks for your attention!