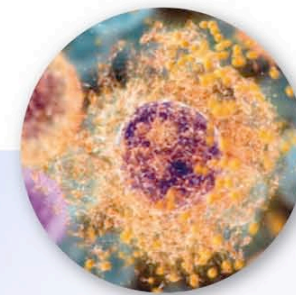
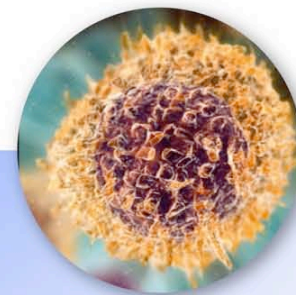
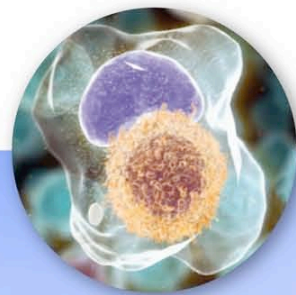


Les Ateliers Lymphomes et LLC

22 – 24 octobre 2009

Le Moulin de la Forge – Le Vaumain (60)



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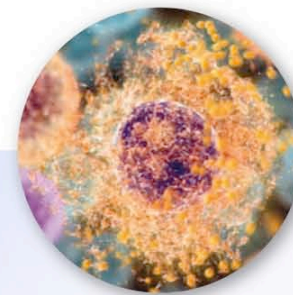
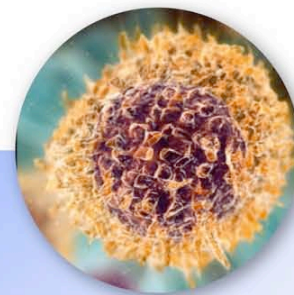
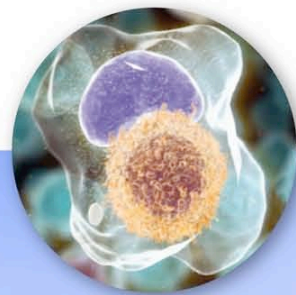
Avec le soutien institutionnel de





5^{ème} session : Leucémie Lymphoïde Chronique

Modérée par Hervé GHESQUIERES



Sous le patronage de



En collaboration avec



En partenariat avec



Avec le soutien institutionnel de





Programme de la session

5^{ème} session : LLC - Modérée par H. Ghesquières

Facteurs pronostiques cliniques et biologiques	A. Delmer
Objectifs thérapeutiques de 1 ^{ère} ligne	V. Leblond
Place des greffes	M. Mohty
Complications infectieuses de la LLC : pourquoi les LLC font plus d'infections ? Prophylaxie	S. Leprêtre
Cas clinique interactif	Présenté par H. Ghesquières

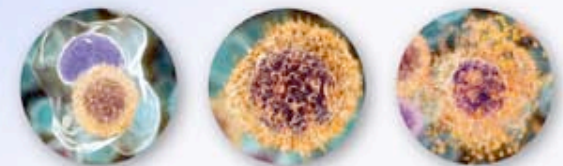




Allogeneic stem cell transplantation CLL

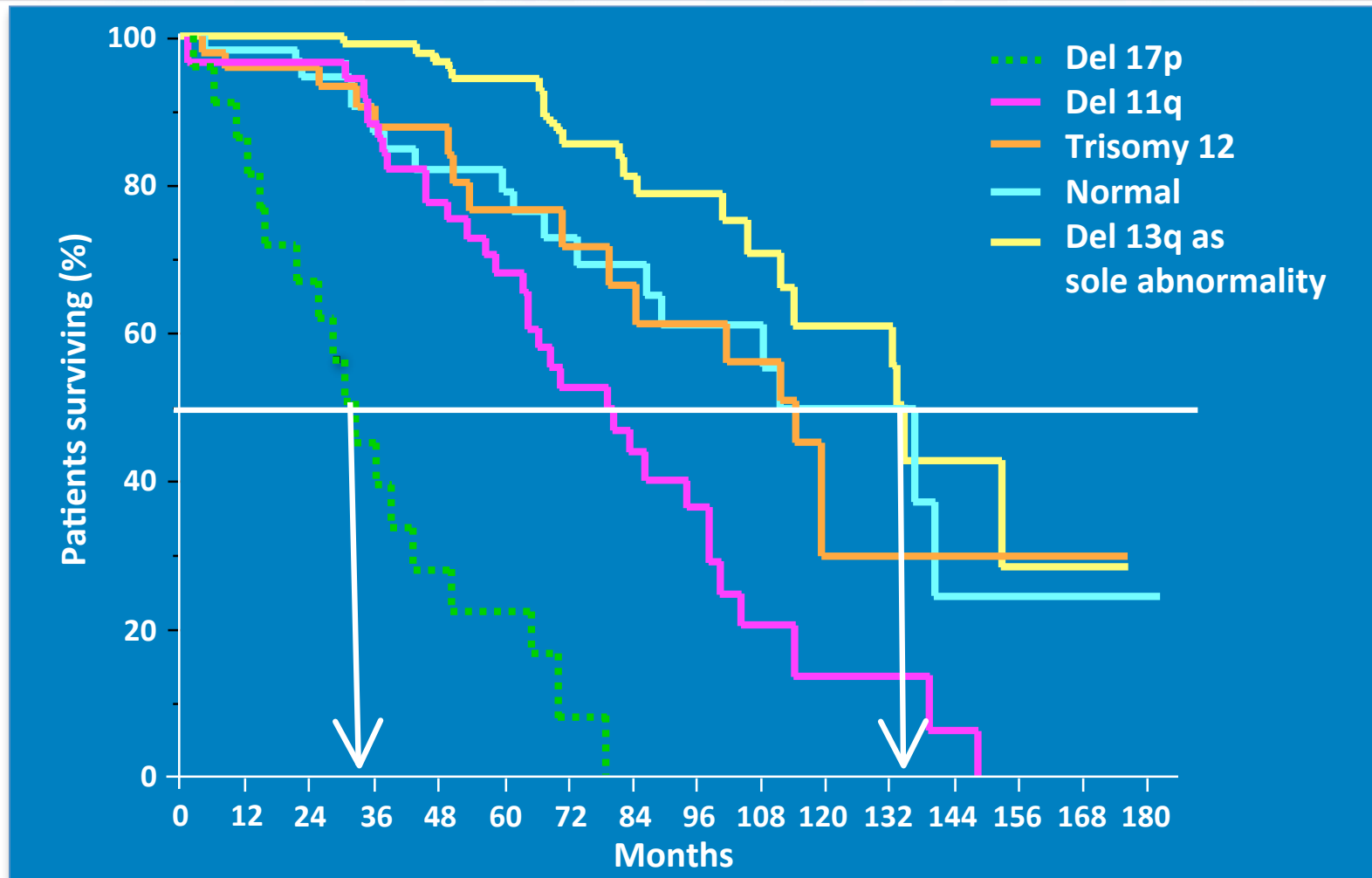
Mohamad MOHTY

***Service Hématologie Clinique, CHU Hotel-Dieu,
INSERM UMR 852, Université de Nantes***





Probability of survival



Döhner et al. *N Engl J Med.* 2000



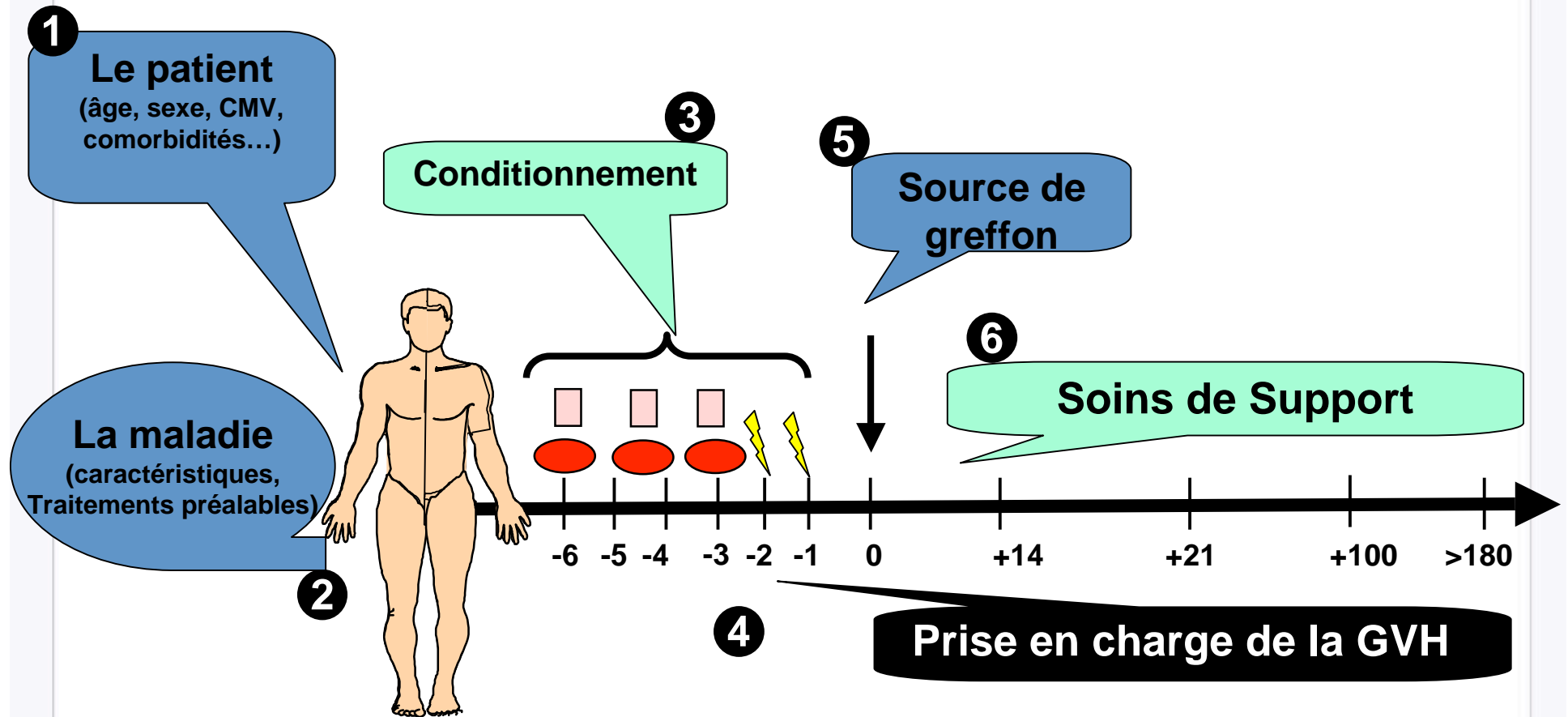


Allogeneic-SCT

- **Advantages:**
 - Healthy donors
 - Graft vs leukemia effect (adoptive immunity)
 - Donor lymphocyte infusions restore remission
 - Long-term disease free-survival (*plateau*) is seen
- **Limitations:**
 - Identifying suitable HLA-matched donors
 - High treatment related mortality, especially when using myeloablative regimens
 - Not possible to separate graft vs leukemia from GVHD

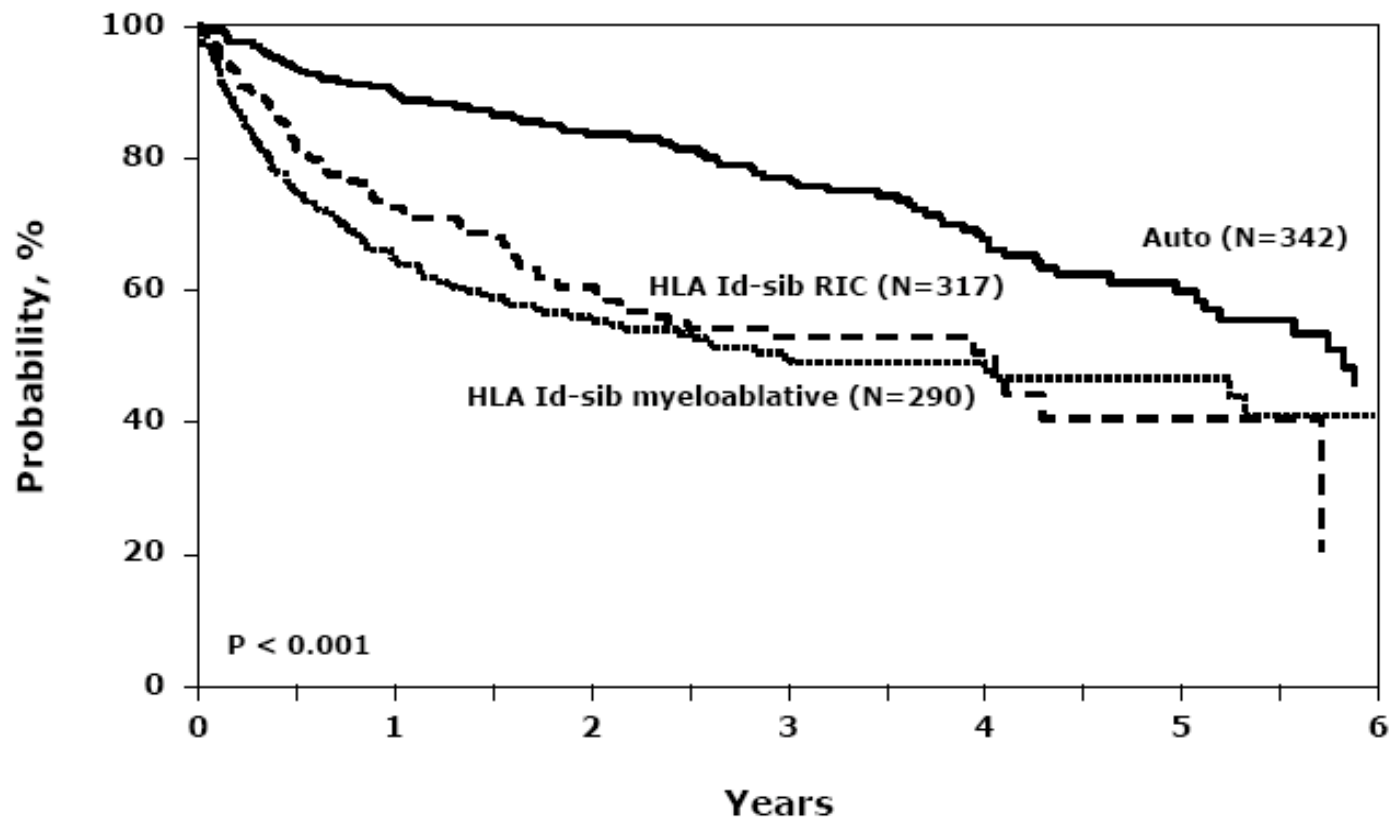


Déroulement d'une Allogreffe: QUI? QUAND? COMMENT?



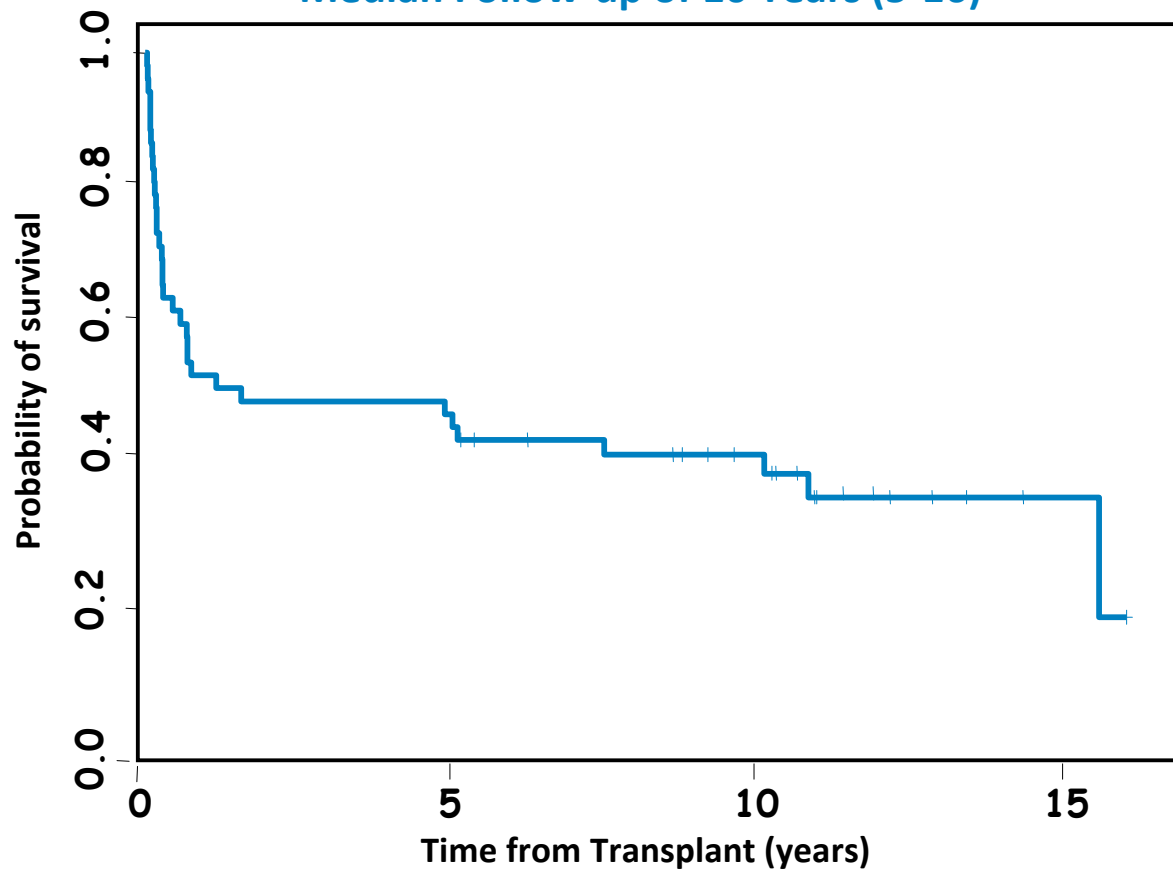


CIBMTR database



Study of EBMT/IBMTR update

Median Follow-up of 10 Years (5-16)



Of the 23 patients : **19 (83%) are still alive** : 17 in CHR, 1 in VGPR (Rituximab for relapse) and 1 in Relapse

4 patients died 7, 10, 11, 16 years after Transplant : 3 from **progressive disease (2 T-Depletion)** and 1 from a Bacterial Sepsis

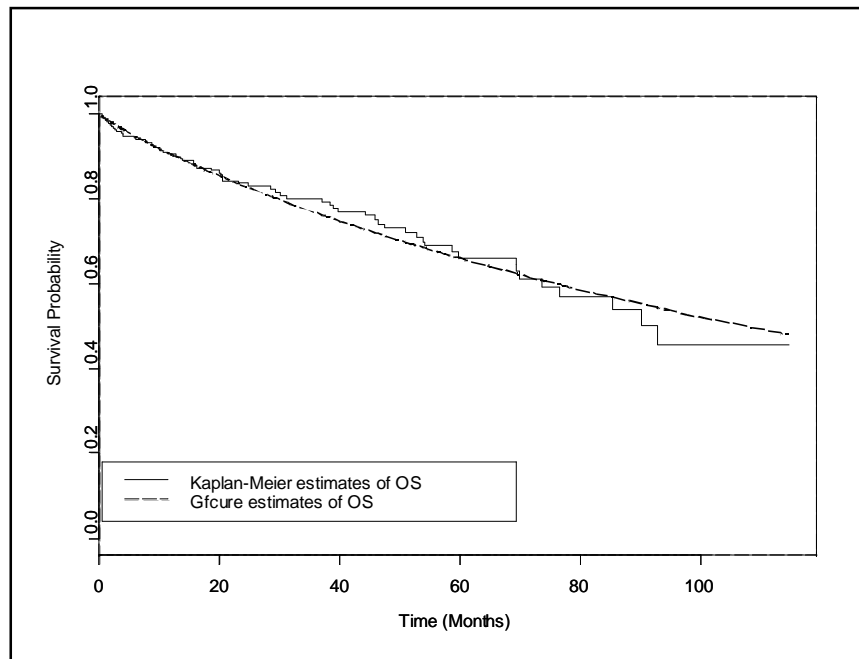


10-year Probability of survival : 41.2% (95%CI 27.9-54.6)

10-year Leukemia-Free survival : 36.6% (95% CI 25.9-49.8)

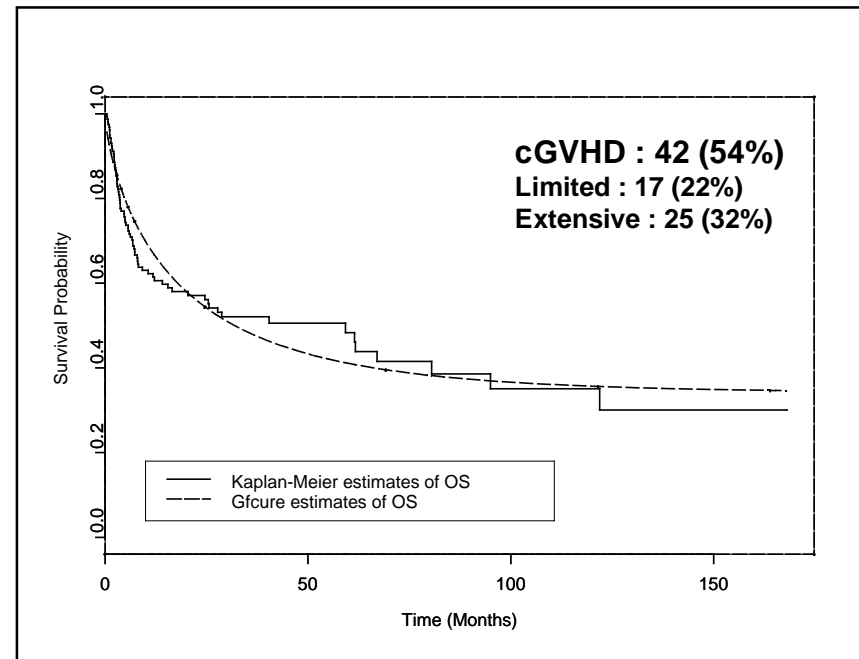


Analysis of long survivors



Autologous transplantation
(n=313)

3 years OS = 80%
5 years OS = 66% % Long-term survivors = 1.2%
8 years OS = 45.5%



Allogeneic transplantation
(n=158)

3 years OS = 52%
5 years OS = 48% % Long-term survivors = 34%
8 years OS = 35%





Evidence for GVL in CLL

- Few late relapses after allo-SCT in contrast to auto-SCT (*Esteve, Michallet 2001*)
- Long-term remissions possible (*Michallet 2003*)
- Detrimental effect of T cell depletion (*Gribben 2005*)
- Frequent responses to DLI (*Gribben 2005*)
- Importance of MRD kinetics post-transplant (*Moreno 2005*)



Myeloablative allo-SCT in CLL: increase of TRM

Reference	Design	N	Age (median)	Regimen	TRM (%)	OS
IBMTR/EBMT USA-Europe	Registry data	54	41	TBI/CY (94%)	46%	41% 10-yrs
Esteve et al.	Registry data	46	43	Mixed	31%	56% 5-yrs
Doney et al.	Prospective single arm	25	47	TBI/CY (68%)	48%	32% 5-yrs
Pavletic et al. USA	Prospective single arm	23	46	TBI/CY/VP16 (70%)	30%	62% 5-yrs
Pavletic et al. USA	Registry data	38	45	TBI-based (76%)	38%	33% 5-yrs
Toze, et al. Canada	Prospective single arm	30	48	TBI/CY (50%)	47%	39% 5-yrs

Michallet M, et al. *Blood* 2003; 102; 474a

Esteve J, et al. *Blood* 2001; 98: 482a

Doney KC, et al. *Bone Marrow Transplant.* 2002; 29: 817-23

Pavletic ZS, et al. *Bone Marrow Transplant.* 2000; 25: 717-22

Pavletic ZS, et al. *J Clin Oncol.* 2005; 23: 5788

Toze C, et al. *Bone Marrow Transplant* 2005; 36: 825-30





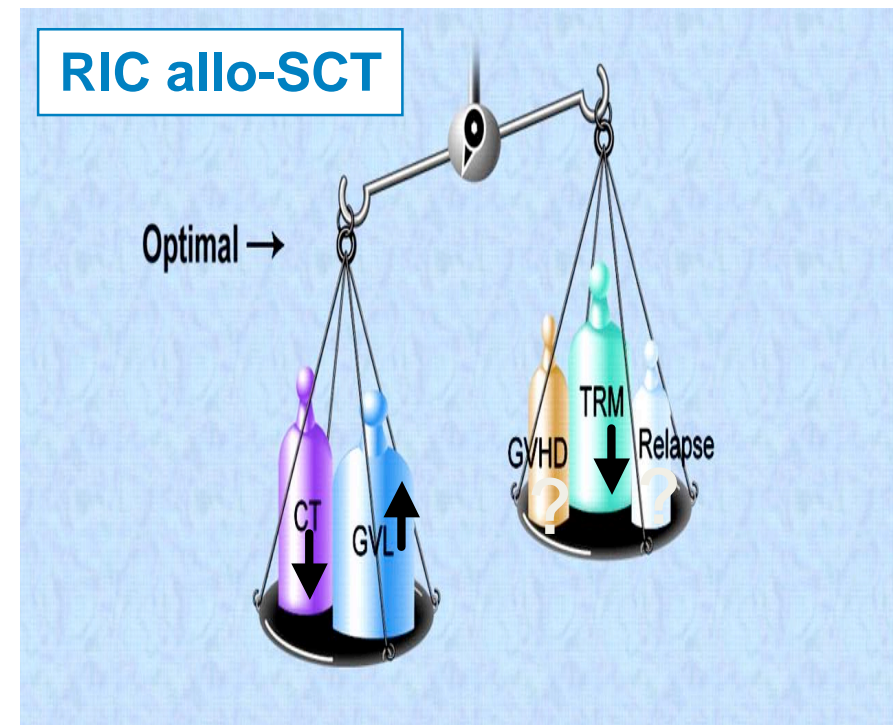
- **Conditioning**
- **Alternative Donors**
- **MRD Monitoring**



RIC allo-SCT: rationale

- As a possible less toxic alternative to standard myeloablative allo-SCT, the use of RIC allo-SCT aims to:

Shift the burden tumor eradication
From
Chemo-radiotherapy
To
Donor immune Cells



RIC allo-SCT in CLL improves TRM

Reference	Design	N	Age (median)	Regimen	TRM (%)	OS
<i>Dreger P et al EBMT</i>	Registry data	73	53	mixed	19%	70% 2-yrs
<i>Scheteling et al.</i>	Prospective single arm	30	50	FLU-BU-ATG	15%	72% 2-yrs
<i>Sorrer et al. Seattle</i>	Prospective single arm	64	56	FLU-TBI (2Gy)	22%	60% 2-yrs
<i>Brown et al. DFCI</i>	Prospective single arm	46	53	FLU-BU	17%	54% 2-yrs
<i>Caballero et al. Europe</i>	Prospective single arm	30	46	FLU-MEL	20%	70% 6-yrs

Dreger P, et al. Leukemia 2005; 19: 1029-33

Scheteling J, et al. J Clin Oncol 2003; 21: 2747-53

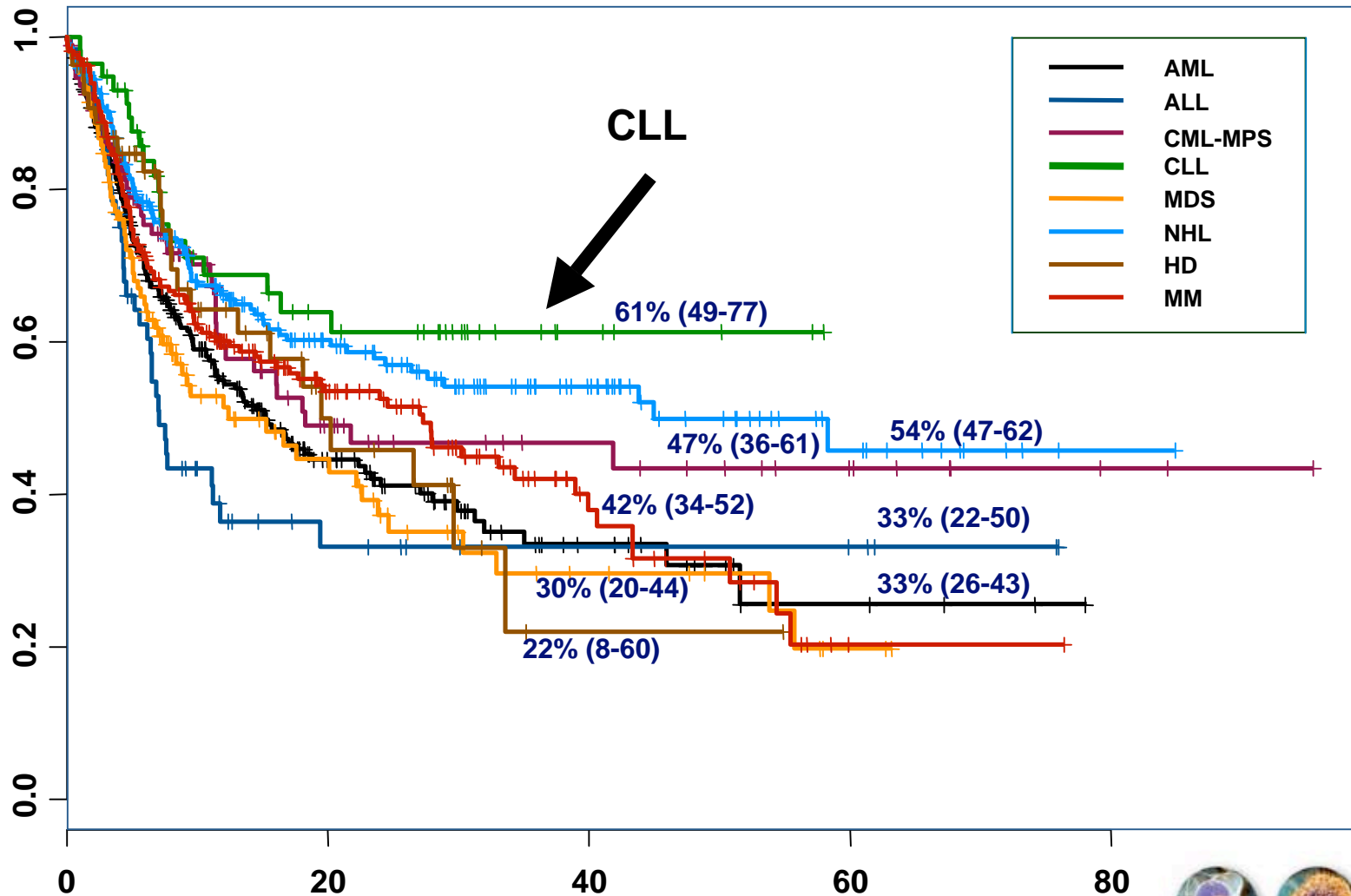
Sorrer M, et al. J Clin Oncol . 2005; 23: 3819-29

Brown J, et al. Biol Blood Marrow Transplant. 2006; 12: 1056-1064

Caballero, et al. Clin Cancer Res. 2005; 11: 7757-63



Overall survival according to diagnosis





Conditioning with rituximab

- **17 CLL patients**
- **Preparative regimen:**
 - Fludarabine (30 mg/m² /d x 3 d)
 - Cyclophosphamide (750 mg/ mg/m² /d x 3 d)
 - + Rituximab for 10 Patients
- **Diagnosis - Transplant: 67 months**
- **Complete remission: 12 Patients**
 - Partial Remission : 4 patients
 - Overall Response : 94%.
- **Overall survival: 100% for patients with Rituximab vs 14% for patients with chemotherapy alone (p=0.03)**

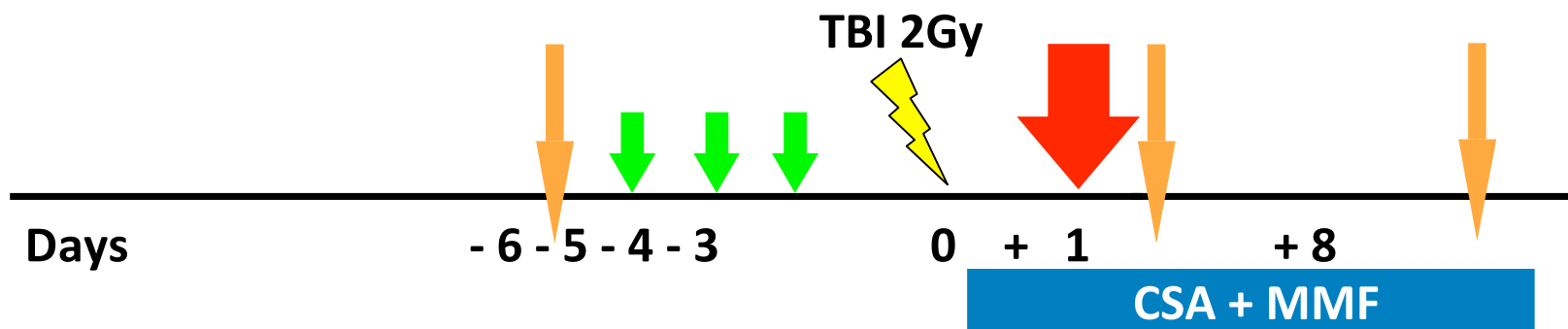
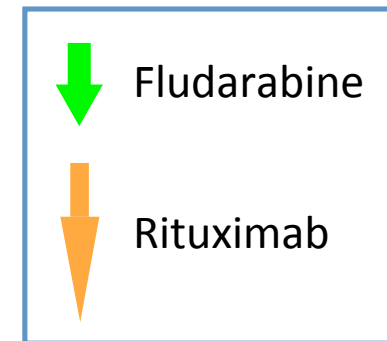




RIC for CLL French ITAC trial

- **Eligibility**

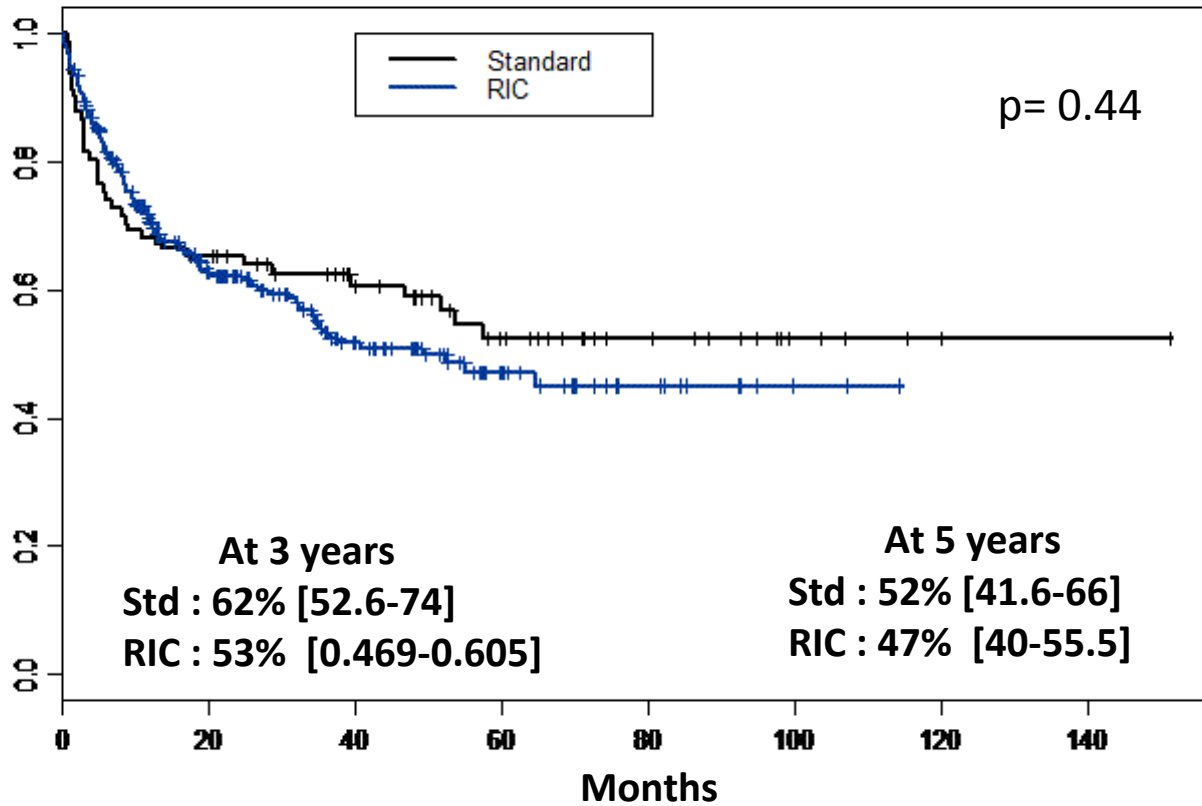
- B-CLL, 18-65 years, Binet B/C,
- HLA-id. sibling donor available
- + failure after purine analogues (<12 mo)
or failure of auto-SCT





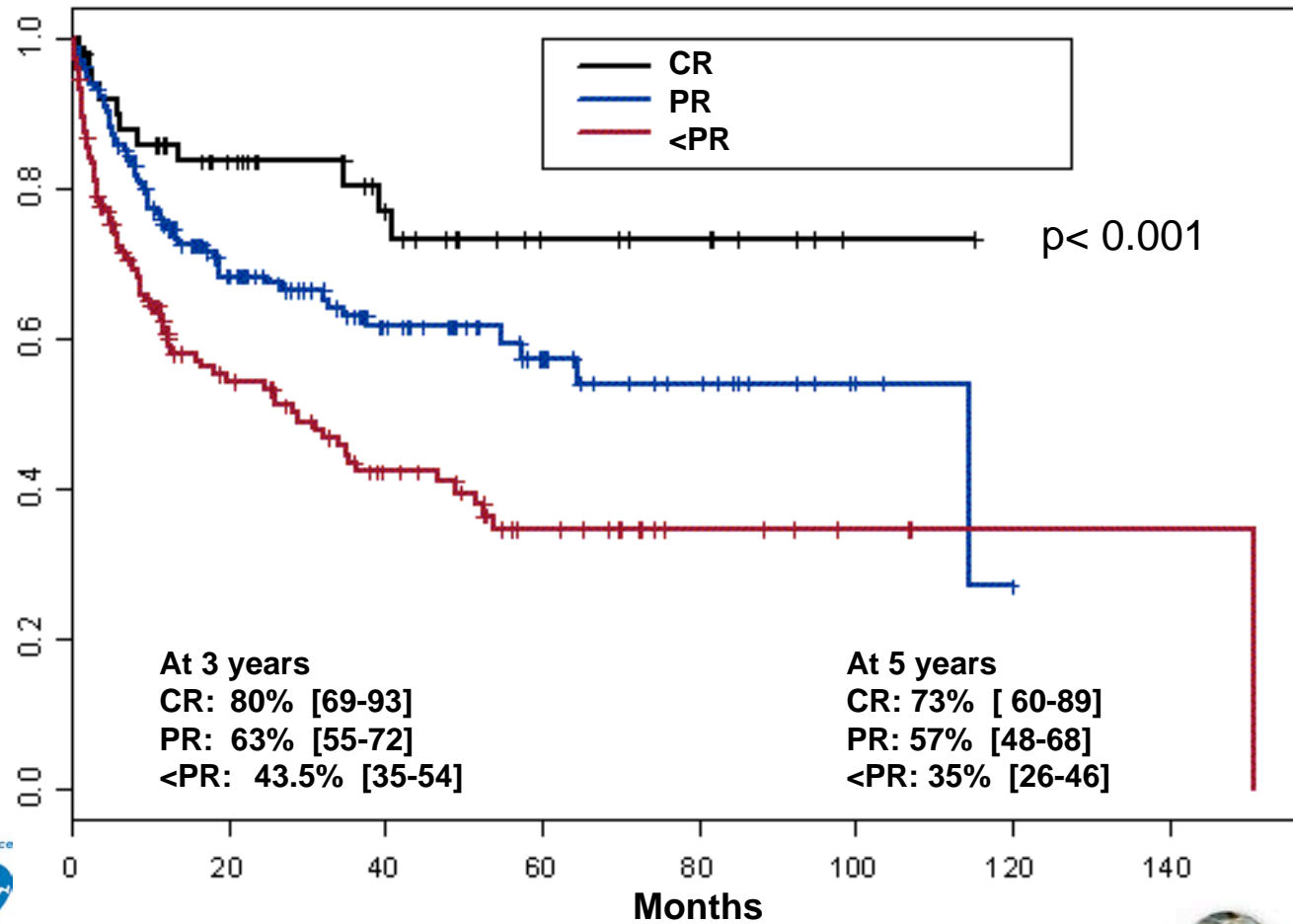
RIC vs MAC in CLL: overall survival

Median follow-up= 38 months



Overall survival (according to pre-transplant-status)

374 B-CLL Patients registered in the EBMT registry





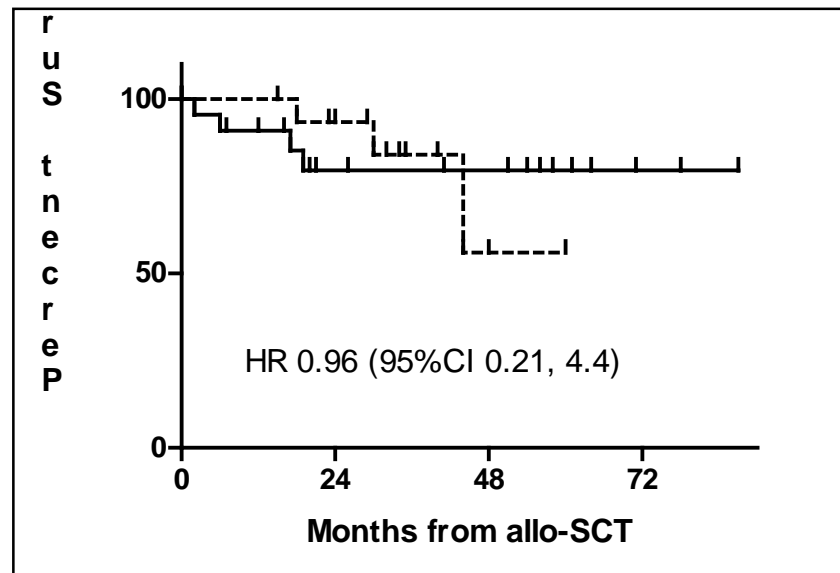
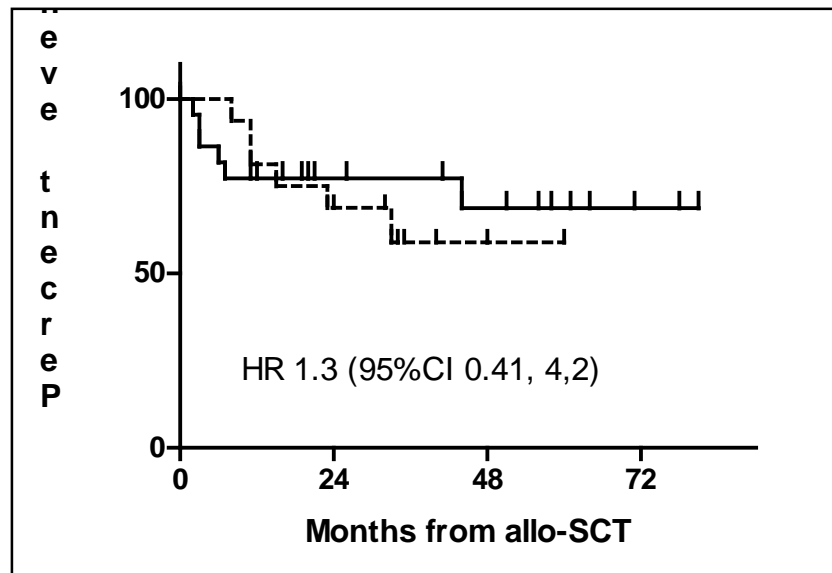
Related and unrelated RIC Allo-SCT for CLL

- 64 advanced CLL patients
- Conditioning: 2 Gy TBI with [n=53] or without [n=11] Fludarabine
- Related (n=44) or unrelated (n=20) donors
- Acute GVHD grades 2, 3 and 4: 39%, 14% and 2%
Chronic GVHD: 50%
- The overall response rate: 67% (50% CR)
- 2-year relapse/progression: 26%
2-year relapse and non-relapse mortalities: 18% and 22%
2-year overall and disease-free survivals: 60% and 52%
- Unrelated HCT: higher CR + lower relapse than related



Allo-SCT for CLL after auto-SCT

- Allo-SCT after ASCT failure seems to be quite feasible when performed with reduced-intensity conditioning
- Preceding ASCT had no adverse impact on outcome in a prospective study on RIC allo-SCT (BSBMT)

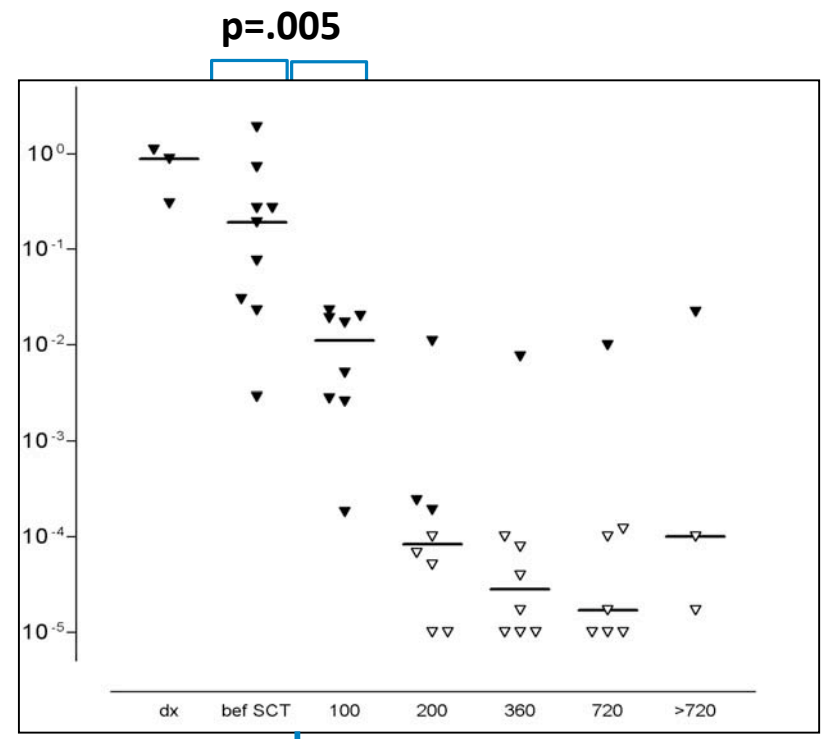
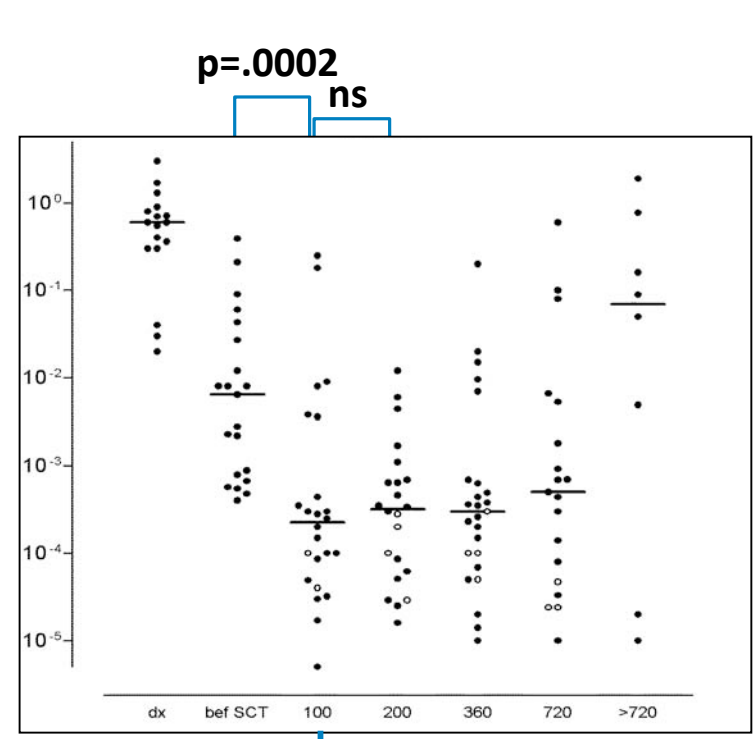


Event-free (A) and overall survival of 16 patients with (broken line) and 22 patients without previous ASCT (GCLLSG CLL3X study)





CLL : MRD after auto and RIC allo-SCT

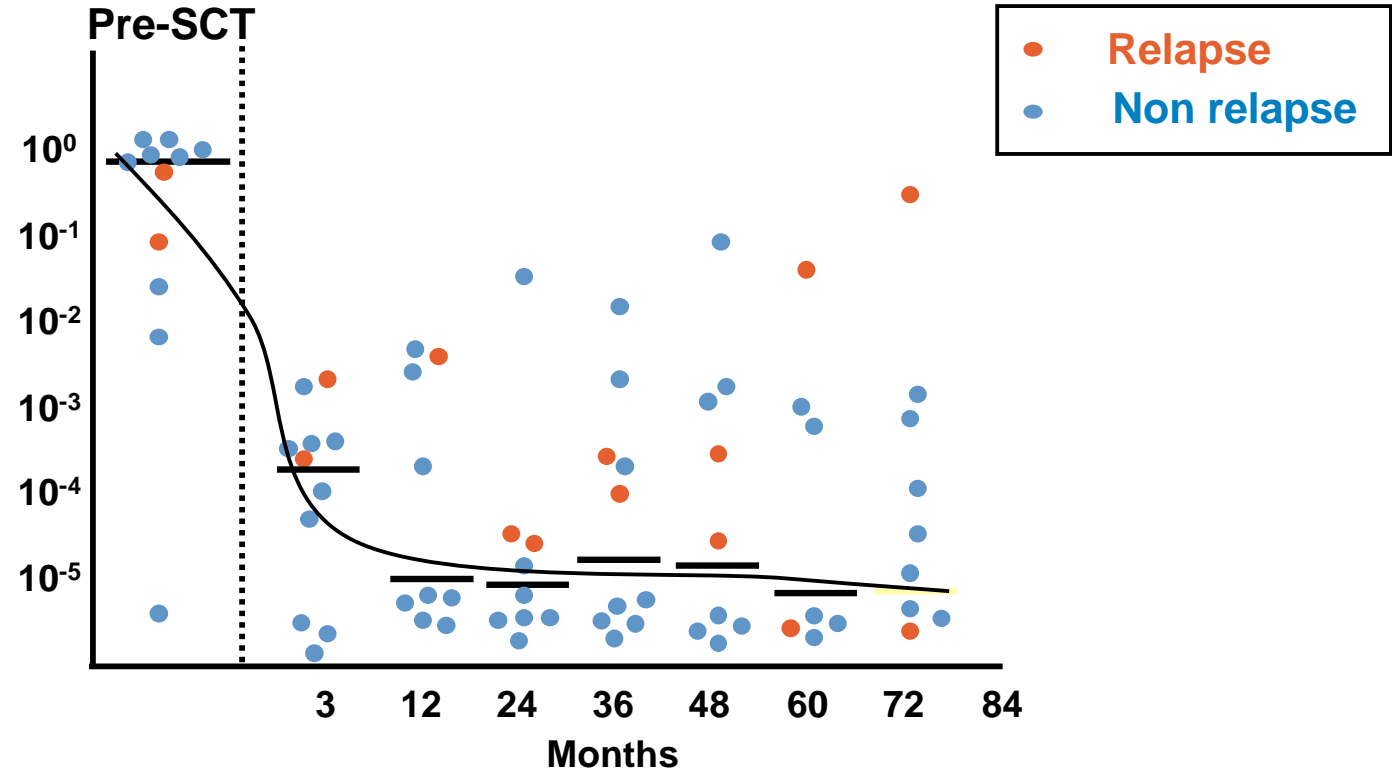


Ritgen et al. IWCLL





MRD level after allo-SCT



Moreno et al.





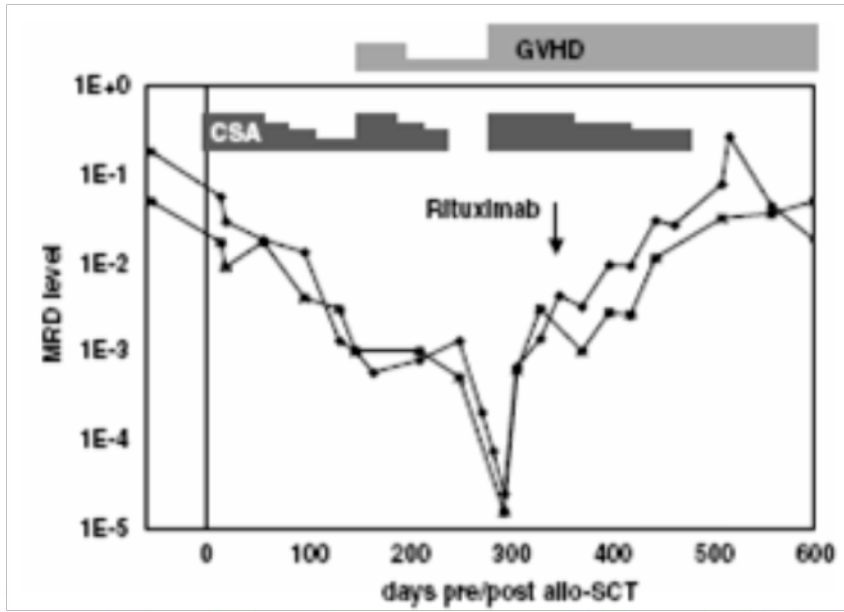
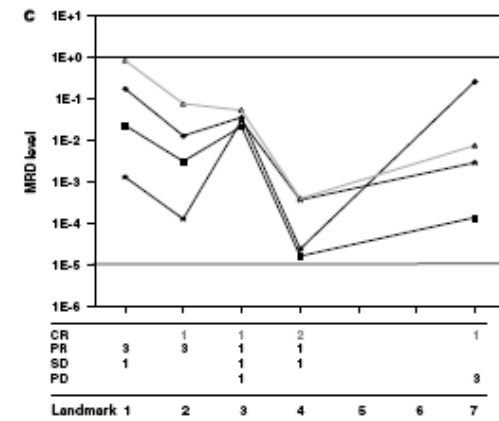
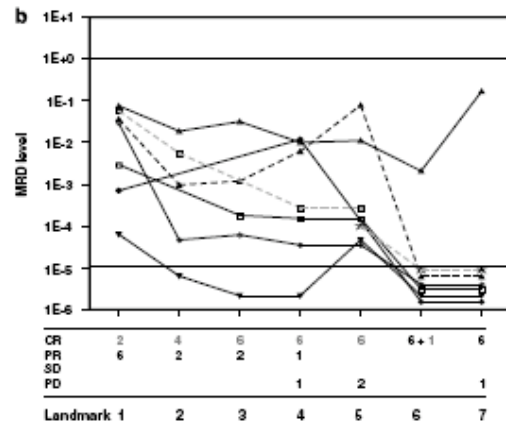
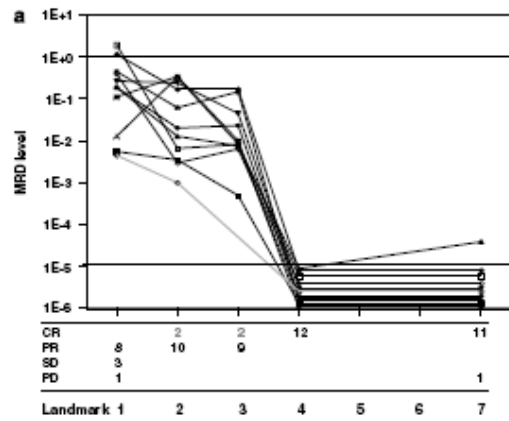
MRD monitoring after allo-SCT (1/2)

- **RQ-PCR and/or Flow-based MRD monitoring: 37 Patients**
- **Kinetics : 5 patterns**
 - Patients who promptly achieved durable MRD negativity without evidence of GVL (n=4, no relapse)
 - Patients with complete and sustained MRD response with GVL after tapering immunosuppression
 - Patients with complete and sustained MRD response with GVL after DLI (n=18, 1 relapse)
 - Patients without MRD response with no GVL (n=2, 2 relapses)
 - Patients with incomplete and transient MRD response to GVL (n=4, 3 relapses)

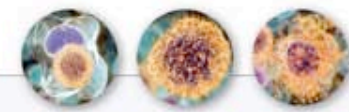




MRD monitoring after allo-SCT (2/2)



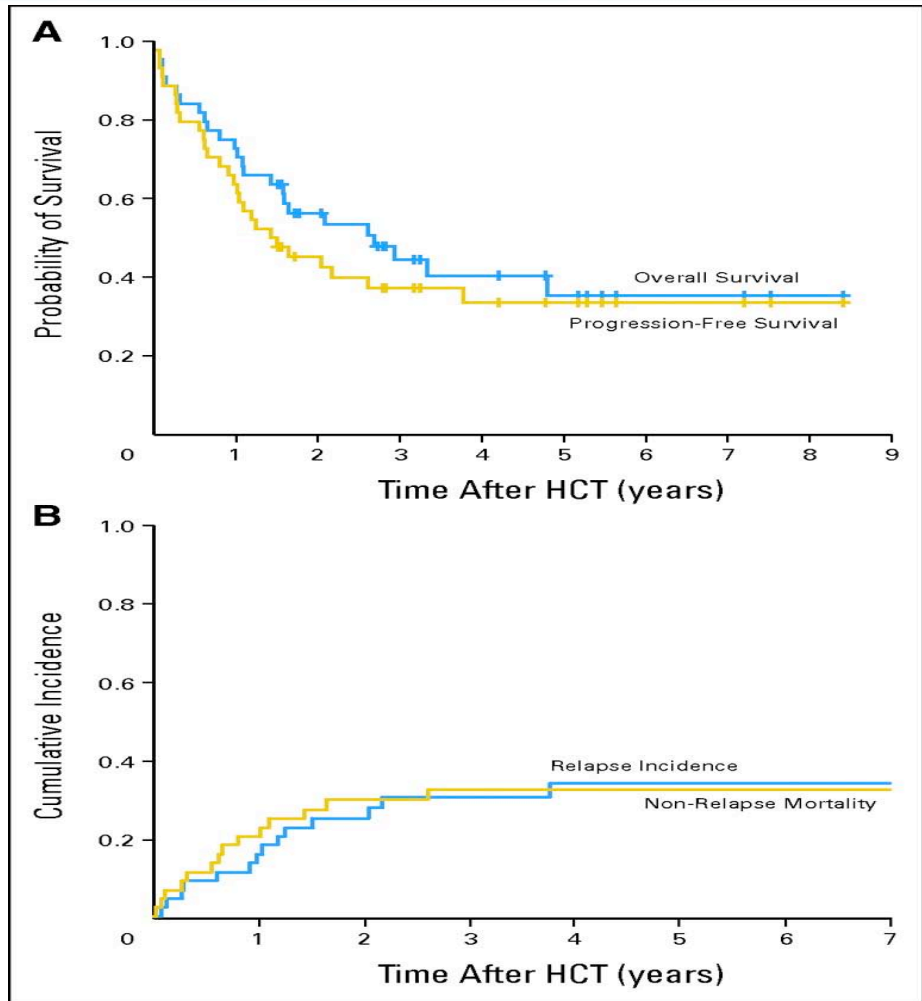
M. Ritgen et al. Leukemia 2008





Allogreffe 17p- LLC

- 44 patients
- EBMT
- 3 years overall survival: 44%
- 3 years disease-free survival: 37%

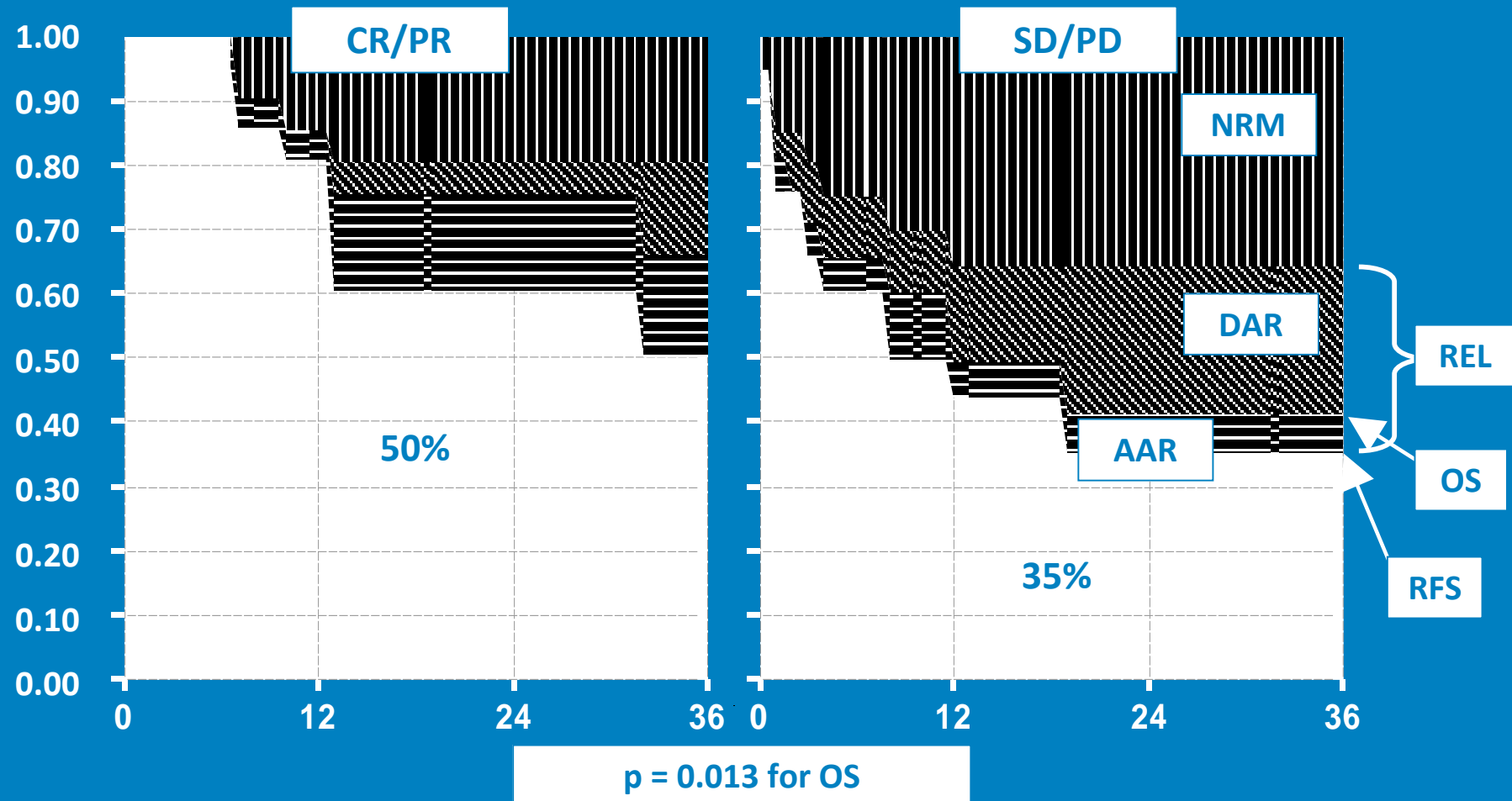


Schetelig et al. J Clin Oncol 2008, 26 : 5094-5100



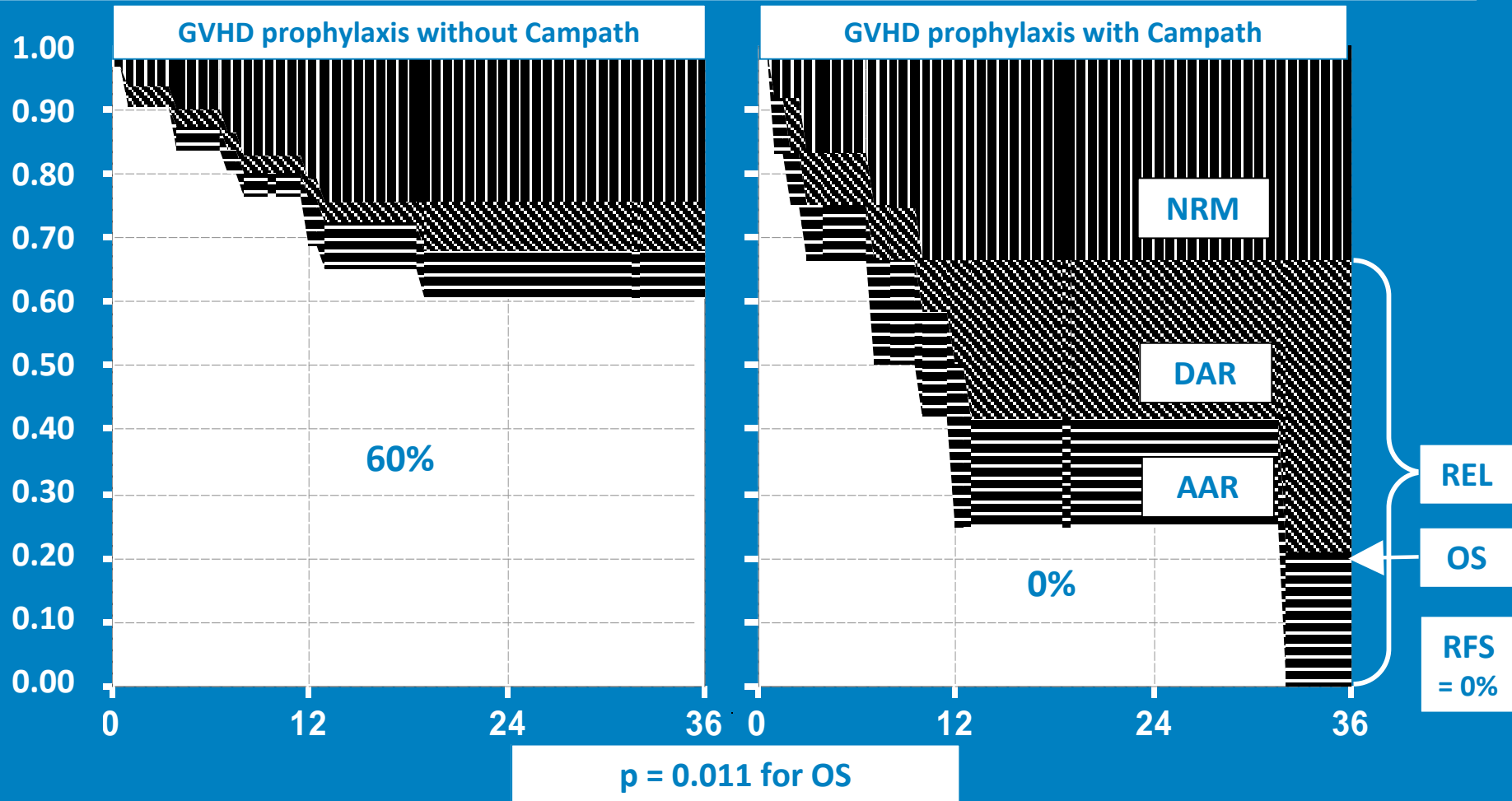
Outcome of allo-SCT for CLL with del 17: Impact of disease status at SCT

NRM = non-relapse mortality DAR = death-after-relapse AAR = alive-after-relapse REL = relapse incidence RFS = relapse-free survival OS = overall survival



Outcome of allo-SCT for CLL with del 17: Impact of in-vivo TCD

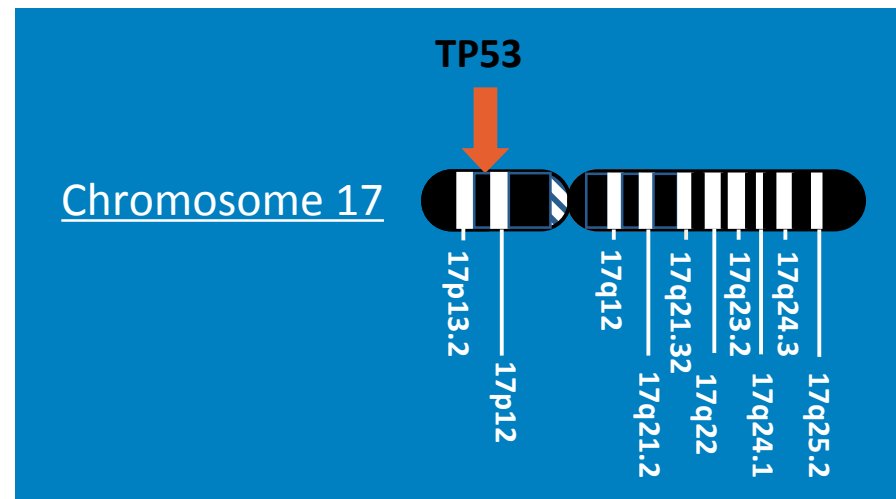
NRM = non-relapse mortality DAR = death-after-relapse AAR = alive-after-relapse REL = relapse incidence RFS = relapse-free survival OS = overall survival



Indications for allo-SCT in patients with CLL: EBMT Transplant Consensus

- **Non-response or early relapse (≤ 12 months) after fludarabine-based regimens or relapse within 24 months after having achieved a response with purine-analogue-based combination therapy (FCR, FR, PCR, etc.)**
- **Del 17p- and/or p53 abnormalities (mutations or deletions) requiring treatment**

81% of del 17p has p53 mutations



Dreger P, et al. *Leukemia*. 2007 Jan;21(1):12-7
Zenz T, et al. *Blood*. 2008;112:3322-29

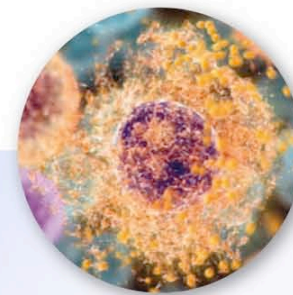
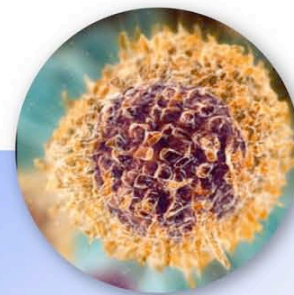
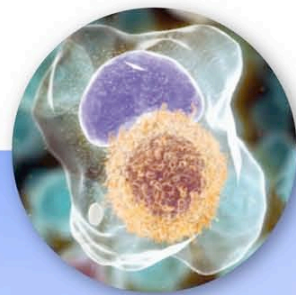




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