



2nd International Workshop on the Biology, Prevention, and Treatment of Relapse After Hematopoietic Stem Cell Transplantation; November 5-6, 2012, Bethesda, MD



Adjunctive Strategies to Improve Cell Therapy for Relapse

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European Group of Blood and
Marrow Transplantation (EBMT)





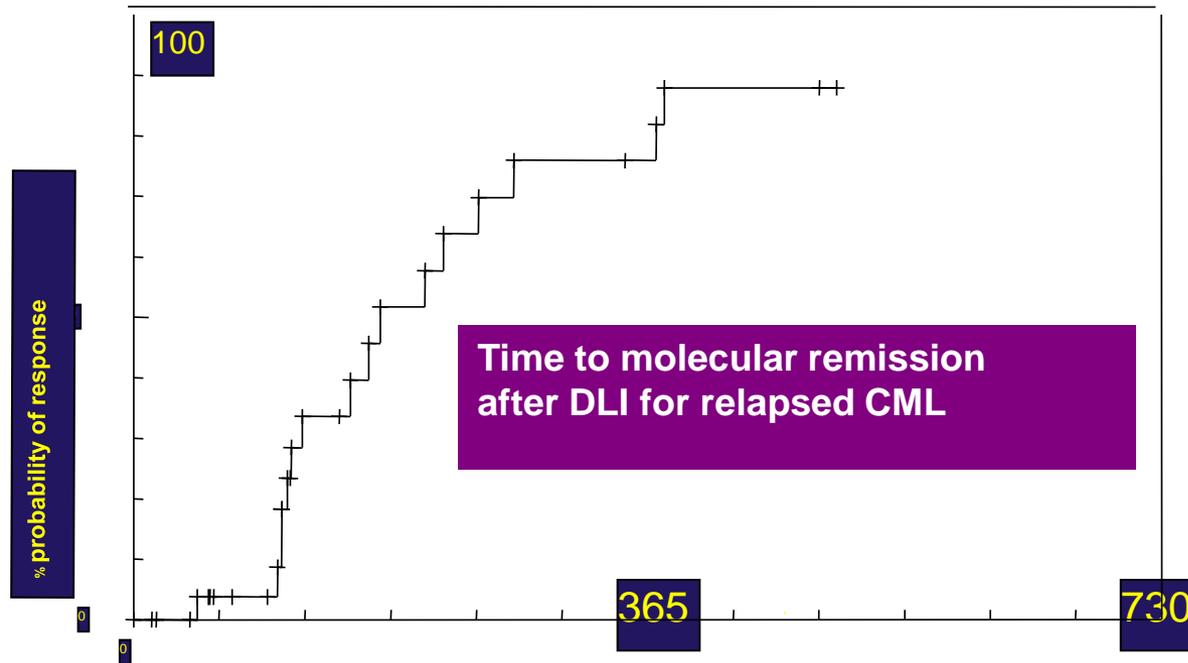
Adjunctive Strategies to Improve Cell Therapy for Relapse



- remission induction prior to cellular therapy
- novel agents
- cytokines
- second transplants



Remission induction prior to cellular therapy



GvL reaction takes time

(Munich data, courtesy of H. Kolb)



Remission induction prior to cellular therapy – AML

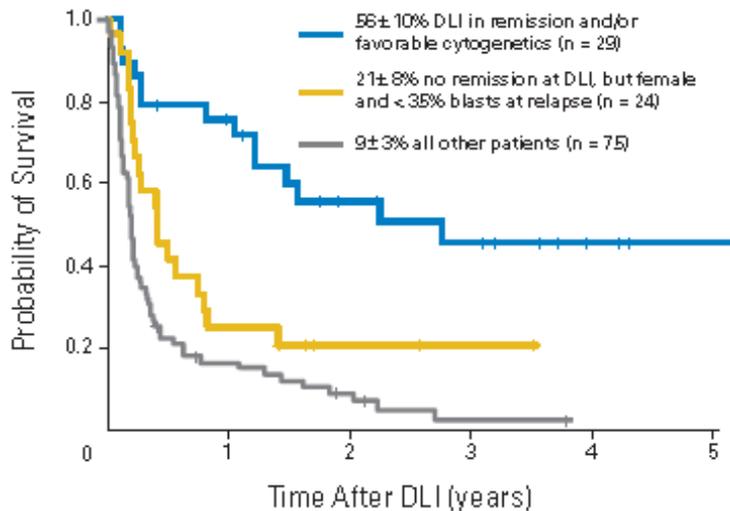


Risk factor analysis for outcome after DLI

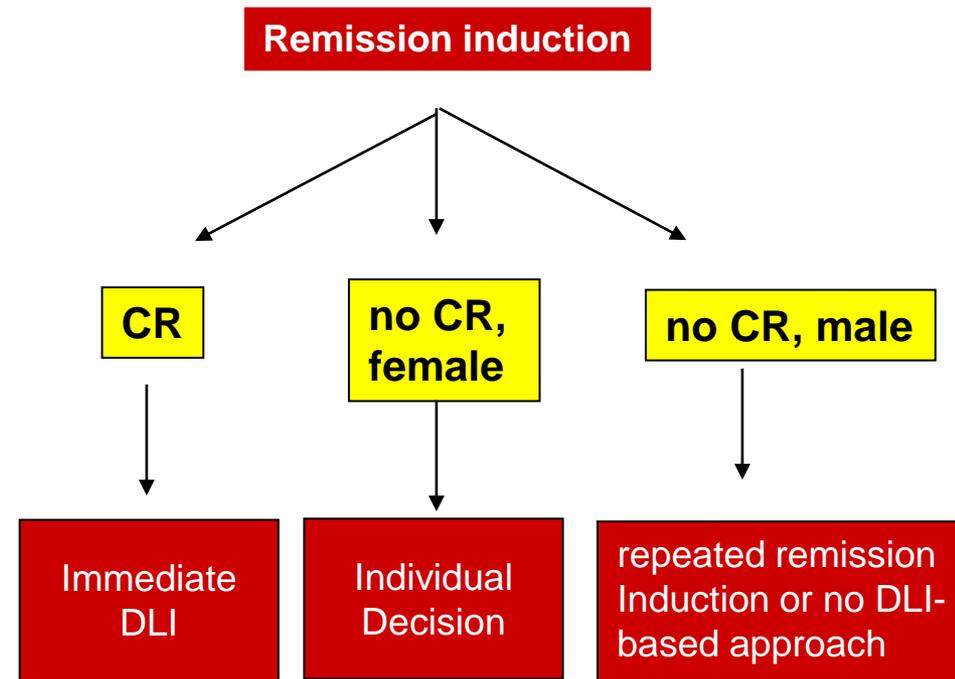
Blasts in BM at rel. <median $p=.0008$

female gender $p=.02$

remission at time of DLI $p=.0002$



Proposed Algorithm





Which drugs should be used ?

Levine et al., JCO 2003, prospective trial

“A combination of cytarabine (100 mg/m² a day for 7 days) and anthracycline (daunorubicin 30 mg/m² a day for 3 days) was recommended as the cytoreductive chemotherapy, but other chemotherapy was used if the clinician deemed it more appropriate”

12 different combinations in 63 pts., ORR pre DLI not reported

Schmid et al., Blood 2012, retrospective ALWP registry study on relapse after RIC

- > 40 different regimen in 263 pts.
- „High or intermediate dose AraC + an anthracycline +/- a third drug such as fludarabine or etoposide, induced CR in 32/71 evaluable patients (45%)“.

Clofarabine

- Frequently used, although not systematically evaluated in relapse after allo SCT
- CR rates of 45-50% reported in relapsed / refractory AML
- used in 15/20 patients before haplo – id HSCT2 (Tischer et al., meeting abstract)



Cellular therapy after remission induction in AML

Chemotherapy as primary intervention for relapsed AML following RIC

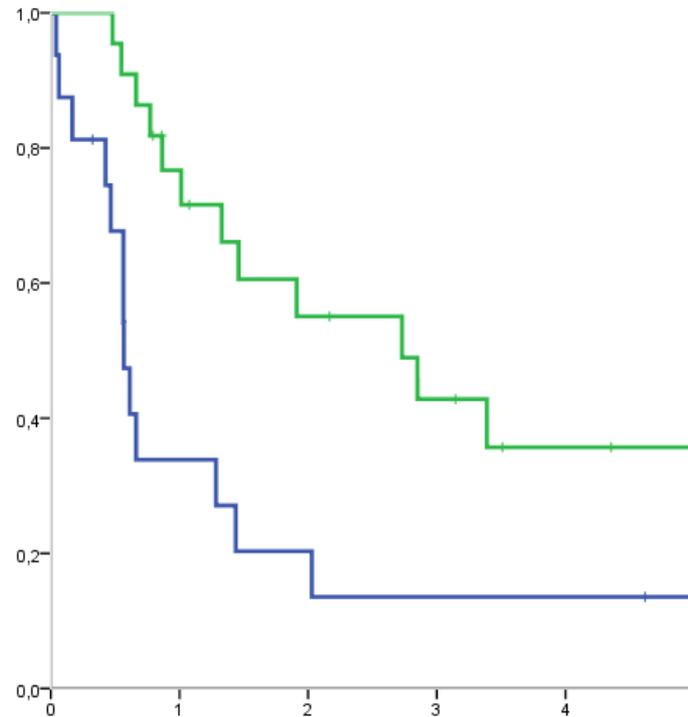
		median OS
no CR post chemo (n=89)	52 no donor cells	2.6 mo
	29 DLI (27 with active disease and 2 in aplasia)	5.1 mo
	10 second Tx (including 2 with DLI)	9.2 mo
CR post chemo (n=38)	16 no infusion	6.9 mo
	12 DLI	22.9 mo
	10 second Tx in CR	22 mo

**ALWP results,
Blood 2012**



Cellular therapy after remission induction

Overall survival from relapse



P<.001

Patients in CR after chemotherapy :
DLT/2nd transplant* versus no donor-based strategy

* analysed as a time dependant variable

**ALWP results,
Blood 2012**



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Novel agents

What to expect ?

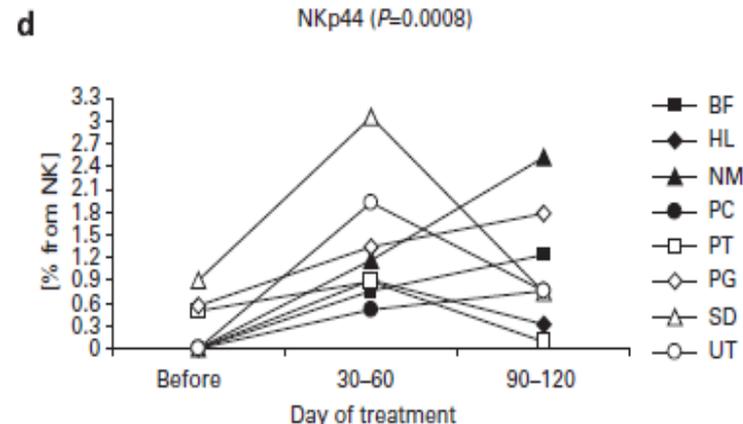
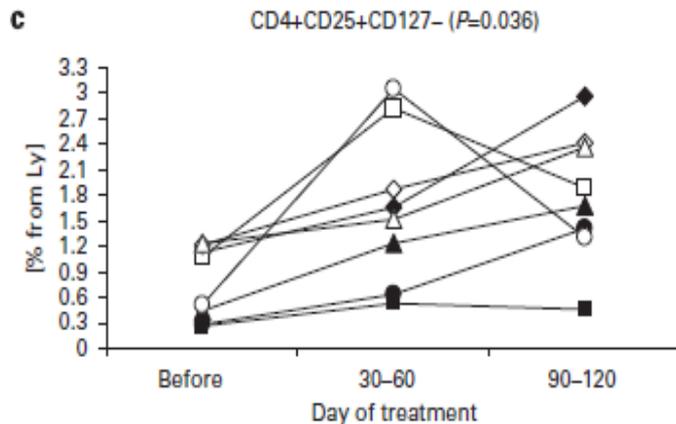
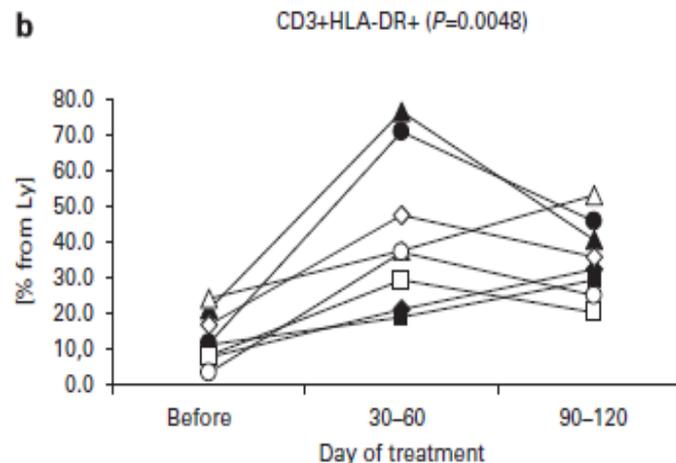
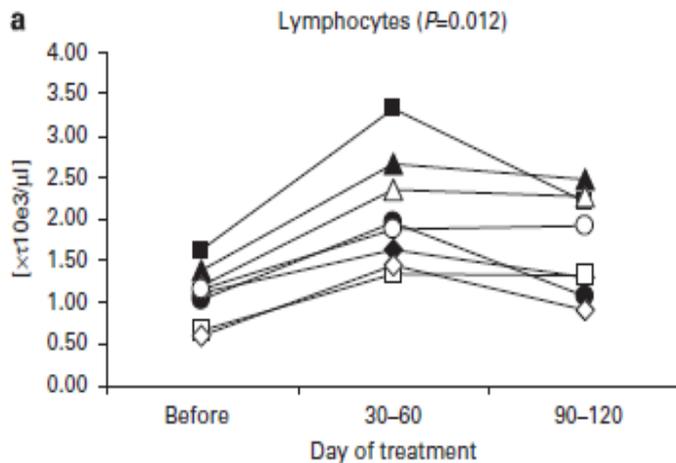
- favourable toxicity profile for early application after allogeneic SCT
- anti-proliferative effect
- increasing immunological mediated graft vs tumor effect
- properties to inhibit immunosuppressive and tolerance mechanisms in the host
- reducing the risk of GvHD without jeopardizing GvL



Novel agents modulating GvM reactions – Thalidomide, Lenalidomide, Pomalidomide

- Increase in T- cell co-stimulation
- Stimulation of NK and NK-T-cells

- Increase in Th1-type cytokine production
- Treg suppression?





Novel agents modulating GvM reactions – Hypomethylating agents (5-Aza, Decitabine)

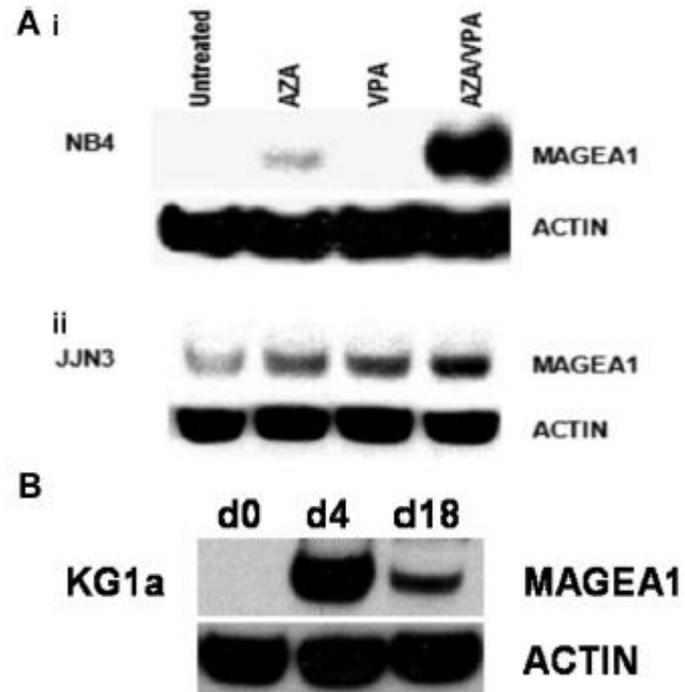
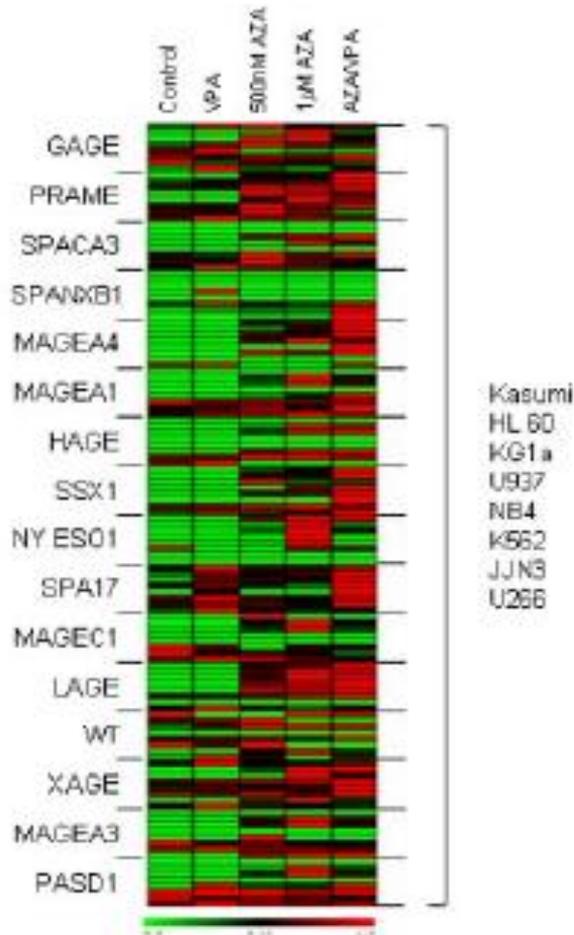
Upregulation of CTA's in leukemic blasts after treatment with 5-Aza

Patient no.	Diagnosis	FAB	T	BM blasts, %	PB blasts, %	MAGE-1	SSX	NY-ESO-1
1	de novo AML	M1	0	90	87	-	-	-
			15	nd	66	+	+	+
			30	nd	64	+	-	+
2	de novo AML	M1	0	80	86	-	+	-
			15	nd	75	+	+	+
			30	nd	5	-	+	+
3	de novo AML	M1	0	95	90	-	-	-
			15	nd	18	+	+	+
			30	nd	67	+	+	+
4	de novo AML	M4	0	90	75	-	-	+
			15	nd	63	+	+	+
			30	nd	66	+	+	+
5	de novo AML	M4	0	65	58	-	-	-
			15	nd	12	-	+	+
			30	nd	67	+	+	+
6	de novo AML	M4	0	70	44	-	-	-
			15	nd	25	+	+	+
			30	nd	49	+	+	+
7	de novo AML	M5	0	85	67	-	-	-
			15	nd	45	+	+	+
			30	nd	49	+	+	+
8	secondary AML ^z	M1	0	60	58	-	-	-
			15	nd	45	+	+	+
			30	nd	49	+	+	+
9	MDS	AREB-t	0	25	2	-	-	-
			15	20	1	+	+	+
10	MDS	AREB-t	0	22	0	-	-	-
			15	7	1	+	+	+
11	MDS	CMML	0	15	12†	-	-	-
			15	nd	10†	+	+	+
			30	nd	13†	-	-	-



Novel agents modulating GvM reactions – Hypomethylating agents (5-Aza, Decitabine)

Upregulation of **CTA's** in AML and myeloma cell lines after treatment with 5-Aza + **Valproate**

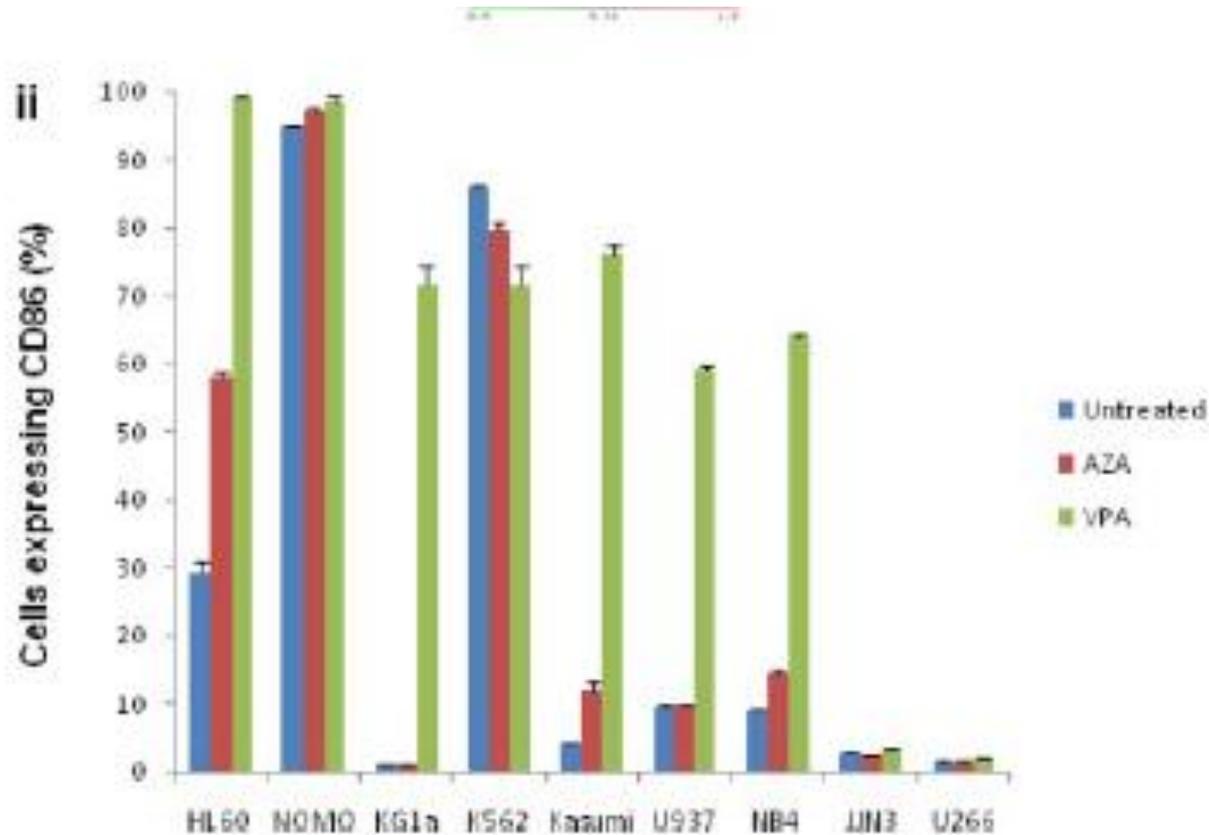


Goodyear et al.,
Blood 2010



Novel agents modulating GvM reactions – Hypomethylating agents (5-Aza, Decitabine)

Upregulation of costimulatory molecule expression after treatment with 5-Aza + Valproate

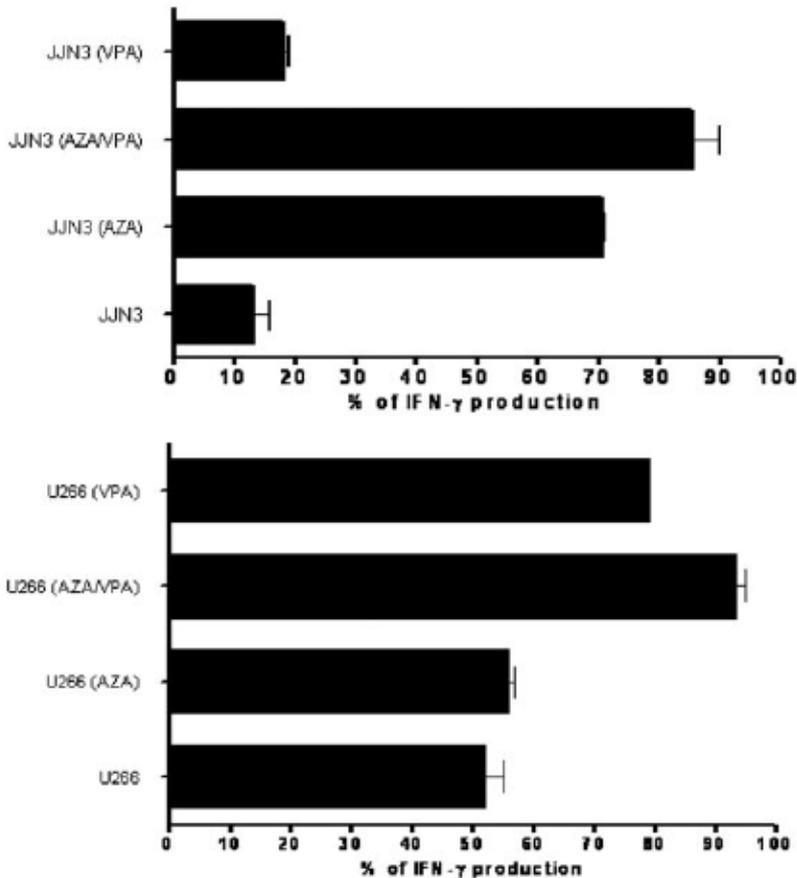


Goodyear et al.,
Blood 2010

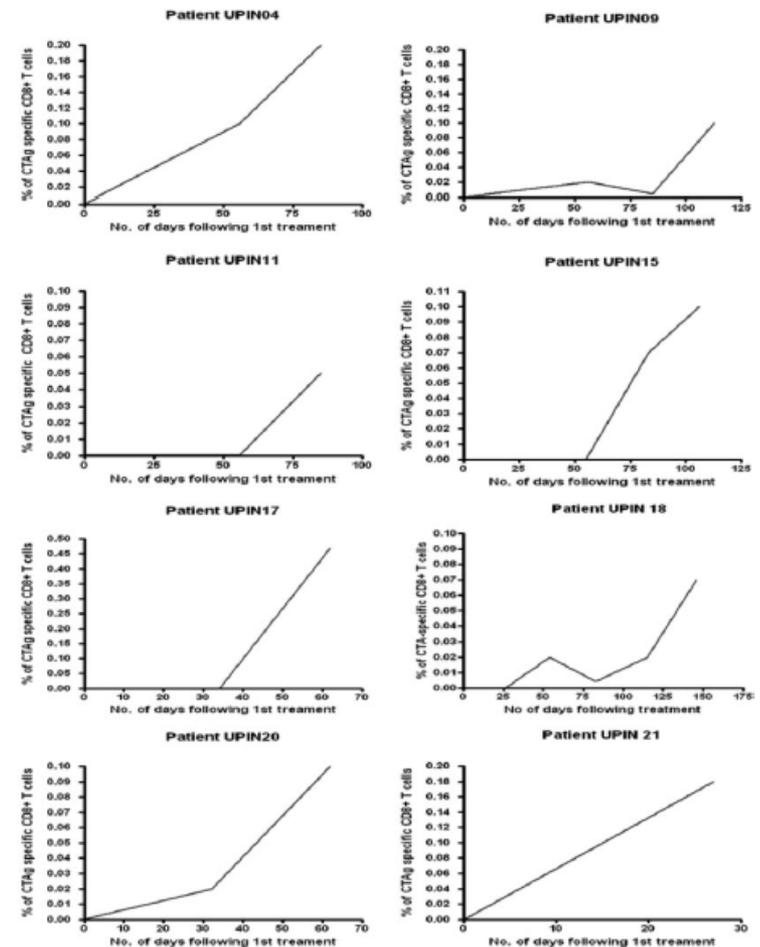
Novel agents modulating GvM reactions – Hypomethylating agents (5-Aza, Decitabine)

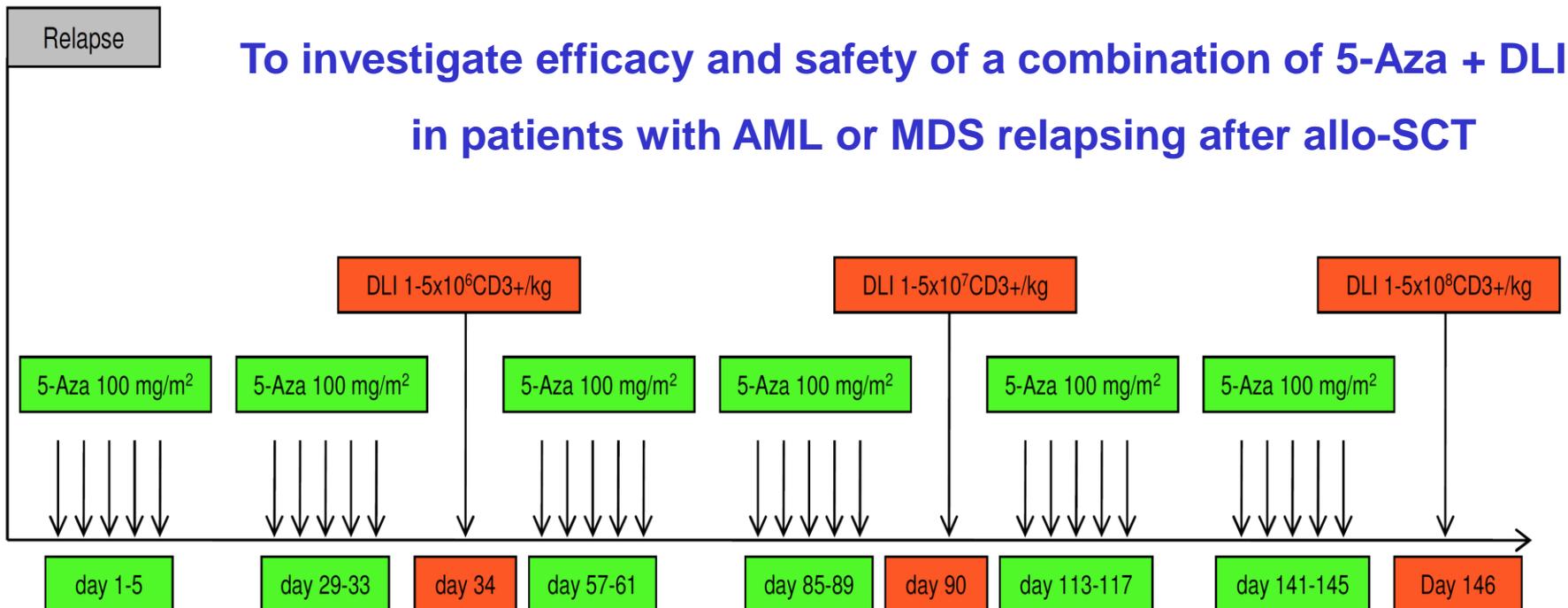
MAGE specific CTL recognition of a hematopoietic target

In vitro....



... and in vivo





- 30 patients in 6 centers 02/2009-05/2010
- Final data lock 12/2011
- Median Follow up - all patients 117 days (25 - 974)
- Median Follow up - surviving patients 817 days (732 – 974)

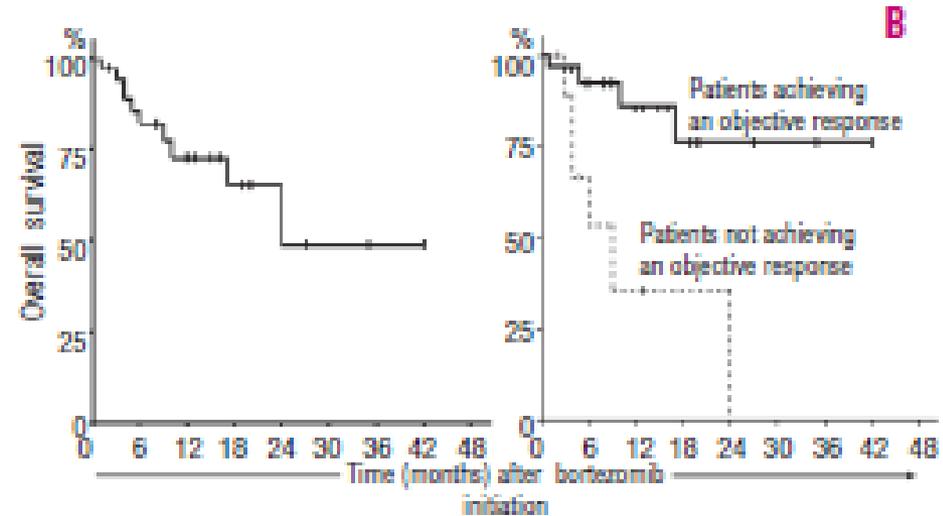
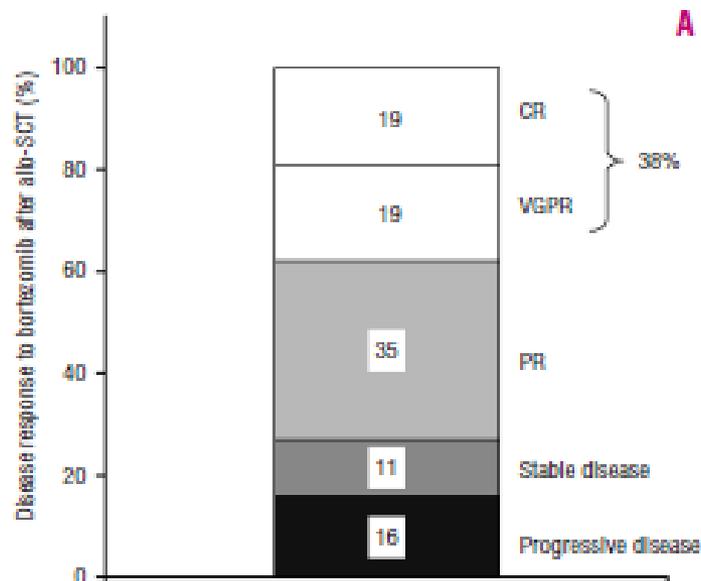


Novel agents modulating GvM reactions – Bortezomib

- *increased sensitivity for CD8+ and NK cells*
- *upregulation of FAS and TRAIL*
- *immunosuppressive*
 - *depletion of allotreactive T-cells*
 - *decreased maturation of APC*

Kröger et al., , Exp. Hematol 2006,
Blanco et al., 2009

Bortezomib as Salvage treatment after allo SCT



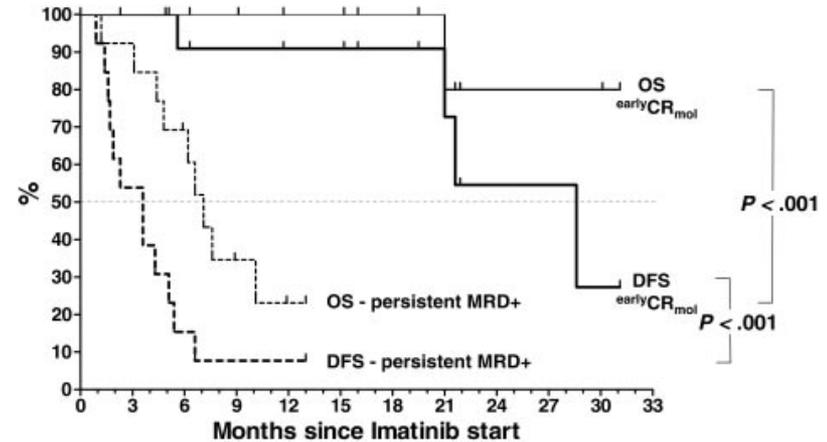
El-Cheikh et al., Haematologica 2008



Novel agents modulating GvM reactions – Thyrosine Kinase Inhibitors

Imanitib for MRD/mol. Relapse in bcr/abl + ALL

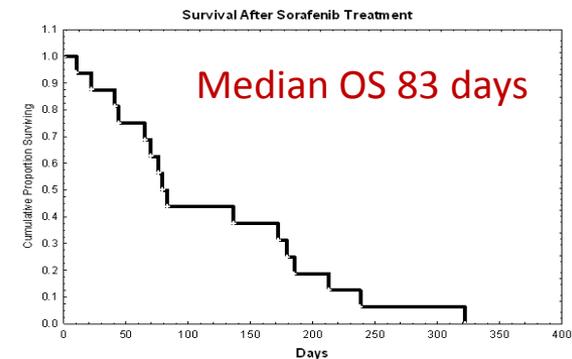
Wassmann et al.,
Blood 2005



Sorafenib for FLT3-ITD + AML

Sharma et al.,
BBMT 2011

N = 16, median remission 3 months
med. BM blasts 58%, 75% circ. blasts
0 CR, 3 PR, median blast red.
in PB 50%, in BM 0%

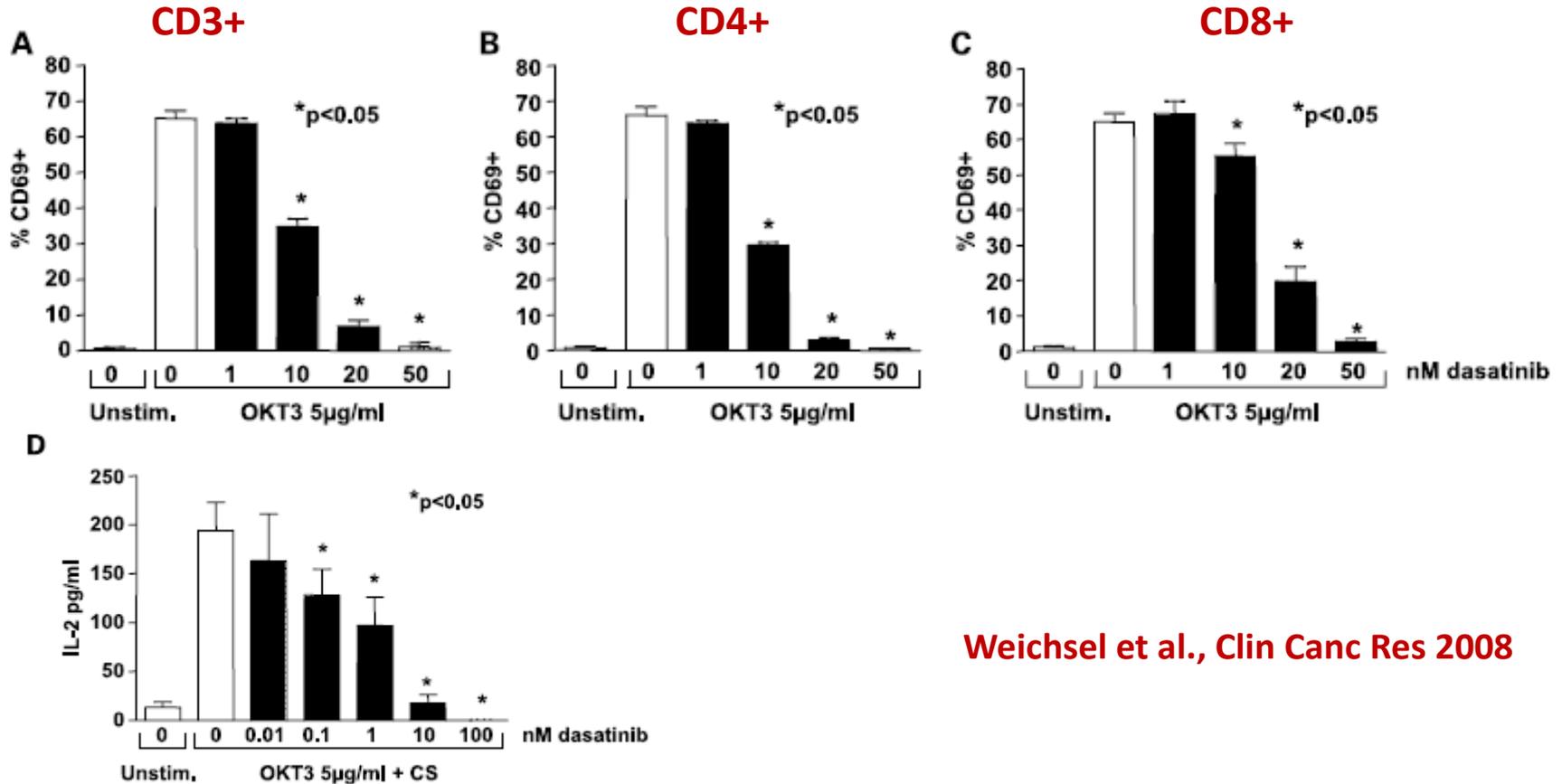




Novel agents modulating GvM reactions – Thyrosine Kinase Inhibitors - Dasatinib

Dose dependant inhibition of

- T-Cell activation,
- cytokine production
- proliferation
- degranulation



Weichsel et al., Clin Canc Res 2008



Novel agents for relapse after SCT – Clinical Studies

	Number of pts.
Hypomethylating agents	
5-Aza-Cytidine	97
Thyrosin kinase inhibitors*	
Imatinib	27
Nilotinib	1
Dasatinib	4
Sorafenib	21
Immuno modulatory drugs	
Thalidomide	18
Lenalidomide	37
Bortezomib	46
Monoclonal antibodies	
Rituximab	27
Bi 20 (FBTA05)	6

Published Data: (all drugs, all diseases):

N = 284

Very few prospective trials



Adjunctive Strategies to Improve Cell Therapy for Relapse

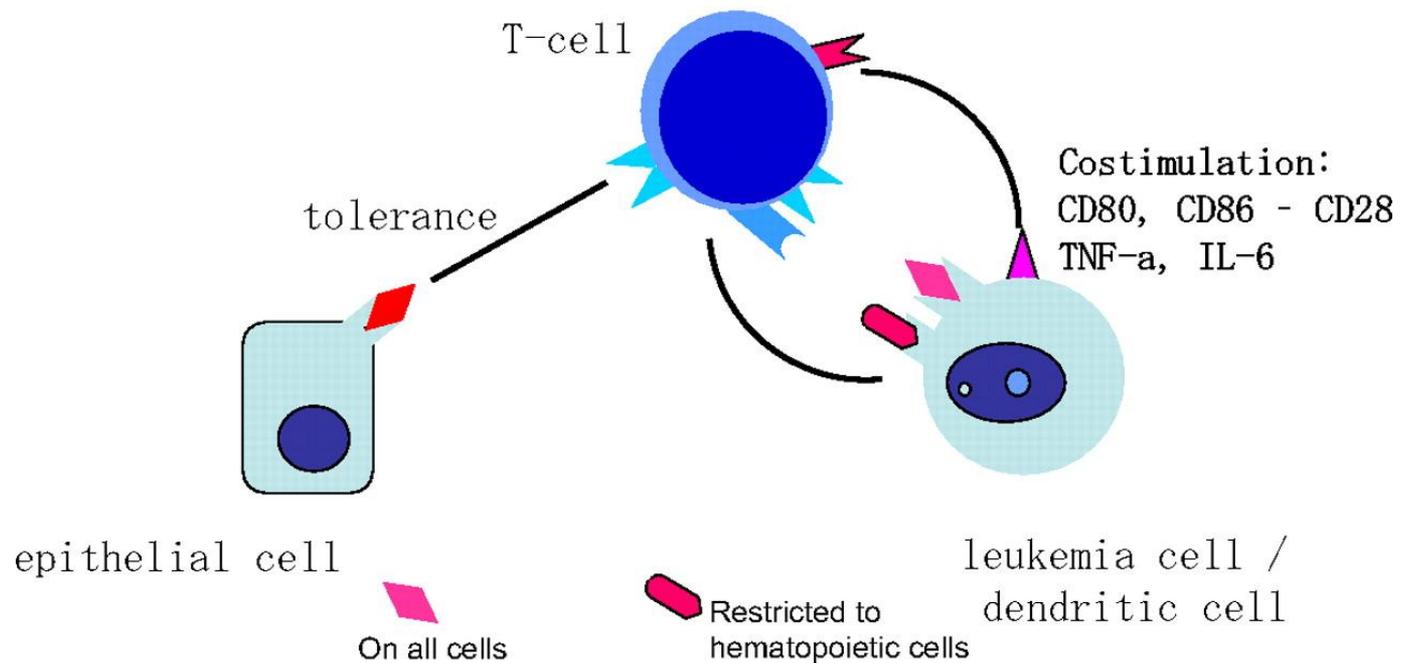


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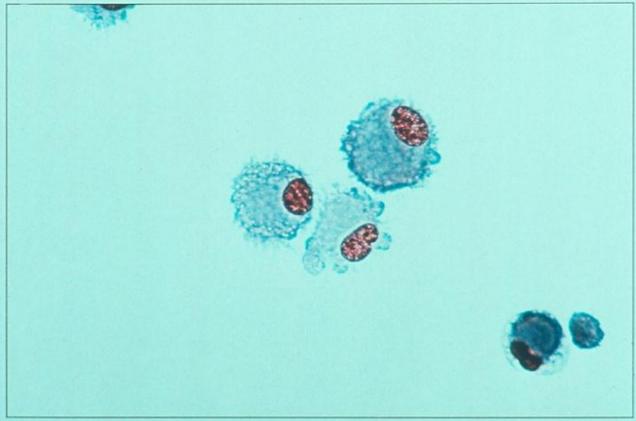
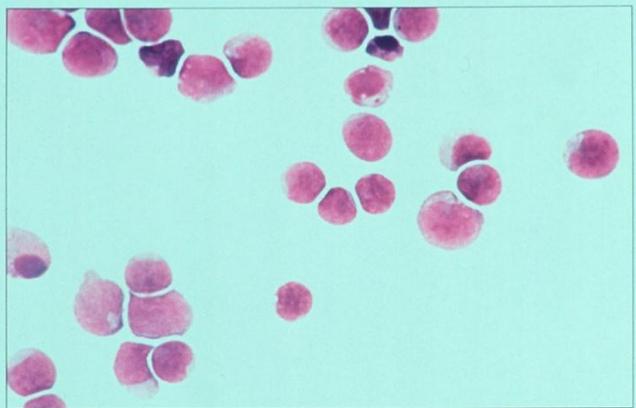
Adoptive Immunotherapy in Chimerism

GVL-Reaction



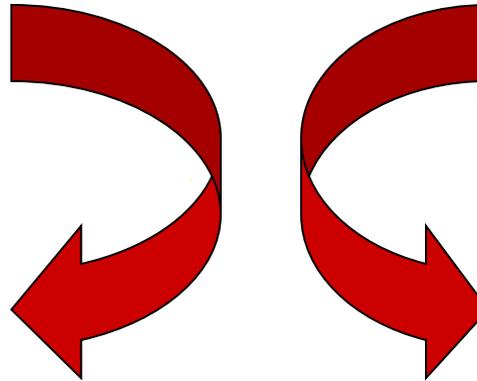


Improving Leukemic Antigen Presentation

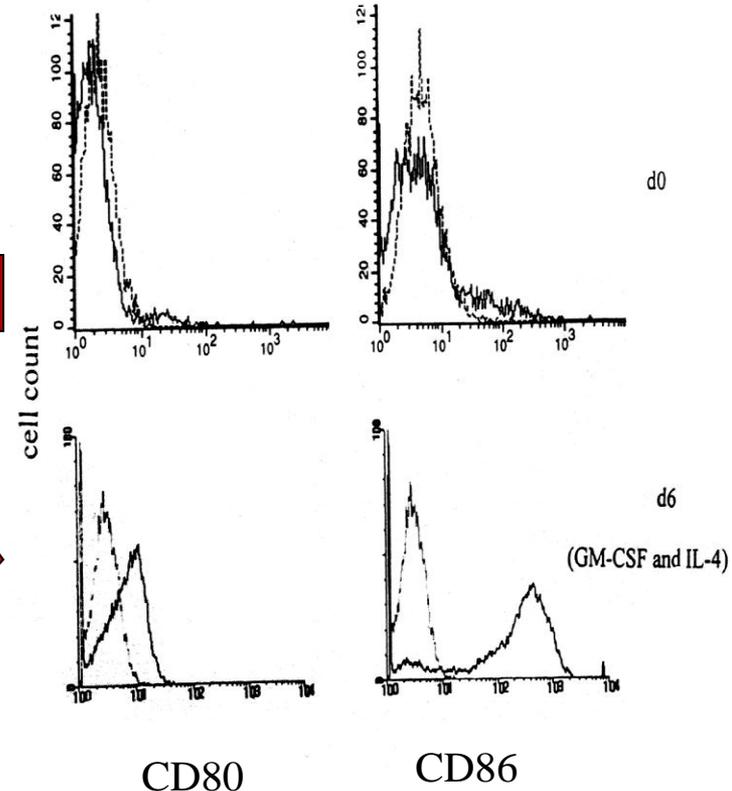


DC-like morphology

cytokine cocktails
containing GM-CSF



Upregulation of costimulatory molecules in AML blasts



upregulation of
costimulatory molecules



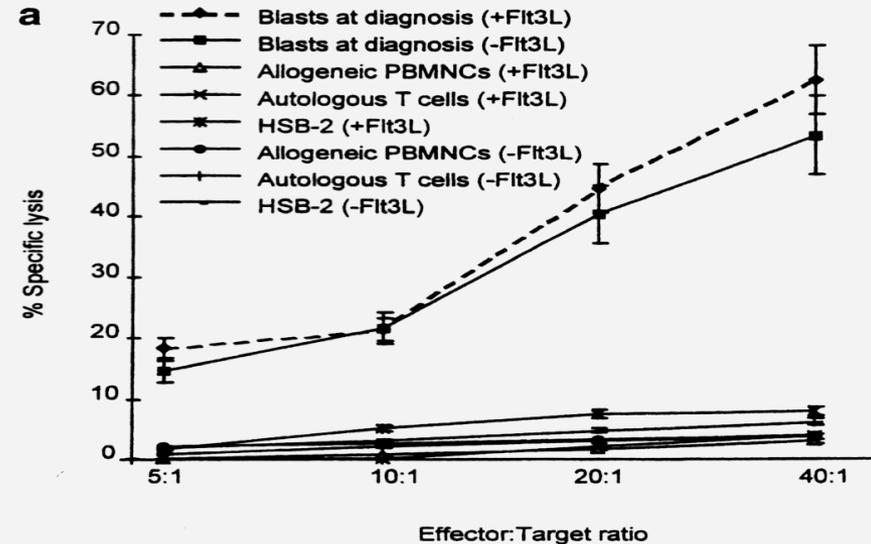
Generation of DC_{leu} from leukemic blasts

Cytotoxicity by T-cells that were stimulated in co-culture with DC_{leu}

Woiciechowsky et al, Leukemia 2000

High rates of DC_{leu}/DC in culture, as well as generation of mature and migratory DC correlate with clinical outcome after cellular immunotherapy

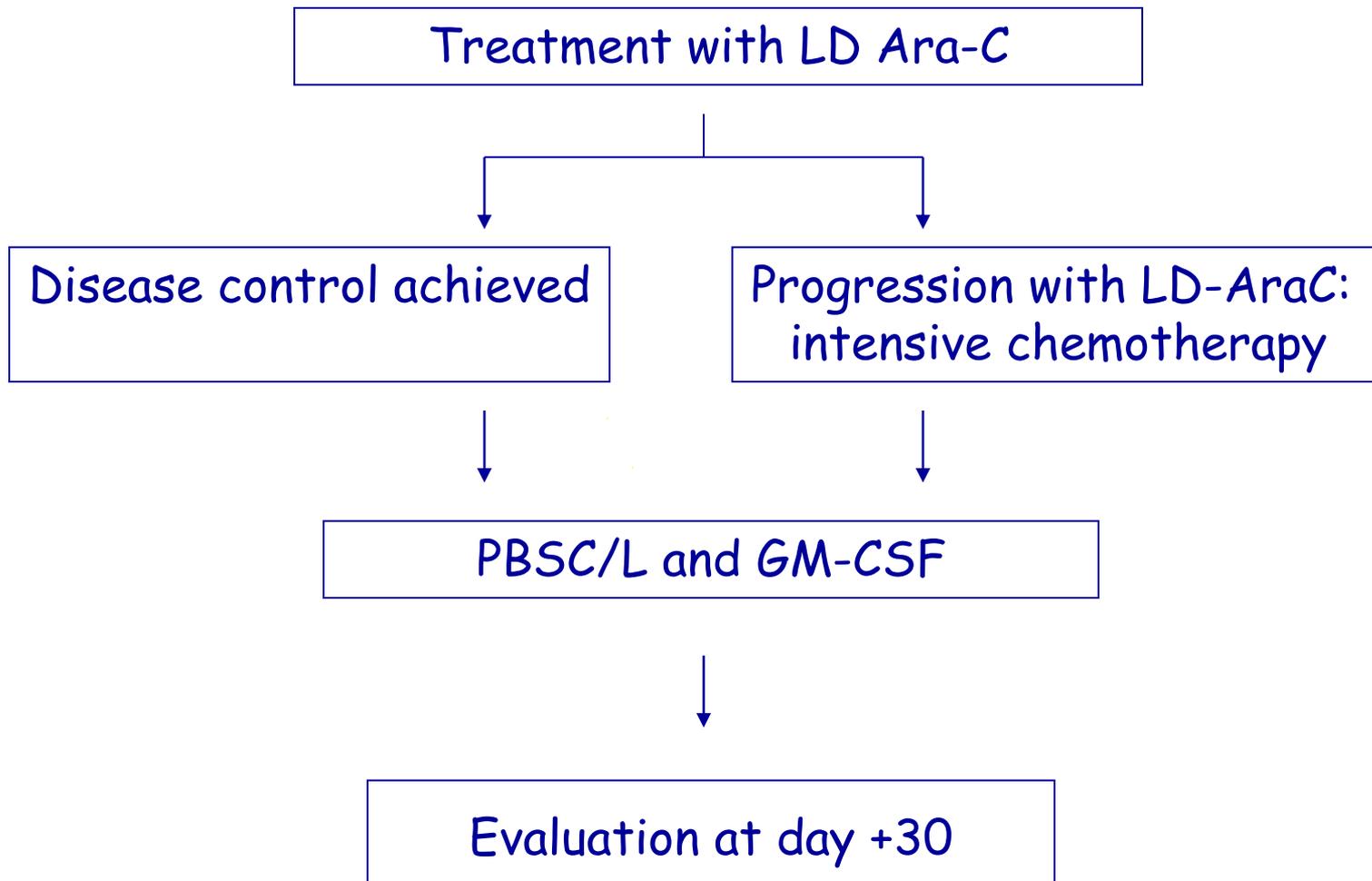
DCs capable of stimulating an AML-specific CTL response
A Woiciechowsky et al



Grabrucker et al., J Immunotherapy, 2010



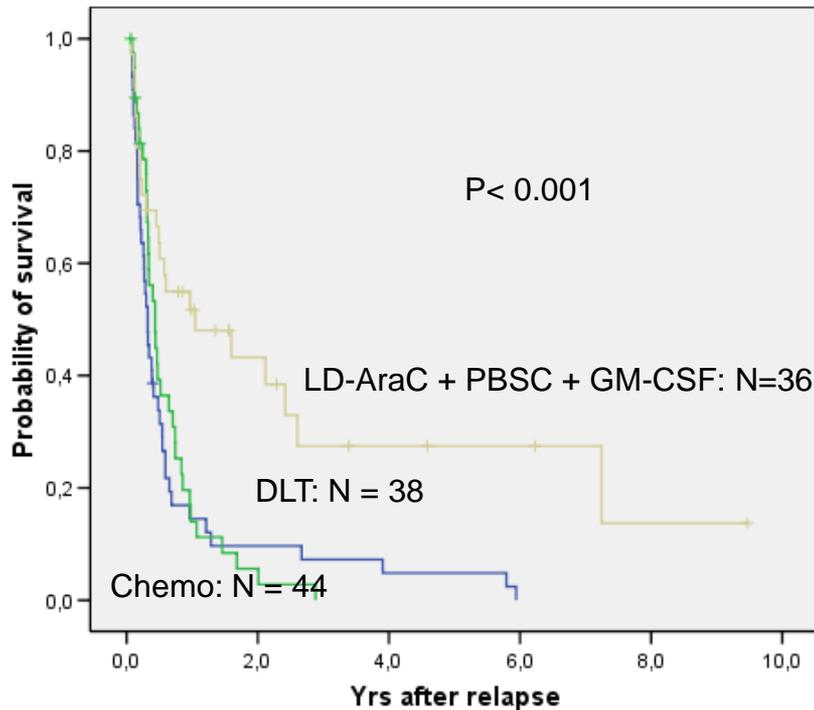
Donor PBSC/L and GM-CSF for AML Relapse post Transplant – Munich pilot study





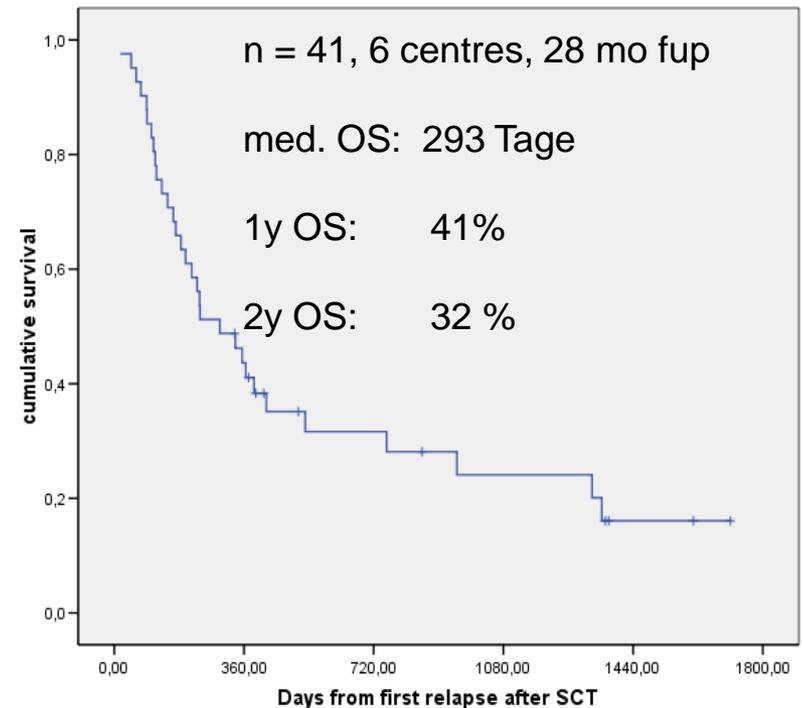
Donor PBSC/L and GM-CSF for AML Relapse post Transplant – Confirmatory Results

Different approaches to post transplant relapse in Munich



Kolb, Blood 2008

Prospective German Multicentre Phase II-Study
AG zelluläre Immuntherapie und SZT,
German Leukemia Net



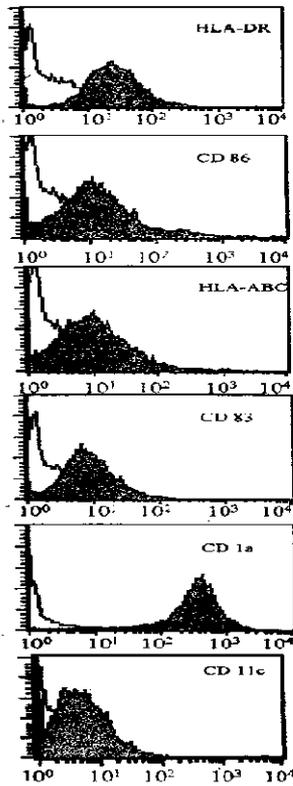
Schmid, unpublished



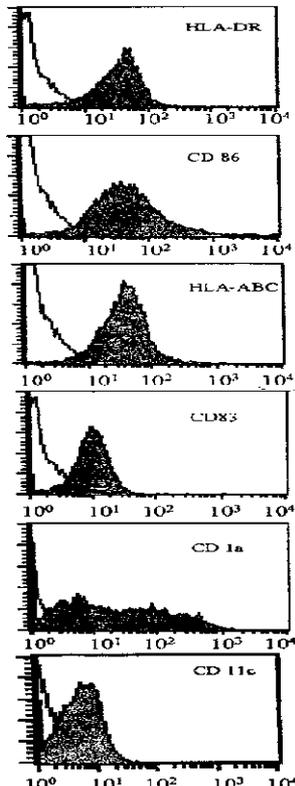
Improved antigen presentation on myeloid cells by IFNa and GM-CSF

CML cells in culture

GM-CSF + IL4



GM-CSF + IFN



HLA-DR

CD 86

HLA-ABC

CD83

CD1a

CD11c

Tang, X., et al (ASH 2011)

- IFNa + donor PBSC/L in ALL/AML (n=16)
- CR rate 75%,
66% in pts. without chemotherapy
- 2-year LFS: 50%
- Outcome improved as compared to DLI

X. Chen et al.,
Br. J. Hematol, 2000



Adjunctive Strategies to Improve Cell Therapy for Relapse

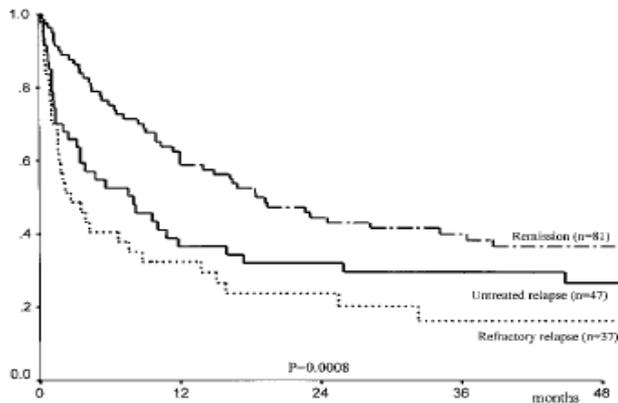


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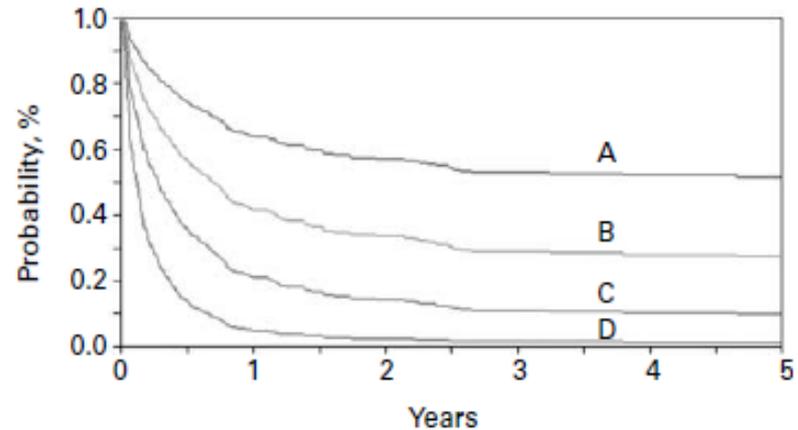


Second Allogeneic Transplant

- Only studied in leukemias
- Retrospective registry data, including mostly 2nd SCT after related first transplant
- overall survival at 5 years around 25 %
- Patient age, remission duration and stage at SCT2 are decisive for outcome



**Bosi et al., EBMT data, JCO 2001
n = 170, AML + ALL**



**Eapen et al., CIBMTR data, BMT 2004
n = 279, acute + chronic leukemia**



Second Allogeneic Transplant

Open questions:

- Role for second HSCT after unrelated first transplant ?
- Does change to a new donor improve the outcome by a better GvL reaction ?



Second Allogeneic Transplant

Role for second HSCT after **un**related first transplant ?

Retrospective analysis of the
German Stem Cell Registry:

179 second transplants

AML, n = 132

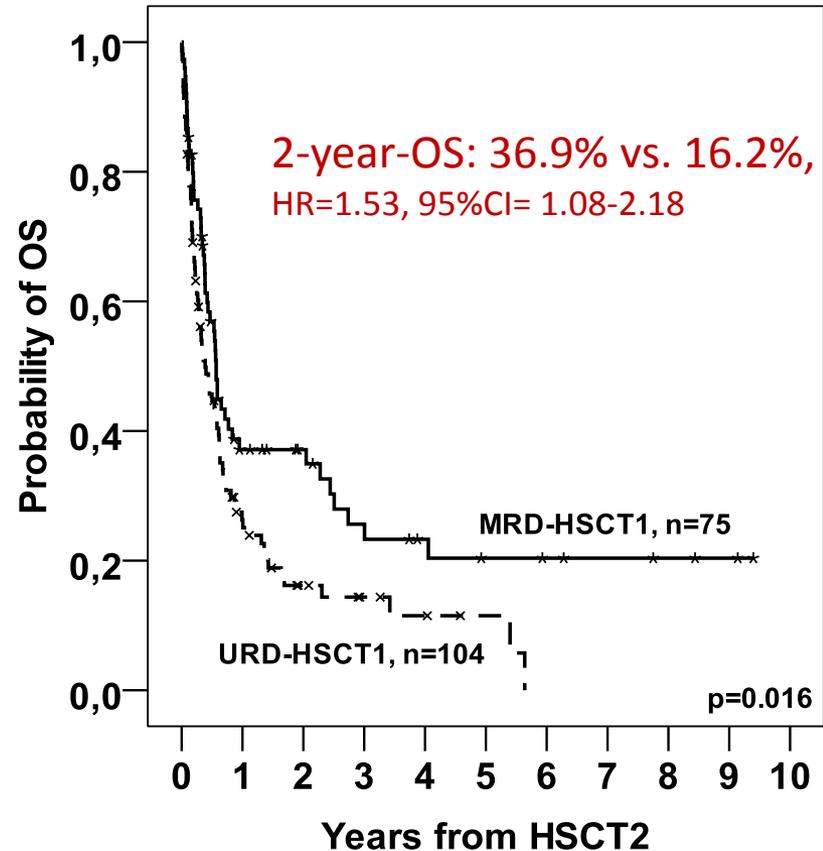
ALL, n = 46

AUL, n = 1

Relapse after

- related SCT1, n = 75

- unrelated SCT1, n = 104



Christopeit et al., submitted



Conclusions

- Remission induction followed by cellular therapy is the only strategy showing long-term outcome after post-transplant relapse in acute leukemias
- Some novel agents have promising effects on the immunogenicity of malignant cells; however, so far, clinical efficacy has been moderate at best
- Immunosuppressive properties of some agents have to be considered in the allogeneic setting
- The role of cytokines for improvement of antigen presentation needs to be studied further
- Second transplants are feasible also in the unrelated setting and with new donors, however, new approaches are warranted to improve long term results



Acknowledement

Many thanks to all friends and colleagues from

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Thank you

