

Toxizitäts-reduzierte
Konditionierung mit Treosulfan

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Wirkprinzipien

Transplantation 1970 - 2000:

- Applikation einer
maximal toxische Behandlung
zur Eradikation von malignen Zellen

Transplantation > 2000:

- Durch die Konditionierung werden maligne Zellen reduziert - die Heilungschance wird aber zusätzlich durch einen
Graft-versus Leukämie Effekt
verbessert

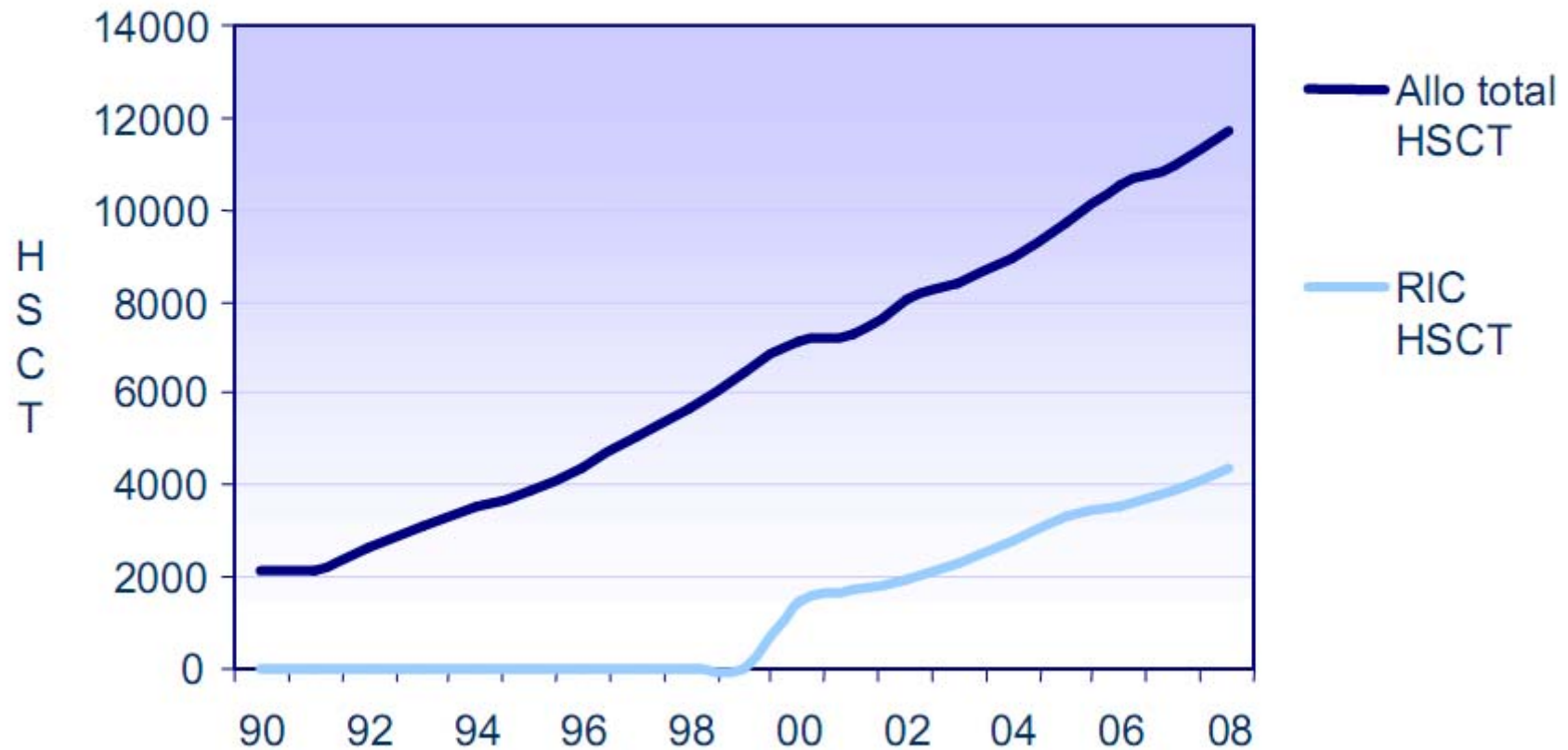
Allogene Blutstammzelltransplantation

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Adoptive Immuntherapie



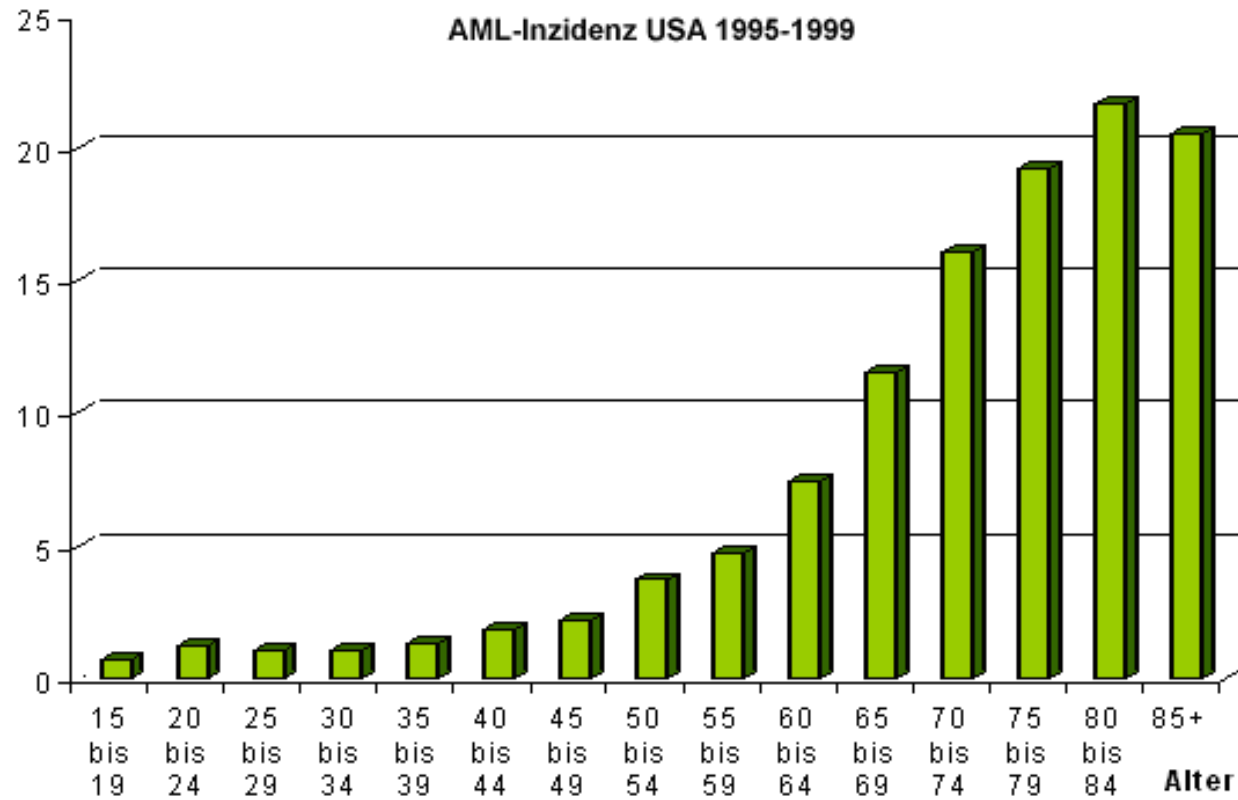
Evolution of RIC allogeneic HSCT in Europe 1990-2008



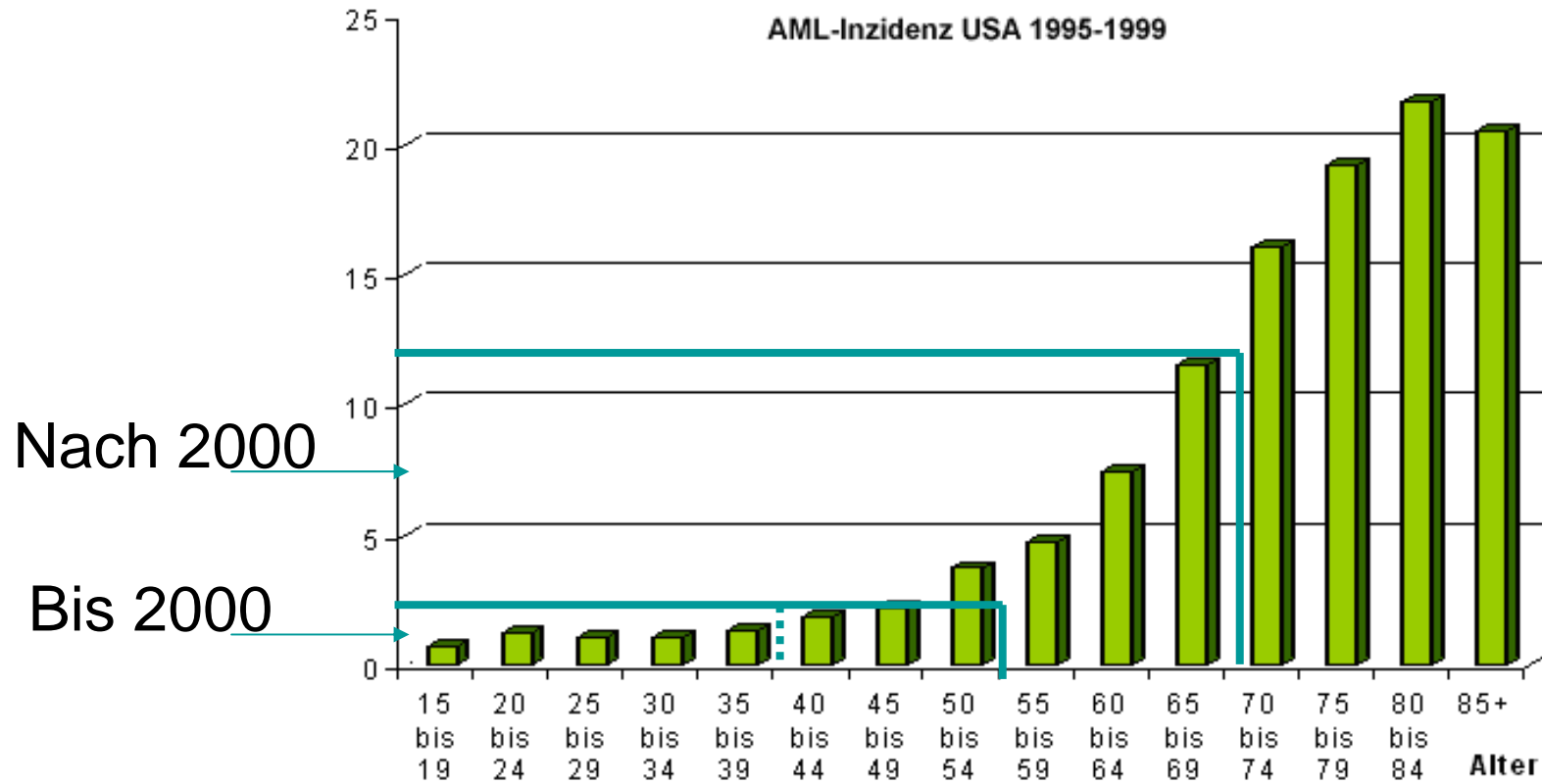
2008: final data

The European Group for Blood and Marrow Transplantation

Inzidenz der AML

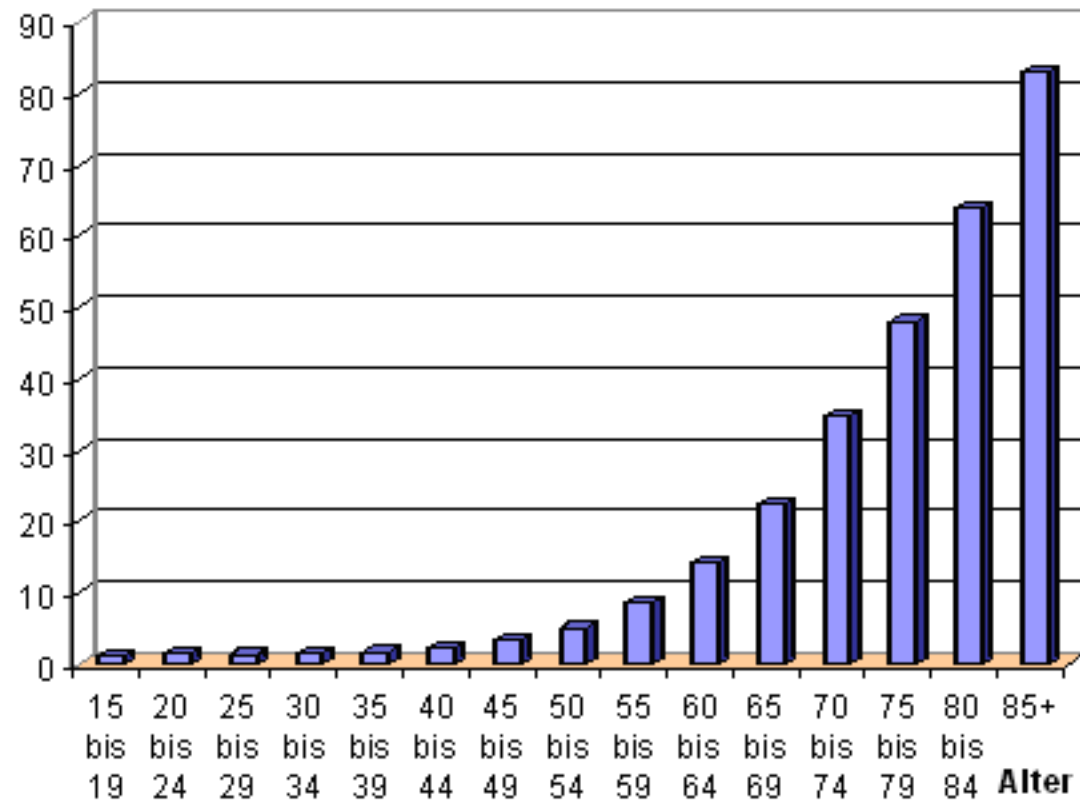


Inzidenz der AML



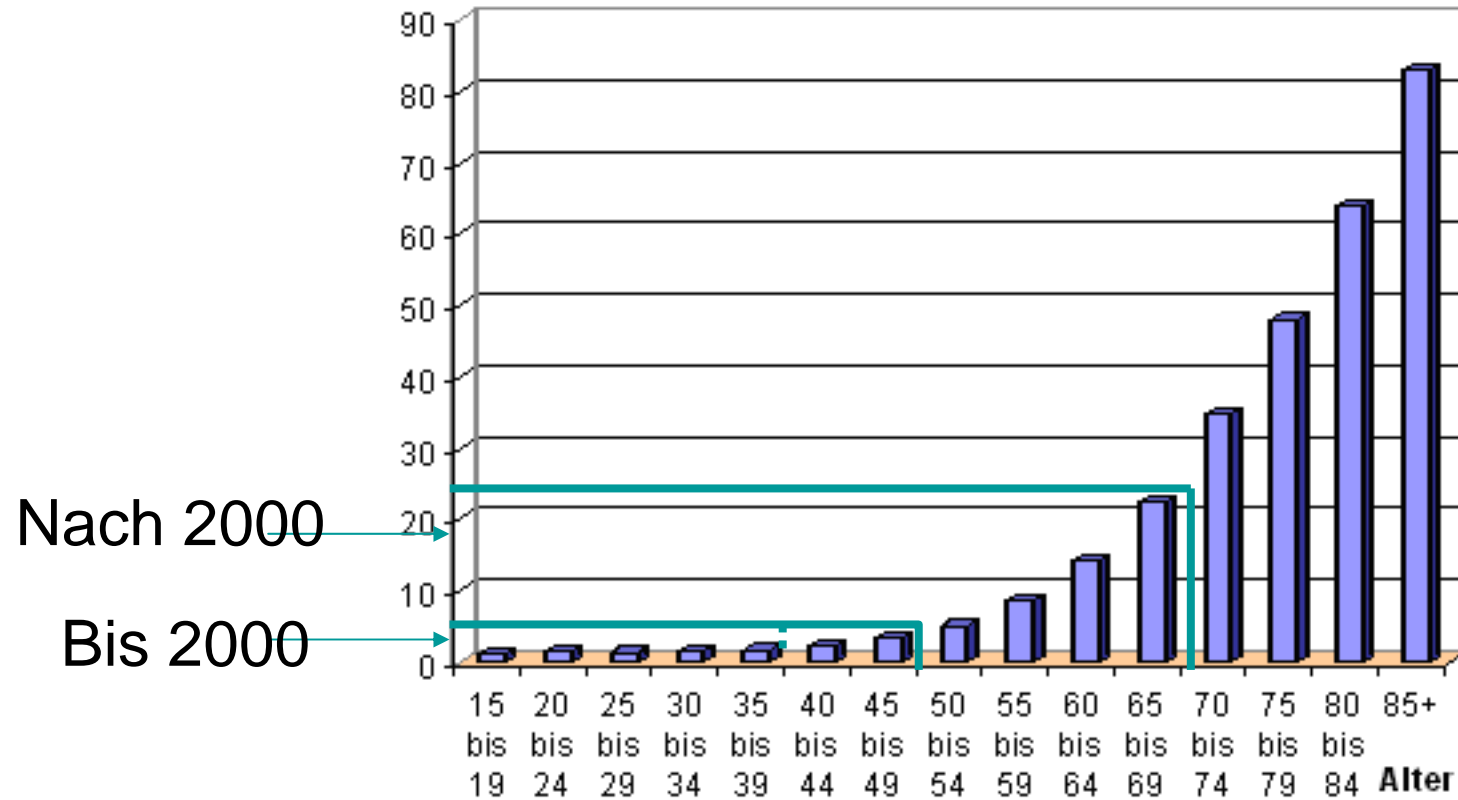
Inzidenz des MDS

Inzidenz Leukämie USA 1995 - 1999



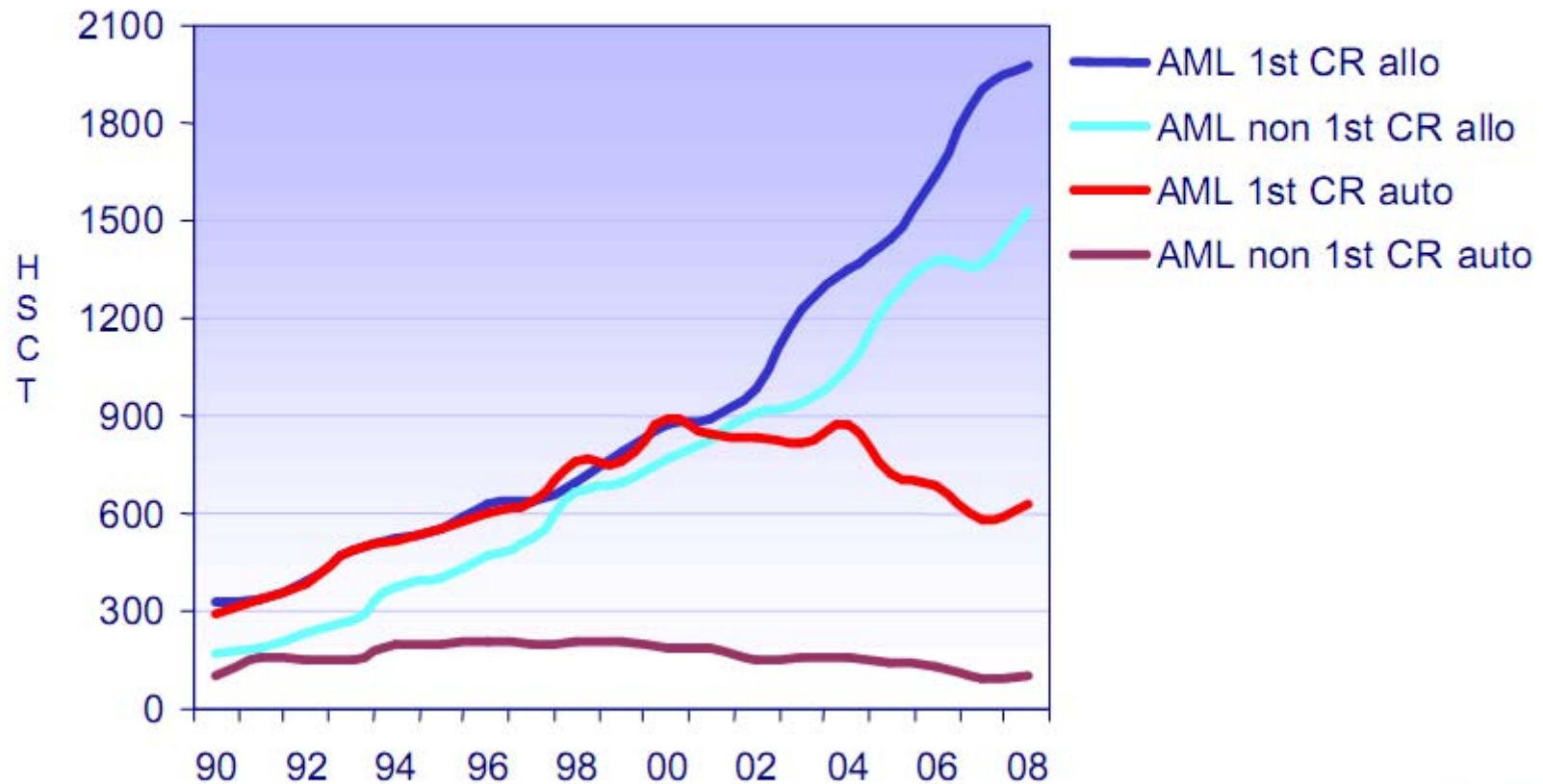
Inzidenz des MDS

Inzidenz Leukämie USA 1995 - 1999





EBMT Activity Survey on HSCT 1990-2008 changes in AML

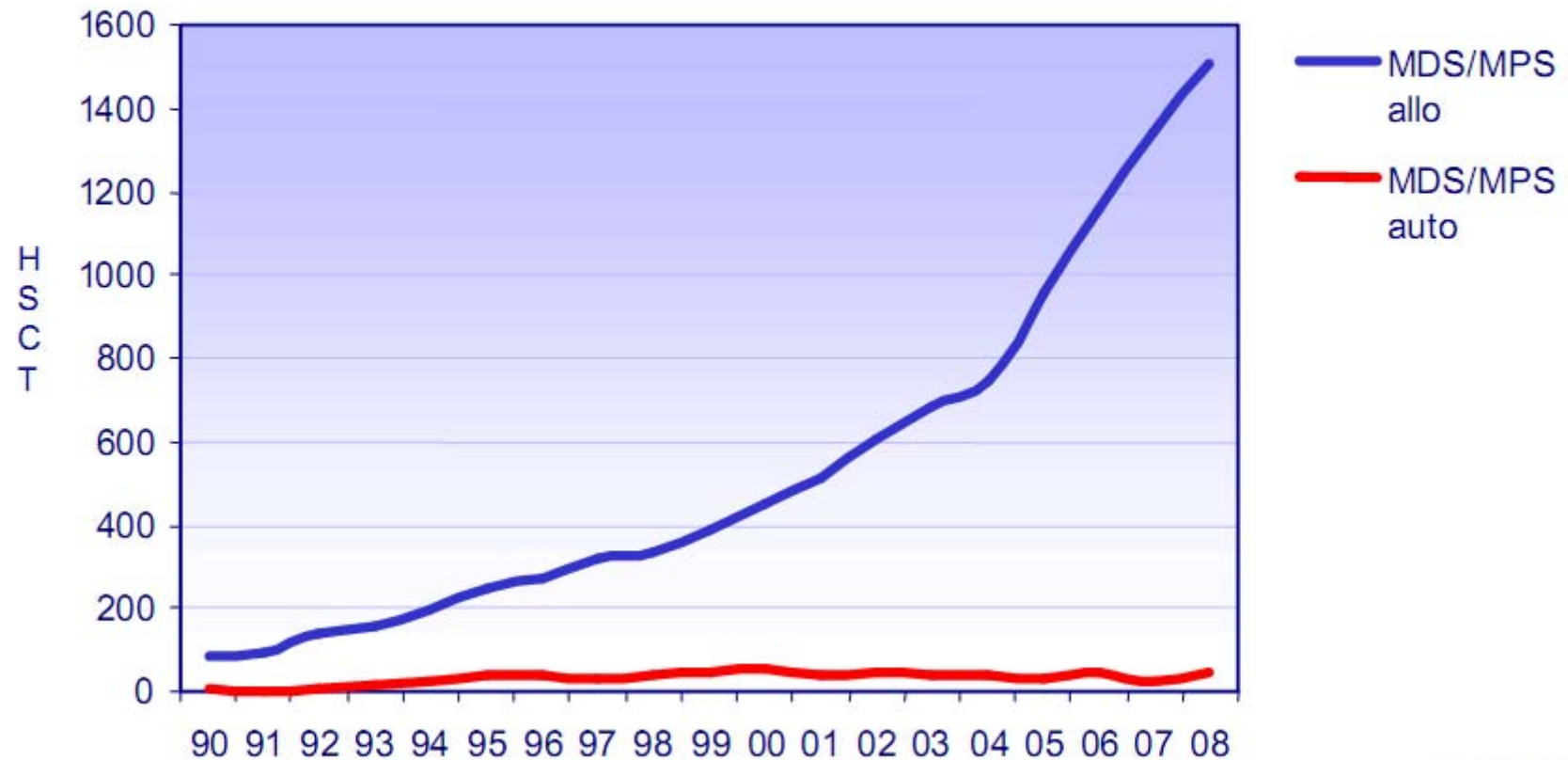


2008: final data

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EBMT Activity Survey on HSCT 1990-2008 changes in MDS/MPS



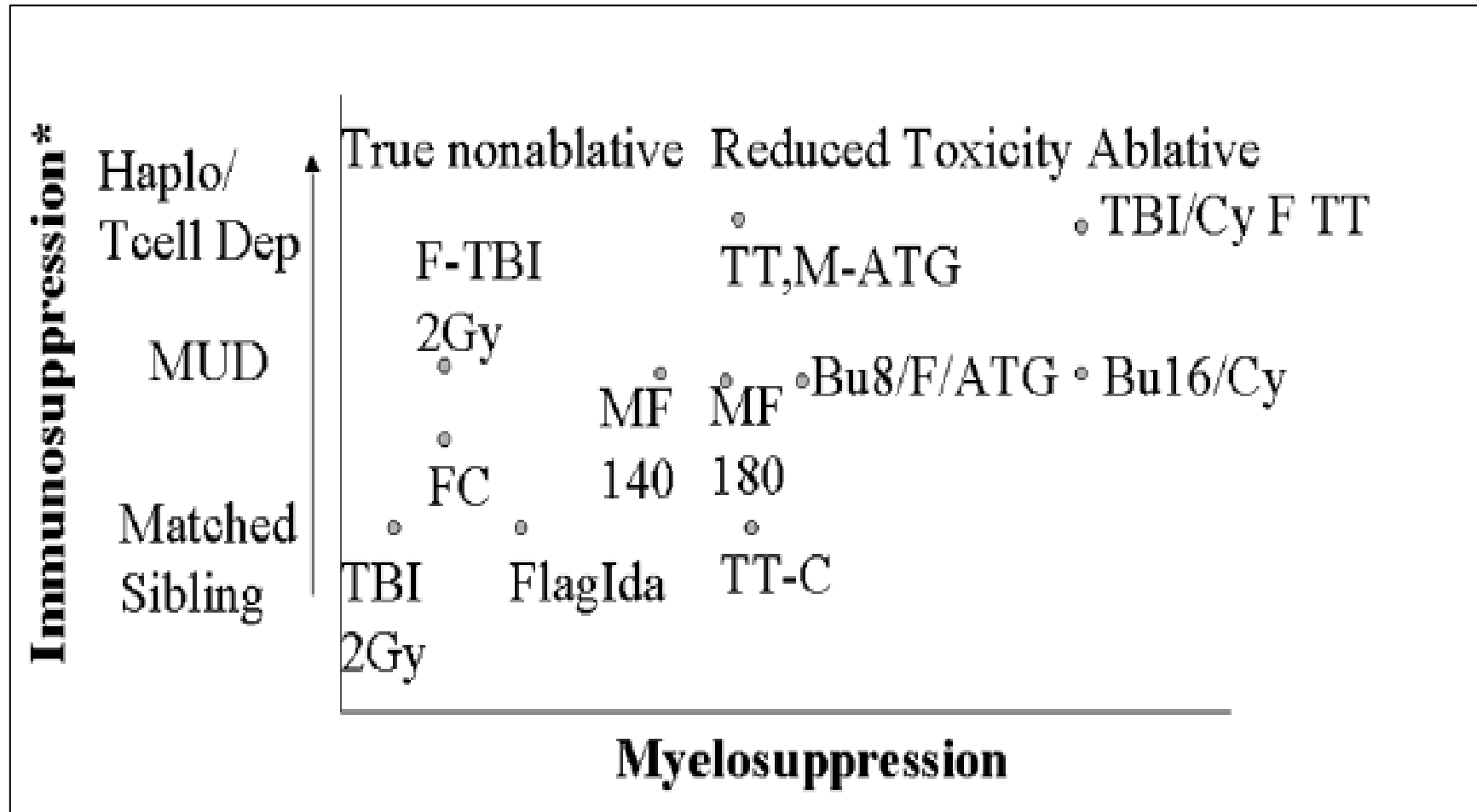
2008: final data

The European Group for Blood and Marrow Transplantation

Neue Indikationen

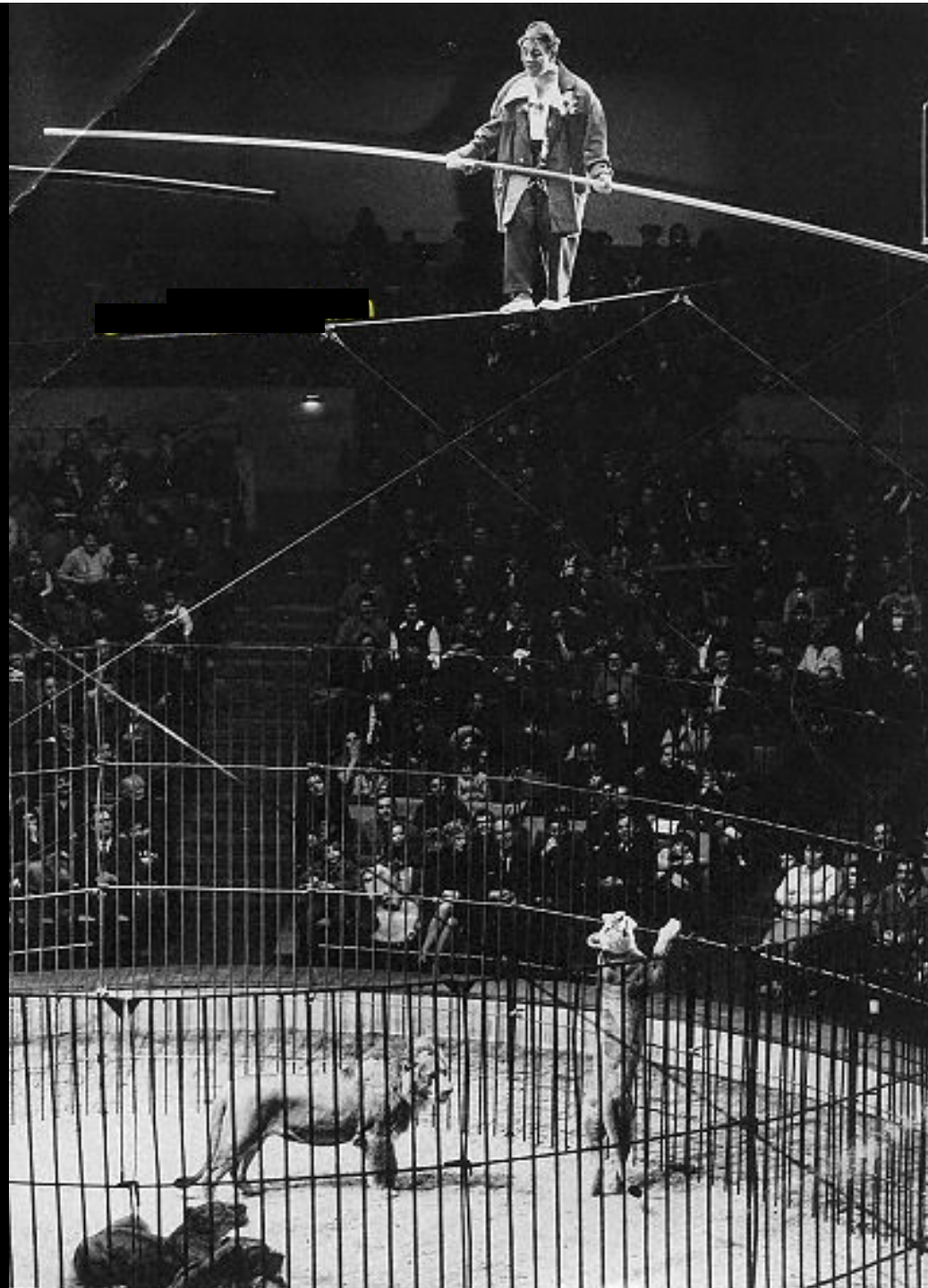
- MDS
- Myelofibrose
- CLL?

Konditionierungen



Toxizität

GvH

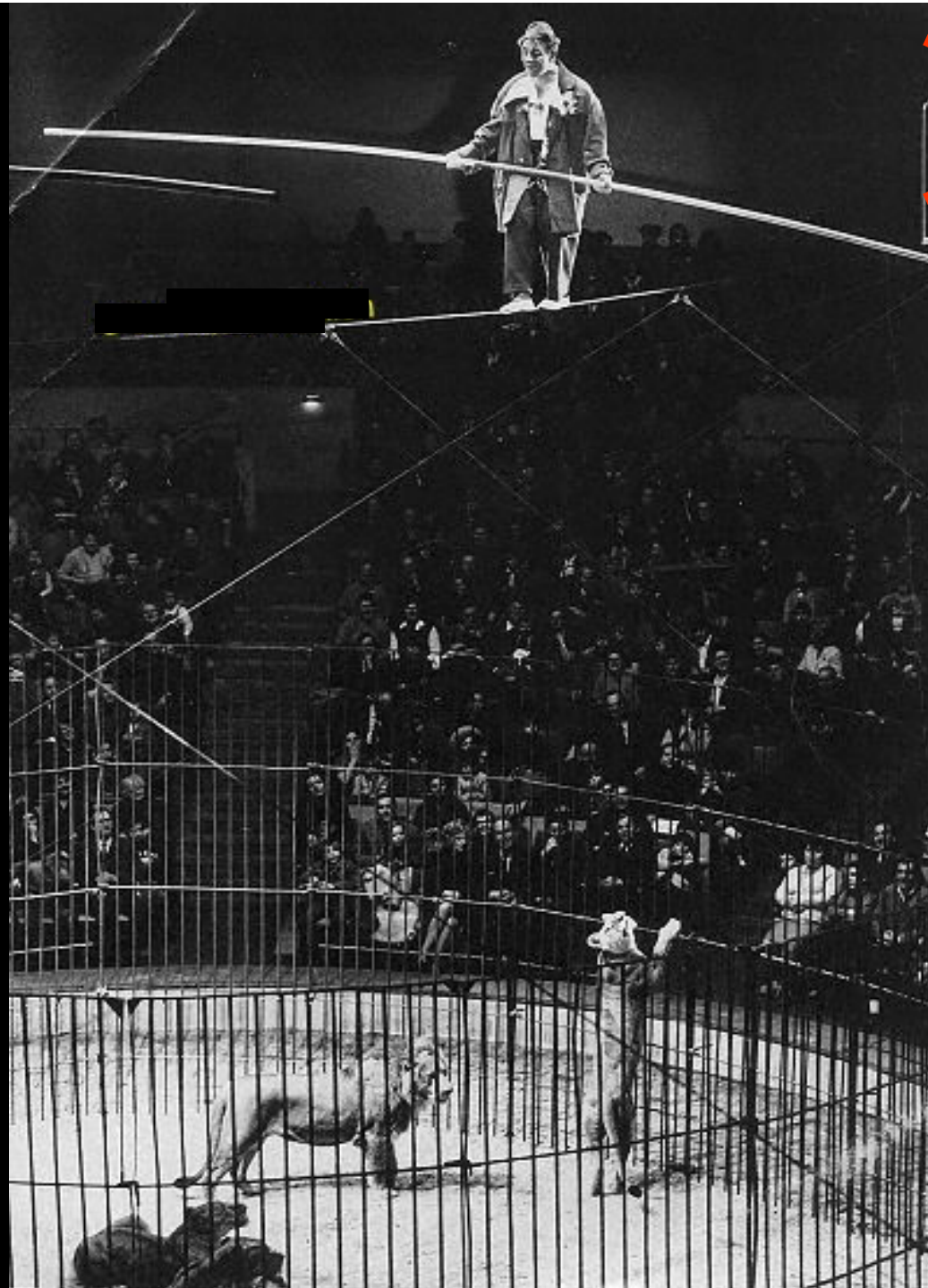


Rezidiv

Infektion

~~Toxizität~~

GvH



~~Rezidiv~~

?

Infektion

Treosulfan Präklinik

- Stammzell Toxizität in vitro

Westerhof et al. Cancer Res. 2000
Ploemacher et al. BMT 2000

- Immunsuppressiv

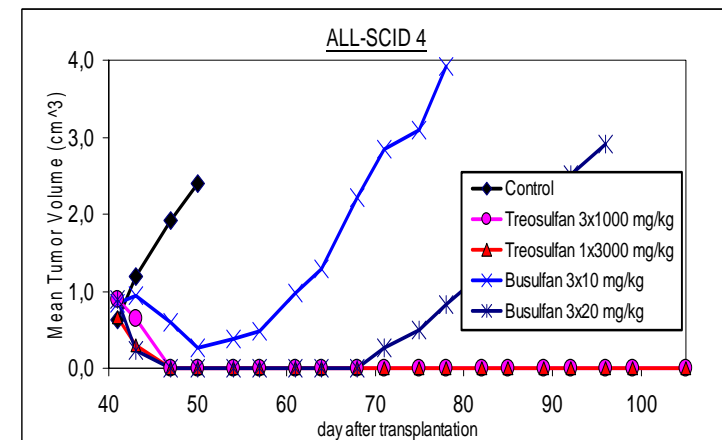
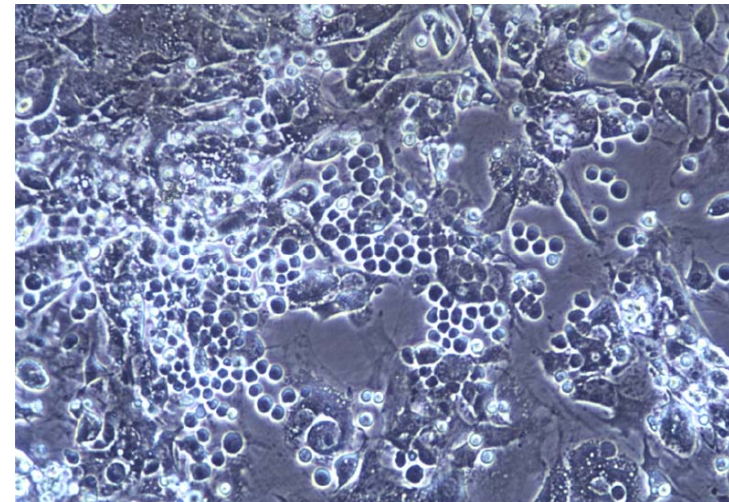
Melchers et al. Immunobiology 2000

- Engraftment in vivo

Ploemacher et al. BMT 2000
van Pel et al. BMT 2003
Andersson et al. Blood 2003

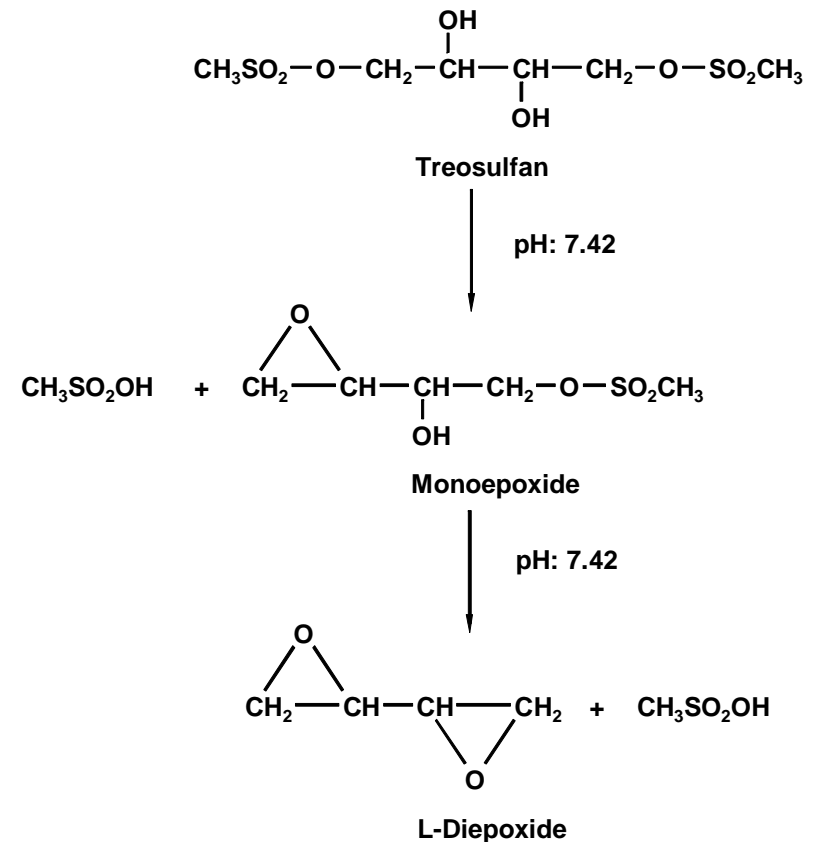
- Anti-Leukämie /Myeloma
Aktivität in vivo / in vitro

Melchers et al. 2002
Meinhardt et al. Br J Hematol 2003 (MM)
Fichtner et al. Eur J Cancer 2003 (ALL)
Schmidmaier et al. Exp. Hematol. 2004 (AML)



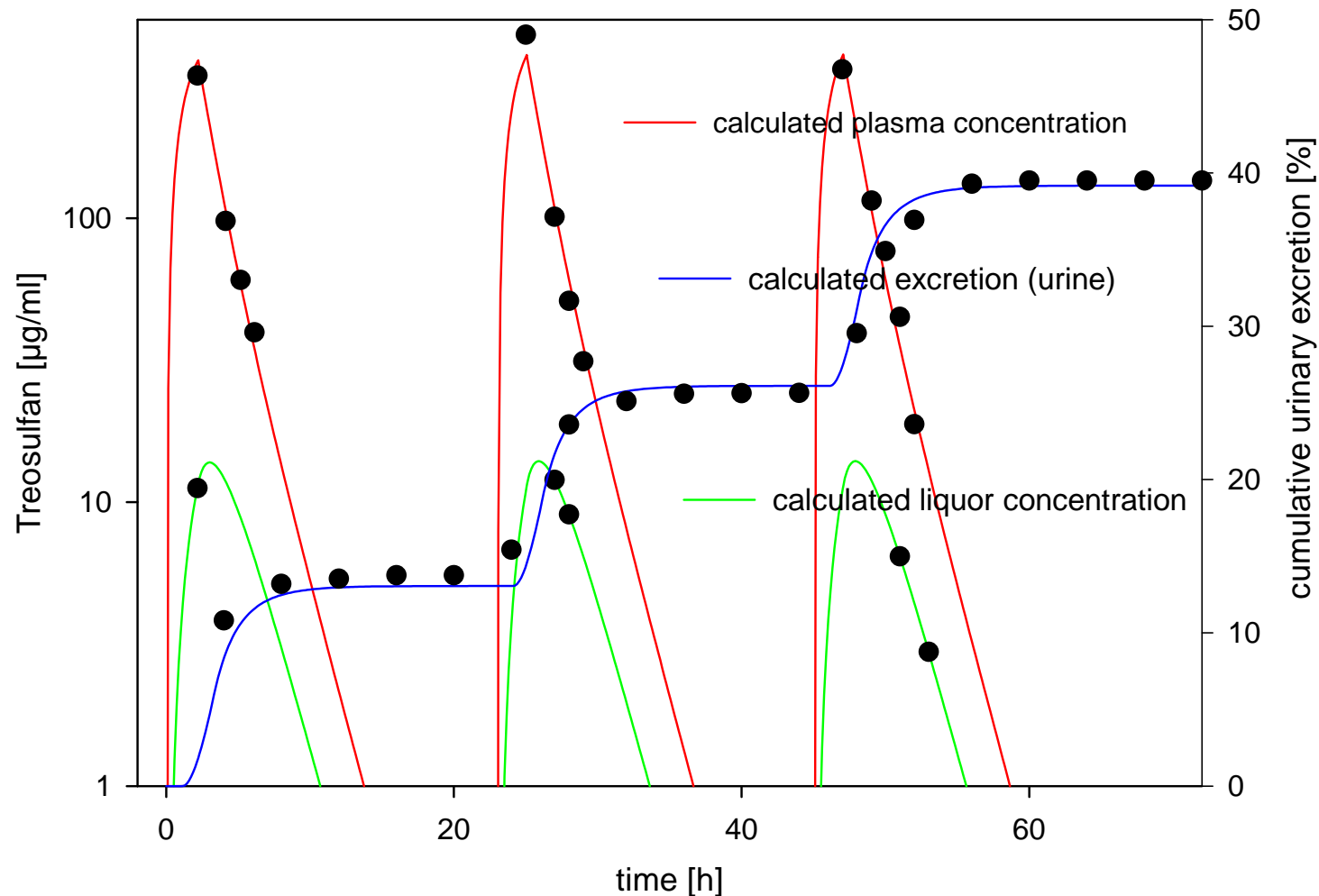
Treosulfan

- Struktur analog zu Busulfan
- Prodrug
- i.v. oder oral
- Kaum/keine VOD
- Geringe nicht-hämatologisch Toxizität
- nicht-enzymatische Aktivierung
- Gut voraussagbare Pharmakokinetik



Treosulfan Plasma und Liquor Konzentration (Hilger et al. 2003)

Treosulfan Study MC-TC.2/L Analysis of Treosulfan in Liquor Cerebrospinalis



Treosulfan Dose Escalation and Autologous Transplantation (Scheulen et al. 2000)

Dose level (g/m ²)	No. of patients	No. of CD34+ cells reinfused (no./kg b.w.); mean (range)	WBC nadir ^a below 0.5 × 10 ⁹ /liter		Thrombocyte nadir ^a below 25 × 10 ⁹ /liter	
			Median (days)	Range (days)	Median (days)	Range (days)
20.0	4	2.15 (1.7–2.8)	0	0	0	0–1 ^b
26.0	3	2.50 (1.6–4.6)	0	0–1	0	0–1
32.5	3	5.33 (2.3–11.2)	2	1–3	3	1–10 ^c
39.0	3	1.80 (1.1–2.7)	2	2–3	3	0–3
47.0	3	5.90 (3.4–8.4)	4	3–4	2	1–3
56.0	6	2.59 (1.3–3.4)	3	3–10 ^d	2	1–7 ^d

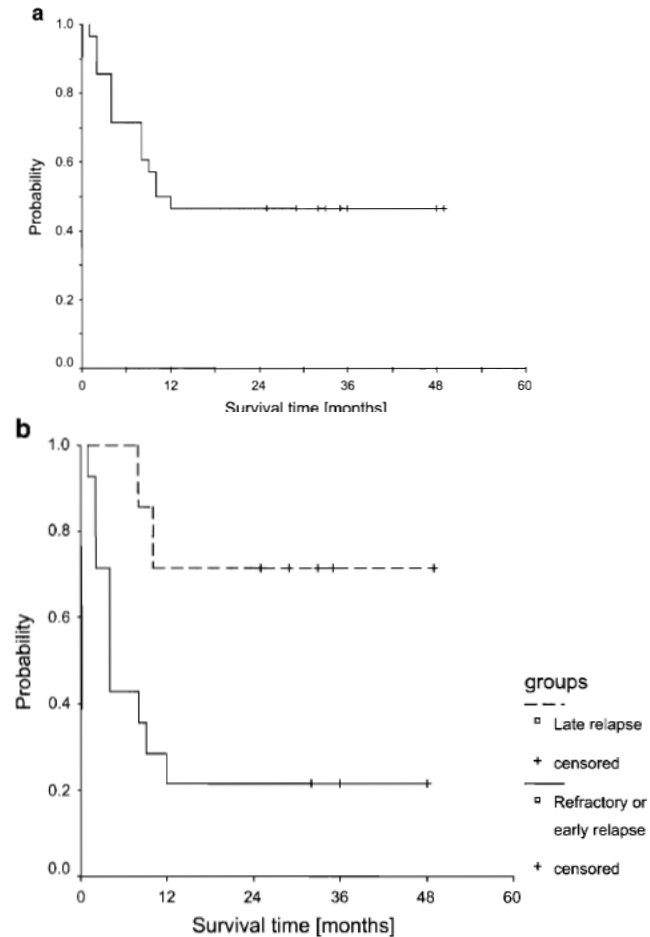
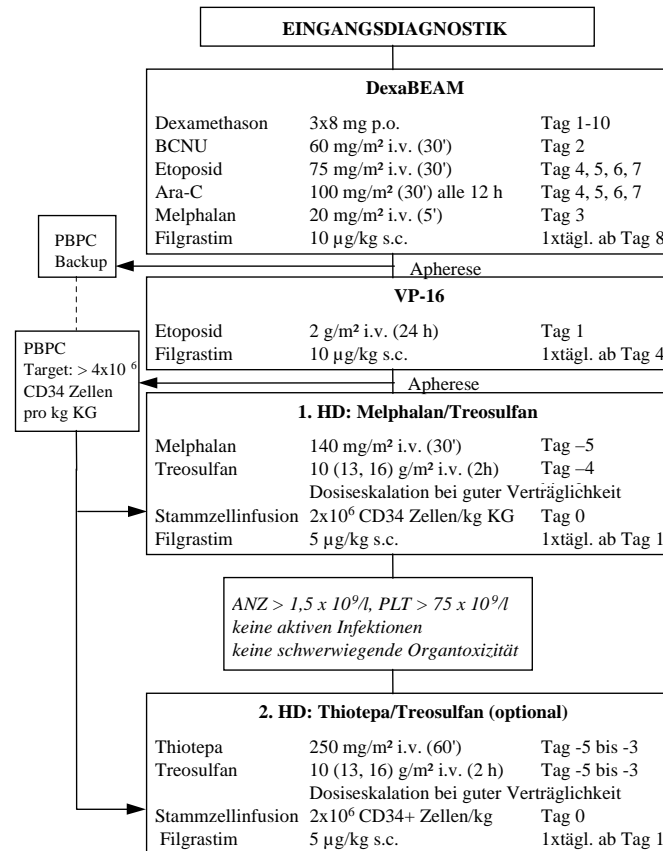
Table 3 Drug-related, nonhematological toxicities: worst toxicity per patient and dose level

Dose level (g/m ²)	No. of patients	CTC grade	Diarrhea	Mucositis/Stomatitis	Acidosis	Skin	Vomiting	Pain	Fever/Infection
20.0	4	II		1			1	1	
		III							
		IV							
26.0	3	II							
		III							
		IV							
32.5	3	II							1
		III							1
		IV							1 ^a
39.0	3	II							
		III							
		IV							
47.0	3	II	2			2		1	1
		III							
		IV							
56.0	6	II	1		2	3	2	3	2
		III		1	1				1
		IV	2	1		1			

^a Patient 10 (Hodgkin's disease) died 19 days after autologous PBSCT because of fungal sepsis despite hematological recovery.

Treosulfan for Relapsed or Refractory NHL and Autologous Transplantation (Königsmann et al. 2004)

Studienübersicht



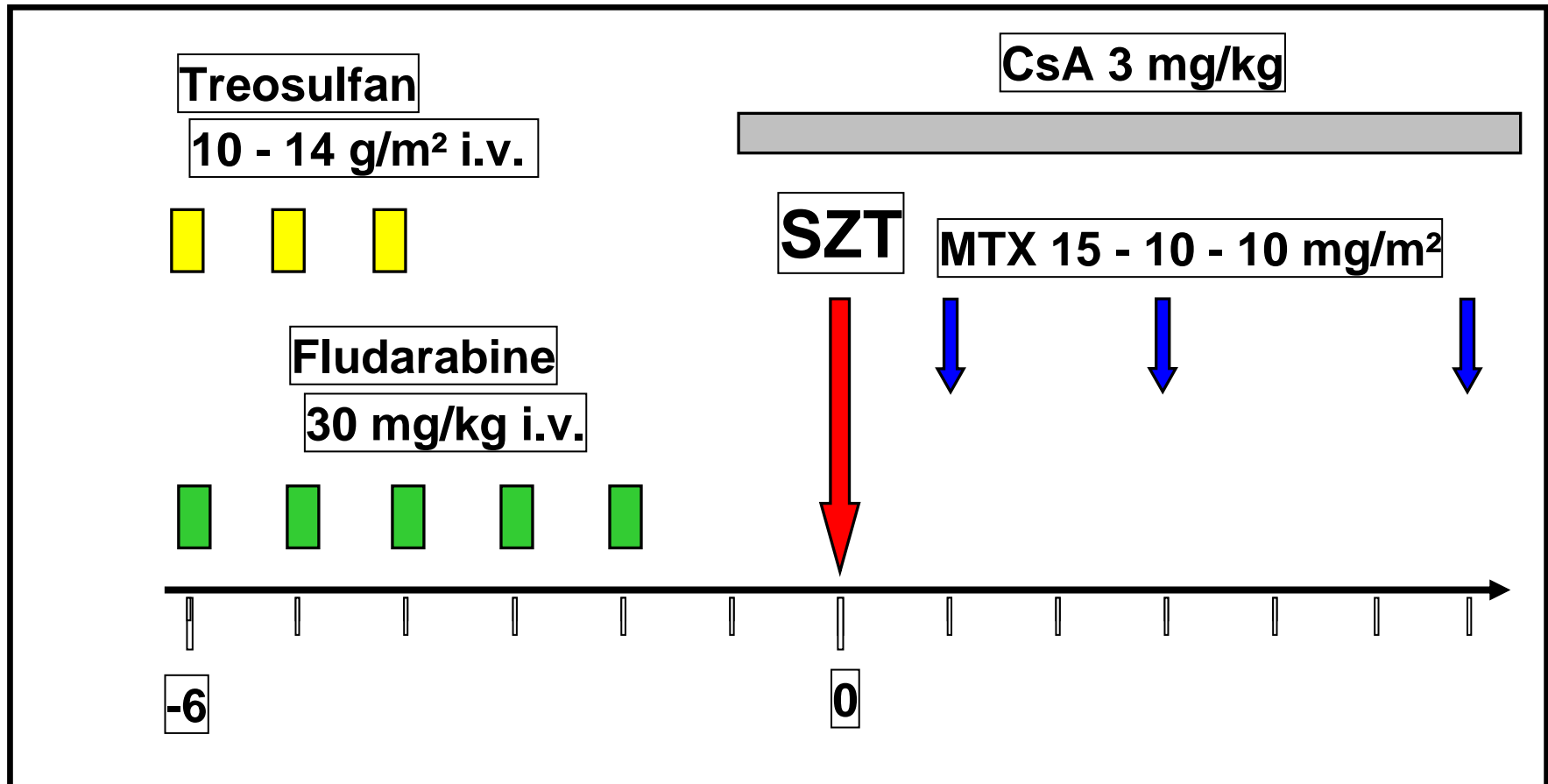
Treosulfan Kombinationen autologe Transplantation

- Treosulfan 3x10 g/m² + Thiotepa 3x250 mg/m²
- Treosulfan 3x10 g/m² + Melphalan 140 mg/m²
- Treosulfan 3x14 g/m² + Carboplatin 3x300 mg/m² + Etoposide 3x500 mg/m²
- Treosulfan 3x10 g/m² + Cytarabine 5x2 g/m² + Fludarabine 5x30 mg/m²

Die “Optimale” Konditionierung

- Anwachsen des Transplantates
 - Immunosuppression
 - Myeloablation
- Pharmakokinetik problemlos
- Geringe Toxizität
- Effektive anti-Tumor/Leukämia Aktivität
- Gut kombinierbar mit anderen Substanzen
- Einfache Handhabung

Treosulfan/Fludarabine



Treosulfan/Fludarabine Studien

Prospective Multizenter Studien:

- Treosulfan 3x10g/m² i.v. Phase I/II, patients not eligible for standard conditioning (Casper et al. Blood 2004)
- Treosulfan dose escalation 3x10, 3x12 and 3x14g/m² Phase I/II (Casper et al. JCO 2010)
- Treosulfan 3x14g/m² in AML Phase II (Casper et al. Leukemia submitted 2010)
- Treosulfan 3x14g/m² in MDS Phase II (Ruutu et al. Leukemia submitted 2010)
- Treosulfan 3x14g/m² in CML Phase II (Holowiecki et al. Br. J. Hematol. 2008)
- Treosulfan vs Busulivex in AML und MDS Phase III (Beelen)

Retrospektive Studien:

- Treosulfan/Fludarabine vs standard TBI conditioning in MDS (Hilgendorf et al. BMT 2010)

Engraftment und Chimerismus

Treosulfan	Number of patients	Granulocytes > 500/ μ l (Median; days)	Platelets > 50.000/ μ l (Median; days)	Complete Chimerism d28 (median)	Complete Chimerism d100 (median)	Primary graft failure	
3x10 g/m ²	30	11.5	16.5	81%	90%	1/30 (3%)	no MTX, G-CSF
3x10 to 3x14 g/m ²	56	14.5	17	77%	94%	0/56	MTX, no G-CSF
MDS 3x14 g/m ²	44	18	21	75%	93%	0/44	MTX, no G-CSF
AML 3x14 g/m ²	75	21	19	72%	92%	0/75	MTX, no G-CSF
CML 3x14 g/m ²	40	21	21	77.5%	92.5%	0/40	MTX, no G-CSF

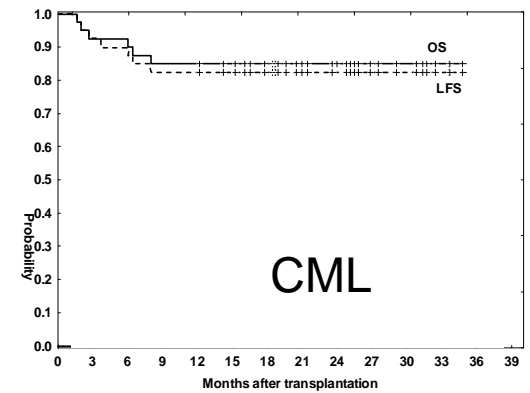
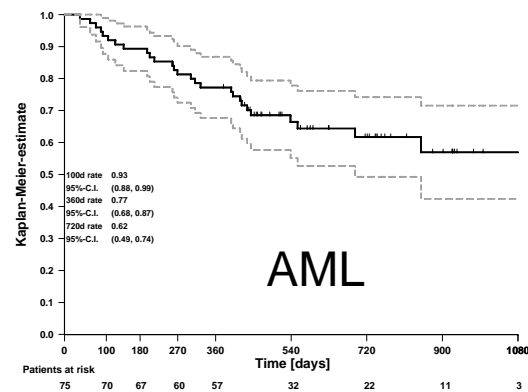
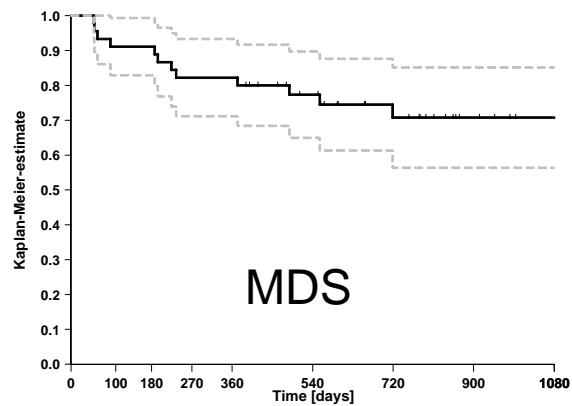
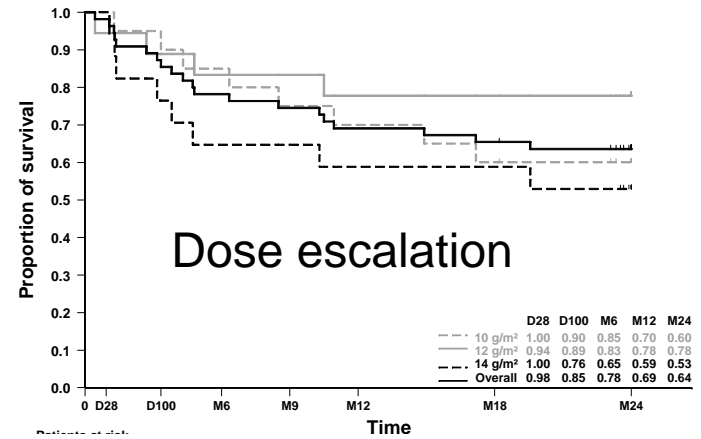
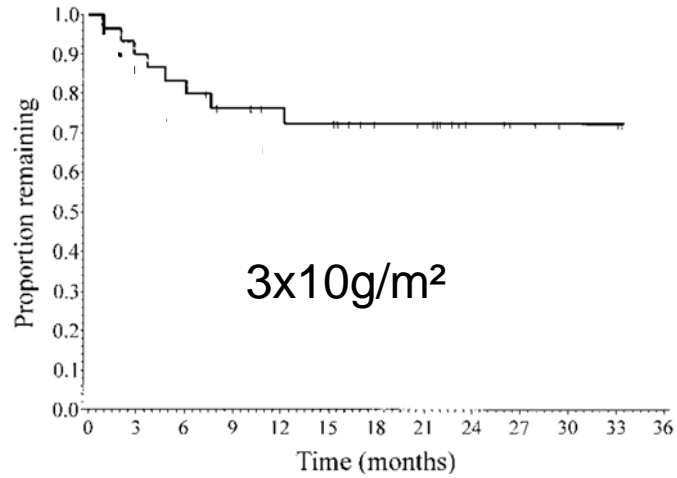
Toxicity – CTC ° III/IV Dose Escalation Study

	Treosulfan Dose			Total
	3 × 10 g/m ²	3 × 12 g/m ²	3 × 14 g/m ²	
Patients (N)	20	18	17	55
Any adverse event (%)	18 (90)	12 (67)	13 (76)	43 (78)
CTC AE category/term (%)				
Cardiac dysrhythmia	0	3 (17)	2 (12)	5 (9)
Cardiac general	2 (10)	1 (6)	2 (12)	5 (9)
Coagulation/PTT	0	2 (11)	3 (18)	5 (9)
Constitutional symptoms	0	1 (6)	3 (18)	4 (7)
Gastrointestinal	4 (20)	2 (11)	1 (6)	7 (13)
Diarrhea	3 (15)	0	0	3 (5)
Mucositis/stomatitis	1 (5)	1 (6)	1 (6)	3 (5)
Hemorrhage/bleeding	1 (5)	0	2 (12)	3 (5)
Infection	12 (60)	9 (50)	9 (53)	30 (55)
Metabolic/laboratory	13 (65)	10 (56)	9 (53)	32 (58)
ALT (SGPT)	7 (35)	5 (28)	4 (24)	16 (29)
AST (SGOT)	3 (15)	4 (22)	2 (12)	9 (16)
GGT	7 (35)	7 (39)	6 (35)	20 (36)
Alkaline phosphatase	2 (10)	2 (11)	0	4 (7)
Hyperbilirubinemia	1 (5)	1 (6)	2 (12)	4 (7)
Hyperglycemia	4 (20)	1 (6)	1 (6)	6 (11)
Neurology	1 (5)	1 (6)	3 (18)	5 (9)
Pulmonary	0	1 (6)	3 (18)	4 (7)
Renal failure	1 (5)	2 (11)	3 (18)	6 (11)

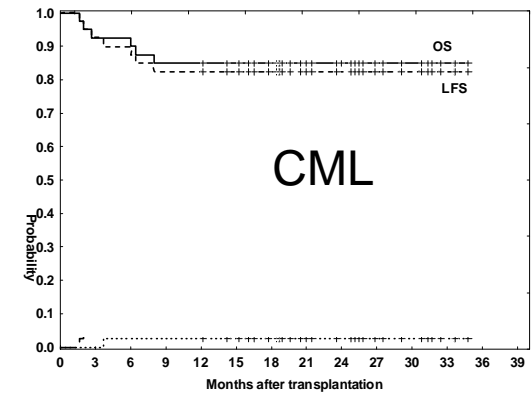
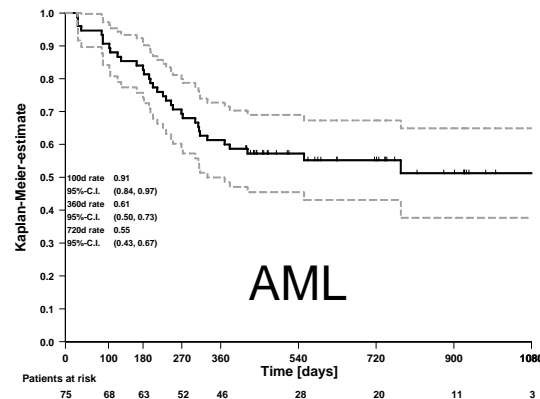
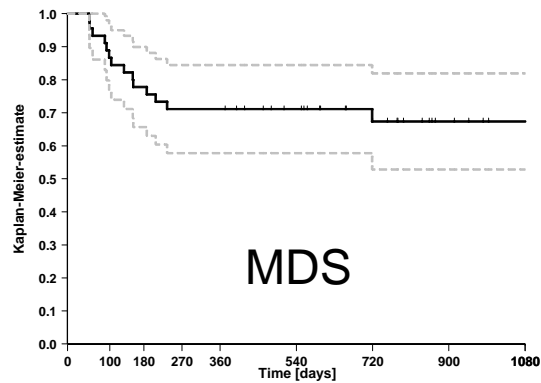
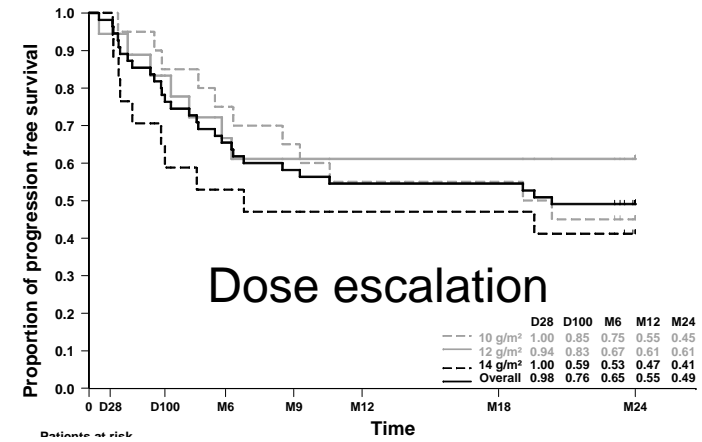
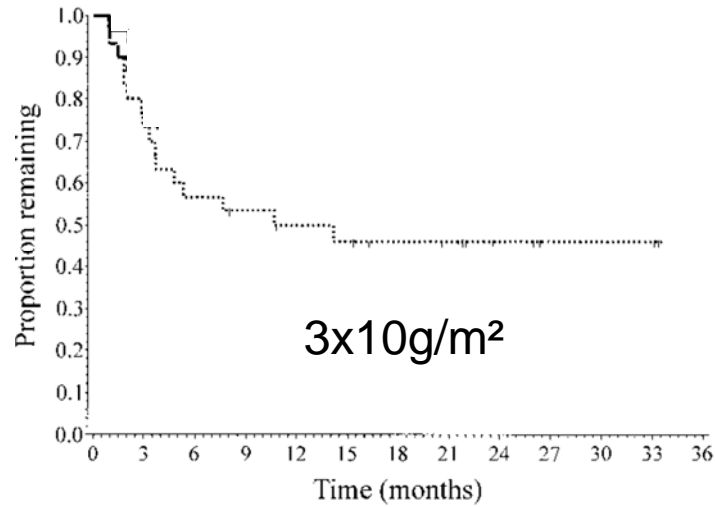
Graft versus Host Disease

Treosulfan	Number of patients	MRD / MUD (+misMRD)	PBSC / BM	aGvHD III/IV	cGvHD limited	cGvHD extensive
3x10 g/m ²	30	47% / 53%	53% / 47%	7%	8%	31%
3x10 to 3x14 g/m ²	56	47% / 53%	78% / 22%	5%	lim.+ext. 54%	24%
MDS 3x14 g/m ²	44	32% / 68%	89% / 11%	14%	lim.+ext. 54%	30%
AML 3x14 g/m ²	75	40% / 60%	63% / 37%	21% (II-IV)	39%	16%
CML 3x14 g/m ²	40	45% / 55%	30% / 70%	4%	42,5%	17%

Overall Survival



Progression-free Survival

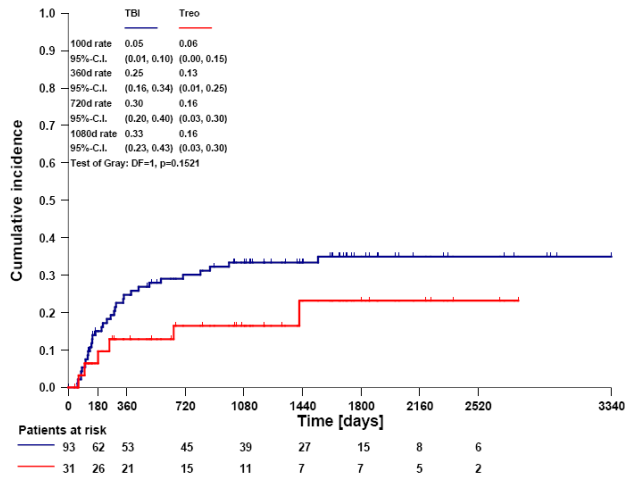


Relapse and Non-Relapse Mortality

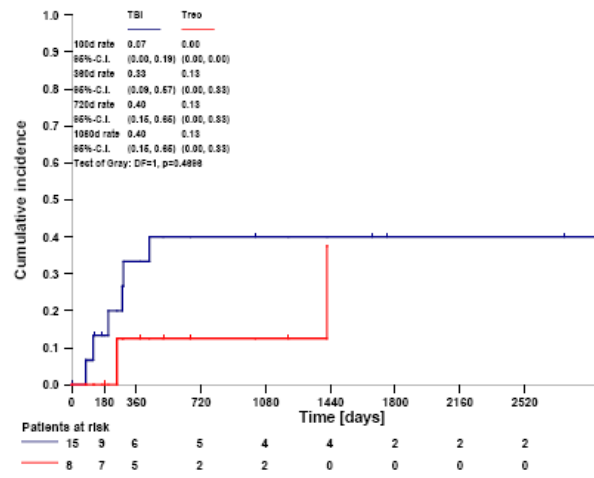
Treosulfan	Number of patients	NRM d+100	NRM 1 year	NRM 2 years	Relapse 1 year	Relapse 2 years
3x10 g/m ²	30	7%	17%	17%	28%	33%
3x10 to 3x14 g/m ²	56	13%	18%	20%	28%	31%
MDS 3x14 g/m ²	44	9%	12%	12%	15%	15%
AML 3x14 g/m ²	75	3%	9%	11%	30%	34%
CML 3x14 g/m ²	40	7.5%		15%	2,5%	2,5%

TBI vs Treosulfan – AML Relapse

Retrospective Analysis

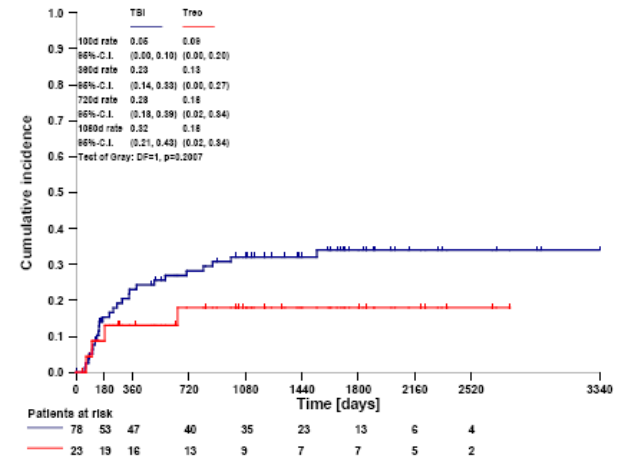


AML in CR



AML in CR

Sorrow Score ≥ 3

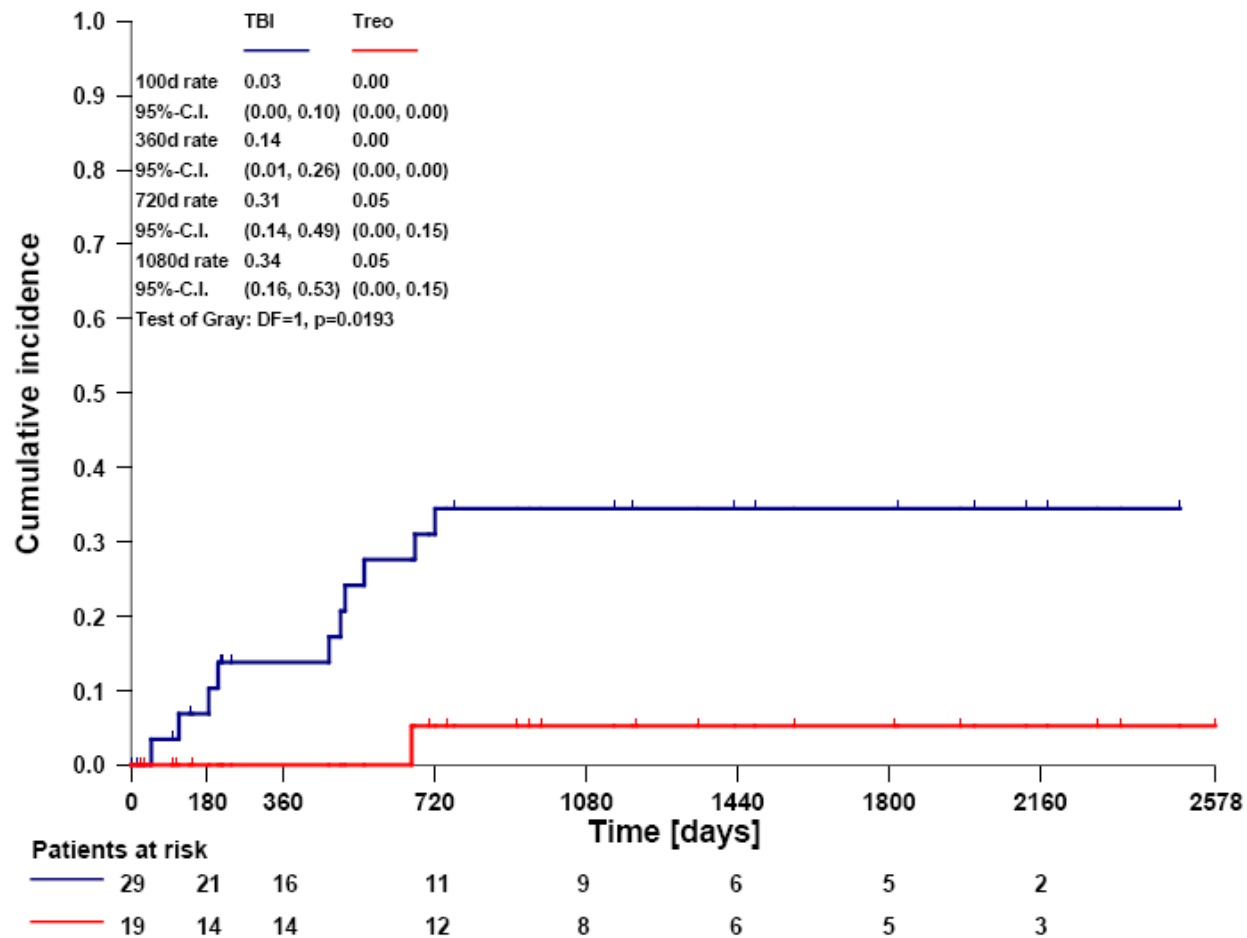


AML in CR

Sorrow Score < 3

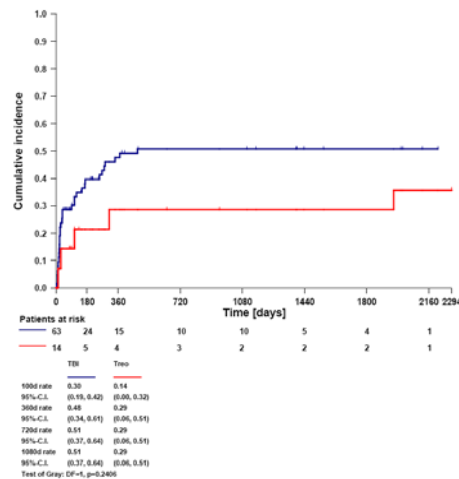
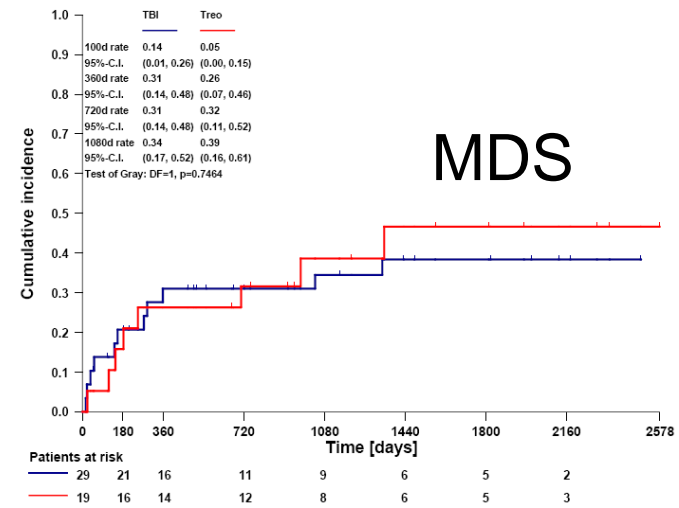
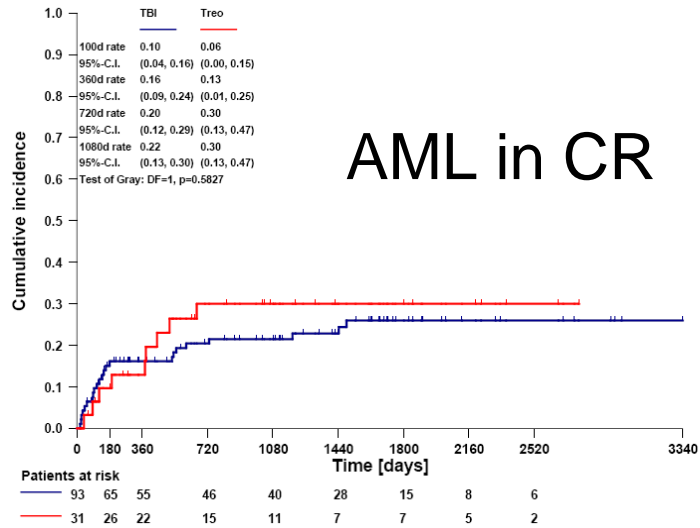
TBI vs Treosulfan – MDS Relapse

Retrospective Analysis



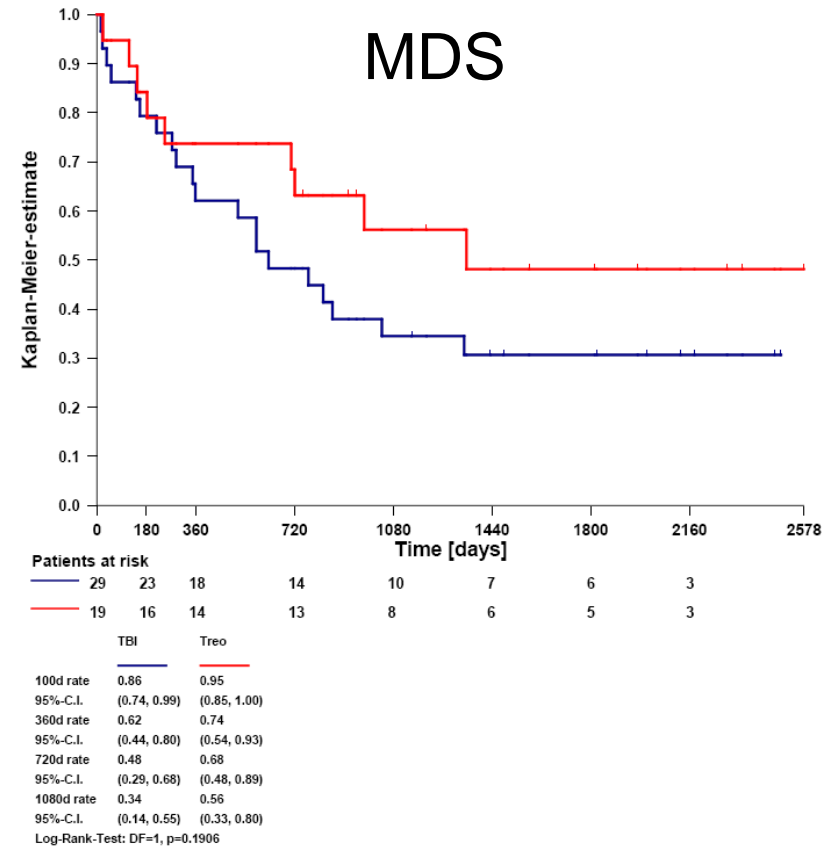
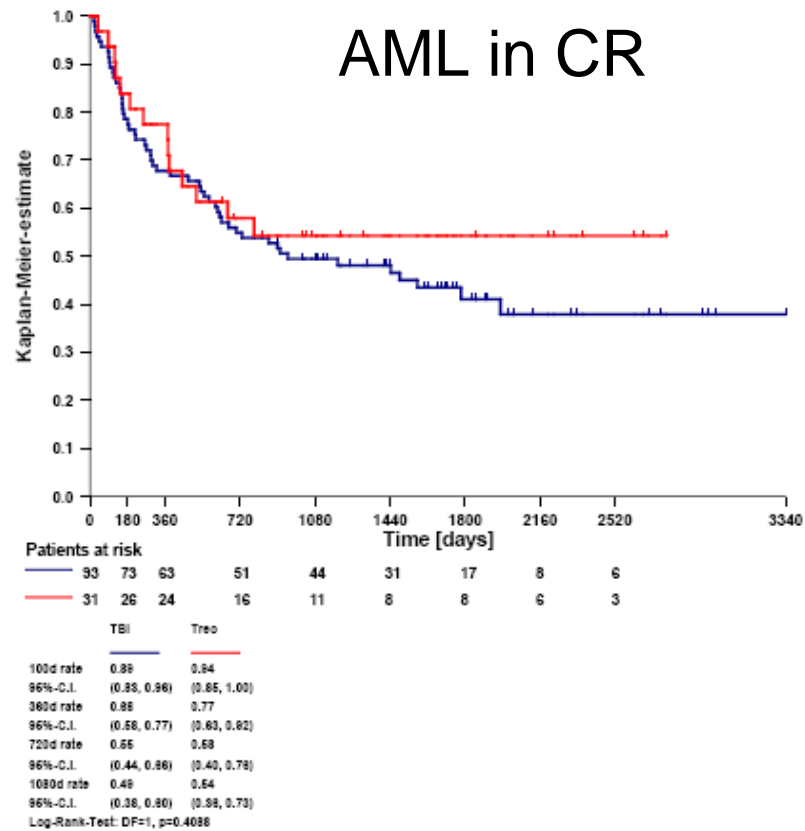
TBI vs Treosulfan - Non Relapse Mortality

Retrospective Analysis



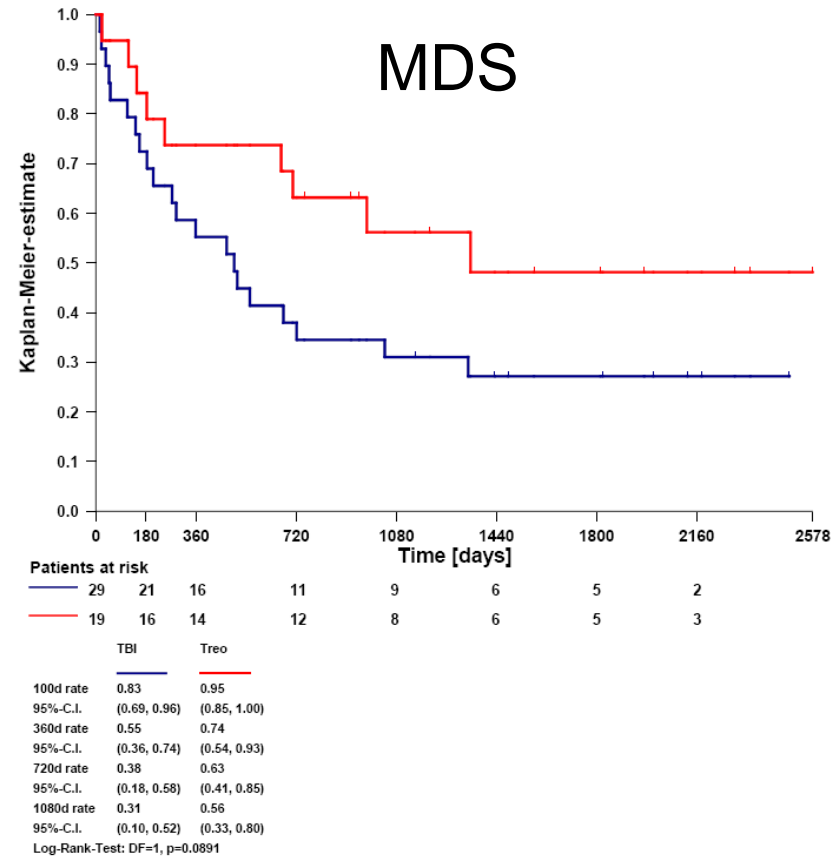
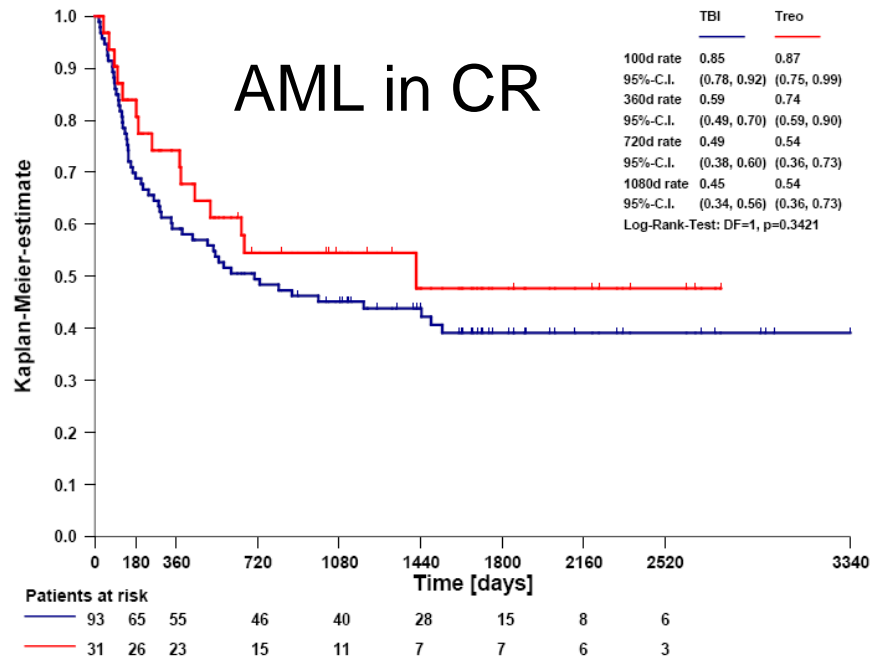
TBI vs Treosulfan - Overall Survival

Retrospective Analysis



TBI vs Treosulfan - Progression-free Survival

Retrospective Analysis



Treosulfan Konditionierung

- Engraftment und kompletter Chimerismus
- Sehr selten kein Engraftment
- Myeloablativ
- Niedrige nicht-hämatologische Toxizität
- 100 Tages Mortalität gering
- Nicht mehr GvHD
- Effektivität vergleichbar zu TBI
 - AML
 - MDS
 - CML

Mögliche Vorteile Treosulfan

- Kaum VOD
- Keine kardiale oder pulmonale Spättoxizität
- Kaum Mucositis
- Regelblutung tritt früh wieder ein (median nach 3 Monaten) - (Holowiecki et al. 2008 CML study)

Ausblick

- Studien!!!!
- Vergleich der Konditionierungsverfahren
- Erkrankungsspezifische Konditionierungsprotokolle
- GvHD!!!
- Infektionen !!
- Lebensqualität!